December 2011 Issue 6


FETAL ALCOHOL FORUM©

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# The International Medical e-Network devoted to Fetal Alcohol Spectrum Disorders

**NOFAS-UK**
National Organisation for Fetal Alcohol Syndrome – UK
165 Beaufort Park, London NW11 6DA, England
Tel: 020 8458 5951, Fax: 020 8209 3296
Helpline 08 700 333 700
Email: info@nofas-uk.org
Website: www.nofas-uk.org
Charity No. 1101935

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## INTRODUCTION


Susan Fleisher

As the FETAL ALCOHOL FORUM has gained more recognition, so too has the issue of Fetal Alcohol Spectrum Disorder (FASD). Millions of people around the world live with this challenging disorder. We hope, by putting FASD research on the international medical radar, support for all the people affected will increase and education will help decrease the number of babies born with alcohol related brain damage.

In this issue you will find abstracts of FASD studies from 28 countries along with a selection of articles, full studies and FASD news.

As always, we begin with original articles contributed by leading FASD experts: Albert E. Chudley, MD, FRCPC, FCCMG, Canada; Piyadasa W. Kodituwakku, PhD, USA; Carmen Rasmussen, PhD, Canada and researcher Leigh Anne Davies who worked closely with Professor Denis Viljoen in South Africa.

In the 2nd section you will find abstracts of studies linking alcohol to DNA damage, investigating gene interaction and bio-markers, new studies on low level and moderate drinking, the effects of early postnatal ethanol exposure, prevalence studies in Ireland and Australia recording higher alcohol consumption in pregnancy than previously estimated, predicting a rise in FASD births, and thought provoking articles by FASD legal experts from 'THE JOURNAL OF PSYCHIATRY & LAW'.

Italy and Spain, in the absence of epidemiological studies, did surveys to assess the knowledge and confidence of medical professionals in diagnosing FAS and FASD.

Study #99 in the Ukraine suggests that 'partner based' interventions could make a significant contribution to FASD prevention. (Contact NOFAS-UK for our prevention support "Fathers Leaflet")

Several animal studies investigate antioxidant agents with neuro-protective properties that could ameliorate some ethanol damage.

The debate about the benefits of alcohol in pregnancy is also represented

I invite you to review the articles from our experts and the abstracts of the enlightening studies that follow.

In the past 6 months, since the last publication of the FETAL ALCOHOL FORUM, we have located FASD studies in 28 countries.

The United States produced the most FASD research in the world with 73 studies. However, based on population, (US - 307,006,550 and Canada – 34,108,752 in 12/2011), the 31 studies produced by Canada, per capita, is 9 times as many as the US.

NOTE: FASD studies worldwide during the past 6 months.

| | |
|---|---|
| USA | 73 |
| CANADA | 31 |
| AUSTRALIA | 10 |
| SPAIN | 7 |
| DENMARK | 5 |
| ITALY | 5 |
| BRAZIL | 3 |
| SOUTH AFRICA | 3 |
| SOUTH KOREA | 4 |
| CHINA | 3 |
| GERMANY | 3 |
| IRAN | 2 |
| THE NETHERLANDS | 3 |
| FINLAND | 2 |
| RUSSIA | 2 |
| SWITZERLAND | 2 |
| UNTIED KINGDOM | 2 |
| ARGENTINA | 1 |
| BELGIUM | 1 |
| CôTE D'IVOIRE | 1 |
| ISRAEL | 1 |
| JAPAN | 1 |
| NORWAY | 1 |
| POLAND | 1 |
| PORTUGAL | 1 |
| REPUBLIC OF IRELAND | 1 |
| SWEDEN | 1 |
| TURKEY | 1 |

Please let us have your feedback at info@nofas-uk.org. You can download all 6 issues of the FETAL ALCOHOL FORUM from our website: www.nofas-uk.org. To be added to our mailing list click here. Please also let us know if you would like to make a contribution to the next issue of the FETAL ALCOHOL FORUM.

Thank you for your interest in the world of Fetal Alcohol Spectrum Disorders and beyond.

Susan Fleisher
Publisher

Vandana Alimchandani
Editor/Technical Supervisor

Elizabeth Mitchell
Associate Editor

Leigh-Anne Davies
Researcher

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## ORIGINAL ARTICLES BY FASD EXPERTS

### I. COMMENTARY: A PERSONAL REFLECTION: FETAL ALCOHOL SPECTRUM DISORDER- WHY IS IT STILL WITH US?

Albert E. Chudley, MD, FRCPC, FCCMG
Professor, Department of Paediatrics and Child Health,
and Department of Biochemistry and Medical Genetics,
University of Manitoba; Medical Director, Program in
Genetics and Metabolism, Winnipeg Regional Health Centre


Dr. Albert Chudley

My involvement and interest in Fetal Alcohol Spectrum Disorder (FASD) began when I was a medical student at the University of Manitoba and a resident in Paediatrics at the Winnipeg Children's Hospital in the early 1970's. I was intrigued with issues of the health of children and disabilities, and especially with the new area, at the time, of clinical genetics and dysmorphology. Learning dysmorphology was not easy. I believe you have to have a natural knack for it, or at the very least have outstanding teachers and see lots of rare cases. It was during those formative years that many syndromes were being described, including Fetal Alcohol Syndrome (FAS). Shortly after FAS was "re-discovered" by David W. Smith and his brilliant fellow Ken Jones, I had the pleasure of meeting David at a Society of Paediatric research meeting in Denver, and was able to discuss with him the children with FAS we had seen in Winnipeg. We had seen numerous unexplained growth retarded, dysmorphic and failure to thrive infants from Northern Manitoba at Children's Hospital. David and his colleagues, with their two Lancet articles in 1973 had revealed to us the aetiology.

Unfortunately, my colleagues and I continue to see many affected children. Indeed, over the past 10 years, we have diagnosed over 1000 children with FASD in the Manitoba FASD Centre in Winnipeg. From our perspective, the rates do not appear to be decreasing despite public service messages, posters, pamphlets, workshops, health care provider counselling, paraprofessional mentorship programmes, etc. Over the past 20 years, my efforts in FASD expanded to include involvement in activities with colleagues to develop a multidisciplinary team approach to diagnosis and care. We met regularly with professionals from social work (as many of these kids are in care because of neglect and/or abuse due to alcoholism in the family), teachers, school psychologists and child psychiatrists (who saw these children as a challenge in the classroom with school failure and attention difficulties), the justice system with lawyers, judges, police (many adolescents and adults with FASD often have difficulties with the law), occupational therapists and speech and language pathologists (for issues of motor-sensory and language impairments). The coming together of these disciplines has resulted in the provincial and federal governments responding to unmet needs of diagnosis, intervention and prevention. At the federal level, I was fortunate to be appointed to a national advisory committee on FASD, and as a group we developed guidelines for FASD diagnosis in Canada. This was a priority and a serious concern, as many centres and professionals did not have a consistent approach to diagnosis (especially with those affected in the expanded "invisible" spectrum), and physicians, alone in their offices, were reluctant to make a diagnosis without more resources, support and training. We believed that once teams developed and started to diagnose children, then this would drive the development of services and treatment protocols. To a large extent, this proved to be correct, although the issue of capacity for diagnosis remains a challenge.

For the third and most recent phase concerning my interests in FASD, I have been fortunate to work with many research colleagues in Winnipeg, across Canada and in France and Israel to incorporate my interests in the genome and how genetic factors may either predispose to, or protect against

FASD. In addition, with our colleagues in the NeuroDevNet, a research initiative through the National Centre of Excellence, we are exploring the connection between genetic factors, psychological findings, MR imaging and electro-physiologic findings in children with FASD in Canada. In Manitoba, we plan to investigate the role of some key developmental pathways, study maternal characteristics and nutritional factors to define their role in FASD. The topic of epigenetics is also hot in medicine these days, as this mechanism may be key to influencing a number of human diseases, such as cancer, but also FASD. Epigenetics refers to changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence. Many of the effects from alcohol on gene expression probably are due to epigenetic effects, rather than direct changes in DNA sequences. Our goal is to find a "molecular signature" or reliable biomarker that would aid in the diagnosis and hopefully prevention of FASD. Some of my colleagues are now developing research protocols to better understand speech, language and psychological patterns or profiles in FASD children. It certainly is an exciting time to be involved with the advances in technology that will allow us a better understanding of the biological consequences of FASD.

There are many mysteries surrounding FASD. One is the prevalence rate. Research has identified that neonates in intensive care units, children in protective care, children experiencing school failure and youth and adults involved with the justice system have the highest rates. A decade ago, Europeans were sceptical of the existence of FASD, despite the fact that Dr. Lemoine in France was one of the first to describe the outcome of children of alcoholics in 1968. Slowly, Europe, including the UK, is awakening to the reality of FASD and not in small part, due to the efforts of organizations such as NOFAS-UK and SAF in France.

One of the greatest challenges in FASD is primary prevention. This brings me to the title of this commentary. We have made the fewest strides in prevention than in any other aspect of FASD. What are the reasons for this? It has always puzzled me why governments have not fully, vigorously and urgently tackled the issue and impact of prenatal exposure to alcohol. Research has shown the effects of prenatal alcohol to be associated with high lifetime costs and is devastating to the lives of children exposed. I believe it is a combination of lack of political will and the strong lobby of the alcohol industry. Take the situation with smoking. It took two generations before the evidence of harm from smoking was acknowledged and stiff action was finally taken by governments. Governments banned smoking advertising in the media, and have kept the sale of tobacco hidden from view. Governments have developed multi-component community interventions, active campaigns to discourage smoking and require manufacturers to place rather distasteful and scary pictures on cigarette packages. This works and smoking prevalence dropped and people live longer. I have been told by senior government officials in Canada and the United States that drinking alcohol is different. It is considered a food, with health benefits when taken at low to moderate levels. Few would argue that low alcohol use is beneficial in pregnant women, nor is there conclusive scientific evidence to suggest this. The low alcohol use and cardiovascular protection benefits may be overstated, and the harms of excessive alcohol intake such as cancer, liver disease and deaths due to drunk driving far outweigh the benefits. I performed a quick search on the web using PubMed to view scientific publications on "smoking prevention". There were 34,801 publications retrieved. Under the heading of "Fetal alcohol syndrome and prevention", there were 681 publications retrieved. I was shocked - over a 50-fold less in interest within the scientific community in FASD prevention! I would not be surprised to see a similar deficiency of research dollars going to FASD research compared to other more attractive research subjects.

So, is there hope for a similar outcome and approach on alcohol use and prevention of FASD? Probably not soon, and not in my generation, but I believe and hope that it is inevitable. It has to happen, for the sake of our children, and it needs to begin now.

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**Biography**
Dr. Albert Chudley is a professor at the University of Manitoba and is Medical Director of the Winnipeg Regional Health Authority Program in Genetics and Metabolism. He is a medical geneticist and pediatrician with experience in the etiology and gene discovery of disorders that cause birth defects and/or intellectual disabilities. Dr. Chudley has a particular interest in the recognition, diagnosis, prevention and intervention strategies related to Fetal Alcohol Spectrum Disorders (FASD). He is the lead author of the Canadian Diagnostic Guidelines for FASD (CMAJ 2005). He served on Health Canada's National Advisory Committee on FASD. He is currently a member of the National FASD Screening Tool Steering Committee of the Canadian Association of Paediatric Health Centres, and Public Health Agency Canada. He is one of the Team Leaders in the FASD stream of the NeurDevNet, established by the National Centres of Excellence. He previously served as a Board member on the Canada Northwest FASD Research Network, and remains a member of the clinical network. He is a former President of the Canadian College of Medical Geneticists. Dr. Chudley has been a consultant to provincial, national and international organizations and governments on issues related to FASD. He is co-Chair of the Second International French FASD meeting to be held on December 15-16, 2011 in
Strasbourg, France.

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## II. SLOW INFORMATION PROCESSING UNDERLIES COGNITIVE BEHAVIORAL DIFFICULTIES IN CHILDREN WITH FASD

P.W. Kodituwakku, Ph.D.
Center for Development and Disability/Pediatrics
University of New Mexico School of Medicine
Pkodituwakku@salud.unm.edu

It is now known that children exposed to alcohol during pregnancy exhibit a wide spectrum of physical (morphological) and neurocognitive outcomes, which are collectively called fetal alcohol spectrum disorders (FASD). While physical anomalies are observed only in a minority of alcohol exposed children, neurocognitive deficits are seen in children across the spectrum. Therefore, the clinician

working in a diagnostic clinic faces an important question: How can alcohol-exposed children without physical features (those labeled as having alcohol related neurodevelopmental disorder or ARND) be differentiated from those children with disabilities who do not have prenatal alcohol exposure such as ADHD or conduct disorder? This question of differential diagnosis can be answered if children with FASD exhibit a unique profile of cognitive-behavioral functioning. Therefore, over the past 3 decades, researchers have invested a great deal of effort to identify such a profile.

In their efforts to delineate the neurocognitive profile of FASD, researchers have probed "different levels of functioning" of alcohol-exposed children, e.g. neural, cognitive and behavioral. We have recently argued that there is a pattern emerging from these investigations, which we characterized as a deficit in the processing and integration of information. We also proposed that *slow processing underlies such deficits in the integration of information* [1]. Summarized below is the evidence that we presented to support these hypotheses.

*Neuronal*: Evidence converging from basic science (e.g. animal models) and neuroimaging studies shows that a number of regions of the brain are vulnerable to alcohol's teratogenicity (causing developmental malformations). Studies using neuroimaging methods like voxel-based morphometry and diffusion tensor imaging have revealed that children with FASD show various structural abnormalities of the brain. These include reduced white matter (neural fibers connecting different regions of the brain) and abnormal grey matter in some regions [2]. Our research team has obtained evidence that neural responses of alcohol exposed children's brains, as measured by magneto encephalography, are slower than those of typically developing children.

*Cognitive*: There exists a large body of literature on the effects of prenatal alcohol exposure on both elementary and complex cognitive functions. We have used the term elementary functions to label such basic processes like reflexes and conditioning [3]. Since these elementary functions are mediated by the brain structures that mature early such as the brainstem and cerebellum, researchers have studies them to find clues (biomarkers) of alcohol-induced brain damage at the early stages of development. For example, consistent with the findings from animal models of FASD, children with prenatal alcohol exposure show deficits in eyeblink conditioning [4]. Infants with prenatal alcohol exposure have been observed to be slow in information processing (e.g. attending to environmental stimuli)[5]

Neuropsychological studies of school age children and adults have revealed evidence of diminished intellectual functioning in alcohol-affected children, with those exposed heavily earning IQ scores, on average, in the Borderline range [6]. Another consistent finding is that children and adults with FASD display deficient skills in attention, particularly on tasks involving executive attention. Numerous investigators have reported that heavy prenatal alcohol exposure is associated with deficient skills in cognitive planning, attentional set shifting (shifting attention in a flexible and adaptive manner), rapid generation of responses (e.g. verbal and nonverbal fluency), concept formation, working memory, and response inhibition (controlling irrelevant responses to a novel situation)[7]. Some investigators have obtained evidence that children with FASD are slow at information processing. The pattern of test results revealed by the studies of specific domains of cognitive functioning (e.g. language, memory etc.) is that children with FASD show performance decrement with increase task complexity [8, 9]. For example, alcohol-exposed children are unimpaired at simple linguistic tasks, but impaired at complex social communication tasks[10]; they are unimpaired at object recognition, but impaired at visual-motor integration[11]they are unimpaired at procedural memory (knowing how) task, but unimpaired at declarative memory tasks (knowing that)[12]; they unimpaired at simple recognition memory tasks, but impaired at effortful free recall tasks[8]; they are unimpaired at simple social awareness interaction tasks, but unimpaired at complex social cognition tasks ; and the are unimpaired at simple motor tasks, but impaired at complex motor sequencing tasks. It is now known that performance of complex tasks involves a number of regions of the brain working together under the supervisory control of the prefrontal cortex.

*Behavioral*: Included under the heading of behavioral are observations made by caregivers, teachers and supervisors. Investigators have utilized various rating scales in the assessment of social and emotional functioning and adaptive behavior of children with FASD. One methodological challenge to the study of behavior in this clinical group is that social behavioral problems in alcohol affected children are highly variable because their problems often have multiple sources such as adverse life experiences and genetic factors. Despite such variability, researchers have identified some behaviors that are often seen in children with alcohol exposure irrespective of their socio-cultural backgrounds. These include acting young[13], inattentiveness[14], and deficient adaptive skills, specifically in socialization[15].

*Summary*: The foregoing summary of the results points to the conclusion that slow information processing is at the core of the cognitive behavioral profile of children with FASD. At a neuronal level, children with FASD show reduced white matter and abnormalities of the grey matter suggesting problems with the neural substrates that support information processing in the brain. Children with FASD are slow in their neural and behavioral responses to environmental stimuli. This slowness in information processing has been observed even in infants with prenatal alcohol exposure. At the level of neuropsychological functioning, children with FASD exhibit performance decrement with increased task complexity. Since performance of complex tasks involves the management and integration of multiple elements and relations, efficient information processing is essential for success on such tasks. Similarly, behavioral concerns reported by caregivers and teachers, particularly acting young, inattentiveness, and limited social skills, can be understood as related to fundamental deficit in the processing and integration of multiple facets of information.

Implication for interventions: The hypothesis that slow processing is at the core of the cognitive-behavioral profile of children with FASD has implications for the development of interventions for children with FASD. Parents and teachers have indeed already discovered some of the effective interventions through trial and error. To address the issue of slow intake of information, strategies such as repetition of information and presentation of information at a slower rate will be helpful. To increase the efficiency of processing, strategies such as avoidance of multi-tasking, structuring the environment to reduce distraction, and development of schedules and routines may also prove to be effective. Furthermore, repeated practice of specific elements of a task will also decrease cognitive demands associated with those elements, eventually allowing the child to combine them. In children with FASD who displayed increased emotional reactivity may benefit a combination of specific medications and cognitive-behavioral strategies.

Click here to Read Corresponding Study

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## III. FASD: PERSONAL EXPERIENCE, RESEARCH, AND INTERVENTION

Carmen Rasmussen, PhD
Department of Pediatrics
University of Alberta

My journey into FASD began in adolescence when my family provided a home for many children, some who were affected by FASD. I also worked directly with children with FASD as a youth worker. I saw first-hand the devastating impact of prenatal alcohol exposure on affected children and their families. I personally witnessed the challenges these children face in almost every facet of daily living including difficulties with school, adapting to society, social relations, communication, attention, understanding consequences and mental health issues. I also saw how these difficulties worsened during adolescence, a period when adolescents with FASD tend to deviate even more from their typically developing peers. Not only do societal demands for intact behavioral regulation, reasoning

and decision making (i.e., executive function skills) increase during adolescence, the area of the brain that regulates executive functions (the frontal cortex)(1) still develops through adolescence and is known to be negatively affected by prenatal alcohol exposure (for a review see 2, 3).

My interests in FASD led me to purse an honours degree in Psychology at the University of Calgary, in Calgary, Alberta, Canada. After completion of my degree in 2000, I attended graduate school in Developmental Psychology under the supervision of Dr. Jeffrey Bisanz at the University of Alberta, in Edmonton, Alberta, Canada. I completed my PhD in 2006 focussing on neurobehavioral deficits in children with FASD, specifically in the areas of executive functioning and mathematics. I now work as an Assistant Professor in Pediatrics at the University of Alberta. My research laboratory is focussed on FASD and is located at the Glenrose Rehabilitation Hospital allowing me to work closely with their FASD diagnostic clinic, which is led by Dr. Gail Andrew. I have many students and research assistants working in my lab, all learning about and conducting research in FASD.

FASD is a unique disorder. Not only are individuals with FASD affected by neurobehavioral impairments and brain damage, they may also experience a number of other life circumstances including involvement in foster care, abuse and violence, exposure to other drugs, instability and/or poor quality home environment (4) that can also affect their functioning. Consequently, individuals with FASD have multiple areas of impairment across many systems of care including medical, mental health, social services, education, addictions, family supports (5) and justice. FASD is also distinctive in that it involves the birth mother (who may also be affected by prenatal alcohol exposure) and other family members and truly spans from prevention to intervention.

Given both the uniqueness and breadth of FASD, my area of research is accordingly quite broad. My program of research in FASD is aimed at addressing three critical needs: 1) neurobehavioral outcomes, 2) interventions and 3) prevention. Within the neurobehavioral domain, I research executive functioning and decision making, mathematics, memory, neuropsychological impairments, and behavior problems. I collaborate with Dr. Christian Beaulieu (University of Alberta) on a program of research examining diffusion tensor brain imaging (mapping white matter integrity or the 'wiring' of the brain) among individuals with FASD (6). I am also currently conducting a large FASD study funded by the Canadian Institutes of Health Research (CIHR) looking at outcomes of children and adolescence with prenatal alcohol exposure and FASD. This study examines the developmental course of behavioral, mental health, adaptive and executive function outcomes, the effect of risk and protective factors and specifically the impact of types of service utilization on these outcomes, and the impact of FASD on the family. The next goal of this outcomes study is to follow these children and their families longitudinally. I am also an investigator on the FASD Demonstration Project funded by NeuroDevNet, which is a multi-site study being conducted across Canada headed by Dr. James Reynolds (Queen's University). The goal of this study is to examine gene-environment interactions, predictive biomarkers and the relationship between structural brain alterations and functional outcomes in FASD (7).

Within the Interventions domain, I have conducted studies collaborating with Catholic Social Services in Edmonton, Alberta, evaluating three of their FASD programs (one aimed at preventing FASD among high risk women, one for families of affected children, and one for parents with FASD who are parenting). Through our evaluation, we found all three programs to be highly successful (8, 9, 10). In collaboration with Dr. Jacqueline Pei (University of Alberta), we are examining the efficacy of a mentoring program for youth with FASD and a computerized executive functioning training program. More recently, I am collaborating with Drs. Claire Coles and Julie Kable (Emory University, Atlanta, USA) on a math intervention program for children with FASD. Finally, in terms of prevention, I am collaborating with Dr. Lola Baydala (University of Alberta) to evaluate a program to prevent substance abuse (and ultimately FASD) among high risk communities and youth (11).

Although research on FASD has increased substantially over the last few decades, there is still so much to be learned through future research, with the ultimate goal of improving the lives of children

with FASD and their families. I would like to thank my collaborators, research assistants and graduate and undergraduate students who all work very hard to make this research possible. I would also like to acknowledge the funders for my research including CIHR, NeuroDevNet, Natural Sciences and Engineering Research Council of Canada (NSERC), Public Health Agency of Canada (PHAC), Alberta Centre for Child, Family and Community Research (ACCFCR), Women's and Children's Health Research Institute (WCHRI), and the Glenrose Hospital Clinical Research Fund. Finally, and most importantly, I would like to thank the true champions behind it all: the individuals with FASD and their families who everyday overcome obstacles created by prenatal alcohol exposure. I am grateful for each and every person affected by FASD who take time out of their lives to participate in research to help inform science, knowledge and outcomes of FASD.

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Kennedy, M., &, Kootenay, B. (2009). A culturally adapted drug and alcohol abuse prevention program for Aboriginal children and youth. Progress in Community Health Partnerships: Research, Education, and Action, 3, 7.

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## IV. TIME TO REFLECT~ FETAL ALCOHOL SPECTRUM DISORDER (FASD): NORTHERN CAPE PROVINCE OF SOUTH AFRICA

Leigh-Anne Davies
Doctoral Scholar
Department of Psychology
University of Witwatersrand
leighanne.davies@gmail.com

*Wisdom is the power to put our time and our knowledge to the proper use* ~ Thomas J. Watson

Most professionals reading this article will appreciate the time, energy and costs involved in conducting research studies. They too will have some experience of the positive relationships formed with individual families and communities, as well as the contribution their findings make to existing knowledge. Over the last 20 years, time spent on research studies specific to prenatal alcohol exposure has increased substantially, with findings contributing a wealth of information regarding Fetal Alcohol Spectrum Disorders (FASD). This article serves as a personal overview of my time spent in research in the field of FASD, while at the same time, pulling together key findings I have been involved in.

Fetal Alcohol Spectrum Disorder (FASD) is among the commonest cause of learning disability worldwide, and is totally preventable [1]. The term FASD describes the effects that can occur in an individual who is prenatally exposed to alcohol, encompassing those of Fetal Alcohol Syndrome (FAS), partial FAS, Alcohol Related Birth Defects (ARND) and Alcohol Related Neurodevelopmental Disorder (ARND) [2].

Globally, some of the highest FAS rates occur in South Africa, with several studies suggesting an increase in these rates [3-5]. The reasons for South Africa's high FAS burdens are complex and incompletely understood but may relate to risky maternal alcohol consumption and other maternal factors that increase the risk [5]. High rates of binge drinking (heavy episodic drinking of more than 5 or more units of alcohol per occasion) are common among women in many parts of South Africa with evidence of high drinking patterns amongst pregnant women attending antenatal clinics in the Western Cape [6-8]. The now abolished dop system (where alcohol formed part of labourer's wages on wine farms) is also believed to have played a role in entrenching this heavy pattern. Other known maternal factors linked to an increased risk of having a child with FASD include older age at pregnancy, smoking and low socio-economic status [4, 9-12]. Maternal depression, unintended pregnancies and poor nutrition are further factors which interact with the effects of high-risk drinking patterns [5].

My interest in Fetal Alcohol Syndrome (FAS) began when I joined the Foundation for Alcohol Related Research (FARR) as a research assistant in 2002. Based in South Africa, and established in 1997 by Professor Denis Viljoen, the Foundation aims at primarily increasing the awareness and prevention of alcohol use with specific focus on Fetal Alcohol Spectrum Disorder (FASD). Secondly, offering professional services for diagnosis, management and research related to various areas of FASD and

thirdly, providing training and education of the risks associated with alcohol use at both a grass root and professional level. As a researcher you travel to areas and communities you need to be in, often on limited funds but usually with like-minded colleagues who share an interest in the subject. The team you work with fast become your family, your friends and your mentors, as you collect the research data but more importantly, as you interact in the lives of others. Being a part of the FARR team provided me the entry-point into the FASD speciality with opportunities for research studies in both the Western and Northern Cape regions of South Africa. Many who visit South Africa fall in love with the beauty of Cape Town, in the Western Cape, her sea's, her mountain and the political history of Robben Island. I too love Cape Town but for me, as a South African, the dry and dusty town of De Aar in the Northern Cape, holds beauty almost invisible to the 'untrained' research eye and is the place I will credit to starting me on my research journey.

*Time is precious*~ Unknown

In the late 1990s, a study in Wellington in the Western Cape Province reported a prevalence of FASD of 40.5 – 46.6 per 1000 children 5 – 9 years[3]. Even higher levels of between 65.2 - 74.2 per 1000 in 2000 [12] and 68.0 -89.2 per 1000 in 2002 [4] were reported in subsequent surveys in the same area, using similar methods. In order to determine whether these FASD rates were specific to only wine-growing regions or were more widespread over other South African provinces, further epidemiological studies were necessary.

Local government invited the Foundation for Alcohol Related Research (FARR) to De Aar (2002) and Upington (2003) two communities in the Northern Cape Province to conduct epidemiological studies. The aim was to describe the prevalence, characteristics and risk factors for FAS and partial FAS among schoolchildren in Grade 1, aged 7 years of age. With a background in psychology and sociology, my interests lay specifically in the relationships between early childhood development and socio-economic variables, including that of prenatal alcohol exposure. The combined rates of FAS reported amongst both communities were astounding, with 67.2 per 1000 children presenting with the full FAS features[5]. Cognitively, findings compare to previously conducted studies where children with FASD performed poorly across a broad range of neurodevelopmental outcomes particularly language skills, speed and accuracy of problem solving 13,14 and practically implementing tasks when compared with expected developmental age[14,15]. Mothers of children with FAS were less likely to have attended secondary school and have full time employment. When compared to the controls, they were more likely to smoke, have a lower body mass index and drink during pregnancy while low maternal education levels and employment rates indicate the general low socio-economic status of the study sample[5].

Diagnosing FAS/PFAS is multifaceted with the FAS phenotype evolving with *time* [17-19]. In South Africa, FASD surveys frequently target school-entry children since the diagnosis is believed to be easier and more accurate at this age. Identifying FAS during infancy may be complicated, but guidelines exist for providing an early diagnosis [2]. This early detection would allow for appropriate referrals and intervention, significantly decreasing secondary disabilities in later childhood [19]. It was for this reason that it was necessary to return to both communities to determine baseline infant FASD rates.

So far, in my research experience and in speaking to colleagues involved in various spheres of FASD, I am convinced that all who work in this field are touched by the people, families and communities we work with. In light of this, it was wonderful to be able to return to the De Aar and Upington communities, as part of the FARR team yet again and assess the effectiveness of universal interventions in increasing FASD awareness and altering social norms about drinking during pregnancy.

*Time moves in one direction, memory in another* ~ William Gibson

My Masters degree, part of the larger FARR prevention study, aimed at describing the extent and nature of developmental delay at two points: during infancy (7-12 months of age) and early childhood (17-21 months of age) amongst the De Aar community. Findings suggest that infants with FASD perform worse than their non-FASD counterparts over all subscales of the Griffiths Mental Developmental Scales (GMDS) namely: Locomotor, Personal-Social, Speech-Hearing, Eye-Hand Coordination and Performance as well as the General Quotient. Mean quotients for both groups decline between assessments across subscales with a particularly marked decline in the Hearing-Language scale at 17-21 months of age. By 17-21 months of age the developmental gap between those exposed to prenatal alcohol and the controls widens with low maternal education, maternal depression, high parity and previous loss of sibling/s influencing developmental achievement at 17-21 months of age[18].

Findings from the larger pre and post intervention studies, conducted for the combined De Aar and Upington communities, suggest that maternal knowledge of alcohol harms, pre-intervention, were low with baseline infant FASD prevalence at 8.9% (72/809). With the increase in universal interventions, post-intervention knowledge levels increased substantially, with infant FASD rates dropping to 5.7% (43/751)[20]. These findings, deserve an article of their own, but suggest that universal prevention might reduce FASD by 30% and supports intensifying universal interventions especially where knowledge of harms of maternal drinking are low.

*The present is a point just passed* ~ David Russel

Regardless of the high reported FASD rates in South Africa, a paucity of research still exists on the impact of prenatal alcohol exposure on early childhood development. A clear need for further investigations into the long-term developmental profiles of infants exposed to varying degrees of prenatal alcohol, using an instrument which assesses development over various developmental domains, prompted me to return to the De Aar community to follow-up the infants, now 5 years of age, who formed part of the Pre-Intervention study. Analysis of these findings is currently underway.

At present, I find myself in London, writing up my PhD and am pleased to have connected with Susan Fleisher and other professionals and organizations, such as NOFAS-UK, working at preventing FASD through education, training and support. As we each continue on with our personal, FASD work, research, support, advocacy and/or education it is difficult to hold our focus on the people, the lives and the communities we have changed in conducting the work we have done, often because *time*, deadlines and research commitments force us otherwise.

As I review the literature, crunch the data and write up my results, I think back to all those families who have shared their *time* with me. The colleagues, I have learnt from and spent so much *time* with and the experts who, over *time*, have contributed to the research knowledge, which I now find myself referencing, with admiration.

A final thought emerges - *Time* itself IS precious BUT *Time* spent working with families affected by FASD is...immeasurable.

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PubMed, J Inherit Metab Dis. 2011 Dec 2. [Epub ahead of print]

**1) GLYCOSYLATION DEFECTS UNDERLYING FETAL ALCOHOL SPECTRUM DISORDER: A NOVEL PATHOGENETIC MODEL : "WHEN THE WINE GOES IN, STRANGE THINGS COME OUT" - S.T. COLERIDGE, THE PICCOLOMINI**

Binkhorst M, Wortmann SB, Funke S, Kozicz T, Wevers RA, Morava E.
Department of Pediatrics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

**ABSTRACT**
Fetal alcohol spectrum disorder (FASD) is an umbrella term used to describe the craniofacial dysmorphic features, malformations, and disturbances in growth, neurodevelopment and behavior occurring in individuals prenatally exposed to alcohol. Fetal alcohol syndrome (FAS) represents the severe end of this spectrum. Many pathophysiological mechanisms have hitherto been proposed to account for the disrupted growth and morphogenesis seen in FAS. These include impaired cholesterol-modification of the Sonic hedgehog morphogen, retinoic acid deficiency, lipoperoxidative damage due to alcohol-induced reactive oxygen species combined with reduced antioxidant defences, and malfunctioning cell adhesion molecules. In this report, we propose a completely novel concept regarding the pathogenesis of FAS. Based on our observation that transferrin isoelectric focusing (TIEF) - the most widely used screening tool for congenital disorders of glycosylation (CDG) - was transiently abnormal in a newborn with FAS and a confirmed maternal history of gestational alcohol abuse, we came to believe that FAS exemplifies a congenital disorder of glycosylation secondary to alcohol-inflicted disruption of (N-linked) protein glycosylation. Various pieces of evidence were found in the literature to substantiate this hypothesis. This observation implies, among others, that one might need to consider the possibility of maternal alcohol consumption in newborns with transient glycosylation abnormalities. We also present an integrated pathophysiological model of FAS, which incorporates all existing theories mentioned above as well as our novel concept. This model highlights the pivotal role of disrupted isoprenoid metabolism in the origination of FAS.

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PubMed, Pediatr Neurol. 2011 Dec;45(6):387-91.

**2) CORTICAL THICKNESS IN FETAL ALCOHOL SYNDROME AND ATTENTION DEFICIT DISORDER**

Fernández-Jaén A, Fernández-Mayoralas DM, Quiñones Tapia D, Calleja-Pérez B, García-Segura JM, Arribas SL, Muñoz Jareño N.
Pediatric Neurology Unit, Hospital Universitario Quirón Madrid, Medical Director Centro de Atención a la Diversidad Educativa, Madrid, Spain.

**ABSTRACT**
Fetal alcohol syndrome represents the classic and most severe manifestation of epigenetic changes induced by exposure to alcohol during pregnancy. Often these patients develop attention deficit hyperactivity disorder. We analyzed cortical thickness in 20 children and adolescents with fetal alcohol syndrome and attention deficit hyperactivity disorder (group 1), in 20 patients without fetal alcohol syndrome (group 2), and in 20 control cases. The first group revealed total cortical thickness significantly superior to those of the other two groups. In per-lobe analyses of cortical thickness, group

1 demonstrated greater cortical thickness in the frontal, occipital, and right temporal and left frontal lobes compared with the second group, and in both temporal lobes and the right frontal lobe compared with the control group. This study demonstrated greater cortical thickness in patients with attention deficit hyperactivity disorder and heavy prenatal exposure to alcohol, probably as an expression of immature or abnormal brain development.

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PubMed, Curr Drug Abuse Rev. 2011 Dec 1. [Epub ahead of print]

### 3) SCREENING AMERICAN INDIAN/ALASKA NATIVES FOR ALCOHOL ABUSE AND DEPENDENCE IN MEDICAL SETTINGS

Abbott PJ.
University of New Mexico School of Medicine, Department of Psychiatry and the University of New Mexico Hospitals, Addiction and Substance Abuse Programs (ASAP), 2450 Alamo SE, Albuquerque, 87106, New Mexico. PAbbott@salud.unm.edu

**ABSTRACT**
As a result of the lethal effect that alcohol has had on the American Indian and Alaska Native population, it is vital to aggressively screen for hazardous/harmful use, alcohol abuse and dependence among American Indian/Alaska Natives entering medical settings. This is especially true in primary care settings where individuals may come in for a host of medical problems and may not be directly seeking help in reducing their use of alcohol. There are a number of strategies to screen for hazardous/harmful use and abuse of alcohol in primary care settings. These strategies include: screening questions/questionnaires, biochemical markers and collateral information. There is a growing body of literature which validates the use of some of the standard screening questionnaires among adult American Indians and Alaska Natives including the AUDIT and CAGE. Additionally, there are two instruments that have been validated in two vulnerable American Indian and Alaska Native populations: adolescents and pregnant women. These instruments are the CRAFFT for adolescents and the SAQ for pregnant women. There are currently no studies that were identified in this review that looked specifically at biochemical markers for American Indian and Alaska Natives. Finally, it is important to interview a patient's collaterals both to identify early problems with alcohol and as an adjunct to engaging the patient into treatment. Supportive collaterals can assist the patient to decrease or stop the use of alcohol and engage in treatment.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21999696

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PubMed, Matern Child Health J. 2011 Nov 26. [Epub ahead of print]

### 4) VALIDATION OF THE ALCOHOL USE MODULE FROM A MULTIDIMENSIONAL PRENATAL PSYCHOSOCIAL RISK SCREENING INSTRUMENT

Harrison PA, Godecker A, Sidebottom AC.
Minneapolis Department of Health and Family Support, 250 Fourth St. South, Minneapolis, MN, 55415-1384, USA, pat.harrison@minneapolismn.gov

**ABSTRACT**
The purpose of the study was to validate the Prenatal Risk Overview (PRO) Alcohol use domain

against a structured diagnostic interview. The PRO was developed to screen for 13 psychosocial risk factors associated with poor birth outcomes. After clinic staff administered the PRO to prenatal patients, they asked for consent to administration of selected modules of the structured clinical interview for DSM-IV (SCID) by a research assistant. To assess the criterion validity of the PRO, low and moderate/high risk classifications from the alcohol use domain were cross-tabulated with SCID Alcohol Use Disorder variables. The study sample included 744 women. Based on PRO responses, 48.7% reported alcohol use during the 12 months before they learned they were pregnant; 5.4% reported use post pregnancy awareness. The typical quantity consumed pre-pregnancy was four or more drinks per occasion. Based on the SCID, 7.4% met DSM-IV criteria for either Alcohol Abuse or Dependence. Sensitivity and specificity of the PRO for Alcohol Use Disorders were 83.6 and 80.3%, respectively. Negative predictive value was 98.4% and positive predictive value was 25.3%. The results indicate the PRO effectively identified pregnant women with Alcohol Use Disorders. However, prenatal screening must also detect consumption patterns that do not meet diagnostic thresholds but may endanger fetal development. The PRO also identified women who continued to drink after they knew they were pregnant, as well as those whose previous drinking habits put them at risk for resumption of hazardous use.

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http://www.ncbi.nlm.nih.gov/pubmed/22120427

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PubMed, Child Neuropsychol. 2011 Nov 25. [Epub ahead of print]

**5) SUBSTANCE EXPOSURE IN UTERO AND DEVELOPMENTAL CONSEQUENCES IN ADOLESCENCE: A SYSTEMATIC REVIEW**

Irner TB.
a The Family Center, Hvidovre and Copenhagen, Department of Obstetrics and Gynaecology , Hvidovre University Hospital, Denmark and Department of Psychology, University of Copenhagen , Denmark.

**ABSTRACT**
**Background:** The impacts of maternal substance use have been observed in both research and clinical experience. Several studies have shown that preschool children are at heightened risk of developing various cognitive, behavioral, and socioemotional difficulties. Most knowledge has been generated concerning alcohol consumption during pregnancy and the postnatal effects thereof. Less is known about substance use other than alcohol (for instance, opiates, marijuana, and cocaine) during pregnancy and the long-term developmental consequences.

**Objective:** The aims of this review are to identify relevant published data on adolescents who have been exposed in utero to alcohol and/or other substances and to examine developmental consequences across functions and mental health at this point in life.

**Methods:** PubMed, Embase, and PsychInfo were searched for publications during the period of 1980-2011 and titles and abstracts selected according to prespecified broad criteria.

**Results:** Twenty-five studies fulfilled all of the specific requirements and were included in this review. Most research covered prenatal alcohol exposure. Other substances, however, included cocaine, marijuana, opiates, and poly-substances. Results showed that prenatal exposure to alcohol has long-term cognitive, behavioral, social, and emotional developmental consequences depending on amount and timing of exposure in utero. Less evidence exists for long-term consequences of exposure in utero to other substances than alcohol. However, recent brain-imaging studies have provided important

evidence of serious effects of other substance exposure on the developing brain and recent follow-up studies have found an association with deficits in language, attention, areas of cognitive performance and delinquent behavior in adolescence.

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PubMed, Neuroscience. 2011 Nov 20. [Epub ahead of print]

**6) LOBELINE ATTENUATES NEONATAL ETHANOL-MEDIATED CHANGES IN HYPERACTIVITY AND DOPAMINE TRANSPORTER FUNCTION IN THE PREFRONTAL CORTEX IN RATS**

Smith AM, Wellmann KA, Lundblad TM, Carter L, Barron S, Dwoskin LP.
Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536-0082, USA.

**ABSTRACT**
Current therapies for attention deficit hyperactivity disorder (ADHD) have varying efficacy in individuals with fetal alcohol spectrum disorders (FASD), suggesting that alternative therapeutics are needed. Developmental exposure to ethanol produces changes in dopamine (DA) systems, and DA has also been implicated in ADHD pathology. In the current study, lobeline, which interacts with proteins in dopaminergic presynaptic terminals, was evaluated for its ability to attenuate neonatal ethanol-induced locomotor hyperactivity and alterations in dopamine transporter (DAT) function in striatum and prefrontal cortex (PFC). From postnatal days (PND) 1-7, male and female rat pups were intubated twice daily with either 3 g/kg ethanol or milk, or were not intubated (non-intubated control) as a model for "third trimester" ethanol exposure. On PND 21 and 22, pups received acute lobeline (0, 0.3, 1, or 3 mg/kg), and locomotor activity was assessed. On PND 23-25, pups again received an acute injection of lobeline (1 or 3 mg/kg), and DAT kinetic parameters (Km and V(max)) were determined. Results demonstrated that neonatal ethanol produced locomotor hyperactivity on PND 21 that was reversed by lobeline (1 and 3 mg/kg). Although striatal DAT function was not altered by neonatal ethanol or acute lobeline, neonatal ethanol exposure increased the V(max) for DAT in the PFC, suggesting an increase in DAT function in PFC. Lobeline ameliorated this effect on PFC V(max) at the same doses that decreased hyperactivity. Methylphenidate, the gold standard therapeutic for ADHD, was also evaluated for comparison with lobeline. Methylphenidate decreased DAT V(max) and Km in PFC from ethanol-treated pups. Thus, lobeline and methylphenidate differentially altered DAT function following neonatal ethanol exposure. Collectively, these findings provide support that lobeline may be a useful pharmacotherapy for some of the deficits associated with neonatal ethanol exposure.

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http://www.ncbi.nlm.nih.gov/pubmed/22119644

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PubMed, An Pediatr (Barc). 2011 Nov 19. [Epub ahead of print]

**7) VALIDITY OF A MATERNAL ALCOHOL CONSUMPTION QUESTIONNAIRE IN DETECTING PRENATAL EXPOSURE**

[Article in Spanish]
Manich A, Velasco M, Joya X, García-Lara NR, Pichini S, Vall O, García-Algar O.

Unitat de Recerca Infància i Entorn (URIE), Servicio de Pediatría, IMIM-Hospital del Mar, Parc de Salut Mar, Red SAMID, Barcelona, España.

**ABSTRACT**
**Introduction:** Ethanol consumption by pregnant women can produce severe effects in the foetus and the newborn, mainly in neurological and weight-height development, and are included in the term FASD (Fetal Alcohol Spectrum Disorder). Questionnaires are the most used screening method to detect prenatal exposure, but a previous population study questioned its reliability. The objective of this study was to compare alcohol prenatal exposure detection by questionnaire compared with biomarkers in meconium.

**Methodology:** Sixty two meconium samples from mothers who denied alcohol consumption during pregnancy by questionnaire were analysed. The objective analysis was made by determination of FAEEs (fatty acid ethyl esters) as exposure biomarkers in meconium as biological matrix.

**Results:** In the meconium from 10 of 62 newborns from non-alcohol consuming mothers by questionnaire (16.12%) FAEE values were positive (≥ 2 nmol/g).

**Discussion:** Questionnaires as a screening method during pregnancy are not a reliable tool. It is necessary to identify prenatal exposure to alcohol as soon as possible by biomarkers analysis in biological matrices from the newborn or the mother. The early detection will allow these patients to benefit from follow up and treatment to reach the best possible neurological development.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22104595

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PubMed, Neuroimage. 2011 Nov 9. [Epub ahead of print]

**8) ALONG-TRACT STATISTICS ALLOW FOR ENHANCED TRACTOGRAPHY ANALYSIS**

Colby JB, Soderberg L, Lebel C, Dinov ID, Thompson PM, Sowell ER.
Department of Neurology, University of California Los Angeles (UCLA), Los Angeles, CA, USA; UCLA Interdepartmental Program for Biomedical Engineering, Los Angeles, CA, USA; Developmental Cognitive Neuroimaging Laboratory, Children's Hospital Los Angeles, Los Angeles, CA, USA.

**ABSTRACT**
Diffusion imaging tractography is a valuable tool for neuroscience researchers because it allows the generation of individualized virtual dissections of major white matter tracts in the human brain. It facilitates between-subject statistical analyses tailored to the specific anatomy of each participant. There is prominent variation in diffusion imaging metrics (e.g., fractional anisotropy, FA) within tracts, but most tractography studies use a "tract-averaged" approach to analysis by averaging the scalar values from the many streamline vertices in a tract dissection into a single point-spread estimate for each tract. Here we describe a complete workflow needed to conduct an along-tract analysis of white matter streamline tract groups. This consists of 1) A flexible MATLAB toolkit for generating along-tract data based on B-spline resampling and compilation of scalar data at different collections of vertices along the curving tract spines, and 2) Statistical analysis and rich data visualization by leveraging tools available through the R platform for statistical computing. We demonstrate the effectiveness of such an along-tract approach over the tract-averaged approach in an example analysis of 10 major white matter tracts in a single subject. We also show that these techniques easily extend to between-group analyses typically used in neuroscience applications, by conducting an along-tract analysis of differences in FA between 9 individuals with fetal alcohol spectrum disorders (FASDs) and 11

typically-developing controls. This analysis reveals localized differences between FASD and control groups that were not apparent using a tract-averaged method. Finally, to validate our approach and highlight the strength of this extensible software framework, we implement 2 other methods from the literature and leverage the existing workflow tools to conduct a comparison study.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22094644

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J Popul Ther Clin Pharmacol Vol 18(3):e500-e502; November 5, 2011

### 9) MECONIUM TESTING FOR FATTY ACID ETHYL ESTERS: A 2011 STATUS REPORT

Stuart MacLeod, Gideon Koren

**BRIEF REPORT**

The Canadian Association of Pediatric Health Centres, working in partnership with the Public Health Agency of Canada has recently published a toolkit to guide screening for identification of risk of FAS/FASD. One of the tools highlighted is the testing of meconium for fatty acid ethyl esters to identify high risk pregnancies and to support associated prevention programs. This paper describes the conclusions of a workshop held in Prince Edward Island in September 2011 to discuss key issues surrounding the wider deployment of meconium testing for assessment of population risk for FAS/FASD.

**Read Full Article,**
http://www.cjcp.ca/pubmed.php?articleId=342

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PubMed, Drug Alcohol Rev. 2011 Nov 3. doi: 10.1111/j.1465-3362.2011.00374.x. [Epub ahead of print]

### 10) UNDERSTANDING STANDARD DRINKS AND DRINKING GUIDELINES

Kerr WC, Stockwell T.
Alcohol Research Group, Emeryville, USA Centre for Addictions Research of British Columbia, University of Victoria, Victoria, Canada.

**ABSTRACT**

**Introduction and Aims:** For consumers to follow drinking guidelines and limit their risk of negative consequences they need to track their ethanol consumption. This paper reviews published research on the ability of consumers to utilise information about the alcohol content of beverages when expressed in different forms, for example in standard drinks or units versus percentage alcohol content.

**Design and Methods:** A review of the literature on standard drink definitions and consumer understanding of these, actual drink pouring, use of standard drinks in guidelines and consumer understanding and use of these.

**Results:** Standard drink definitions vary across countries and typically contain less alcohol than actual drinks. Drinkers have difficulty defining and pouring standard drinks with over-pouring being the norm

such that intake volume is typically underestimated. Drinkers have difficulty using percentage alcohol by volume and pour size information in calculating intake but can effectively utilise standard drink labelling to track intake.

**Discussion and Conclusions:** Standard drink labelling is an effective but little used strategy for enabling drinkers to track their alcohol intake and potentially conform to safe or low-risk drinking guidelines.[Kerr WC, Stockwell T. Understanding standard drinks and drinking guidelines. Drug Alcohol Rev 2011].

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22050262

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Science Direct, doi:10.1016/j.brainres.2011.11.010
Received 11 July 2011; revised 1 November 2011; Accepted 3 November 2011. Available online 10 November 2011.

## 11) DIFFERENTIAL EFFECTS OF ETHANOL ON C-JUN N-TERMINAL KINASE, 14-3-3 PROTEINS, AND BAX IN POSTNATAL DAY 4 AND POSTNATAL DAY 7 RAT CEREBELLUM

Marieta Barrow Heaton[a, b, c], Michael Paiva[a, b, c], Stacey Kubovic[a], Alexandra Kotler[a], Jonathan Rogozinski[a], Eric Swanson[a], Vladimir Madorsky[a], Michelle Posados[a]
a Department of Neuroscience, University of Florida College of Medicine
b McKnight Brain Institute
c Center for Alcohol Research, Gainesville, FL 32610–0244, USA

**ABSTRACT**
These studies investigated ethanol effects on upstream cellular elements and interactions which contribute to Bax-related apoptosis in neonatal rat cerebellum at ages of peak ethanol sensitivity (postnatal day 4 [P4]), compared to later ages of relative resistance (P7). Analyses were made of basal levels of the pro-apoptotic c-jun N-termimal kinase (JNK), Bax, and the 14-3-3 anchoring proteins, as well as the responsiveness of these substances to ethanol at P4 versus P7. Dimerization of Bax with 14-3-3 was also investigated at the two ages following ethanol treatment, a process which sequesters Bax in the cytosol, thus inhibiting its mitochondrial translocation and disruption of the mitochondrial membrane potential. Cultured cerebellar granule cells were used to examine the protective potential of JNK inhibition on ethanol-mediated cell death. Basal levels of JNK were significantly higher at P4 than P7, but no differences in the other proteins were found. Activated JNK, and cytosolic and mitochondrially-translocated Bax were increased in P4 but not P7 animals following ethanol exposure, while protective 14-3-3 proteins were increased only at P7. Ethanol treatment resulted in decreases in Bax:14-3-3 heterodimers at P4, but not at P7. Inhibition of JNK activity in vitro provided partial protection against ethanol neurotoxicity.

Thus, differential temporal vulnerability to ethanol in this CNS region correlates with differences in both levels of apoptosis-related substances (e.g., JNK), and differential cellular responsiveness, favoring apoptosis at the most sensitive age and survival at the resistant age. The upstream elements contributing to this vulnerability can be targets for future therapeutic strategies.

**Highlights**
► Ethanol-induced apoptosis in neonatal CNS involves Bax mitochondrial translocation. ► Ethanol-induced apoptosis in neonatal CNS involves enhanced JNK activation. ► Ethanol-induced apoptosis

in neonatal CNS involves decreased Bax:14-3-3 dimers. ► JNK inhibition blunts ethanol-induced apoptosis in cerebellar granule cells. ► Differential ethanol sensitivity can be related to events affecting Bax activation.

**Read Full Article,**
http://www.sciencedirect.com/science/article/pii/S0006899311020373

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PubMed, J Womens Health (Larchmt). 2011 Nov 2. [Epub ahead of print]

**12) TRENDS IN HEALTH-RELATED BEHAVIORAL RISK FACTORS AMONG PREGNANT WOMEN IN THE UNITED STATES: 2001-2009**

Zhao G, Ford ES, Tsai J, Li C, Ahluwalia IB, Pearson WS, Balluz LS, Croft JB.
1 Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention , Atlanta, Georgia.

**ABSTRACT**
**Background:** Unhealthy lifestyle behaviors during pregnancy often predispose women to multiple risks including adverse pregnancy outcomes and impaired health status for mothers. This study assessed the trends in the prevalence of health-related behavioral risk factors over time among U.S. pregnant women.

**Methods:** Data from 22,604 pregnant women aged 18-44 years who participated in the 2001-2009 Behavioral Risk Factor Surveillance System were analyzed to assess the trends in the prevalence of behavioral risk factors. Correlates of having individual or clustering healthy behaviors were also assessed among 2295 pregnant women in the 2009 survey.

**Results:** From 2001 to 2009, among pregnant women, the age-adjusted prevalence of engaging in leisure-time exercise and receiving influenza vaccination increased significantly ($p<0.05$ for linear trends); the prevalence of any alcohol consumption decreased marginally ($p=0.065$ for linear trend); and the prevalence of binge drinking, smoking, and consuming fruits and vegetables ≥5 times/day varied little. Over the 9 years, the percentages of pregnant women who reported having all four healthy behaviors (i.e., not currently smoking, no alcohol consumption, engaging in leisure-time exercise, and receiving influenza vaccination) increased linearly from 7.3% in 2001 to 21.2% in 2009 ($p<0.001$). Sociodemographic characteristics, perceived health status, and health-care availability were differentially associated with certain individual or clustered healthy behaviors.

**Conclusions:** Increased efforts emphasizing multiple health-related behavioral risk factors including reducing alcohol use, binge drinking, and smoking and improving fruit and vegetable consumption during pregnancy are needed.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22047097

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PubMed, Matern Child Health J. 2011 Nov 2. [Epub ahead of print]

**13) EGO-DYSTONIC PREGNANCY AND PRENATAL CONSUMPTION OF ALCOHOL AMONG FIRST-TIME MOTHERS**

O'Brien PL; The Centers for the Prevention of Child Neglect.
Heller School for Social Policy and Management, Brandeis University, Waltham, MA, USA, pegmlob@brandeis.edu

**ABSTRACT**

This study examines predictors of drinking during pregnancy among first-time mothers, in order to distinguish those in need of targeted screening and intervention. Data from the prenatal panel of the Parenting for the First Time study were used in hierarchical linear regressions to determine likelihood of prenatal alcohol consumption among a sample of 645 women. African-American women and those of race/ethnicities other than White were less likely to drink, regardless of age or level of education. Among all women, being in school was associated with abstention (P = 0.05). Among teens, endorsing a perception of feeling "pushed around" was a significant indicator of prenatal alcohol consumption (P = 0.05), as was not having plans for infant feeding shortly before delivery (P = 0.05). Among adults with some level of college education, having a first prenatal visit after the fourth month of pregnancy was a significant predictor of drinking (P = 0.01). This study indicates that women who evidence behaviors or attitudes indicating an ego-dystonic pregnancy (one that is psychologically or emotionally uncomfortable), may be more likely to self-medicate and cope via avoidance through drinking. These behaviors and attitudes may be indicators of the need for targeted screening and intervention, as well as indicators of underlying problems to be targeted in treatment. Further, among all women for whom continued education is a possibility, retaining the ability to attend school during the pregnancy can be protective.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22045021

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PubMed, J Health Commun. 2011 Nov 1. [Epub ahead of print]

**14) CRITIQUING FETAL ALCOHOL SYNDROME HEALTH COMMUNICATION CAMPAIGNS TARGETED TO AMERICAN INDIANS**

Rentner TL, Dixon LD, Lengel L.
a School of Media and Communication, Bowling Green State University , Bowling Green , Ohio , USA.

**ABSTRACT**

It is widely recognized American Indians and Alaska Natives have suffered from far worse health status than that of other Americans. Health communication campaigns directed to American Indians and Alaska Natives and their outcomes must be grounded in an understanding of the historical and ongoing marginalization and cultural dislocation of these groups. The authors draw upon the specific case of health communication campaigns to reduce cases of fetal alcohol syndrome among American Indians and Alaska Natives. Counteracting stereotyping of American Indians and alcohol consumption by mainstream American popular culture and mediated discourses, coverage of fetal alcohol syndrome in the media is assessed. The study analyzes 429 American Indian news articles from 1990 to 2010. Mainstream American and American Indian media should cover health concerns such as fetal alcohol syndrome more extensively. Researchers, health communication campaign developers, health policy makers, and mainstream media must be knowledgeable about American Indian and Alaskan Native identity, cultures, and history, and diversity across Nations. Last, and most important, health communication strategists and health policy makers must welcome American Indians and Alaska

Natives to take leadership roles in communicating culture- and Nation-specific health campaign strategies to eliminate health disparities.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22044046

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PubMed, Nutr Rev. 2011 Nov;69(11):642-59. doi: 10.1111/j.1753-4887.2011.00417.x.

**15) EFFECT OF ALCOHOL CONSUMPTION IN PRENATAL LIFE, CHILDHOOD, AND ADOLESCENCE ON CHILD DEVELOPMENT**

Foltran F, Gregori D, Franchin L, Verduci E, Giovannini M.
Laboratories of Epidemiological Methods and Biostatistics, Department of Environmental Medicine and Public Health, University of Padova, Padova, Italy Department of Paediatrics, San Paolo Hospital and University of Milan, Milan, Italy.

**ABSTRACT**

The effects of alcohol consumption in adults are well described in the literature, while knowledge about the effects of alcohol consumption in children is more limited and less systematic. The present review shows how alcohol consumption may negatively influence the neurobiological and neurobehavioral development of humans. Three different periods of life have been considered: the prenatal term, childhood, and adolescence. For each period, evidence of the short-term and long-term effects of alcohol consumption, including neurodevelopmental effects and associations with subsequent alcohol abuse or dependence, is presented.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22029831

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PubMed, J Neurochem. 2011 Nov;119(4):859-67. doi: 10.1111/j.1471-4159.2011.07467.x. Epub 2011 Oct 11.

**16) ETHANOL CAUSES THE REDISTRIBUTION OF L1 CELL ADHESION MOLECULE IN LIPID RAFTS**

Tang N, Farah B, He M, Fox S, Malouf A, Littner Y, Bearer CF.
Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland, USA Duke-NUS Graduate Medical School, Singapore Department of Neurosciences, Case Western Reserve University, Cleveland, Ohio, USA NineSigma, Cleveland, Ohio, USA Department of Pediatrics, Cleveland Clinic, Cleveland, Ohio, USA.

**ABSTRACT**

Fetal alcohol spectrum disorder is estimated to affect 1% of live births. The similarities between children with fetal alcohol syndrome and those with mutations in the gene encoding L1 cell adhesion molecule (L1) implicates L1 as a target of ethanol developmental neurotoxicity. Ethanol specifically inhibits the neurite outgrowth promoting function of L1 at pharmacologic concentrations. Emerging evidence shows that localized disruption of the lipid rafts reduces L1-mediated neurite outgrowth. We

hypothesize that ethanol impairment of the association of L1 with lipid rafts is a mechanism underlying ethanol's inhibition of L1-mediated neurite outgrowth. In this study, we examine the effects of ethanol on the association of L1 and lipid rafts. We show that, in vitro, L1 but not N-cadherin shifts into lipid rafts following treatment with 25 mM ethanol. The ethanol concentrations causing this effect are similar to those inhibiting L1-mediated neurite outgrowth. Increasing chain length of the alcohol demonstrates the same cutoff as that previously shown for inhibition of L1-L1 binding. In addition, in cerebellar granule neurons in which lipid rafts are disrupted with methyl-beta-cyclodextrin, the rate of L1-mediated neurite outgrowth on L1-Fc is reduced to background rate and that this background rate is not ethanol sensitive. These data indicate that ethanol may inhibit L1-mediated neurite outgrowth by retarding L1 trafficking through a lipid raft compartment.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21884525

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PubMed, Can Fam Physician. 2011 Nov;57(11):e430-5.

### 17) COMPREHENSIVE TREATMENT PROGRAM FOR PREGNANT SUBSTANCE USERS IN A FAMILY MEDICINE CLINIC

Ordean A, Kahan M.
St Joseph's Health Centre, Family Medicine, 30 The Queensway, Toronto, ON M6R 1B5; e-mail ordeaa@stjoe.on.ca

**ABSTRACT**

**Problem being addressed:** Substance use during pregnancy is a substantial public health problem and a risk factor for poor neonatal outcomes. Prenatal care is often provided in high-risk pregnancy units, separate from addiction treatment.

**Objective of program:** To provide comprehensive prenatal care and addiction treatment in a family medicine setting.

**Description of program:** The Toronto Centre for Substance Use in Pregnancy (T-CUP) is a family medicine-based program in a large urban city in Ontario. The T-CUP program comprises an interdisciplinary team using a one-stop access model to provide comprehensive services for pregnant women with a history of alcohol or drug abuse, including prenatal and postnatal medical care, addiction counseling, and assistance with complex psychosocial needs.

**Evaluation:** A retrospective chart review was performed, including charts for 121 women who received care at T-CUP from August 2000 to January 2006. Women demonstrated a high compliance rate with prenatal care attendance. Most women reported reduction in a variety of drug use categories. Significant differences were found especially among women who presented earlier in their pregnancies ($P < .05$). As a result, neonatal outcomes were satisfactory and approximately 75% of newborns were discharged home in the care of their mothers.

**Conclusion:** Pregnant substance-using women have positive maternal and infant health outcomes when they receive comprehensive care in a family medicine setting.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22084472

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PubMed, Alcohol Alcohol. 2011 Oct 27. [Epub ahead of print]

**18) UNIVERSAL PREVENTION IS ASSOCIATED WITH LOWER PREVALENCE OF FETAL ALCOHOL SPECTRUM DISORDERS IN NORTHERN CAPE, SOUTH AFRICA: A MULTICENTRE BEFORE-AFTER STUDY**

Chersich MF, Urban M, Olivier L, Davies LA, Chetty C, Viljoen D.
Centre for Health Policy, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand.

**ABSTRACT**

**Aims:** Prevalence of fetal alcohol spectrum disorders (FASDs) is remarkably high in several provinces of South Africa; yet population-level knowledge of the harms of maternal drinking remains low. In two heavily affected areas, we assessed effectiveness of interventions to heighten awareness of these harms and to alter social norms about drinking in pregnancy.

**Methods:** FASD prevalence, maternal knowledge and drinking behaviours were investigated in two Northern Cape Province towns, before and after interventions which included highlighting FASD using local media and health promotion talks at health facilities. Independently, two dysmorphologists and a neuropsychometrist examined children at 9 and 18 months.

**Results:** Pre-intervention maternal knowledge of alcohol harms was low and FASD prevalence 8.9% (72/809). Interventions reached high coverage and knowledge levels increased substantially. FASD prevalence was 5.7% post-intervention (43/751; P = 0.02); 0.73 lower odds, controlling for maternal age and ethnicity (95% confidence interval = 0.58-0.90). No change was detected in more severe FASD forms, but in the whole population, median dysmorphology scores reduced from 4 [inter-quartile range (IQR) = 2-7] to 3 (IQR = 1-6; P = 0.002).

**Conclusion:** This, the first prevention study using FASD outcomes, suggests that universal prevention might reduce FASD by ~30% and have population-level effects. This supports intensifying universal interventions where knowledge of harms of maternal drinking is low. These efforts need to be accompanied by alcohol-dependence treatment to lower more severe FASD forms.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22037537

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PubMed, Neurology. 2011 Oct 25;77(17):e96.

**19) TEACHING NEUROIMAGES: SCHIZENCEPHALY IN FETAL ALCOHOL SYNDROME**

Spalice A, Del Balzo F, Nicita F, Papetti L, Ursitti F, Salvatori G, Mattiucci C, Mancini F, Tarani L.
Division of Child Neurology, Department of Pediatrics, University "La Sapienza," Rome, Viale Regina Elena 324, 00161 Rome, Italy childneurology.sapienzaroma@live.it

No abstract available.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22025464

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PubMed, Alcohol Clin Exp Res. 2011 Oct 21. doi: 10.1111/j.1530-0277.2011.01661.x. [Epub ahead of print]

**20) A REVIEW OF SOCIAL SKILLS DEFICITS IN INDIVIDUALS WITH FETAL ALCOHOL SPECTRUM DISORDERS AND PRENATAL ALCOHOL EXPOSURE: PROFILES, MECHANISMS, AND INTERVENTIONS**

Kully-Martens K, Denys K, Treit S, Tamana S, Rasmussen C.
From the Department of Pediatrics (KK-M, KD, CR), Centre for Neuroscience (ST), and Department of Educational Psychology (ST), University of Alberta, Edmonton, AB, Canada.

**ABSTRACT**

**Background:** Individuals gestationally exposed to alcohol experience a multitude of sociobehavioral impairments, including deficits in adaptive behaviors such as social skills.

**Methods:** The goal of this report is to critically review research on social skills deficits in individuals with prenatal alcohol exposure, including individuals with and without fetal alcohol spectrum disorders (FASD).

**Results:** Social deficits are found in alcohol-exposed children, adults, and adolescents with and without a clinical presentation. These deficits tend to persist across the lifespan and may even worsen with age. Social deficits in this population appear to be independent of facial dysmorphology and IQ and are worse than can be predicted based on atypical behaviors alone. Abnormalities in neurobiology, executive function, sensory processing, and communication likely interact with contextual influences to produce the range of social deficits observed in FASD.

**Conclusions:** Future investigations should strive to reconcile the relationship between social skills deficits in FASD and variables such as gender, age, cognitive profile, and structural and functional brain impairments to enable better characterization of the deficits observed in this population, which will enhance diagnosis and improve remediation.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22017360

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PubMed, J Biomed Sci. 2011 Oct 21;18:77.

**21) NEUROPROTECTIVE PEPTIDE ADNF-9 IN FETAL BRAIN OF C57BL/6 MICE EXPOSED PRENATALLY TO ALCOHOL**

Sari Y, Segu ZM, Youssefagha A, Karty JA, Isailovic D.
Department of Pharmacology, College of Pharmacy and Pharmaceutical Sciences, University of Toledo, Toledo, OH. youssef.sari@utoledo.edu

**ABSTRACT**

**Background:** A derived peptide from activity-dependent neurotrophic factor (ADNF-9) has been shown to be neuroprotective in the fetal alcohol exposure model. We investigated the neuroprotective effects of ADNF-9 against alcohol-induced apoptosis using TUNEL staining. We further characterize in this study the proteomic architecture underlying the role of ADNF-9 against ethanol teratogenesis during early fetal brain development using liquid chromatography in conjunction with tandem mass spectrometry (LC-MS/MS).

**Methods:** Pregnant C57BL/6 mice were exposed from embryonic days 7-13 (E7-E13) to a 25%

ethanol-derived calorie [25% EDC, Alcohol (ALC)] diet, a 25% EDC diet simultaneously administered i.p. ADNF-9 (ALC/ADNF-9), or a pair-fed (PF) liquid diet. At E13, fetal brains were collected from 5 dams from each group, weighed, and frozen for LC-MS/MS procedure. Other fetal brains were fixed for TUNEL staining.

**Results:** Administration of ADNF-9 prevented alcohol-induced reduction in fetal brain weight and alcohol-induced increases in cell death. Moreover, individual fetal brains were analyzed by LC-MS/MS. Statistical differences in the amounts of proteins between the ALC and ALC/ADNF-9 groups resulted in a distinct data-clustering. Significant upregulation of several important proteins involved in brain development were found in the ALC/ADNF-9 group as compared to the ALC group.

**Conclusion:** These findings provide information on potential mechanisms underlying the neuroprotective effects of ADNF-9 in the fetal alcohol exposure model.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22017746

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ScienceDirect, doi:10.1016/j.neuropharm.2011.10.006
Received 5 May 2011; revised 7 October 2011; Accepted 8 October 2011. Available online 20 October 2011.

## 22) ANXIETY- AND DEPRESSION-LIKE BEHAVIORS ARE ACCOMPANIED BY AN INCREASE IN OXIDATIVE STRESS IN A RAT MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS: PROTECTIVE EFFECTS OF VOLUNTARY PHYSICAL EXERCISE

Patricia S. Brocardo[a], Fanny Boehme[a, b], Anna Patten[a, b], Adrian Cox[a, b], Joana Gil-Mohapela, Brian R. Christie[a, b, c, d]

a Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada
b Department of Biology, University of Victoria, Victoria, British Columbia, Canada
c Brain Research Centre and Program in Neuroscience, University of British Columbia, Vancouver, British Columbia, Canada
d Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, British Columbia, Canada

**ABSTRACT**
Prenatal ethanol exposure can damage the developing nervous system, producing long-lasting impairments in both brain structure and function. In this study we analyzed how exposure to this teratogen during the period of brain development affects the intracellular redox state in the brain as well as the development of anxiety- and depressive-like phenotypes. Furthermore, we also tested whether aerobic exercise might have therapeutic potential for fetal alcohol spectrum disorders (FASD) by increasing neuronal antioxidant capacity and/or by alleviating ethanol-induced behavioral deficits. Sprague-Dawley rats were administered ethanol across all three-trimester equivalents (i.e., throughout gestation and during the first 10 days of postnatal life). Ethanol-exposed and control animals were assigned to either sedentary or running groups at postnatal day (PND) 48. Runners had free access to a running wheel for 12 days and at PND 60 anxiety- and depressive-like behaviors were assessed. Perinatal ethanol exposure resulted in the occurrence of depressive and anxiety-like behaviors in adult rats without affecting their locomotor activity. Voluntary wheel running reversed the depressive-like behaviors in ethanol-exposed males, but not in ethanol-exposed females. Levels of lipid peroxidation and protein oxidation were significantly increased in the hippocampus and cerebellum of ethanol-exposed rats, and there was a concomitant reduction in the levels of the endogenous antioxidant glutathione. Voluntary exercise was able to reverse the deficits in glutathione both in ethanol-exposed

males and females. Thus, while voluntary physical exercise increased glutathione levels in both sexes, its effects at the behavioral level were sex dependent, with only ethanol-exposed male runners showing a decrease in depressive-like behaviors.

**Highlights**
► Perinatal ethanol exposure leads to anxiety and depression-like behaviors in rats. ► Exercise reverses depression-like behaviors in ethanol-exposed adult male rats. ► Perinatal ethanol exposure leads to an increase in oxidative stress in adult rats. ► Exercise restores glutathione levels in ethanol-exposed adult female and male rats. ► Exercise reduces oxidative stress by enhancing glutathione levels.

**Link to the Article,**
http://www.sciencedirect.com/science/article/pii/S0028390811004618

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PubMed, Alcohol Clin Exp Res. 2011 Oct 20. doi: 10.1111/j.1530-0277.2011.01625.x. [Epub ahead of print]

**23) CHILDREN WITH HEAVY PRENATAL ALCOHOL EXPOSURE EXHIBIT DEFICITS WHEN REGULATING ISOMETRIC FORCE**

Simmons RW, Nguyen TT, Levy SS, Thomas JD, Mattson SN, Riley EP.
From the Motor Control Laboratory (RWS, SSL), School of Exercise and Nutritional Sciences, San Diego State University, San Diego, California; Center for Behavioral Teratology (TTN, JDT, SNM, EPR), Department of Psychology, San Diego State University, San Diego, California; and SDSU/UCSD Joint Doctoral Program in Clinical Psychology (TTN), San Diego, California.

**ABSTRACT**
**Background:** Production of isometric (i.e., constant) force is an essential component of performing everyday functional tasks, yet no studies have investigated how this type of force is regulated in children with confirmed histories of heavy prenatal alcohol exposure.

**Methods:** Children 7 to 17 years old with heavy prenatal alcohol exposure (n = 25) and without exposure (n = 18) applied force to a load cell to generate an isometric force that matched a criterion target force displayed on a computer monitor. Two levels of target force were investigated in combination with 3 levels of visual feedback frequency that appeared on the computer monitor as a series of yellow dots. Force was maintained for 20 seconds and participants completed 6 trials per test condition.

**Results:** Root-mean-square error, signal-to-noise ratio, and sample entropy indexed response accuracy, response variability, and signal complexity, respectively. The analyses revealed that in comparison with controls, children with gestational ethanol exposure were significantly less accurate and more variable in regulating their force output and generated a response signal with greater regularity and less complexity in the time domain.

**Conclusions:** Children with prenatal alcohol exposure experience significant deficits in isometric force production that may impede their ability to perform basic motor skills and activities in everyday tasks.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22014260

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ScienceDirect, doi:10.1016/j.pbb.2011.10.013
Received 20 May 2011; revised 3 October 2011; Accepted 14 October 2011. Available online 20 October 2011.

**24) BEHAVIORAL DEFICITS AND CELLULAR DAMAGE FOLLOWING DEVELOPMENTAL ETHANOL EXPOSURE IN RATS ARE ATTENUATED BY CP-101,606, AN NMDAR ANTAGONIST WITH UNIQUE NR2B SPECIFICITY**

B. Lewis[a], K.A. Wellmann[a], A.M.H. Kehrberg[1, a], M.L. Carter[a], T. Baldwin[a], M. Cohen[a], S. Barron[a]
a Dept. of Psychology, University of Kentucky, Lexington, KY 40506, USA

**ABSTRACT**
NMDAR-mediated excitotoxicity has been implicated in some of the impairments following fetal ethanol exposure. Previous studies suggest that both neuronal cell death and some of the behavioral deficits can be reduced by NMDAR antagonism during withdrawal, including antagonism of a subpopulation of receptors containing NR2B subunits. To further investigate NR2B involvement, we selected a compound, CP-101,606 (CP) which binds selectively to NR2B/2B stoichiometries, for both in vitro and in vivo analyses. For the in vitro study, hippocampal explants were exposed to ethanol for 10 days and then 24 h following removal of ethanol, cellular damage was quantified via propidium iodide fluorescence. In vitro ethanol withdrawal-associated neurotoxicity was prevented by CP (10 and 25 nM). In vivo ethanol exposure was administered on PNDs 1–7 with CP administered 21 h following cessation. Activity (PNDs 20–21), motor skills (PNDs 31–33), and maze navigation (PNDs 43–44) were all susceptible to ethanol insult; treatment with CP (15 mg/kg) rescued these deficits. Our findings show that CP-101,606, a drug that blocks the NR2B/2B receptor, can reduce some of the damaging effects of “3rd trimester” alcohol exposure in our rodent model. Further work is clearly warranted on the neuroprotective potential of this drug in the developing brain.

**Link to the Article,**
http://www.sciencedirect.com/science/article/pii/S009130571100342X

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PubMed, Neuroscience. 2011 Oct 18. [Epub ahead of print]

**25) PERIADOLESCENT ETHANOL EXPOSURE REDUCES ADULT FOREBRAIN CHAT+IR NEURONS: CORRELATION WITH BEHAVIORAL PATHOLOGY**

Ehlers CL, Criado JR, Wills DN, Liu W, Crews FT.
Department of Molecular and Integrative Neurosciences, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.

**ABSTRACT**
Substance abuse typically begins in adolescence; therefore, the impact of alcohol during this critical time in brain development is of particular importance. Epidemiological data indicate that excessive alcohol consumption is prevalent among adolescents and may have lasting neurobehavioral consequences. Loss of cholinergic input to the forebrain has been demonstrated following fetal alcohol exposure and in adults with Wernicke-Korsakoff syndrome.

In the present study, immunohistochemistry for choline acetyltransferase (ChAT) was determined to assess forebrain cholinergic neurons (Ch1-4), and behavioral changes following periadolescent alcohol exposure. Wistar rats were exposed to intermittent ethanol vapor (14 h on/10 h off/day) for 35 days from postnatal day (PD) 22 to PD 57 (average blood alcohol concentration (BAC): 163 mg%). Rats were withdrawn from vapor and assessed for locomotor activity, startle response, conflict behavior in the open field, and immobility in the forced swim test, as adults. Rats were then sacrificed

at day 71/72 and perfused for histochemical analyses. Ethanol vapor-exposed rats displayed: increased locomotor activity 8 h after the termination of vapor delivery for that 24 h period at day 10 and day 20 of alcohol vapor exposure, significant reductions in the amplitude of their responses to prepulse stimuli during the startle paradigm at 24 h withdrawal, and at 2 weeks following withdrawal, less anxiety-like and/or more "disinhibitory" behavior in the open field conflict, and more immobility in the forced swim test. Quantitative analyses of ChAT immunoreactivity revealed a significant reduction in cell counts in the Ch1-2 and Ch3-4 regions of the basal forebrain in ethanol vapor-exposed rats.

This reduction in cell counts was significantly correlated with less anxiety-like and/or more "disinhibitory" behavior in the open field conflict test. These studies demonstrate that behavioral measures of arousal, affective state, disinhibitory behavior, and ChAT+IR, are all significantly impacted by periadolescent ethanol exposure and withdrawal in Wistar rats.

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http://www.ncbi.nlm.nih.gov/pubmed/22033458

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PubMed, Environ Health Perspect. 2011 Oct 17. [Epub ahead of print]

**26) IN UTERO EXPOSURES, INFANT GROWTH, AND DNA METHYLATION OF REPETITIVE ELEMENT AND DEVELOPMENTALLY RELATED GENES IN HUMAN PLACENTA**

Wilhelm-Benartzi CS, Houseman EA, Maccani MA, Poage GM, Koestler DC, Langevin SM, Gagne LA, Banister C, Padbury JF, Marsit CJ.
Brown University.

**ABSTRACT**
**Background:** Fetal programming describes the theory linking environmental conditions during embryonic and fetal development with risk of diseases later in life. Environmental insults in-utero may lead to changes in epigenetic mechanisms potentially affecting fetal development.

**Objectives:** We examined associations between in-utero exposures, infant growth, repetitive element and gene-associated DNA methylation in human term placenta tissue samples.

**Methods:** Placental tissues and associated demographic and clinical data were obtained from subjects delivering at Women and Infants Hospital in Providence, RI. LINE-1 and AluYb8 methylation levels were determined in 380 placental samples from term deliveries using bisulfite pyrosequencing. Genome-wide DNA methylation profiles were obtained in a subset of 184 samples using the Illumina Infinium HumanMethylation27 BeadArray. Multiple linear regression, model-based clustering methods and gene set enrichment analysis examined the association between birthweight percentile, demographic variables, repetitive element methylation and gene-associated CpG locus methylation.

**Results:** LINE-1 and AluYb8 methylation levels were found to be significantly positively associated with birthweight percentile ($p=0.01$ and $p<0.0001$ respectively), and were found to differ significantly amongst tobacco smoke and alcohol exposed infants. Increased placental AluYb8 methylation was positively associated with average methylation among CpG loci found in polycomb group target genes; developmentally related transcription factor binding sites were over-represented for differentially methylated loci associated with both elements.

**Conclusions:** Our results suggest that epigenetic alterations in repetitive element methylation markers, most notably AluYb8 methylation, may be susceptible to the intrauterine environment, play a

critical role in mediating placenta function and ultimately inform on the developmental basis of health and disease.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22005006

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J Popul Ther Clin Pharmacol Vol 18(3):e494-e499; October 16, 2011

## 27) THE CANADIAN GUIDELINES AND THE INTERDISCIPLINARY CLINICAL CAPACITY OF CANADA TO DIAGNOSE FETAL ALCOHOL SPECTRUM DISORDER

Sterling K Clarren, Jan Lutke, Michelle Sherbuck

**ABSTRACT**

**Background:** In 2005, the CMAJ published the Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. The intent of this publication was to encourage a more consistent interdisciplinary team approach and diagnostic procedure for FASD diagnoses. That same year, the Canada Northwest FASD Research Network (CanFASD Northwest) determined the locations and capacity for interdisciplinary FASD diagnosis across Canada. Six years later, we wondered how successfully these Guidelines had been in bringing consistency to FASD clinical work.

**Method:** All clinical programs in Canada that routinely performed FASD evaluations were identified through membership in either our Network Action Team on FASD Diagnosis, professional meetings, organizational memberships, websites, programs lists available from Provincial or Federal offices or by word of mouth. Surveys were sent to all of the programs identified.

**Results:**A total of 55 clinics had been identified in seven provinces and one territory in 2005 that did FASD multidisciplinary diagnostics. In 2011 only 44 clinics were identified in six provinces and one territory using the same methodology. Survey responses were completed by 89% of these 44 clinics identified in 2011. The Guidelines were well known to all programs and actively referred to by most. Only 46% of respondents had a full staff of professionals on site for diagnosis, however 90% did use the team approach in determining final FASD diagnosis, while 79% used the team to help in developing a treatment plan. Among the clinics reporting, 74% of them used the new diagnostic schema proposed in the Guidelines and another 12% report using both the Guidelines and another system for diagnosis.

**Interpretation:** The Guidelines have become well known to the medical community. They have contributed to increased consistency in approach and in diagnosis. The variations in clinical ability to fully staff themselves, and the 20% decline in clinic numbers suggest important funding gaps. Many provinces and territories still have no local interdisciplinary programs for FASD diagnosis, and the need across Canada is still many times greater than what is currently available.

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http://www.cjcp.ca/pubmed.php?articleId=341

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PubMed, Childs Nerv Syst. 2011 Oct 15. [Epub ahead of print]

**28) HEAD CIRCUMFERENCE AT BIRTH AND EXPOSURE TO TOBACCO, ALCOHOL AND ILLEGAL DRUGS DURING EARLY PREGNANCY**

Ortega-García JA, Gutierrez-Churango JE, Sánchez-Sauco MF, Martínez-Aroca M, Delgado-Marín JL, Sánchez-Solis M, Parrilla-Paricio JJ, Claudio L, Martínez-Lage JF.
Pediatric Environmental Health Specialty Unit, Virgen de la Arrixaca University Hospital, 30120, El Palmar, Murcia, Spain, ortega@pehsu.org

**ABSTRACT**

**Aims:** We aimed to assess the effects of exposure to tobacco smoke, alcohol and illegal drugs during early pregnancy on the head circumference (HC) at birth of otherwise healthy neonates.

**Methods:** A follow-up study from the first trimester of pregnancy to birth was carried out in 419 neonates. An environmental reproductive health form was used to record data of substance exposure obtained during the first obstetric visit at the end of the first trimester. A multiple linear regression model was created for this purpose.

**Results:** Alcohol intake during pregnancy and medical ionizing radiation exposure were the most significant predictors of HC. The mothers' alcohol consumption increased with the mothers' and fathers' education level, net family income and fathers' alcohol consumption. In contrast, maternal smoking decreased with increasing mothers' and fathers' education level and net family income. About 13% of the surveyed embryos were exposed to illegal drugs.

**Conclusions:** Mild to moderate alcohol consumption diminishes the at-birth HC of theoretically healthy newborns in a linear form. There was no threshold dose. We perceived a need for increasing the awareness, and for training, of health care professionals and parents, in regard to risks of alcohol consumption and for recommending abstinence of these substances in both parents during pregnancy. It should also be remembered that medical ionizing radiation should be performed only during the first half of the cycle in fertile women. We think that our study has an important social impact as it affords data for implementing policies for promoting "healthy pregnancies".

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22002105

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PubMed, Am J Med Genet A. 2011 Oct 14. doi: 10.1002/ajmg.a.34276. [Epub ahead of print]

**29) PATTERNS OF PRENATAL ALCOHOL EXPOSURE AND ASSOCIATED NON-CHARACTERISTIC MINOR STRUCTURAL MALFORMATIONS: A PROSPECTIVE STUDY**

Feldman HS, Jones KL, Lindsay S, Slymen D, Klonoff-Cohen H, Kao K, Rao S, Chambers C.
Department of Pediatrics, University of California, San Diego, California. sawada@ucsd.edu

**ABSTRACT**

The characteristic facial features of the more severe end of Fetal Alcohol Spectrum Disorders (FASD) include smooth philtrum, thin vermillion of the upper lip, and short palpebral fissures. A systematic evaluation of a comprehensive list of minor structural defects in association with varying patterns of prenatal exposure to alcohol has not been performed. We examined the patterns and timing of prenatal alcohol exposure to minor structural malformations occurring in at least 5% of the sample. Patterns of drinking were evaluated by drinks per day, number of binge episodes, and maximum number of drinks. Timing of exposure was evaluated 0-6 weeks post-conception, 6-12 weeks post-

conception, first trimester, second trimester, and third trimester. Naevus flammeus neonatorum is significantly associated with various patterns of drinking during the second half of the first trimester (RR 1.14, 95% CI 1.04, 1.24 for average number of drinks per day; RR 1.04, 95% CI 1.02, 1.07 for number of binge episodes; RR 1.08, 95% CI 1.01, 1.15 for maximum number of drinks in one episode) and similar for number of binge episodes in all categories of timing of exposure and in the second trimester for average number of drinks per day. Other minor malformations occurring in at least 5% of the sample were not found to be significantly associated with prenatal alcohol exposure. Expected minor malformations were not found to be significantly associated with prenatal alcohol exposure. Naevus flammeus neonatorum appears to be part of the spectrum of features associated with prenatal alcohol exposure.

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http://www.ncbi.nlm.nih.gov/pubmed/22002918

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PubMed, Eur J Neurosci. 2011 Oct;34(8):1200-11. doi: 10.1111/j.1460-9568.2011.07857.x. Epub 2011 Oct 13.

**30) A CIS-ACTING REGION IN THE N-METHYL-D-ASPARTATE R1 3'-UNTRANSLATED REGION INTERACTS WITH THE NOVEL RNA-BINDING PROTEINS BETA SUBUNIT OF ALPHA GLUCOSIDASE II AND ANNEXIN A2 - EFFECT OF CHRONIC ETHANOL EXPOSURE IN VIVO**

Anji A, Kumari M.
Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA.

**ABSTRACT**
A cis-acting region, Δ4, located in the 3'-untranslated region of N-methyl-d-aspartate R1(NR1) mRNA interacts with several trans-acting proteins present in polysomes purified from fetal cortical neurons. Chronic ethanol exposure of fetal cortical neurons increases Δ4 RNA-protein interactions. This increased interaction is due to an increase in one of the Δ4-binding trans-acting proteins identified as beta subunit of alpha glucosidase II (GIIβ). In this study, we examined whether ethanol-mediated regulation of NR1 mRNA in vivo is similar to that in vitro and whether Δ4-trans interactions are important for ethanol-mediated NR1 mRNA stability. Our data show that polysomal proteins from adult mouse cerebral cortex (CC) formed a complex with Δ4 RNA, suggesting the presence of NR1 mRNA-binding trans-acting proteins in CC polysomes. The intensity of the Δ4 RNA-protein complex was increased with polysomes from chronic ethanol-exposed CC. The Δ4 RNA-protein complex harbored GIIβ and a second trans-acting protein identified as annexin A2 (AnxA2). Ethanol-sensitive GIIβ was upregulated by 70% in ethanol-exposed CC. Heparin, a known binding partner of AnxA2, inhibited Δ4 RNA-protein complex formation. Transient transfection studies using chimeric constructs with and without the Δ4 region revealed that cis-trans interactions are important for ethanol-mediated stability of NR1 mRNA. Furthermore, our data highlight, for the first time, the presence of a binding site on the 3'-untranslated region of NR1 mRNA for AnxA2 and demonstrate the regulation of NR1 mRNA by AnxA2, GIIβ and a third NR1 mRNA-binding protein, which is yet to be identified.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21995826

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PubMed, Alcohol Clin Exp Res. 2011 Oct 13. doi: 10.1111/j.1530-0277.2011.01657.x. [Epub ahead of print]

### 31) LOW TO MODERATE ALCOHOL INTAKE DURING PREGNANCY AND RISK OF PSYCHOMOTOR DEFICITS

Bay B, Støvring H, Wimberley T, Denny CH, Mortensen EL, Eriksen HL, Kesmodel US.
From the Department of Epidemiology (BB, H-LFE, USK), School of Public Health, Aarhus University, Aarhus, Denmark; Department of Biostatistics (HS, TW), School of Public Health, Aarhus University, Aarhus, Denmark; Centers for Disease Control and Prevention (CDC) (CHD), Atlanta, Georgia; Institute of Public Health (ELM), University of Copenhagen, Copenhagen, Denmark.

**ABSTRACT**
**Background:** To examine the effects of low to moderate alcohol consumption during pregnancy on child motor function at age 5.

**Methods:** A prospective follow-up study of 685 women and their children sampled from the Danish National Birth Cohort based on maternal alcohol consumption during pregnancy. At 5 years of age, the children were tested with the "Movement Assessment Battery for Children" (MABC). Parental education, maternal IQ, prenatal maternal smoking, the child's age at testing, and gender of child were considered core confounders, while the full model also controlled for prenatal maternal binge drinking episodes, age, maternal prepregnancy body mass index, parity, home environment, postnatal parental smoking, health status, and indicators for hearing and vision impairment.

**Results:** There were no systematic or significant differences in motor function between children of mothers reporting low to moderate levels of average alcohol consumption during pregnancy and children of mothers who abstained.

**Conclusions:** In this study, we found no systematic association between low to moderate maternal alcohol intake during pregnancy and child motor function at age 5.

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http://www.ncbi.nlm.nih.gov/pubmed/21995343

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J Popul Ther Clin Pharmacol Vol 18(3):e486-e493; October 10, 2011

### 32) AN ANALYSIS OF THIRD YEAR MEDICAL STUDENTS' KNOWLEDGE AND PERCEIVED SELF-EFFICACY TO COUNSEL AND SCREEN FOR ALCOHOL USE AMONG PREGNANT WOMEN

Katherine Ott Walter, Dianne L Kerr

**ABSTRACT**
**Background :** Fetal Alcohol Spectrum Disorders (FASDs) are one of the leading preventable causes of mental retardation and birth defects in the United States. FASDs are 100% preventable if a mother does not consume alcohol during pregnancy. Research suggests that physician advice is one of the most important factors in determining whether or not a pregnant woman decreases her alcohol intake. However, most physicians receive very little training on counseling and screening pregnant women for alcohol use.

**Objective:** To assess the knowledge and perceived self-efficacy to counsel and screen for alcohol use among pregnant women in third year medical students at two Midwestern medical schools.

**Methods:** Third year medical students (n = 259) from two Midwestern medical schools were administered a questionnaire via Survey Monkey assessing their knowledge and perceived self-efficacy to counsel for alcohol use among pregnant women as well as their perceived self-efficacy to screen for alcohol use among pregnant women using the T-ACE, CAGE, TWEAK, MAST and AUDIT.

**Results:** Findings revealed that most participants were knowledgeable about the health risks associated with consuming alcohol while pregnant and the screening tools, but less knowledgeable about the self-help/group support and treatment programs available to patients. In contrast, when asked about their confidence in using the different screening tools, although reporting being knowledgeable, they were most confident in using the CAGE and least confident in using the TACE, TWEAK, MAST and AUDIT respectively.

**Conclusions:** Recommendations are offered to medical schools for incorporating additional training in screening instruments and self-help/group support and treatment programs available to patients.

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http://www.cjcp.ca/pubmed.php?articleId=340

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PubMed, Med Hypotheses. 2011 Oct 8. [Epub ahead of print]

### 33) DOES LIGHT ALCOHOL CONSUMPTION DURING PREGNANCY IMPROVE OFFSPRING'S COGNITIVE DEVELOPMENT?

Liang W, Chikritzhs T.
National Drug Research Institute, Curtin University, Perth, Western Australia, Australia.

**ABSTRACT**
We posit that: (i) light alcohol consumption during pregnancy does not improve the cognitive development of human offspring and (ii) observational study outcomes indicating apparent protective effects arise from residual confounding due to socioeconomic status. Our hypotheses counter emerging hypotheses apparent in the epidemiological literature that light alcohol consumption during pregnancy improves offspring's cognitive development. Determining the plausibility of this proposition is important given its potential to influence women's alcohol consumption behavior during pregnancy. However, given ethical concerns, it is unlikely that a randomized control trial will be conducted to test this hypothesis. The veracity of alcohol's purported positive effect on cognitive development is therefore explored here by comparing research evidence on light alcohol consumption to the evidence for folate and DHA supplementation intake during pregnancy. An alternative approach for further testing this hypothesis in observational studies is also suggested.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21985759

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PubMed, Neurotoxicol Teratol. 2011 Oct 7. [Epub ahead of print]

### 34) CHARACTERISTICS AND BEHAVIORS OF MOTHERS WHO HAVE A CHILD WITH FETAL ALCOHOL SYNDROME

Cannon MJ, Dominique Y, O'Leary LA, Sniezek JE, Floyd RL.

**ABSTRACT**
Fetal alcohol syndrome (FAS) is a leading cause of birth defects and developmental disabilities. The

objective of this study was to identify the characteristics and behaviors of mothers of children with FAS in the United States using population-based data from the FAS Surveillance Network (FASSNet). FASSNet used a multiple source methodology that identified FAS cases through passive reporting and active review of records from hospitals, specialty clinics, private physicians, early intervention programs, Medicaid, birth certificates and other vital records, birth defects surveillance programs, and hospital discharge data. The surveillance included children born during January 1, 1995-December 31, 1997. In the four states included in our analysis - Arizona, New York, Alaska, and Colorado - there were 257 confirmed cases and 96 probable cases for a total of 353 FAS cases. Compared to all mothers in the states where surveillance occurred, mothers of children with FAS were significantly more likely to be older, American Indians/Alaska Natives, Black, not Hispanic, unmarried, unemployed, and without prenatal care, to smoke during pregnancy, to have a lower educational level, and to have more live born children. A significant proportion of mothers (9-29%) had another child with suspected alcohol effects. Compared to all US mothers, they were also significantly more likely to be on public assistance, to be on Medicaid at their child's birth, to have received treatment for alcohol abuse, to have confirmed alcoholism, to have used marijuana or cocaine during pregnancy, to have their baby screen positive for alcohol or drugs at birth, to have had an induced abortion, to have had a history of mental illness, to have been involved in binge drinking during pregnancy, and to have drunk heavily (7days/week) during pregnancy. These findings suggest that it is possible to identify women who are at high risk of having a child with FAS and target these women for interventions.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22001355

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PubMed, Neurosci Lett. 2011 Nov 14;505(2):82-6. Epub 2011 Oct 6.

### 35) AMELIORATIVE EFFECT OF BDNF ON PRENATAL ETHANOL AND STRESS EXPOSURE-INDUCED BEHAVIORAL DISORDERS

Popova NK, Morozova MV, Naumenko VS.
Department of Behavioral Neurogenomics, Institute of Cytology and Genetics, Siberian Division of the Russian Academy of Sciences, Lavrentyeva av. 10, 630090 Novosibirsk, Russia.

**ABSTRACT**
Brain-derived neurotrophic factor (BDNF) plays critical role in neuronal development, function, survival and plasticity of mature neurons. The present experiments investigated whether BDNF ameliorates the damaging effect of prenatal ethanol and stress exposure on behavior in offspring. Prenatal exposure of ethanol and stress combined during gestation inverted sexual partner preference of male offspring, increased social contacts with juvenile male mouse and stereotypic burying activity in the marble-burying test suggesting predisposition to homosexuality and to obsessive-compulsive disorder. Centrally administered BDNF (300ng i.c.v.) restored sexual female preference of male adult offspring and decreased marble-burying activity. Ameliorative effect was shown in 7-10 days after BDNF administration. The results provide the first evidence that BDNF improves epigenetic impairment of behavior and may have profound implications in the treatment of neurologic disorders induced by early environmental challenges.

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http://www.ncbi.nlm.nih.gov/pubmed/22005582

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PubMed, Matern Child Health J. 2011 Oct 5. [Epub ahead of print]

**36) ASSOCIATIONS BETWEEN DEPRESSIVE AND ANXIOUS SYMPTOMS AND PRENATAL ALCOHOL USE**

Leis JA, Heron J, Stuart EA, Mendelson T.
Department of Pediatrics, Johns Hopkins University, School of Medicine, 200 North Wolfe Street, Baltimore, MD, 21287, USA, jleis2@jhmi.edu

**ABSTRACT**
Symptoms of depression and anxiety are prevalent during pregnancy and may influence women's health behaviors. The impact of women's mental health on alcohol use may be particularly important to consider as prenatal alcohol use is common and may have serious negative consequences for the developing fetus. The objectives of this study were to investigate the relationships between elevated symptoms of depression and anxiety and subsequent likelihood of any alcohol use and binge drinking during pregnancy. The sample consisted of 12,824 women from a prospective, population-based study from the United Kingdom, the Avon Longitudinal Study of Parents and Children. Participants completed questionnaires assessing alcohol use and depressive and anxious symptoms during the first and third trimesters of pregnancy. A series of multivariable regression models was fit using multiply imputed data. Thirty four percent of women reported having at least one alcoholic drink at 32 weeks' gestation and 17% reported binge drinking. We found a weak association between elevated symptoms of anxiety and any alcohol use but not between elevated symptoms of depression and any alcohol use. Modest associations were found between both elevated symptoms of depression and anxiety at 18 weeks' gestation and binge drinking at 32 weeks' gestation. Elevated symptoms of depression and anxiety may increase risk for binge drinking during pregnancy. Further research into the impact of symptoms of depression and anxiety on binge drinking during pregnancy is needed as this could represent an opportunity for public health intervention.

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http://www.ncbi.nlm.nih.gov/pubmed/21971680

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Mol Psychiatry. 2011 Oct 4. doi: 10.1038/mp.2011.126. [Epub ahead of print]

**37) MECHANISMS OF INITIATION AND REVERSAL OF DRUG-SEEKING BEHAVIOR INDUCED BY PRENATAL EXPOSURE TO GLUCOCORTICOIDS**

Rodrigues AJ, Leão P, Pêgo JM, Cardona D, Carvalho MM, Oliveira M, Costa BM, Carvalho AF, Morgado P, Araújo D, Palha JA, Almeida OF, Sousa N.
1] Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal [2] ICVS/3B's-PT Government Associate Laboratory, Braga/Guimarães, Portugal.

**ABSTRACT**
Stress and exposure to glucocorticoids (GC) during early life render individuals vulnerable to brain disorders by inducing structural and chemical alterations in specific neural substrates. Here we show that adult rats that had been exposed to in utero GCs (iuGC) display increased preference for opiates and ethanol, and are more responsive to the psychostimulatory actions of morphine. These animals presented prominent changes in the nucleus accumbens (NAcc), a key component of the mesolimbic reward circuitry; specifically, cell numbers and dopamine (DA) levels were significantly reduced, whereas DA receptor 2 (Drd2) mRNA expression levels were markedly upregulated in the NAcc. Interestingly, repeated morphine exposure significantly downregulated Drd2 expression in iuGC-exposed animals, in parallel with increased DNA methylation of the Drd2 gene. Administration of a

therapeutic dose of L-dopa reverted the hypodopaminergic state in the NAcc of iuGC animals, normalized Drd2 expression and prevented morphine-induced hypermethylation of the Drd2 promoter. In addition, L-dopa treatment promoted dendritic and synaptic plasticity in the NAcc and, importantly, reversed drug-seeking behavior. These results reveal a new mechanism through which drug-seeking behaviors may emerge and suggest that a brief and simple pharmacological intervention can restrain these behaviors in vulnerable individuals.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21968930

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PubMed, Child Neuropsychol. 2011 Oct 3. [Epub ahead of print]

**38) FACIAL MEMORY DEFICITS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS**

Wheeler SM, Stevens SA, Sheard ED, Rovet JF.
a Neuroscience and Mental Health Program , The Hospital for Sick Children , Toronto , Ontario , Canada.

**ABSTRACT**
Prenatal exposure to alcohol may lead to a range of neurobehavioral effects, including impaired learning and memory. Although children with fetal alcohol spectrum disorders (FASD) exhibit both verbal and nonverbal memory impairments, their memory for faces has not been as thoroughly investigated and the extent literature provides inconsistent results. The aim of the current study was to determine whether difficulties in face memory exist in children with FASD and whether the difficulties are mediated by task demands. To address this, we used two measures of immediate and delayed facial recognition memory, the Children's Memory Scale (CMS) and Test of Memory and Learning (TOMAL). Compared to typically developing controls, children with FASD showed memory deficits on all tests and were more likely to perform in a clinically significant range. As well, children performed more poorly on the CMS compared to TOMAL, a finding consistent with the greater difficulty of the CMS task. Our results are consistent with our hypothesis that children with FASD show impairment in facial memory, particularly on demanding memory tasks.

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http://www.ncbi.nlm.nih.gov/pubmed/21967603

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J Popul Ther Clin Pharmacol Vol 18(3):e475-e485; October 3, 2011

**39) FEELING DIFFERENT: THE EXPERIENCE OF LIVING WITH FETAL ALCOHOL SPECTRUM DISORDER**

Brenda Stade, Joseph Beyene, Kathryn Buller, Shannon Ross, Kayla Patterson, Bonnie Stevens, Michael Sgro, Wendy Ungar, William Watson, Gideon Koren

**ABSTRACT**
**Background**: In Canada the incidences of Fetal Alcohol Spectrum Disorder (FASD) is estimated to be in 1 in 100 live births caused by prenatal exposure to alcohol, the disorder is the leading cause of developmental and cognitive disabilities among Canadian children and its effects are life lasting. No research has attempted to describe the experience of living with FASD from the perspective of

Canadian children.

**Purpose:** The main purpose of this study was to describe the children's experience of living with FASD.

**Methods:** A qualitative method was used to examine the children's experiences. Twenty-two (22) children, aged 6 to 18 years, living in urban and rural communities across Canada participated in an unstructured in-depth interview. Data was analysed using Colaizzi's qualitative method.

**Results:** For all children in this study, living day-to-day with FASD meant feeling different. Within this construct knowing the disability; feeling alone-feeling supported, and overcoming the disability were dominant themes which emerged.

**Conclusion:** Implications for practice and research have been described.

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http://www.cjcp.ca/pubmed.php?articleId=339

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J Popul Ther Clin Pharmacol Vol 18(3):e471-e474; October 1, 2011

**40) LEGAL AND ETHICAL CONSIDERATIONS IN MECONIUM TESTING FOR FETAL EXPOSURE TO ALCOHOL**

Bernard M Dickens

**REVIEW**

In Canadian law, pregnant women are held to owe no enforceable duties of care to their children before birth, but healthcare providers may be held accountable once children are born alive for causing injuries prenatally. When children are born in hospitals, recovered meconium may be tested without consent, but there may be an ethical duty to inform mothers. Meconium belongs to the newborns, and mothers may be required to make decisions about its use in their children's best interests. Proposals to test meconium from particular populations raise concern about stigmatization.

**Read Full Article,**
http://www.cjcp.ca/pubmed.php?articleId=338

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PubMed, J Matern Fetal Neonatal Med. 2011 Oct;24 Suppl 1:34-7.

**41) FETAL ALCOHOL SYNDROME: NEW PERSPECTIVES FOR AN ANCIENT AND UNDERESTIMATED PROBLEM**

de Sanctis L, Memo L, Pichini S, Tarani L, Vagnarelli F.
Department of Pediatric Sciences, University of Torino, Italy. luisa.desanctis@unito.it

**ABSTRACT**

The knowledge of the dangers of alcohol consumption during pregnancy isn't indeed a new issue, but the recent evidences of ethyl-glucuronide and ethyl-sulfate in meconium as novel biomarkers of

prenatal ethanol exposure open new perspectives for the early diagnosis of the alcohol-related birth defects. This is crucial for a better developmental outcome of the affected patients and for preventing additional cases in at risk families. The fetal alcohol syndrome is not a single entity but represents the most severe form of a spectrum of disorders, including distinctive craniofacial alterations, stunted growth and behavioral abnormalities, caused by complex gene-environment interactions. FAS must always be a diagnosis of exclusion and have to be differentiated from many conditions caused by other embryotoxin agents and genetic syndromes that share some phenotypic features. Even if the first trimester is considered the most vulnerable period, nowadays is known that a fetal damage might occur throughout all gestation. Since ethanol consumption is constantly increasing among young women, a substantial amount of work has to be made to implement the knowledge on alcohol fetal effects among women of childbearing age; moreover, awareness and training among professionals in the health care system might play a critical role in the early diagnosis of these serious conditions.

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PubMed, Med Monatsschr Pharm. 2011 Oct;34(10):363-74; quiz 375-6.

**42) PREGNANT OPIOID ADDICTED PATIENTS AND ADDITIONAL DRUG INTAKE. PART I. TOXIC EFFECTS AND THERAPEUTIC CONSEQUENCES**

[Article in German]
Hoell I, Havemann-Reinecke U.
Klinik für Psychiatrie und Psychotherapie, Universitätsmedizin Göttingen, Von-Siebold-Str. 5, 37075 Göttingen. imke.hoell@med.uni-goettingen.de

**ABSTRACT**
Opioid dependent patients often are dependent from the illegal consumption of heroin and, in addition, perform a polytoxicomanic way of consuming drugs. They suffer of various somatic and psychiatric diseases. Moreover, pregnancies of drug addicted women are classified as high-risk pregnancies. With respect to the particular consumed drug substances other than opioids during pregnancy variable forms of teratogenic and toxic effects can be assigned to the baby. Critical values of maternal substance abuse referring to fetal impairment do not exist. With regard to the possible teratogenic and toxic fetal effects of maternal consume of alcohol, tobacco, sedativa, cannabis, cocaine and amphetamines, withdrawal treatment of polytoxicomanic pregnant patients under inpatient medical supervision including medication if necessary represent the first-line-treatment.

With respect to smoking, it is possible to detoxicate the patients also by an outpatient treatment. However, referring to heroin addiction, a maintenance therapy with L-methadone, D/L-methadone or buprenorphine should be preferred since fetal withdrawal symptoms of opioids otherwise can cause severe complications which even can lead to the loss of the fetus and also increase the risks for the mother. Increasing the dose of the opioid substitute may be necessary, for example, to avoid premature uterus contractions. It is to be pointed out that substitution treatment with methadone or buprenorphine also improve the medicinal compliance and psychosocial circumstances of the pregnant patients.Subsequent to delivery, the maintenance treatment should initially be pursued over a further period of time. In the follow up, the question of continuing with maintenance treatment or starting a withdrawal treatment of opioids should be discussed on an individual basis. To sum up, proceeded interdisciplinary care during pregnancy and afterwards by all the professions involved like general practioners as well as social workers, gynaecologists, paediatrists, pharmacists, psychologists

and psychiatrists should be ensured. Futhermore, diagnosis and therapy of the comorbid psychiatric and infectious diseases like hepatitis A, B, C and HIV are necessary and described (see Part II. Comorbidity and their treatment).

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22010420

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PubMed, Dan Med Bull. 2011 Oct;58(10):A4327.

### 43) LACK OF CONSENSUS BETWEEN GENERAL PRACTITIONERS AND OFFICIAL GUIDELINES ON ALCOHOL ABSTINENCE DURING PREGNANCY

Kesmodel US, Kesmodel PS, Iversen LL.
Department of Obstetrics and Gynaecology, Aarhus University Hospital, Skejby, 8200 Aarhus N, Denmark. ukes@soci.au.dk

**ABSTRACT**

**Introduction:** Many pregnant women in Denmark have been advised that some alcohol intake is acceptable. In the 1999-2007-period, the Danish National Board of Health advised pregnant women that some alcohol intake was acceptable. From 2007, alcohol abstinence has been recommended. We aimed to describe the attitudes towards and knowledge about alcohol in pregnancy among general practitioners (GPs) in Denmark in 2000 and in 2009.

**Material and Methods:** In 2000, we invited a representative sample of GPs in the catchment area of the Antenatal Care Centre in Aarhus to participate in the study. Participants were interviewed about their attitudes, beliefs, knowledge and information practice in relation to alcohol in pregnancy. Identical questions were sent to all GPs in the area in 2009.

**Results:** In 2000, most GPs (71%) considered that some alcohol intake in pregnancy was acceptable, mostly on a weekly level. There was considerable interperson variation in the participants' attitudes and recommendations to pregnant women. In 2009, significantly more GPs (51%) considered abstinence to be preferable, and significantly more GPs (53%) gave this advice to pregnant women than in 2000. Their knowledge about the official recommendations on alcohol was good. Older GPs were more likely to recommend abstinence.

**Conclusion:** The attitudes towards and knowledge about drinking in pregnancy among GPs have changed along with the change in official policy.

**Funding:** In 2000, data collection was funded by The Danish National Board of Health (J.no. 407-15-1999).

**Trial Registration:** Not relevant.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21975156

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PubMed, Internist (Berl). 2011 Oct;52(10):1185-90.

**44) EFFECTS OF ALCOHOL AND SMOKING IN PREGNANCY**

[Article in German]
Thäle V, Schlitt A.
Universitätsklinik und Poliklinik für Geburtshilfe und Reproduktionsmedizin, Universitätsklinikum der Martin-Luther-Universität Halle-Wittenberg, Ernst-Grube-Straße 40, 06097, Halle (Saale), Deutschland. volker.thaele@uk-halle.de

**ABSTRACT**
Nicotine and alcohol are legal drugs, which damage not only the health of the consumer, but also the society due to health-economic costs. In pregnancy, the consequences of alcohol consumption and smoking for the unborn life in pregnancy are dramatic. The irreversibly damaging effect of alcohol is proven in each stage of the pregnancy, whereby the phase of the organogenesis is the most sensitive period. Beside a higher incidence for deformations of all organs, the damage of the central nervous system is leading, since mental-intellectual retardation of children after alcohol consumption in pregnancy is proven. Smoking in pregnancy leads likewise to harmful effects, with the intrauterine growth retardation of the fetus being the leading smoking-induced pathology. Smoking- and alcohol-induced damages for the unborn life are irreversible with no therapeutic options. The only therapy is prevention, which means complete cessation of alcohol and smoking in pregnancy.

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http://www.ncbi.nlm.nih.gov/pubmed/21953067

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PubMed, Drug Alcohol Rev. 2011 Sep 29. doi: 10.1111/j.1465-3362.2011.00331.x. [Epub ahead of print]

**45) GUIDELINES FOR PREGNANCY: WHAT'S AN ACCEPTABLE RISK, AND HOW IS THE EVIDENCE (FINALLY) SHAPING UP?**

O'Leary CM, Bower C.
National Drug Research Institute, Curtin University, Perth, Australia Division of Population Sciences, Telethon Institute for Child Health Research, Perth, Australia Centre for Child Health Research, University of Western Australia, Perth, Australia.

**ABSTRACT**
**Issues:** The lack of consensus about whether low to moderate levels of prenatal alcohol exposure are a risk factor for fetal development has generated considerable debate about what advice policies and guidelines should provide.

**Approach:** This paper reviews the evidence from systematic reviews and meta-analyses examining the risk from low and moderate levels of prenatal alcohol exposure, along with the results of articles published 2009-2010, after the reviews.

**Key Findings:** The reported significant effects from low levels of prenatal alcohol exposure are likely due to methodological issues such as confounding and/or misclassification of exposure or outcome and there is no strong research evidence of fetal effects from low levels of alcohol exposure. However, harm is well-documented with heavy exposure and moderate levels of exposure, 30-40 g per occasion and no more than 70 g per week, have been demonstrated to increase the risk of child behaviour problems. Implications. With such a small margin before there is increased risk to the fetus, it would be morally and ethically unacceptable for policies and guidelines to condone consumption of

alcohol during pregnancy. Not all women will follow this advice and some women will inadvertently consume alcohol prior to pregnancy awareness requiring non-judgmental counselling and the provision of rational advice about the likelihood of risk to the fetus.

**Conclusions:** The policy advice that 'the safest choice for pregnant women is to abstain from alcohol during pregnancy' should be maintained. However, the abstinence message needs to be presented in a balanced and rational manner to prevent unintended negative consequences.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21955332

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PubMed, Anat Cell Biol. 2011 Sep;44(3):210-7. Epub 2011 Sep 29.

**46) MODULATION BY THE GABA(B) RECEPTOR SIRNA OF ETHANOL-MEDIATED PKA-A, CAMKII, AND P-CREB INTRACELLULAR SIGNALING IN PRENATAL RAT HIPPOCAMPAL NEURONS**

Lee HY, Yang BC, Lee ES, Chung JI, Koh PO, Park MS, Kim MO.
Department of Biology, College of Natural Sciences (RINS), Gyeongsang National University, Jinju, Korea.

**ABSTRACT**
Fetal alcohol syndrome (FAS) is a developmental neuropathology resulting from in utero exposure to ethanol; many of ethanol's effects are likely to be mediated by the neurotransmitter γ-aminobutyric acid (GABA). We studied modulation of the neurotransmitter receptor GABA(B)R and its capacity for intracellular signal transduction under conditions of ethanol treatment (ET) and RNA interference to investigate a potential role for GABA signaling in FAS. ET increased GABA(B1)R protein levels, but decreased protein kinase A-α (PKA-α), calcium/calmodulin-dependent protein kinase II (CaMKII) and phosphorylation of cAMP-response element binding protein (p-CREB), in cultured hippocampal neurons harvested at gestation day 17.5. To elucidate GABA(B1)R response to ethanol, we observed the effects of a GABA(B)R agonist and antagonist in pharmacotherapy for ethanol abuse. Baclofen increased GABA(B)R, CaMKII and p-CREB levels, whereas phaclofen decreased GABA(B)R, CaMKII and p-CREB levels except PKA-α. Furthermore, when GABA(B1)R was knocked down by siRNA treatment, CaMKII and p-CREB levels were reduced upon ET. We speculate that stimulation of GABA(B1)R activity by ET can modulate CaMKII and p-CREB signaling to detrimental effect on fetal brain development.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22025973

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PubMed, Alcohol Clin Exp Res. 2011 Sep 20. doi: 10.1111/j.1530-0277.2011.01644.x. [Epub ahead of print]

**47) A LIMITED ACCESS MOUSE MODEL OF PRENATAL ALCOHOL EXPOSURE THAT PRODUCES LONG-LASTING DEFICITS IN HIPPOCAMPAL-DEPENDENT LEARNING AND MEMORY**

Brady ML, Allan AM, Caldwell KK.
From the Department of Neurosciences (MLB, AMA, KKC), School of Medicine, University of New

Mexico, Albuquerque, New Mexico.

**ABSTRACT**
**Background:** It has been estimated that approximately 12% of women consume alcohol at some time during their pregnancy, and as many as 5% of children born in the United States are impacted by prenatal alcohol exposure (PAE). The range of physical, behavioral, emotional, and social dysfunctions that are associated with PAE are collectively termed fetal alcohol spectrum disorder (FASD).

**Methods:** Using a saccharin-sweetened ethanol solution, we developed a limited access model of PAE. C57BL/6J mice were provided access to a solution of either 10% (w/v) ethanol and 0.066% (w/v) saccharin or 0.066% (w/v) saccharin (control) for 4 h/d. After establishing consistent drinking, mice were mated and continued drinking during gestation. Following parturition, solutions were decreased to 0% in a stepwise fashion over a period of 6 days. Characterization of the model included measurements of maternal consumption patterns, blood ethanol levels, litter size, pup weight, maternal care, and the effects of PAE on fear-conditioned and spatial learning, and locomotor activity.

**Results:** Mothers had mean daily ethanol intake of 7.17 ± 0.17 g ethanol/kg body weight per day, with average blood ethanol concentrations of 68.5 ± 9.2 mg/dl after 2 hours of drinking and 88.3 ± 11.5 mg/dl after 4 hours of drinking. Food and water consumption, maternal weight gain, litter size, pup weight, pup retrieval times, and time on nest did not differ between the alcohol-exposed and control animals. Compared with control offspring, mice that were exposed to ethanol prenatally displayed no difference in spontaneous locomotor activity but demonstrated learning deficits in 3 hippocampal-dependent tasks: delay fear conditioning, trace fear conditioning, and the delay nonmatch to place radial-arm maze task.

**Conclusions:** These results indicate that this model appropriately mimics the human condition of PAE and will be a useful tool in studying the learning deficits seen in FASD.

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http://www.ncbi.nlm.nih.gov/pubmed/21933200

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PubMed, Midwifery. 2011 Sep 20. [Epub ahead of print]

**48) SCREENING FOR ALCOHOL AND DRUG USE IN PREGNANCY**

Seib CA, Daglish M, Heath R, Booker C, Reid C, Fraser J.
School of Nursing and Midwifery, Queensland University of Technology, Victoria Park Road, Kelvin Grove, Queensland 4059, Australia.

**ABSTRACT**
**Objective:** This study examined the clinical utility and precision of routine screening for alcohol and other drug use among women attending a public antenatal service.

**Study design:** A survey of clients and audit of clinical charts.

**Participants and setting:** Clients attending an antenatal clinic of a large tertiary hospital in Queensland, Australia, from October to December 2009.

**Measurements and findings:** Data were collected from two sources. First, 32 women who reported use of alcohol or other drugs during pregnancy at initial screening were then asked to complete a full

substance use survey. Second, data were collected from charts of 349 new clients who attended the antenatal clinic during the study period. Both sensitivity (86%, 67%) and positive predictive value (100%, 92%) for alcohol and other drug use respectively, were high. Only 15% of surveyed women were uncomfortable about being screened for substance use in pregnancy, yet the chart audit revealed poor staff compliance. During the study period, 25% of clients were either not screened adequately or not at all.

**Key conclusions and implications for practise:** Despite recommended universal screening in pregnancy and the apparent acceptance by our participants, alcohol and other drug (A&OD) screening in the antenatal setting remains problematic. Investigation into the reasons behind, and ways to overcome, the low screening rate could improve health outcomes for mothers and children in this at-risk group. Targeted education and training for midwives may form part of the solution as these clinicians have a key role in implementing prevention and early intervention strategies.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21940079

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PubMed, Tokai J Exp Clin Med. 2011 Sep 20;36(3):63-70.

**49) TOXIC EFFECTS OF ELAEAGNUS ANGUSTIFOLIA FRUIT EXTRACT ON CHONDROGENESIS AND OSTEOGENESIS IN MOUSE LIMB BUDS**

Talaei-Khozani T, Vojdani Z, Dehghani F, Heidari E, Kharazinejad E, Panjehshahin MR.
School of Medicine, Zand Street, Shiraz University of Medical Sciences, Shiraz, Iran. talaeit@sums.ac.ir

**ABSTRACT**
**Objectives:** We determined the effect of Elaeagnus angustifolia extract on chondrogenesis and osteogenesis in mouse embryo limb buds in vitro and in vivo. Limb bud mesenchyme from day 12.5 embryos were used for high-density micromass cultures. Water/alcohol extract was added to culture media at 10, 100, 1000 and 10000 µg/L. Cytotoxicity was tested with neutral red. Chondogenesis was detected by alcian blue and osteogenesis was detected by alizarin red S and alkaline phosphatase activity. For in vivo experiments, 40 pregnant mice were given 0.5, 5.0 or 50.0 mg/kg of the extract between days 8 and 18 of gestation. Embryos were stained with alizarin red S and alcian blue to measure femur and ossified region lengths. Total bone mass volume was measured stereometrically. Data were compared with ANOVA and LSD.

**Results:** In limb bud cultures 10 µg/mL of extract reduced chondrogenesis but not osteogenesis. Higher concentrations had no effect on chondrogenesis or osteogenesis. In pregnant mice 50 mg/kg of the extract significantly increased fetal femur and ossified zone length, but significantly decreased bone and cartilage volumes.

**Significance:** The extract had no favorable effects on chodrification or ossification and appeared to reduce chondrogenesis. This is in apparent contradiction to its empirical effects in human adults.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21932186

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PubMed, Environ Toxicol Pharmacol. 2011 Nov;32(3):465-71. Epub 2011 Sep 10.

**50) ENHANCEMENT OF PLACENTAL ANTIOXIDATIVE FUNCTION AND P-GP EXPRESSION BY SODIUM FERULATE MEDIATED ITS PROTECTIVE EFFECT ON RAT IUGR INDUCED BY PRENATAL TOBACCO/ALCOHOL EXPOSURE**

Li Y, Yan YE, Wang H.
Department of Pharmacology of Basic Medical College, Wuhan University, Wuhan 430071, China.

**ABSTRACT**
This study was aimed to explore the therapeutic effect of sodium ferulate (SF) on rats with intrauterine growth retardation (IUGR), and then to clarify the corresponding mechanism. Pregnant rats were divided into normal group, tobacco/alcohol exposure group, and tobacco/alcohol+SF groups. Fetal developmental indices, placental weight, histological alteration, oxidative and antioxidative-function (e.g. MDA, SOD, CAT) and Mdr1 levels were assayed. Results showed exposure to tobacco/alcohol resulted in reduced fetal developmental indices and placental histological alteration, as well as the increased MDA content, decreased SOD and CAT activities and decreased Mdr1a level. After SF treatment, fetal developmental indices, and placental weight, histological alteration, oxidative and antioxidative-function and mdr1a levels were reversed. Our study indicated SF may be effective in reversing IUGR production, and its underlying mechanism may be due to enhanced placental antioxidative function and P-gp expression, which may be related to IUGR formation by tobacco/alcohol exposure.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22004967

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PubMed, J Womens Health (Larchmt). 2011 Sep 6. [Epub ahead of print]

**51) THE ASSOCIATION BETWEEN MATERNAL ALCOHOL USE AND SMOKING IN EARLY PREGNANCY AND CONGENITAL CARDIAC DEFECTS IN INFANTS**

Mateja WA, Nelson DB, Kroelinger CD, Ruzek S, Segal J.
1 Delaware Division of Public Health , Dover, Delaware.

**ABSTRACT**
**Background:** Alcohol use is an extremely prevalent but preventable risk factor among women seeking to become pregnant. Many women continue to use alcohol in the early stages of pregnancy before they are aware they are pregnant. Research is unclear about the role of maternal alcohol use during pregnancy and congenital cardiac defects, one of the leading types of birth defects in the United States.

**Methods:** Data from the Pregnancy Risk Assessment Monitoring Survey (PRAMS) were used to examine maternal alcohol use and its association with congenital cardiac defects. Various measures of alcohol use in the 3 months prior to pregnancy, as well as smoking and other risk factors for congenital cardiac defects, were linked to birth certificate data for nine states over a 10-year period (1996-2005). In this case-control study, cases included infants with a congenital cardiac defect indicated on the birth certificate, and the control group consisted of healthy, normal weight infants with no indication of a congenital abnormality on their birth certificate. Complex samples logistic regression models were used to study the relationships between several measures of alcohol use, including binge drinking and binge drinking on more than once occasion, and the interaction between alcohol use and smoking with the odds of congenital cardiac defects.

**Results:** A significant increase in congenital cardiac defects was found among mothers who reported binge drinking more than once in the 3 months prior to pregnancy compared to mothers who did not report binge drinking (adjusted odds ratio [aOR] 2.99, 95% confidence interval [CI] 1.19-7.51). There was a significant interaction between any binge drinking or binge drinking more than once and cigarette use, which corresponded to a substancial increase in congenital cardiac defects (aOR 12.65, 95% CI 3.54-45.25 and aOR 9.45, 95% CI 2.53-35.31, respectively).

**Conclusions:** Multiple episodes of maternal binge drinking in early pregnancy may increase the odds of congenital cardiac defects, and we found this relationship was more dramatic when combined with maternal smoking.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21895513

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J Popul Ther Clin Pharmacol Vol 18(3):e440-e453; September 5, 2011

**52) A DIFFERENTIAL APPROACH FOR EXAMINING THE BEHAVIOURAL PHENOTYPE OF FETAL ALCOHOL RESEARCH DISORDERS**

Kelly Nash, Gideon Koren, Joanne Rovet

**Background:** In 2006, Nash and colleagues published results suggesting that individual items from the Child Behavior Checklist (CBCL) could be used as a screening tool that was highly sensitive in differentiating children with FASD from controls and children with Attention Deficit Hyperactivity Disorder (ADHD). Since many of the items referred to features of Oppositional Defiant/Conduct Disorder (ODD/CD), it was not clear whether the items reflected comorbidity with ODD/CD, or were unique to children with FASD.

**Objectives:** The present study sought to replicate the results of our 2006 paper using a new and larger sample, which also includes a group of children diagnosed with ODD/CD.
Methods Retrospective psychological chart review was conducted on 56 children with FASD, 50 with ADHD, 60 with ODD/CD, and 50 normal control (NC) children. Receiver operating characteristic curve (ROC) analysis of CBCL items discriminating FASD from NC was used to compare FASD to the ADHD and ODD/CD groups.

**Results:** ROC analyses showed scores of a) 3 or higher on 10 items differentiated FASD from NC with a sensitivity of 98%, specificity of 42% and b) 2 or higher on 5 items reflecting oppositional behaviors differentiated FASD from ADHD with a sensitivity of 89% and specificity of 42%.

**Conclusion:** Our findings partially replicate the results of our 2006 study and additionally elucidate the behavioural differences between children with FASD and those with ODD/CD. The proposed screening tool is currently the only tool available that is empirically derived and able to differentiate children with FASD from children with clinically similar profiles.

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J Popul Ther Clin Pharmacol Vol 18(3):e426-e439; September 1, 2011

**53) A NEED FOR CLOSER EXAMINATION OF FASD BY THE CRIMINAL JUSTICE SYSTEM: HAS THE CALL BEEN ANSWERED?**

Karina Royer Gagnier, Timothy E Moore, Justice Melvyn Green

**ABSTRACT**

Individuals with FASD exhibit deficits in many domains that can include memory, learning, behavioural inhibition, executive functioning, interpersonal skills, and language. These deficits have serious implications for affected persons when they become engaged in the legal system. In 2004, Moore and Green reviewed case law and psychological literature which suggested that FASD-related deficits placed affected individuals at a significant disadvantage in the justice system. According to them, this disadvantage stemmed from the limited awareness and knowledge of FASD demonstrated by key players in the justice system, as well as the scarcity of effective interventions in place to rehabilitate affected defendants. The aim of the current paper is to assess the extent to which awareness of FASD-related issues in the Canadian justice system has advanced since the publication of Moore and Green's conclusions. First, the deficits associated with FASD and their implications for the justice system are described. Next, recent case law and psychological evidence are reviewed as we consider issues of witness reliability and false confessions. The significance of FASD for sentencing, fitness to stand trial, and the Not Criminally Responsible by Reason of Mental Disorder defence are also briefly discussed. Finally, emerging system wide responses to FASD-related issues are presented. Overall, it appears that the call for closer examination of FASD by the justice system has been answered, but a need for increased education and awareness remains.

**Read Full Article,**
http://www.cjcp.ca/pubmed.php?articleId=333

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PubMed, Afr J Psychiatry (Johannesbg). 2011 Sep;14(4):298-305. doi:

**54) DEVELOPMENTAL DELAY OF INFANTS AND YOUNG CHILDREN WITH AND WITHOUT FETAL ALCOHOL SPECTRUM DISORDER IN THE NORTHERN CAPE PROVINCE, SOUTH AFRICA**

Davies L, Dunn M, Chersich M, Urban M, Chetty C, Olivier L, Viljoen D.
Institute for Child, Youth and Family Studies, Hugenote College, University of Stellenbosch, Stellenbosch, South Africa.

**ABSTRACT**

**Objective:** To describe the extent and nature of developmental delay at different stages in childhood in a community in South Africa, with a known high rate of Fetal Alcohol Spectrum Disorder (FASD).

**Method:** Cohort of infants, clinically examined for FASD at two time periods, 7-12 months (N= 392; 45 FASD) and 17-21 months of age (N= 83, 35 FASD) were assessed using the Griffiths Mental Developmental Scales (GMDS).

**Results:** Infants and children with FASD perform worse than their Non-FASD counterparts over all scales and total developmental quotients. Mean quotients for both groups decline between assessments across subscales with a particularly marked decline in the hearing and language scale at Time 2 (scores dropping from 110.6 to 83.1 in the Non-FASD group and 106.3 to 72.7 in the FASD group; P=0.004). By early childhood the developmental gap between the groups widens with low

maternal education, maternal depression, high parity and previous loss of sibling/s influencing development during early childhood.

**Conclusion:** The FASD group show more evidence of developmental delay over both time points compared to their Non-FASD counterparts. Demographic and socio-economic factors further impact early childhood. These findings are important in setting up primary level psycho-educational and national prevention programmes especially in periurban communities with a focus on early childhood development and FASD.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22038428

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PubMed, Can J Public Health. 2011 Sep-Oct;102(5):336-40.

### 55) FETAL ALCOHOL SPECTRUM DISORDER PREVALENCE ESTIMATES IN CORRECTIONAL SYSTEMS: A SYSTEMATIC LITERATURE REVIEW

Popova S, Lange S, Bekmuradov D, Mihic A, Rehm J.
Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, ON. lana_popova@camh.net

**ABSTRACT**
**Objectives:** The objective of this study was to conduct a systematic search of the literature for studies that estimated the prevalence/incidence of Fetal Alcohol Spectrum Disorder (FASD) in correctional systems in different countries and, based on these data, to estimate a) the number of people with Fetal Alcohol Syndrome (FAS)/FASD within the criminal justice system population, and b) the relative risk of becoming imprisoned for individuals with FAS/FASD compared with those without FAS/FASD.

**Method:** A systematic world literature review of published and unpublished studies concerning the prevalence/incidence of FASD in correctional systems was conducted in multiple electronic bibliographic databases.

**Synthesis:** Very little empirical evidence is available on the prevalence of FASD in correctional systems. There were no studies estimating the prevalence/incidence of FASD in correctional systems found for any country other than Canada and the USA. The few studies that have identified incarcerated individuals with FASD estimate that the number of undiagnosed persons in correctional facilities is high. Based on available Canadian data, this study estimates that youths with FASD are 19 times more likely to be incarcerated than youths without FASD in a given year.

**Conclusion:** More studies investigating the prevalence/incidence of alcohol-affected people in the criminal justice system are required. There is an urgent need to raise awareness about the prevalence and disabilities of individuals with FASD in the criminal justice system and about appropriate responses. The criminal justice system is an ideal arena for intervention efforts aimed at the rehabilitation and prevention or reduction of recidivism in this unique population.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/22032097

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PubMed, J Law Med. 2011 Sep;19(1):69-87.

**56) "MUMMY BEEREST": A STUDY OF FETAL ALCOHOL SPECTRUM DISORDER, A MOTHER'S DUTY OF CARE AND STRATEGIES FOR INTERVENTION**

Nolan EJ.
Office of the Director of Public Prosecutions, Queensland. Elise.Nolan@justice.qld.gov.au

**ABSTRACT**
Fetal alcohol spectrum disorder can occur in children when a mother consumes alcohol while pregnant. It can manifest in a range of both physical and mental impairments and in varying degrees of seriousness. The act of consuming alcohol while pregnant arguably constitutes a breach of the duty of care that a mother owes to her unborn child and may lead to an award of damages for children with the disorder. However, to conclude that a duty is owed to an unborn child may be legally problematic. Further, an award of compensation may be of little utility to the child. It is therefore suggested that intervention strategies should instead be implemented which target relevant population groups and which prevent and assist in the management of the disorder.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21988011

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PubMed, J Ark Med Soc. 2011 Sep;108(4):62-4.

**57) MAKE YOUR OFFICE ALCOHOL-EXPOSED PREGNANCY PREVENTION FRIENDLY**

Rhoads S, Mengel M; Arkansas Team of the Midwest Fetal Alcohol Syndrome Training Center

**ABSTRACT**
This article is third in a series on fetal alcohol spectrum disorders (FASD), and centers on preventing an alcohol exposed pregnancy (AEP). FASDs are 100% preventable if a woman does not drink alcohol during pregnancy. As many pregnancies are unintended, Arkansas providers would best serve childbearing women if they would routinely screen for alcohol use in all childbearing-aged women and encourage women to consider drinking reduction or elimination, or use of an effective method of contraception if they continue to drink alcohol. A systematic process in the clinical setting involving all office personnel enables screening to be a feasible process, otherwise busy clinicians alone often do not have the time to provide these services. A provider other than a physician, such as a trained nurse, can conduct brief interventions after a positive screen while the patient is in the clinic. These brief interventions have been shown to reduce the risk of an AEP. Additionally, there are multiple resources in Arkansas for women who need further treatment for an alcohol use disorder.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21916382

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PubMed, J Addict Med. 2011 Sep;5(3):221-6.

**58) SELF-REPORTED ALCOHOL AND DRUG USE IN PREGNANT YOUNG WOMEN: A PILOT STUDY OF ASSOCIATED FACTORS AND IDENTIFICATION**

Chang G, Orav EJ, Jones JA, Buynitsky T, Gonzalez S, Wilkins-Haug L.
Department of Psychiatry, Brigham and Women's Hospital, Boston, MA, USA. Gchang@partners.org

**ABSTRACT**

**Objectives:** This study describes the factors associated with self-reported substance use in pregnant young women attending a hospital clinic and evaluates 3 ways in its identification.

**Methods:** A cross-sectional study of 30 pregnant young adults who responded to a mail survey containing the CRAFFT screening tool. All completed a diagnostic interview that included self-report information on their use of alcohol and drugs before and during pregnancy, the T-ACE screening tool, and the contexts in which they would be likely to use. Medical records were reviewed.

**Results:** One-third of participants consumed alcohol, marijuana, or both while pregnant. Many had lifetime diagnoses of alcohol (23%) or cannabis (30%) use disorders, but only 1 met criteria for current diagnosis. Age, race, education, and children at home were not associated with either prenatal alcohol or cannabis use. Before pregnancy, alcohol drinking was associated with prenatal alcohol use (P = .02) and prenatal cannabis use (P = .06). Another trend of the before-pregnancy cannabis use being associated with prenatal cannabis use (P = .08) was observed. Most participants indicated little likelihood of substance use in convivial, intimate, or negative coping contexts while pregnant. However, participants with prenatal substance use had significantly higher convivial (P = .02) and intimate (P = .01) subscale scores of the Drinking Context Scale before pregnancy. Compared to the medical record and the T-ACE, the CRAFFT was best in identifying prenatal substance use (c-statistic = 0.9).

**Conclusions:** The CRAFFT screening instrument and asking about the contexts during which alcohol might have been consumed before pregnancy are promising approaches in the identification of prenatal substance use.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21844837

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PubMed, Alcohol. 2011 Aug 31. [Epub ahead of print]

**59) PROCEEDINGS OF THE 2010 ANNUAL MEETING OF THE FETAL ALCOHOL SPECTRUM DISORDERS STUDY GROUP**

Kane CJ, Smith SM, Miranda RC, Kable J.
Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

**ABSTRACT**

The annual meeting of the Fetal Alcohol Spectrum Disorders Study Group (FASDSG) was held on June 26, 2010 in San Antonio, TX, as a satellite of the Research Society on Alcoholism meeting. The FASDSG membership includes clinical, basic, and social scientists who meet to discuss recent advances and issues in Fetal Alcohol Spectrum Disorder (FASD) research. The central theme of the meeting was "Glia and Neurons: Teamwork in Pathology and Therapy." Alcohol disruption of neuron development and alcohol-induced neurodegeneration is central to the pathology and clinical

expression of FASD. The active role of glia as perpetrator, victim, or bystander in neurotoxicology and neurodegenerative processes has emerged at the forefront of adult central nervous system (CNS) disorders and therapy. Glia- and neuron-glial interactions hold the potential to elucidate causes and offer treatment of FASD as well. Growing evidence indicates that neurons and glia are direct targets of alcohol, but may also be vulnerable to molecules produced in peripheral systems as a result of alcohol exposure. Diagnostics and therapies can take advantage of these processes and biomarkers, and these may be applicable to CNS pathology in FASD. Two keynote speakers, Howard E. Gendelman, M.D., and Ernest M. Graham, M.D, addressed the role of glia and neuroinflammation in brain development and neurodegeneration. The invited speakers and FASDSG members discussed new paradigms in CNS development and discuss new strategies for understanding and treating neurodegenerative disease. Members of the FASDSG provided updates on new findings through presentation of breaking research in the FASt data sessions. Representatives of national agencies provided updates on programs, activities, and funding priorities. The Henry Rosett Award was presented to R. Louise Floyd, R.N., D.S.N., for her career contributions to the field of fetal alcohol research. The Student and Postdoctoral Fellow Research Merit Award was presented to Shonagh O'Leary-Moore, Ph.D., for her contributions to the field as a young investigator.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21889288

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PubMed, Clin Exp Pharmacol Physiol. 2011 Aug 30. doi: 10.1111/j.1440-1681.2011.05597.x. [Epub ahead of print]

### 60) MECHANISM OF ALCOHOL-INDUCED IMPAIRMENTS IN RENAL DEVELOPMENT: COULD IT BE REDUCED RETINOIC ACID?

Gray SP, Cullen-McEwen LA, Bertram JF, Moritz KM.
Department of Anatomy & Developmental Biology, Monash University, Clayton, VIC 3800, Australia School of Biomedical Sciences, University of Queensland, QLD 4072, Australia.

**ABSTRACT**

1. Prenatal alcohol exposure impairs kidney development resulting in a reduced nephron number. However, the mechanism through which alcohol acts to disrupt renal development is largely unknown. Retinoic acid is critically involved in kidney development and it has been proposed that a diminished concentration is a contributing factor to fetal alcohol syndrome.

2. In this study we proposed that the ethanol-induced inhibition of ureteric branching morphogenesis and glomerular development in the cultured rat kidney would be ameliorated by co-culture with exogenous retinoic acid, and that examining the expression profile of key genes involved in the development of the kidney would provide insights into potential molecular pathways involved.

3. Whole rat metanephroi cultured in the presence of exogenous retinoic acid without ethanol appeared larger and had significantly more ureteric branch points, tips and glomeruli than metanephroi cultured in control media. Those cultured in the presence of ethanol alone (0.2%) had 20% fewer ureteric branch points, tips and glomeruli, which was ameliorated by co-culture with retinoic acid.

4. Gene expression analysis identified changes in the expression levels of enzymes involved in the metabolism of alcohol, in conjunction with changes in key regulators of kidney development including cRET.

5. These results demonstrate that the teratogenic effects of alcohol in vitro on kidney development

resulting in reduced ureteric branching morphogenesis and glomerular development can be ameliorated through co-culture with retinoic acid. These results provide the foundation for future research into the mechanism through which alcohol acts to disrupt kidney development.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21883382

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PubMed, Int J Circumpolar Health. 2011 Sep;70(4):428-33. Epub 2011 Aug 29.

**61) DEVELOPING EFFECTIVE, CULTURALLY APPROPRIATE AVENUES TO FASD DIAGNOSIS AND PREVENTION IN NORTHERN CANADA**

Salmon A, Clarren SK.
Canada Northwest FASD Research Network, Vancouver, Canada.

**ABSTRACT**
This article describes 2 research initiatives that are being undertaken by members of the Canada Northwest FASD Research Network, involving collaborations between researchers, clinicians, service providers and community members in the Canadian North. Improving both the diagnosis and prevention of FASD requires evidence-based approaches to clinical and social service delivery that are capable of accounting for the unique contours of the geographic, regional and cultural diversities in which women become pregnant and in which families live. Although FASD has been a priority for communities and governments in northern Canada, research capacity has not been available to support the development of the context-specific knowledge needed to inform policy and practice in this region. Moreover, there have not been adequate mechanisms for transferring practice-based knowledge from the Canadian North to researchers and service providers in the South, who might make use of this knowledge to inform their own practice. Herein, we highlight the ways in which reciprocal knowledge exchange involving CanFASD Northwest researchers at academic health science centres and diverse stakeholder groups is supporting multi-directional capacity building in FASD diagnosis and prevention.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21878184

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PubMed, Rev Saude Publica. 2011 Oct;45(5):864-9. Epub 2011 Aug 19.

**62) ASSOCIATION BETWEEN ALCOHOL ABUSE DURING PREGNANCY AND BIRTH WEIGHT**

[Article in English, Portuguese]
Silva I, Quevedo Lde A, Silva RA, Oliveira SS, Pinheiro RT.
Programa de Pós-Graduação em Saúde e Comportamento, Universidade Católica de Pelotas, Pelotas, RS, Brasil. ivelissadasilvat@hotmail.com

**ABSTRACT**
**Objective:** To assess the association between alcohol abuse during gestation and low birth weight.

**Methods:** Cross-sectional, population-based nested study from a cohort of 957 pregnant women who received prenatal assistance through Sistema Único de Saúde (National Health System) in the city of Pelotas, Southern Brazil, and delivered their babies between September 2007 and September 2008.

The mothers were interviewed at two distinct moments: prenatal and postpartum periods. In order to verify alcohol abuse, the CAGE (Cut down, Annoyed by criticism, Guilty and Eye-opener) scale was used. Bivariate analyses were carried out, as well as multiple logistic regression adjusted by the variables prematurity and alcohol abuse. The level of significance that was adopted was 95%.

**Results:** Of the women who participated in the study, 2.1% abused alcohol during pregnancy and, among these, 26.3% had low birth weight children. There was an association between alcohol abuse and low birth weight ($p<0.038$).

**Conclusions:** The findings indicate that alcohol abuse during pregnancy is associated with low birth weight.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21860911

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ScienceDIrect, doi:10.1016/j.ntt.2011.08.002
Received 8 February 2011; revised 20 June 2011; Accepted 4 August 2011. Available online 16 August 2011.

## 63) SELECTIVE EFFECTS OF PERINATAL ETHANOL EXPOSURE IN MEDIAL PREFRONTAL CORTEX AND NUCLEUS ACCUMBENS

R. Charles Lawrence[a], Nicha K.H. Otero[a], Sandra J. Kelly[a]
a Department of Psychology, University of South Carolina, Columbia, SC 29208, United States

**ABSTRACT**
Ethanol exposure during development is the leading known cause of mental retardation and can result in characteristic physiological and cognitive deficits, often termed Fetal Alcohol Spectrum Disorders (FASD). Previous behavioral findings using rat models of FASD have suggested that there are changes in the nucleus accumbens (NAC) and medial prefrontal cortex (mPFC) following ethanol exposure during development. This study used a rat model of FASD to evaluate dendritic morphology in both the NAC and mPFC and cell number in the NAC. Dendritic morphology in mPFC and NAC was assessed using a modified Golgi stain and analyzed via three dimensional reconstructions with Neurolucida (MBF Bioscience). Cell counts in the NAC (shell and core) were determined using an unbiased stereology procedure (Stereo Investigator (MBF Bioscience)). Perinatal ethanol exposure did not affect neuronal or glial cell population numbers in the NAC. Ethanol exposure produced a sexually dimorphic effect on dendritic branching at one point along the NAC dendrites but was without effect on all other measures of dendritic morphology in the NAC. In contrast, spine density was reduced and distribution was significantly altered in layer II/III neurons of the mPFC following ethanol exposure. Ethanol exposure during development was also associated with an increase in soma size in the mPFC. These findings suggest that previously observed sexually dimorphic changes in activation of the NAC in a rat model of FASD may be due to altered input from the mPFC.

**Highlights**
► Developmental ethanol exposure did not affect cell number in the nucleus accumbens. ► Developmental ethanol exposure did not impact dendrites in the nucleus accumbens. ►

Developmental ethanol exposure reduced spine density in the medial prefrontal cortex. ► Developmental ethanol altered spine distribution in the medial prefrontal cortex.

**Link to the Article,**
http://www.sciencedirect.com/science/article/pii/S0892036211001620

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PubMed, J Womens Health (Larchmt). 2011 Nov;20(11):1627-33. Epub 2011 Aug 12.

**64) PRECONCEPTION MARKERS OF DUAL RISK FOR ALCOHOL AND SMOKING EXPOSED PREGNANCY: TOOLS FOR PRIMARY PREVENTION**

Ingersoll KS, Hettema JE, Cropsey KL, Jackson JP.
1 University of Virginia School of Medicine , Department of Psychiatry and Neurobehavioral Sciences, Charlottesville, Virginia.

**ABSTRACT**
**Objective:** Effective preconception primary prevention strategies are needed for women who are at dual risk for alcohol and smoking exposed pregnancies. The current study seeks to identify risk factors that can be used to target intervention strategies at women who are at dual risk.

**Methods:** During a 2-year period from January 2007 through December 2009, 109 women at dual risk for alcohol exposed pregnancy (AEP) and smoking exposed pregnancy (SEP) and 108 women at risk only for AEP were recruited from central Virginia cities. All participants completed a battery of instruments, including assessments of sexual, smoking, and alcohol history and current behavior in each area.

**Results:** Several factors differentiated women at dual risk for SEP/AEP vs. AEP alone, including lower educational level and employment, higher frequency of sexual intercourse, less use of contraception, and higher frequency of alcohol use and mental disorders.

**Conclusions:** Several measurable factors differentiate SEP/AEP women, and these factors could be used to efficiently target primary prevention. The increased severity of women at dual risk of SEP/AEP on a variety of factors demonstrates the importance of preconception prevention efforts for these women.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21838526

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PubMed, Paediatr Perinat Epidemiol. 2011 Nov;25(6):559-65. doi: 10.1111/j.1365-3016.2011.01229.x. Epub 2011 Aug 10.

**65) MATERNAL PRENATAL CIGARETTE, ALCOHOL AND ILLICIT DRUG USE AND RISK OF INFANT LEUKAEMIA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP**

Slater ME, Linabery AM, Blair CK, Spector LG, Heerema NA, Robison LL, Ross JA.
Division of Pediatric Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, 55455, USA.

**ABSTRACT**
Several case-control studies have evaluated associations between maternal smoking, alcohol

consumption and illicit drug use during pregnancy and risk of childhood leukaemia. Few studies have specifically focused on infants (<1 year) with leukaemia, a group that is biologically and clinically distinct from older children. We present data from a Children's Oncology Group case-control study of 443 infants diagnosed with acute leukaemia [including acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML)] between 1996 and 2006 and 324 population controls. Mothers were queried about their cigarette, alcohol and illicit drug use 1 year before and throughout pregnancy. Odds ratios (ORs) and 95% confidence intervals [CI] were calculated using adjusted unconditional logistic regression models. Maternal smoking (>1 cigarette/day) and illicit drug use (any amount) before and/or during pregnancy were not significantly associated with infant leukaemia. Alcohol use (>1 drink/week) during pregnancy was inversely associated with infant leukaemia overall [OR = 0.64; 95% CI 0.43, 0.94], AML [OR = 0.49; 95% CI 0.28, 0.87], and leukaemia with mixed lineage leukaemia gene rearrangements ('MLL+') [OR = 0.59; 95% CI 0.36, 0.97]. While our results agree with the fairly consistent evidence that maternal cigarette smoking is not associated with childhood leukaemia, the data regarding alcohol and illicit drug use are not consistent with prior reports and are difficult to interpret. It is possible that unhealthy maternal behaviours during pregnancy, some of which carry potential legal consequences, may not be adequately measured using only self-report. Future case-control studies of childhood leukaemia that pursue these exposures may benefit from incorporation of validated instruments and/or biomarkers when feasible.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21980945

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PubMed, Eur J Obstet Gynecol Reprod Biol. 2011 Aug 8. [Epub ahead of print]

### 66) SMOKE, ALCOHOL CONSUMPTION AND ILLICIT DRUG USE IN AN ITALIAN POPULATION OF PREGNANT WOMEN

De Santis M, De Luca C, Mappa I, Quattrocchi T, Angelo L, Cesari E.
Telefono Rosso - Teratology Information Service, Department of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, Rome, Italy.

**ABSTRACT**
**Objective:** High-risk behaviours are associated with an increased risk of adverse pregnancy outcomes. Exposure to drugs, infection or radiation is a cause of concern for pregnant women, who contact Teratology Information Services (TIS) to have a counseling but with an accurate medical history is possible to detect additional behavioural risk factors that can significantly interfere with pregnancy outcome. The aim of this study is to describe risk behaviours in a population of Italian women calling our TIS and to identify related maternal factors.

**Study Design:** Between December 2008 and January 2010 we collected data from 503 pregnant women calling our TIS (Telefono Rosso, Rome). We investigated about smoke, alcohol and abuse substances addiction and we also collected demographic data.

**Results:** Of the 503 women consenting to participate 34% were found to have an additional risk marker during the current pregnancy. Within this group were 22.7% (n=119) who reported smoking, the 17.7% (n=89) admitted to drink and 2 women (0.4%) used illicit drugs. In 13.7% of cases (n=69) reason for calling represented an exposure to teratogenic agents. Unmarried status and previous induced abortion represent a risk factor for all high-risk behaviours. Lower education (p<0.001) and use of neurological drugs (p<0.001) are related with cigarette consumption. A lower parity was a risk factor for alcohol assumption (p=0.04). Women with high-risk behaviours tend to be exposed to more than a risk factor.

**Conclusions:** Teratogen Information Services are an important system to identify women with pregnancy risk markers. These services should have the ability to provide risk reduction information to women who smoke cigarettes or with alcohol or drug use. In addition to the phone based information these women may benefit from referral back to their physician for assessment and management of substance use/abuse during pregnancy. Substance abuse risks are often underestimated by pregnant women. Single mothers or women with an history of terminations of pregnancy represents an high-risk population. Physicians should inform their patients about possible risks related to high-risk behaviours during preconception counseling or during the first obstetric visit.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21831510

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PubMed, J Womens Health (Larchmt). 2011 Oct;20(10):1517-24. Epub 2011 Aug 8.

### 67) A RANDOMIZED PHASE I TRIAL OF A BRIEF COMPUTER-DELIVERED INTERVENTION FOR ALCOHOL USE DURING PREGNANCY

Tzilos GK, Sokol RJ, Ondersma SJ.
Wayne State University, Department of Psychology, Detroit, Michigan, USA. golfo_tzilos@brown.edu

**ABSTRACT**
**Background:** Drinking alcohol during pregnancy has a range of negative consequences for the developing fetus. Screening and brief intervention approaches have significant promise, but their population impact may be limited by a range of challenges to implementation. We, therefore, conducted preliminary acceptability and feasibility evaluation of a computer-delivered brief intervention for alcohol use during pregnancy.

**Methods:** Participants were 50 pregnant women who screened positive for risky drinking during a routine prenatal clinic visit and were randomly assigned to computer-delivered brief intervention or assessment-only conditions.

**Results:** Ratings of intervention ease of use, helpfulness, and other factors were high (4.7-5.0 on a 1-5 scale). Participants in both conditions significantly decreased alcohol use at follow-up, with no group differences; however, birth weights for infants born to women in the intervention group were significantly higher ($p<0.05$, $d = 0.62$).

**Conclusions:** Further development and study of computer-delivered screening and intervention for alcohol use during pregnancy are warranted.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21823917

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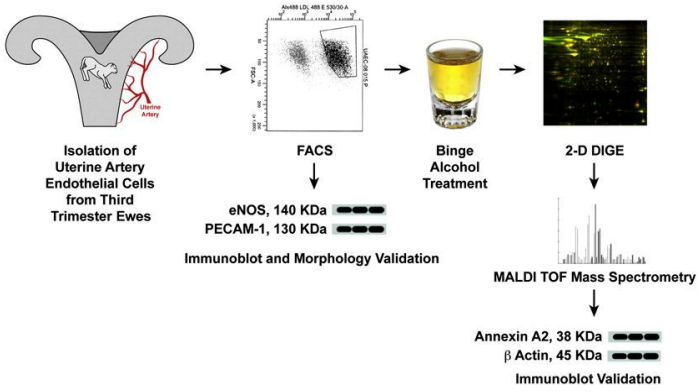
ScienceDirect, doi:10.1016/j.jprot.2011.07.029
Received 4 June 2011; Accepted 25 July 2011. Available online 4 August 2011.

## 68) 2-D DIGE UTERINE ENDOTHELIAL PROTEOMIC PROFILE FOR MATERNAL CHRONIC BINGE-LIKE ALCOHOL EXPOSURE

Jayanth Ramadoss[a], Ronald R. Magness[a, b, c]
a Perinatal Research Laboratories, Department of Obstetrics and Gynecology, University of Wisconsin, Madison, Wisconsin, USA
b Department of Pediatrics, University of Wisconsin, Madison, Wisconsin, USA
c Department of Animal Sciences, University of Wisconsin, Madison, Wisconsin, USA

**ABSTRACT**
Little is known about alcohol effects on the utero-placental compartment during pregnancy. For the first time, we utilized 2-D DIGE quantitative proteomics to evaluate the role of the uterus in Fetal Alcohol Spectrum Disorders (FASD) pathogenesis. Uterine artery endothelial cells were isolated from pregnant ewes, FAC sorted, validated, and maintained in culture. To mimic maternal binge drinking patterns, cells were cultured in the absence or presence of alcohol (300 mg/dl) in a compensating sealed humidified chamber system equilibrated with aqueous alcohol for 3 h on 3 consecutive days for two weeks. CyDye switch combined with 2-D DIGE followed by MALDI-TOF and tandem MS/MS were utilized. Validation was performed using Western immunoblot analysis. Chronic binge-like alcohol significantly ($P < 0.05$) decreased 30 proteins and increased 19 others. Gene-enrichment and functional annotation cluster analysis revealed significant enrichment ($P < 0.05$) in three categories: glutathione S transferase, thioredoxin, and vesicle transport-related. Furthermore, alcohol differentially altered proteins with certain isoforms being downregulated while others were upregulated. In summary, binge alcohol has specific effects on the maternal uterine proteome, especially those related to oxidative stress. The current study also demonstrates a great need to utilize proteomic approaches for diagnostic, mechanistic and therapeutic aspects of FASD.
Graphical abstract




**Highlights**
► Quantitative 2-D DIGE MALDI-TOF MS analysis of late pregnant ovine uterine artery endothelial cells. ► Novel proteomics data on the dynamic processes altered by maternal in vitro binge-like alcohol exposure. ► Important role for the maternal uterine compartment in Fetal Alcohol Spectrum Disorders pathogenesis

**Link to the Article,**
http://www.sciencedirect.com/science/article/pii/S1874391911003836

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PubMed, Alcohol Clin Exp Res. 2011 Aug 4. doi: 10.1111/j.1530-0277.2011.01594.x. [Epub ahead of print]

**69) AUDITORY BRAINSTEM RESPONSE (ABR) ABNORMALITIES ACROSS THE LIFE SPAN OF RATS PRENATALLY EXPOSED TO ALCOHOL**

Church MW, Hotra JW, Holmes PA, Anumba JI, Jackson DA, Adams BR.
From the Department of Obstetrics & Gynecology (MWC, JWH, PAH, JIA, DAJ, BRA), Wayne State University School of Medicine, Detroit, Michigan.

**ABSTRACT**

**Background:** Fetal alcohol syndrome (FAS) is a leading cause of neurodevelopmental impairments (NDIs) in developed countries. Sensory deficits can play a major role in NDI, yet few studies have investigated the effects of prenatal alcohol exposure on sensory function. In addition, there is a paucity of information on the lifelong effects of prenatal alcohol exposure. Thus, we sought to investigate the effects of prenatal alcohol exposure on auditory function across the life span in an animal model. Based on prior findings with prenatal alcohol exposure and other forms of adverse prenatal environments, we hypothesized that animals prenatally exposed to alcohol would show an age-dependent pattern of (i) hearing and neurological abnormalities as postweanling pups, (ii) a substantial dissipation of such abnormalities in young adulthood, and (iii) a resurgence of such abnormalities in middle-aged adulthood.

**Methods:** Pregnant rats were randomly assigned to an untreated control (CON), a pair-fed control (PFC), or an alcohol-treated (ALC) group. The ALC dams were gavaged with 6 mg/kg alcohol daily from gestation day (GD) 6 to 21. The PFC dams were gavaged daily from GD6 to GD21 with an isocaloric and isovolumetric water-based solution of maltose-dextrins and pair-fed to the ALC dams. The CON dams were the untreated group to which the ALC and CON groups were compared. Hearing and neurological functions in the offspring were assessed with the auditory brainstem response (ABR) at the postnatal ages of 22, 220, and 520 days.

**Results:** In accord with our hypothesis, ABR abnormalities were first observed in the postweanling pups, largely dissipated in young adulthood, and then resurged in middle-aged adulthood. This age-related pattern suggests that the ALC pups had a developmental delay that dissipated in young adulthood and an enhanced age-related deterioration that occurred in middle-aged adulthood. Such a pattern is consistent with the fetal programming hypothesis of adult-onset diseases (the Barker hypothesis).

**Conclusions:** Our findings have important clinical implications for the assessment and management of (i) childhood hearing disorders and their comorbidities (i.e., speech-and-language, learning, and attention deficit disorders) and (ii) enhanced age-related hearing and neurological degeneration in middle-aged adulthood that can result from prenatal alcohol exposure. We recommend hearing evaluation be a part of any long-term follow-up for FAS patients and patients exposed to any adverse prenatal environment.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21815896

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PubMed, Drug Alcohol Depend. 2011 Aug 3. [Epub ahead of print]

**70) ALCOHOL CONSUMPTION AMONG HIV-POSITIVE PREGNANT WOMEN IN KWAZULU-NATAL, SOUTH AFRICA: PREVALENCE AND CORRELATES**

Desmond K, Milburn N, Richter L, Tomlinson M, Greco E, van Heerden A, van Rooyen H, Comulada WS, Rotheram-Borus MJ.
Center for Community Health, University of California at Los Angeles, 10920 Wilshire Blvd., Suite 350, Los Angeles, CA 90024-6543, USA.

**ABSTRACT**

**Background:** HIV-positive pregnant women who drink put their children at risk of both HIV and fetal alcohol spectrum disorders. The province of KwaZulu-Natal (KZN) has the highest prevalence of HIV in South Africa, but has not before been considered an area of high alcohol consumption among women. This paper analyzes a large sample of HIV+ pregnant women in KZN to examine alcohol consumption in that population.

**Methods:** Data came from assessments of women enrolled in Prevention of Mother-To-Child Transmission programs at 8 clinics in KZN. Descriptive statistics and logistic regressions were used to examine the prevalence and correlates of alcohol consumption and binge drinking.

**Results:** Of 1201 women assessed, 18% reported drinking during pregnancy, and 67% of drinkers usually binged when drinking (had 3+ drinks in one sitting). Over one-third of drinkers binged twice a month or more. Women living in urban and peri-urban locations were more likely to drink, as were those with indicators of higher economic status and greater social engagement. Married women were less likely to drink, while women who had poorer mental health, used tobacco, or had a greater history of sexual risk-taking were more likely to drink.

**Conclusion:** Health care workers in KZN should be aware that pregnant women who drink are likely to do so at a level that is dangerous for their babies. Some factors associated with drinking indicate social/environmental influences that need to be counteracted by greater dissemination of information about the dangers of drinking, and greater support for abstinence or moderation.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21820252

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PubMed, Obstet Gynecol. 2011 Aug;118(2 Pt 1):383-8.

**71) COMMITTEE OPINION NO. 496: AT-RISK DRINKING AND ALCOHOL DEPENDENCE: OBSTETRIC AND GYNECOLOGIC IMPLICATIONS**

American College of Obstetricians and Gynecologists. Committee on Health Care for Underserved Women.

**ABSTRACT**

Compared with men, at-risk alcohol use by women has a disproportionate effect on their health and lives, including reproductive function and pregnancy outcomes. Obstetrician–gynecologists have a key role in screening and providing brief intervention, patient education, and treatment referral for their patients who drink alcohol at risk levels. For women who are not physically addicted to alcohol, tools such as brief intervention and motivational interviewing can be used effectively by the clinician and incorporated into an office visit. For pregnant women and those at risk of pregnancy, it is important for the obstetrician–gynecologist to give compelling and clear advice to avoid alcohol use, provide

assistance for achieving abstinence, or provide effective contraception to women who require help. Health care providers should advise women that low-level consumption of alcohol in early pregnancy is not an indication for pregnancy termination.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21775870

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PubMed, J Ark Med Soc. 2011 Aug;108(2):38-40.

**72) RECOGNITION, DIAGNOSIS AND TREATMENT OF FETAL ALCOHOL SYNDROME**

Schaefer GB, Deere D.
Arkansas Team of the Midwest Fetal Alcohol Syndrome Training Center, USA.

**ABSTRACT**
Fetal Alcohol spectrum disorders are extremely common. The clinical impact and societal effects are tremendous. Prevention and treatment of these disorders begins with an accurate diagnosis. All health care providers who work with children (and adults) with special health care needs should be alert to these findings. The key to early diagnosis is to always keep the diagnostic possibility in the broad differential diagnoses of growth and developmental disorders. As with most conditions, early recognition and intervention is associated with better outcomes. Once an FASD is identified in a specific patient, prompt referrals and enrollment in indicated services are necessary to get the best outcomes. In this article we review the diagnostic criteria and clues to prompt early identification of FASDs. We also discuss the therapeutic options shown to be most effective for this group of individuals.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21902001

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PubMed, Horm Cancer. 2011 Aug;2(4):239-48.

**73) ALCOHOL EXPOSURE IN UTERO LEADS TO ENHANCED PREPUBERTAL MAMMARY DEVELOPMENT AND ALTERATIONS IN MAMMARY IGF AND ESTRADIOL SYSTEMS**

Polanco TA, Crismale-Gann C, Cohick WS.
Rutgers Endocrine Program, Department of Animal Sciences, Rutgers, The State University of New Jersey, 59 Dudley Rd, New Brunswick, NJ 08901, USA. tpolanco@eden.rutgers.edu

**ABSTRACT**
Exposure to alcohol during fetal development increases susceptibility to mammary cancer in adult rats. This study determined if early changes in mammary morphology and the insulin-like growth factor (IGF)/estradiol axis are involved in the mechanisms that underlie this increased susceptibility. Pregnant Sprague-Dawley rats were fed a liquid diet containing 6.7% ethanol (alcohol), an isocaloric liquid diet (pair-fed), or rat chow ad libitum from days 11 to 21 of gestation. At birth, female pups were cross-fostered to ad libitum-fed control dams. Offspring were euthanized at postnatal days (PND) 20, 40, or 80. Animals were injected with BrdU before euthanasia, then mammary glands, serum, and livers were collected. Mammary glands from animals exposed to alcohol in utero displayed increased epithelial cell proliferation and aromatase expression at PND 20 and 40. Mammary IGF-I mRNA was higher in alcohol-exposed animals relative to controls at PND 20, while mammary IGFBP-5 mRNA was lower in this group at PND 40. Hepatic IGF-I mRNA expression was increased at all time points in alcohol-exposed animals, however, circulating IGF-I levels were not altered. These data indicate that

alcohol exposure in utero may advance mammary development via the IGF and estradiol systems, which could contribute to increased susceptibility to mammary cancer later in life.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21761112

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PubMed, Midwifery. 2011 Aug;27(4):489-96. Epub 2010 May 14.

**74) MIDWIVES AND PREGNANT WOMEN TALK ABOUT ALCOHOL: WHAT ADVICE DO WE GIVE AND WHAT DO THEY RECEIVE?**

Jones SC, Eval M, Telenta J, Cert G, Shorten A, Johnson K.
Centre for Health Initiatives, University of Wollongong, NSW 2522, Australia. sandraj@uow.edu.au

**ABSTRACT**
**Background: T**he Australian National Health and Medical Research Council (NHMRC) recently revised its guidelines for alcohol consumption during pregnancy and breast feeding, moving from a recommendation of minimising intake to one of abstinence. Women are potentially exposed to a variety of messages about alcohol and pregnancy, including from the media and social contacts, and are likely to see midwives as the source of expert advice in understanding these contradictory messages.

**Objective:** To explore the advice that midwives believe they give to pregnant women about alcohol consumption, and the advice that pregnant women believe they receive; the knowledge and attitudes of both groups regarding alcohol consumption and the consistency with the NHMRC guidelines; and the receptivity and comfort of both groups in discussing alcohol consumption in the context of antenatal appointments.

**Design:** Individual semi-structured interviews with midwives and pregnant women.

**Setting:** Face-to-face interviews with midwives and telephone interviews with pregnant women were conducted in two regional areas of New South Wales in 2008-2009.

**Participants:** 12 midwives and 12 pregnant women.

**Findings:** Midwives and pregnant women consistently agreed that conversations about alcohol are generally limited to brief screening questions at the first visit, and the risks are not discussed or explained (except for high-risk women).

**Key Conclusions:** Both groups expressed comfort with the idea of discussing alcohol consumption, but lacked knowledge of the risk and recommendation, and it appears that this opportunity to provide women with information is under-utilised.

**Implications for practice:** There is a need to provide midwives with accurate information about the risks of alcohol consumption during pregnancy and effective communication tools to encourage them to discuss the risks and recommendations with their patients.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/20471731

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J Popul Ther Clin Pharmacol Vol 18 (2)e397-e402; July 29, 2011

**75) COMPARING DAILY LIVING SKILLS IN ADULTS WITH FETAL ALCOHOL SPECTRUM DISORDER (FASD) TO AN IQ MATCHED CLINICAL SAMPLE**

Valerie Temple, Lauren Shewfelt, Leeping Tao, Josee Cassati, Linda Klevnik

**ABSTRACT**

**Background :** Prenatal alcohol exposure is an established risk factor for cognitive deficits. Adults with FASD also have deficits in their Adaptive Daily Living skills (ADLs) relative to age-appropriate norms, but the degree to which this can be attributed to cognitive deficits is unclear.

**Objectives:** To examine ADLs in adults with FASD and compare them to a group of clinic referred individuals with similar IQ scores but without FASD.

**Methods :** Fifteen adults with FASD and 15 IQ matched controls were included. Wechsler Intelligence tests were used to measure IQ, and the Adaptive Behavior Assessment System-II (ABAS-II) was used to measure ADLs.

**Results :** Compared to IQ matched controls, individuals with FASD had significantly lower overall ADLs (p=.03). Mean scores across all sub-domains on the ABAS-II were lower for the FASD group. Mean standard scores for ADLs in the FASD group were 11 points lower than mean IQ. In the control group, the difference was only 2 points.

**Conclusions:** Adults with FASD may have lower daily living skills than individuals with similar IQ scores. This suggests that IQ is not a good predictor of ADLs in adults with FASD.

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http://www.cjcp.ca/pubmed.php?articleId=328

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Oxford Journals, Cereb. Cortex (2011) doi: 10.1093/cercor/bhr193 First published online: July 28, 2011

**76) ABNORMAL CORTICAL THICKNESS ALTERATIONS IN FETAL ALCOHOL SPECTRUM DISORDERS AND THEIR RELATIONSHIPS WITH FACIAL DYSMORPHOLOGY**

Yang Y, Roussotte F, Kan E, Sulik KK, Mattson SN, Riley EP, Jones KL, Adnams CM, May PA, O'Connor MJ, Narr KL, Sowell ER.
Laboratory of NeuroImaging (LONI), Department of Neurology, University of California, Los Angeles, CA 90095, USA.

**ABSTRACT**

Accumulating evidence from structural brain imaging studies on individuals with fetal alcohol spectrum disorder (FASD) has supported links between prenatal alcohol exposure and brain morphological deficits. Although global and regional volumetric reductions appear relatively robust, the effects of alcohol exposure on cortical thickness and relationships with facial dysmorphology are not yet known. The structural magnetic resonance imaging data from 69 children and adolescents with FASD and 58 nonexposed controls collected from 3 sites were examined using FreeSurfer to detect cortical thickness changes across the entire brain in FASD and their associations with facial dysmorphology. Controlling for brain size, subjects with FASD showed significantly thicker cortices than controls in several frontal, temporal, and parietal regions. Analyses conducted within site further revealed

prominent group differences in left inferior frontal cortex within all 3 sites. In addition, increased inferior frontal thickness was significantly correlated with reduced palpebral fissure length. Consistent with previous reports, findings of this study are supportive of regional increases in cortical thickness serving as a biomarker for disrupted brain development in FASD. Furthermore, the significant associations between thickness and dysmorphic measures suggest that the severity of brain anomalies may be reflected by that of the face.

**Read Full Article,**
http://cercor.oxfordjournals.org/content/early/2011/07/28/cercor.bhr193.abstract

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PubMed, Alcohol Clin Exp Res. 2011 Jul 28. doi: 10.1111/j.1530-0277.2011.01591.x. [Epub ahead of print]

**77) TRANSLATION OF AN EVIDENCE-BASED SOCIAL SKILLS INTERVENTION FOR CHILDREN WITH PRENATAL ALCOHOL EXPOSURE IN A COMMUNITY MENTAL HEALTH SETTING**

O'Connor MJ, Laugeson EA, Mogil C, Lowe E, Welch-Torres K, Keil V, Paley B.
From the Department of Psychiatry and Biobehavioral Sciences Semel Institute for Neuroscience and Human Behavior (MJO, EAL, CM, VK, BP), University of California at Los Angeles, Los Angeles California; and the Child and Family Guidance Center (EL, KW-T), Los Angeles, California.

**ABSTRACT**
**Background:** Children with prenatal alcohol exposure (PAE) have significant social skills deficits and are often treated in community mental health settings. However, it remains unclear whether these children can be effectively treated using manualized, evidence-based interventions that have been designed for more general mental health populations.

**Methods:** To shed light on this issue, the effectiveness of Children's Friendship Training (CFT) versus Standard of Care (SOC) was assessed for 85 children ages 6 to 12 years with and without PAE in a community mental health center.

**Results:** Children participating in CFT showed significantly improved knowledge of appropriate social skills, improved self-concept, and improvements in parent-reported social skills compared to children in the SOC condition. Moreover, results revealed that within the CFT condition, children with PAE performed as well as children without PAE. Findings indicated that CFT, an evidence-based social skills intervention, yielded greater gains than a community SOC social skills intervention and was equally effective for children with PAE as for those without PAE.

**Conclusions:** Results suggest that children with PAE can benefit from treatments initiated in community settings in which therapists are trained to understand their unique developmental needs, and that they can be successfully integrated into treatment protocols that include children without PAE.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21797888

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PubMed, Alcohol Clin Exp Res. 2011 Jul 25. doi: 10.1111/j.1530-0277.2011.01566.x. [Epub ahead of print]

**78) DIFFUSION TENSOR IMAGING OF THE CEREBELLUM AND EYEBLINK CONDITIONING IN FETAL ALCOHOL SPECTRUM DISORDER**

Spottiswoode BS, Meintjes EM, Anderson AW, Molteno CD, Stanton ME, Dodge NC, Gore JC, Peterson BS, Jacobson JL, Jacobson SW.

From the Department of Human Biology (BSS, EMM, JLJ, SWJ), the MRC UCT Medical Imaging Research Unit (BSS, EMM), and the Department of Psychiatry and Mental Health (CDM, JLJ, SWJ), University of Cape Town Faculty of Health Sciences, Cape Town, South Africa; Division of Radiology (BSS), University of Stellenbosch Faculty of Health Sciences, Cape Town, South Africa; Vanderbilt University Institute of Imaging Science (AWA, JCG), Department of Biomedical Engineering (AWA), and Department of Radiology and Radiological Sciences, Vanderbilt University (JCG), Vanderbilt University, Nashville, Tennessee; Department of Psychology (MES), University of Delaware, Newark, Delaware; Department of Psychiatry and Behavioral Neurosciences (NCD, JLJ, SWJ), Wayne State University School of Medicine, Detroit, Michigan; Division of Child Psychiatry (BSP), Columbia College of Physicians & Surgeons, New York, New York.

**ABSTRACT**

**Background:** Prenatal alcohol exposure is related to a wide range of neurocognitive effects. Eyeblink conditioning (EBC), which involves temporal pairing of a conditioned with an unconditioned stimulus, has been shown to be a potential biomarker of fetal alcohol exposure. A growing body of evidence suggests that white matter may be a specific target of alcohol teratogenesis, and the neural circuitry underlying EBC is known to involve the cerebellar peduncles. Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that has proven useful for assessing central nervous system white matter integrity. This study used DTI to examine the degree to which the fetal alcohol-related deficit in EBC may be mediated by structural impairment in the cerebellar peduncles.

**Methods:** Thirteen children with fetal alcohol spectrum disorder (FASD) and 12 matched controls were scanned using DTI and structural MRI sequences. The DTI data were processed using a voxelwise technique, and the structural data were used for volumetric analyses. Prenatal alcohol exposure group and EBC performance were examined in relation to brain volumes and outputs from the DTI analysis.

**Results:** Fractional anisotropy (FA) and perpendicular diffusivity group differences between alcohol-exposed and nonexposed children were identified in the left middle cerebellar peduncle. Alcohol exposure correlated with lower FA and greater perpendicular diffusivity in this region, and these correlations remained significant even after controlling for total brain and cerebellar volumes. Conversely, trace conditioning performance was related to higher FA and lower perpendicular diffusivity in the left middle peduncle. The effect of prenatal alcohol exposure on trace conditioning was partially mediated by lower FA in this region.

**Conclusions:** This study extends recent findings that have used DTI to reveal microstructural deficits in white matter in children with FASD. This is the first DTI study to demonstrate mediation of a fetal alcohol-related effect on neuropsychological function by deficits in white matter integrity.

http://www.ncbi.nlm.nih.gov/pubmed/21790667

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PubMed, Neuropharmacology. 2011 Dec;61(8):1248-55. Epub 2011 Jul 23.

**79) PROTECTIVE EFFECT OF PYRUVATE AGAINST ETHANOL-INDUCED APOPTOTIC NEURODEGENERATION IN THE DEVELOPING RAT BRAIN**

Ullah N, Naseer MI, Ullah I, Lee HY, Koh PO, Kim MO.
Division of Life Science, College of Natural Sciences (RINS) and Applied Life Sciences, Gyeongsang National University, Chinju 660-701, Republic of Korea.

**ABSTRACT**
Exposure to alcohol during the early stages of brain development can lead to neurological disorders in the CNS. Apoptotic neurodegeneration due to ethanol exposure is a main feature of alcoholism. Exposure of developing animals to alcohol (during the growth spurt period in particular) elicits apoptotic neuronal death and causes fetal alcohol effects (FAE) or fetal alcohol syndrome (FAS). A single episode of ethanol intoxication (at 5 g/kg) in a seven-day-old developing rat can activate the apoptotic cascade, leading to widespread neuronal death in the brain. In the present study, we investigated the potential protective effect of pyruvate against ethanol-induced neuroapoptosis. After 4h, a single dose of ethanol induced upregulation of Bax, release of mitochondrial cytochrome-c into the cytosol, activation of caspase-3 and cleavage of poly (ADP-ribose) polymerase (PARP-1), all of which promote apoptosis. These effects were all reversed by co-treatment with pyruvate at a well-tolerated dosage (1000 mg/kg). Histopathology performed at 24 and 48 h with Fluoro-Jade-B and cresyl violet stains showed that pyruvate significantly reduced the number of dead cells in the cerebral cortex, hippocampus and thalamus. Immunohistochemical analysis at 24h confirmed that ethanol-induced cell death is both apoptotic and inhibited by pyruvate. These findings suggest that pyruvate treatment attenuates ethanol-induced neuronal cell loss in the developing rat brain and holds promise as a safe therapeutic and neuroprotective agent in the treatment of neurodegenerative disorders in newborns and infants.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21803053

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PubMed, J Ment Health. 2011 Oct;20(5):438-48. Epub 2011 Jul 22.

**80) MENTAL HEALTH ISSUES IN FETAL ALCOHOL SPECTRUM DISORDER**

Pei J, Denys K, Hughes J, Rasmussen C.
Department of Educational Psychology, University of Alberta, Edmonton, AB, Canada. jacqueline.pei@ualberta.ca

**ABSTRACT**
**Background:** High numbers of individuals with Fetal Alcohol Spectrum Disorders (FASD) have been described as having mental health problems.

**Aims:** This article summarizes research about mental health problems in FASD and considers related developmental and environmental issues.

**Method:** A computer-based literature search was conducted in the databases Medline, PsycINFO, Google Scholar, Academic Search Complete, and Education Resources Information Centre for articles addressing the prevalence and types of mental health issues in individuals affected by FASD.

**Results:** High rates of mental disorders within the FASD and prenatal alcohol exposure (PAE) population were found to be consistently reported for both internalizing and externalizing disorders.

Moreover, problems that emerge in childhood may reflect a convergence of genetic, environmental, and neurophysiological factors that persist into adulthood.

**Conclusions:** Researchers are beginning to document the impacts of PAE on later mental health development. Further longitudinal study is needed to determine whether there is an increasing severity of mental health deficits and consequences with age, and whether any such changes reflect increasingly deteriorating environmental factors or brain-based factors. Additionally, research is needed to design interventions to better address the unique mental health needs of this population.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21780939

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PubMed, BMC Public Health. 2011 Jul 22;11:584.

**81) ATTITUDES AND BEHAVIOUR PREDICT WOMEN'S INTENTION TO DRINK ALCOHOL DURING PREGNANCY: THE CHALLENGE FOR HEALTH PROFESSIONALS**

Peadon E, Payne J, Henley N, D'Antoine H, Bartu A, O'Leary C, Bower C, Elliott EJ.
Discipline of Paediatrics and Child Health, Sydney Medical School, The University of Sydney, The Children's Hospital at Westmead, Australia. elizabp5@chw.edu.au

**ABSTRACT**
**Background:** To explore women's alcohol consumption in pregnancy, and potential predictors of alcohol consumption in pregnancy including: demographic characteristics; and women's knowledge and attitudes regarding alcohol consumption in pregnancy and its effects on the fetus.

**Methods:** We conducted a national cross-sectional survey via computer assisted telephone interview of 1103 Australian women aged 18 to 45 years. Participants were randomly selected from the Electronic White Pages. Pregnant women were not eligible to participate. Quotas were set for age groups and a minimum of 100 participants per state to ensure a national sample reflecting the population. The questionnaire was based on a Health Canada survey with additional questions constructed by the investigators. Descriptive statistics were calculated and logistic regression analyses were used to assess associations of alcohol consumption in pregnancy with participants' characteristics, knowledge and attitudes.

**Results:** The majority of women (89.4%) had consumed alcohol in the last 12 months. During their last pregnancy (n = 700), 34.1% drank alcohol. When asked what they would do if planning a pregnancy (n = 1103), 31.6% said they would consume alcohol and 4.8% would smoke. Intention to consume alcohol in a future pregnancy was associated with: alcohol use in the last pregnancy (adjusted OR (aOR) 43.9; 95% Confidence Interval (CI) 27.0 to 71.4); neutral or positive attitudes towards alcohol use in pregnancy (aOR 5.1; 95% CI 3.6 to 7.1); intention to smoke in a future pregnancy (aOR 4.7; 95% CI 2.5 to 9.0); and more frequent and higher current alcohol consumption.

**Conclusions:** Women's past pregnancy and current drinking behaviour, and attitudes to alcohol use in pregnancy were the strongest predictors of alcohol consumption in pregnancy. Targeted

interventions for women at higher risk of alcohol consumption in pregnancy are needed to change women's risk perception and behaviour.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21781309

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ScienceDirect, doi:10.1016/j.brainres.2011.07.027
Accepted 12 July 2011. Available online 21 July 2011.

## 82) NEONATAL ALCOHOL EXPOSURE DISRUPTS HIPPOCAMPAL NEUROGENESIS AND CONTEXTUAL FEAR CONDITIONING IN ADULT RATS

G.F. Hamiltona, N.J. Murawskia, S.A. St.Cyra, S.A. Jablonskia, F.L. Schiffinoa, M.E. Stantona, A.Y. Klintsova
a Psychology Department, University of Delaware, Newark, DE, 19716, USA

**ABSTRACT**
Developmental alcohol exposure can permanently alter brain structures and produce functional impairments in many aspects of behavior, including learning and memory. This study evaluates the effect of neonatal alcohol exposure on adult neurogenesis in the dentate gyrus of the hippocampus and the implications of such exposure for hippocampus-dependent contextual fear conditioning. Alcohol-exposed rats (AE) received 5.25 g/kg/day of alcohol on postnatal days (PD) 4–9 (third trimester in humans), in a binge-like manner. Two control groups were included: sham-intubated (SI) and suckle-control (SC). Animals were housed in social cages (3/cage) after weaning. On PD80, animals were injected with 200 mg/kg BrdU. Half of the animals were sacrificed 2 h later. The remainder were sacrificed on PD114 to evaluate cell survival; separate AE, SI, and SC rats not injected with BrdU were tested for the context preexposure facilitation effect (CPFE; ~ PD117). There was no difference in the number of BrdU+ cells in AE, SI and SC groups on PD80. On PD114, cell survival was significantly decreased in AE rats, demonstrating that developmental alcohol exposure damages new cells' ability to incorporate into the network and survive. Behaviorally tested SC and SI groups preexposed to the training context 24 h prior to receiving a 1.5 mA 2 s footshock froze significantly more during the context test than their counterparts preexposed to an alternate context. AE rats failed to show the CPFE. The current study shows the detrimental, long-lasting effects of developmental alcohol exposure on hippocampal adult neurogenesis and contextual fear conditioning.

**Highlights**
► Neonatal alcohol exposure does not affect hippocampal adult cell proliferation. ► Neonatal alcohol exposure decreases hippocampal adult cell survival. ► Neonatal alcohol exposure alters hippocampus-dependent context fear conditioning.

**Read Full Article,**
http://www.sciencedirect.com/science/article/pii/S0006899311013126

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PubMed, Behav Brain Res. 2011 Nov 20;225(1):235-42. Epub 2011 Jul 20.

**83) COMPARATIVE EFFECTS OF ALCOHOL AND THIAMINE DEFICIENCY ON THE DEVELOPING CENTRAL NERVOUS SYSTEM**

Bâ A.
Université de Cocody, UFR Biosciences, 22 BP 582, Abidjan 22, Cote d'Ivoire. abdouba3000@hotmail.com

**ABSTRACT**
The present study addresses the still unresolved issue of the character of alcohol-thiamine metabolic interferences in the developing central nervous system (CNS). Investigations compare developmental neurotoxicity evoked by three patterns of maternal thiamine deficiency (pre, peri and postnatal), with two patterns of maternal chronic alcohol intake (alcohol alone and alcohol+thiamine cotreatment), on seven neurodevelopmental abilities in the offspring. The three patterns of thiamine deficiency, pair-compared with controls, highlight four sequences of development: (1) embryonic-perinatal sequence; (2) perinatal-postnatal sequence; (3) "ontogeny in ontogeny out" sequence; (4) "off and on" developing sequence. The results suggest a temporally- and regionally emergence of structures and centers underlying functional maturation during CNS ontogenesis. Furthermore, both developmental thiamine deficiencies and ethanol exposure produce two waves of neurofunctional alterations, peaking at P15 (postnatal day 15) and P25, respectively. The first peak of vulnerability is a prenatal event; it may interfere with the periods of intense cellular proliferation and migration. The second peak represents both perinatal and postnatal events; it may interfere with the periods of cellular differentiation, synaptogenesis, axonogenesis and myelinogenesis. Alcohol+thiamine cotreatment fails to reduce the first peak, but neutralizes essentially the second peak. The results suggest that alcohol interferes with thiamine during cellular differentiation and membrane developmental processes mainly. Indeed, among the three conditions of thiamine-deficient diet, only perinatal thiamine deficiency exhibits a closer relationship with developmental alcohol exposure. Together, these observations suggest that the critical period for alcohol-thiamine antagonism occurs perinatally and affects primarily cellular differentiation.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21784107

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PubMed, Alcohol Clin Exp Res. 2011 Jul 18. doi: 10.1111/j.1530-0277.2011.01588.x. [Epub ahead of print]

**84) NUCLEAR CLUSTERIN IS ASSOCIATED WITH NEURONAL APOPTOSIS IN THE DEVELOPING RAT BRAIN UPON ETHANOL EXPOSURE**

Kim N, Han JY, Roh GS, Kim HJ, Kang SS, Cho GJ, Park JY, Choi WS.
Department of Anatomy and Neurobiology (NK, JYH, GSR, HJK, SSK, GJC, WSC) Health Science Institute, Medical Research Center for Neural Dysfunction, School of Medicine, Gyeongsang National University, Jinju, Gyeongnam, South Korea; and Department of Physiology (JYP), School of Medicine, Gyeongsang National University, Jinju, Gyeongnam, South Korea.

**ABSTRACT**
**Background**: Fetal alcohol spectrum disorder (FASD) is often accompanied by reduced brain volumes, reflecting brain cell death induced by ethanol, but the molecular mechanisms were less elucidated. This study was set up to investigate whether clusterin (Clu) was involved in neuronal cell death in developing rats.

**Methods:** Seven-day-old rats were subcutaneously injected with 20% ethanol in normal saline at 3 g/kg twice. The upregulation of Clu and cell death was detected by immunohistochemistry, immunofluorescence microscopy, and/or Western blotting. Protein-protein interaction was detected by immunoprecipitation and immunoblotting. To identify the isoform interacting with Bcl-XL, HT22 mouse hippocampal cells were transfected with nuclear Clu(nClu)- or secretory Clu-expressing vector, and confocal microscopy was performed. Clu transcripts were knocked down in primary cortical cells using siRNA.

**Results:** We found that Clu increased in the cerebral cortex following acute ethanol treatment. The Clu upregulation was related to increased cell death, which was assessed by activated caspase-3 and TUNEL staining. The upregulated Clu was a nuclear isoform that was nuclear translocated upon ethanol exposure and interacted with Bcl-XL, mediating apoptosis.

**Conclusions:** This study shows that nClu plays a pro-apoptotic role in ethanol-induced cell death in the developing brain, providing new insights for development of FASD.

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http://www.ncbi.nlm.nih.gov/pubmed/21762182

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PubMed, Fortschr Neurol Psychiatr. 2011 Sep;79(9):500-6. doi: 10.1055/s-0031-1273360. Epub 2011 Jul 7.

**85) HOW DOES MATERNAL ALCOHOL CONSUMPTION DURING PREGNANCY AFFECT THE DEVELOPMENT OF ATTENTION DEFICIT/HYPERACTIVITY SYNDROME IN THE CHILD**

[Article in German]
Burger PH, Goecke TW, Fasching PA, Moll G, Heinrich H, Beckmann MW, Kornhuber J.
Psychiatrische und Psychotherapeutische Klinik, Universitätsklinikum Erlangen. pascal.burger@uk-erlangen.de

**ABSTRACT**
Besides genetic susceptibility, environmental factors and gene-environment interactions are of central interest in research on attention deficit/hyperactivity disorder in children. Focusing on maternal behaviour during pregnancy, prenatal maternal alcohol consumption is associated with behavioural disorders in children. In animal models, developmental disorders of brain structures as well as subsequent behavioural disorders - similar to findings in attention deficit disorder - were caused by prenatal alcohol exposure. These findings occur in small rodents (mice, rats) as well as in primates and can be caused by even moderate alcohol exposure. In foetal alcohol syndrome (FAS) and foetal alcohol spectrum disease (FASD) in humans, symptoms like hyperactivity, disruptive or impulsive behaviour along with reduced attention and slower reaction time are observed. These findings resemble the symptoms of ADHD. For that reason, children diagnosed with FAS/FASD are frequently diagnosed with ADHD in parallel. Even small amounts of alcohol during pregnancy are responsible for cognitive and behavioural impairments like a significantly decreased IQ. About 50 % of adult ADHD patients show alcohol abuse or dependency and/or other substance disorders. Due to this, a higher rate of prenatal exposition to psychoactive substances for children of mothers affected with ADHD seems probable. However, there are no sufficient data on ADHD and its association to substance abuse in pregnancy, which makes it difficult to quantify the impact of genetic and environmental causes for the development of childhood ADHD. So far, no link could be proven with a high level of evidence between moderate prenatal alcohol consumption and the development of childhood ADHD. It has to be recognised that all present studies are based on self-reported alcohol consumption. Data collected by this methodology are usually severely biased to an underestimation of alcohol abuse.

Objective tests for alcohol abuse in pregnancy, such as the analysis of fatty acid ethyl esters or ethyl glucuronide in foetal feces after birth, show rates of alcohol consumption in pregnant women which are dramatically higher than reported. Therefore, studies investigating the association between prenatal alcohol exposure and ADHD should incorporate the analysis and validation of more objective methods, such as parameters for alcohol degradation.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21739408

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PubMed, Rev Neurol. 2011 Jul 16;53(2):127-8.

**86) FREQUENCY OF FETAL ALCOHOL SYNDROME IN INSTITUTIONALIZED CHILDREN OF EASTERN EUROPEAN COUNTRIES**

[Article in Spanish]
Olivan-Gonzalvo G.
Centro de Pediatría y Adopción Internacional, Zaragoza, España.

Article is without Abstract. Full Text available from link below.

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http://www.ncbi.nlm.nih.gov/pubmed/21720984

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PubMed, Addiction. 2011 Jul 13. doi: 10.1111/j.1360-0443.2011.03569.x. [Epub ahead of print]

**87) WOMEN'S ALCOHOL CONSUMPTION AND RISK FOR ALCOHOL-EXPOSED PREGNANCIES IN RUSSIA**

Balachova T, Bonner B, Chaffin M, Bard D, Isurina G, Tsvetkova L, Volkova E.
University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, St Petersburg State University, St Petersburg, Russia Nizhny Novgorod State Pedagogical University, Nizhniy Novgorod, Russia.

**ABSTRACT**
**Aims:** Alcohol-exposed pregnancies (AEP) are the direct cause of fetal alcohol spectrum disorders (FASD). This study examines drinking patterns among pregnant and non-pregnant women of childbearing age in Russia, a country with one of the highest levels of alcohol consumption in the world.

**Design**: Cross-sectional survey. Setting Seven public women's clinics in two locations: St Petersburg (SPB) and the Nizhny Novgorod region (NNR). Participants A total of 648 pregnant and non-pregnant childbearing-age women. Measurements A face-to-face structured interview assessed alcohol consumption, pregnancy status/possibility of becoming pregnant and consumption before and after pregnancy recognition.

**Findings:** Eighty-nine per cent of non-pregnant women reported consuming alcohol and 65% reported binge drinking in the past 3 months; 47% in NNR and 28% in SPB reported binges at least monthly. Women who might become pregnant consumed alcohol similarly to women who were not likely to become pregnant, and 32% of women in SPB and 54% in NNR were categorized as at risk for

AEP. There was a significant decline in drinking after pregnancy identification. Twenty per cent of pregnant women reported consuming alcohol and 6% in SBP (none in NNR) reported binge drinking; however, a high prevalence of binge drinking was found among women who might become pregnant or who were trying to conceive.

**Conclusions:** Russian women substantially reduce drinking after pregnancy recognition compared to pre-pregnancy levels. No reductions were found prior to pregnancy recognition, either when a woman might become pregnant or when she was trying to conceive. The pre-conception period presents a risk window and, therefore, a prevention opportunity.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21752144

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PubMed, Early Hum Dev. 2011 Jul 12. [Epub ahead of print]

**88) BINGE ALCOHOL EXPOSURE ONCE A WEEK IN EARLY PREGNANCY PREDICTS TEMPERAMENT AND SLEEPING PROBLEMS IN THE INFANT**

Alvik A, Torgersen AM, Aalen OO, Lindemann R.
Institute of Clinical Medicine, University of Oslo, Norway.

**ABSTRACT**
**Background:** Prenatal alcohol exposure can cause several cognitive and behavioral difficulties. Few studies have investigated the associations with infant temperament or sleeping patterns. Our aim was to study potential associations between early prenatal binge exposure and infant temperament and sleeping pattern.

**Methods:** In a population based longitudinal study, representative of pregnant women in Oslo, questionnaires were answered at 17 and 30weeks of pregnancy and 6months after term. Two factors, difficult temperament and sleeping problems, were identified using Principal Component Analysis and dichotomized at the least optimal 14-15%. Logistic regression analyses identified predictive factors.

**Results:** Maternal binge drinking (≥5 drinks per occasion) once a week during pregnancy week 0-6 significantly predicted both difficult temperament (Odds Ratio OR 3.3**; 95% Confidence interval CI 1.4-7.9) and sleeping problems (OR 5.3**; 95% CI 2.1-13.7) in the infant, after adjusting for other confounding factors. Including binge drinking more often than once a week, further increased the OR of sleeping problems (6.0***; 2.7-13.7). Prenatal maternal depressive symptoms also predicted both outcomes. Reduced birth weight predicted difficult temperament. Maternal satisfaction with life reduced the probability of sleeping problems. Maternal smoking, and work stress, during pregnancy had no predictive power. The results were not explained by binge drinking later during pregnancy or higher consumption per occasion.

**Conclusions:** Binge drinking once a week during pregnancy week 0-6 had stronger predictive power of difficult temperament and sleeping problems during infancy, than other covariates. The findings support advising women to avoid binge drinking when planning pregnancy.

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http://www.ncbi.nlm.nih.gov/pubmed/21757302

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PubMed, BMC Pregnancy Childbirth. 2011 Jul 12;11:52.

**89) THE EPIDEMIOLOGY OF ALCOHOL UTILIZATION DURING PREGNANCY: AN ANALYSIS OF THE CANADIAN MATERNITY EXPERIENCES SURVEY (MES)**

Walker MJ, Al-Sahab B, Islam F, Tamim H.
Dalla Lana School of Public Health, Division of Epidemiology, University of Toronto, Toronto, ON, Canada.

**ABSTRACT**

**Background:** Maternal alcohol consumption during pregnancy may potentially constitute a major public health concern in Canada but despite this, the available epidemiological data on both rates and predictors of alcohol consumption during pregnancy is limited. The present study assessed the prevalence and predictors of maternal alcohol consumption during pregnancy of women living in Canada from 2005-2006 who had a singleton live birth and whose child remained in their care 5-9 months following birth. Prevalence of maternal alcohol consumption was examined across the Canadian provinces.

**Methods:** The analysis was based on the Maternity Experience Survey (MES), a population-based survey that assessed pregnancy, delivery and postnatal experiences of mothers and their children between November 2005 and May 2006. The main outcome variable assessed was ever drinking alcohol during pregnancy. The sample of mothers who drank during pregnancy consisted mainly of low to moderate level-alcohol drinkers (95.8%), while only 1.7% of the sample were heavy drinkers (>1 drink per day). Socio-economic factors, demographic factors, maternal characteristics, and pregnancy related factors that proved to be significant at the bivariate level were considered for a logistic regression analysis. Bootstrapping was performed to account for the complex sampling design.

**Results:** Analysis of 5882 mothers, weighted to represent 72,767 Canadian women, found that 10.8% of women drank alcohol at some point during their pregnancies. This mainly reflects prevalence of low to moderate maternal alcohol consumption. Prevalence of drinking alcohol during pregnancy was 13.8% in Eastern-Central provinces, 7.8% in Western Provinces-British Columbia, 4.1% in Eastern-Atlantic provinces and 4.0% in Western-Prairie Provinces. Utilizing alcohol during gestation was significantly associated with several important factors including marital status, smoking status, reaction to the pregnancy and immigrant status. While being an immigrant to Canada appeared to confer a protective effect, women who have partners (odds ratio (OR)=2.00; 95% confidence interval (CI): 1.20, 3.31) and smoked during pregnancy (OR=1.54; 95% CI: 1.12, 1.87) were significantly more likely to drink alcohol during their pregnancies. Perhaps most importantly, pregnant women who reported indifference or being unhappy/very unhappy in regards to their pregnancies exhibited 1.89- and 2.5-fold increased risk of drinking alcohol during their pregnancies, respectively.

**Conclusion:** A number of important factors associated with maternal alcohol utilization during pregnancy have been identified, indicating areas where increased focus may serve to reduce maternal and pediatric morbidity and mortality.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21745414

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PubMed, J Community Health. 2011 Jul 10. [Epub ahead of print]

**90) PREGNANCY, ALCOHOL INTAKE, AND INTIMATE PARTNER VIOLENCE AMONG MEN AND WOMEN ATTENDING DRINKING ESTABLISHMENTS IN A CAPE TOWN, SOUTH AFRICA TOWNSHIP**

Eaton LA, Kalichman SC, Sikkema KJ, Skinner D, Watt MH, Pieterse D, Pitpitan EV.
Center for Health, Intervention and Prevention, University of Connecticut, 2006 Hillside Rd, Storrs, CT, 06269-1020, USA, lisaanne.eaton@gmail.com

**ABSTRACT**
The highest rates of fetal alcohol syndrome worldwide can be found in South Africa. Particularly in impoverished townships in the Western Cape, pregnant women live in environments where alcohol intake during pregnancy has become normalized and interpersonal violence (IPV) is reported at high rates. For the current study we sought to examine how pregnancy, for both men and women, is related to alcohol use behaviors and IPV. We surveyed 2,120 men and women attending drinking establishments in a township located in the Western Cape of South Africa. Among women 13.3% reported being pregnant, and among men 12.0% reported their partner pregnant. For pregnant women, 61% reported attending the bar that evening to drink alcohol and 26% reported both alcohol use and currently experiencing IPV. Daily or almost daily binge drinking was reported twice as often among pregnant women than non-pregnant women (8.4% vs. 4.2%). Men with pregnant partners reported the highest rates of hitting sex partners, forcing a partner to have sex, and being forced to have sex. High rates of alcohol frequency, consumption, binge drinking, consumption and binge drinking were reported across the entire sample. In general, experiencing and perpetrating IPV were associated with alcohol use among all participants except for men with pregnant partners. Alcohol use among pregnant women attending shebeens is alarmingly high. Moreover, alcohol use appears to be an important factor in understanding the relationship between IPV and pregnancy. Intensive, targeted, and effective interventions for both men and women are urgently needed to address high rates of drinking alcohol among pregnant women who attend drinking establishments.

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http://www.ncbi.nlm.nih.gov/pubmed/21744297

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PubMed, Mol Brain. 2011 Jul 7;4:29.

**91) FETAL ALCOHOL EXPOSURE LEADS TO ABNORMAL OLFACTORY BULB DEVELOPMENT AND IMPAIRED ODOR DISCRIMINATION IN ADULT MICE**

Akers KG, Kushner SA, Leslie AT, Clarke L, van der Kooy D, Lerch JP, Frankland PW.
Neurosciences and Mental Health, Hospital for Sick Children, and Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada.

**ABSTRACT**
**Background:** Children whose mothers consumed alcohol during pregnancy exhibit widespread brain abnormalities and a complex array of behavioral disturbances. Here, we used a mouse model of fetal alcohol exposure to investigate relationships between brain abnormalities and specific behavioral alterations during adulthood.

**Results:** Mice drank a 10% ethanol solution throughout pregnancy. When fetal alcohol-exposed offspring reached adulthood, we used high resolution MRI to conduct a brain-wide screen for structural changes and found that the largest reduction in volume occurred in the olfactory bulbs. Next, we tested adult mice in an associative olfactory task and found that fetal alcohol exposure impaired

discrimination between similar odors but left odor memory intact. Finally, we investigated olfactory bulb neurogenesis as a potential mechanism by performing an in vitro neurosphere assay, in vivo labeling of new cells using BrdU, and in vivo labeling of new cells using a transgenic reporter system. We found that fetal alcohol exposure decreased the number of neural precursor cells in the subependymal zone and the number of new cells in the olfactory bulbs during the first few postnatal weeks.

**Conclusions:** Using a combination of techniques, including structural brain imaging, in vitro and in vivo cell detection methods, and behavioral testing, we found that fetal alcohol exposure results in smaller olfactory bulbs and impairments in odor discrimination that persist into adulthood. Furthermore, we found that these abnormalities in olfactory bulb structure and function may arise from deficits in the generation of new olfactory bulb neurons during early postnatal development.

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PubMed, BJOG. 2011 Nov;118(12):1411-21. doi: 10.1111/j.1471-0528.2011.03050.x. Epub 2011 Jul 6.

**92) DOSE-RESPONSE RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION BEFORE AND DURING PREGNANCY AND THE RISKS OF LOW BIRTHWEIGHT, PRETERM BIRTH AND SMALL FOR GESTATIONAL AGE (SGA)-A SYSTEMATIC REVIEW AND META-ANALYSES**

Patra J, Bakker R, Irving H, Jaddoe VW, Malini S, Rehm J.
Centre for Addiction and Mental Health, Toronto, ON, Canada. jayadeep_patra@camh.net

**ABSTRACT**
**Background:** Descriptions of the effects of moderate alcohol consumption during pregnancy on adverse pregnancy outcomes have been inconsistent.

**Objective:** To review systematically and perform meta-analyses on the effect of maternal alcohol exposure on the risk of low birthweight, preterm birth and small for gestational age (SGA).

**Search strategy:** Using Medical Subject Headings, a literature search of MEDLINE, EMBASE, CINAHL, CABS, WHOlist, SIGLE, ETOH, and Web of Science between 1 January 1980 and 1 August 2009 was performed followed by manual searches.

**Selection criteria:** Case-control or cohort studies were assessed for quality (STROBE), 36 available studies were included.

**Data collection and analysis:** Two reviewers independently extracted the information on low birthweight, preterm birth and SGA using a standardised protocol. Meta-analyses on dose-response relationships were performed using linear as well as first-order and second-order fractional polynomial regressions to estimate best fitting curves to the data.
**Main results:** Compared with abstainers, the overall dose-response relationships for low birthweight and SGA showed no effect up to 10 g pure alcohol/day (an average of about 1 drink/day) and preterm birth showed no effect up to 18 g pure alcohol/day (an average of 1.5 drinks/day); thereafter, the relationship showed a monotonically increasing risk for increasing maternal alcohol consumption. Moderate consumption during pre-pregnancy was associated with reduced risks for all outcomes.

**Conclusions:** Dose-response relationship indicates that heavy alcohol consumption during pregnancy

increases the risks of all three outcomes whereas light to moderate alcohol consumption shows no effect. Preventive measures during antenatal consultations should be initiated.

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PubMed, Nurs Health Sci. 2011 Sep;13(3):303-8. doi: 10.1111/j.1442-2018.2011.00618.x. Epub 2011 Jul 6.

### 93) PRENATAL ALCOHOL CONSUMPTION AND KNOWLEDGE ABOUT ALCOHOL CONSUMPTION AND FETAL ALCOHOL SYNDROME IN KOREAN WOMEN

Kim O, Park K.
Division of Nursing Science, Ewha Womans University, Seoul, Korea. ohong@ewha.ac.kr

**ABSTRACT**
The study investigated prenatal alcohol consumption and knowledge of alcohol risks and fetal alcohol syndrome among Korean women. The participants were 221 Korean women who attended the post-partum care centers in Seoul, Korea. The data included the participants' background characteristics, quantity-frequency typology, Student Alcohol Questionnaire, and a scale on the participants' knowledge of fetal alcohol syndrome. Alcohol was consumed during pregnancy by 12.7% of the participants. Of these, 60.7% drank alcohol with their spouse. A few participants reported that nurses identified their drinking habits and gave them information on alcohol consumption and fetal alcohol syndrome. Most of the participants did not have the opportunity for prenatal counseling about fetal alcohol syndrome. The knowledge level regarding alcohol risks and fetal alcohol syndrome among the participants was poor. Alcohol consumption before pregnancy was significantly related to prenatal alcohol consumption. Prenatal alcohol consumption was not related to knowledge about alcohol consumption and fetal alcohol syndrome. The assessment of alcohol consumption and counseling about alcohol are needed for pregnant women in order to prevent fetal alcohol syndrome.

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PubMed, Nature. 2011 Jul 6;475(7354):53-8. doi: 10.1038/nature10192.

### 94) FANCD2 COUNTERACTS THE TOXIC EFFECTS OF NATURALLY PRODUCED ALDEHYDES IN MICE

Langevin F, Crossan GP, Rosado IV, Arends MJ, Patel KJ.
MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 0QH, UK.

**ABSTRACT**
Reactive aldehydes are common carcinogens. They are also by-products of several metabolic pathways and, without enzymatic catabolism, may accumulate and cause DNA damage. Ethanol, which is metabolised to acetaldehyde, is both carcinogenic and teratogenic in humans. Here we find that the Fanconi anaemia DNA repair pathway counteracts acetaldehyde-induced genotoxicity in mice. Our results show that the acetaldehyde-catabolising enzyme Aldh2 is essential for the development of Fancd2(-/-) embryos. Nevertheless, acetaldehyde-catabolism-competent mothers (Aldh2(+/-)) can support the development of double-mutant (Aldh2(-/-)Fancd2(-/-)) mice. However, these embryos are

unusually sensitive to ethanol exposure in utero, and ethanol consumption by postnatal double-deficient mice rapidly precipitates bone marrow failure. Lastly, Aldh2(-/-)Fancd2(-/-) mice spontaneously develop acute leukaemia. Acetaldehyde-mediated DNA damage may critically contribute to the genesis of fetal alcohol syndrome in fetuses, as well as to abnormal development, haematopoietic failure and cancer predisposition in Fanconi anaemia patients.

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PubMed, J Matern Fetal Neonatal Med. 2011 Jul 5. [Epub ahead of print]

**95) HEAVY PRENATAL ALCOHOL EXPOSURE AND RISK OF STILLBIRTH AND PRETERM DELIVERY**

Cornman-Homonoff J, Kuehn D, Aros S, Carter TC, Conley MR, Troendle J, Cassorla F, Mills JL.
Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health, Department of Health and Human Services , Bethesda, MD , USA.

**ABSTRACT**
We prospectively identified 96 women consuming at least 4 drinks/day during pregnancy by screening 9628 pregnant women. In these women with heavy prenatal alcohol use, there were three stillbirths and one preterm delivery; 98 matched nondrinking women had no stillbirths and two preterm births. Preterm rates did not differ significantly. The stillbirth rate was higher in the exposed group ($p = 0.06$). Additional investigation showed the stillbirth rate in the exposed population (3.1%) was significantly higher ($p = 0.019$) than the reported Chilean population rate (0.45%). Our data suggest that heavy alcohol consumption may increase the risk for stillbirth but not preterm delivery.

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http://www.ncbi.nlm.nih.gov/pubmed/21728738

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PubMed, Dev Neuropsychol. 2011 Jul;36(5):566-77.

**96) COMPARING ATTENTIONAL NETWORKS IN FETAL ALCOHOL SPECTRUM DISORDER AND THE INATTENTIVE AND COMBINED SUBTYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER**

Kooistra L, Crawford S, Gibbard B, Kaplan BJ, Fan J.
Department of Pediatrics, University of Calgary, Canada.

**ABSTRACT**
The Attention Network Test (ANT) was used to examine alerting, orienting, and executive control in fetal alcohol spectrum disorder (FASD) versus attention deficit hyperactivity disorder (ADHD). Participants were 113 children aged 7 to 10 years (31 ADHD-Combined, 16 ADHD-Primarily Inattentive, 28 FASD, 38 controls). Incongruent flanker trials triggered slower responses in both the ADHD-Combined and the FASD groups. Abnormal conflict scores in these same two groups provided additional evidence for the presence of executive function deficits. The ADHD-Primarily Inattentive

group was indistinguishable from the controls on all three ANT indices, which highlights the possibility that this group constitutes a pathologically distinct entity.

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http://www.ncbi.nlm.nih.gov/pubmed/21667361

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PubMed, Fam Community Health. 2011 Jul-Sep;34(3):242-5.

**97) FETAL ALCOHOL SPECTRUM DISORDERS: A NATIVE AMERICAN JOURNEY TO PREVENTION**

Beckett CD.
Pediatrics/Perinatal Services and Evidence-Based Practice, Northern Arizona Healthcare-Flagstaff Medical Center, Flagstaff, Arizona 86001, USA. preventingfasd@gmail.com

**ABSTRACT**
Fetal alcohol spectrum disorders, the most common preventable cause for mental retardation, is the result of prenatal alcohol exposure. There is no safe amount of alcohol during pregnancy. Native Americans have a higher risk of alcohol abuse than the general U.S. population. The fetal alcohol spectrum disorders prevalence rates for Native Americans range from 1.0 to 8.97 per 1000 births. Nurses and health care providers working in collaboration with tribal fetal alcohol spectrum disorders prevention specialists can greatly, and positively, impact the physical and mental health and well-being of children in Native American communities.

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http://www.ncbi.nlm.nih.gov/pubmed/21633217

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PubMed, Cad Saude Publica. 2011 Jul;27(7):1403-14.

**98) NEUROPSYCHOMOTOR DEVELOPMENT: THE DENVER SCALE FOR SCREENING COGNITIVE AND NEUROMOTOR DELAYS IN PRESCHOOLERS**

[Article in Portuguese]
Brito CM, Vieira GO, Costa Mda C, Oliveira NF.
Universidade Estadual de Feira de Santana, Brasil. cileidelopes1@bol.com.br

**ABSTRACT**
This study investigated the prevalence of abnormal neuropsychomotor developmental performance and associated factors in children enrolled in the public preschool system in Feira de Santana, Bahia State, Brazil, 2009 (N = 438). This was a cross-sectional epidemiological study with random sampling of schools and children. The study analyzed associated factors with a questionnaire applied to mothers and the Denver Developmental Screening Test (DDST) II in the preschool children. Statistical analysis used the $\chi(2)$ test with 95% confidence interval and $\alpha = 5\%$. Prevalence of abnormal developmental performance was 46.3%. According to logistic regression analysis, variables showing statistically significant association were: male gender (PR = 1.43; p = 0.00), age five years (PR = 1.42; p = 0.00), lack of prenatal care (PR = 1.41; p = 0.00), first prenatal visit ≥ 3 months gestation (PR = 1.25; p = 0.00), and alcohol consumption during pregnancy (PR = 1.55; p = 0.00). Prevalence of abnormal development was high, thus highlighting the need for early prenatal care, warnings against

alcohol consumption during pregnancy, and early childhood monitoring, aimed at prevention or early treatment.

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PubMed, J Stud Alcohol Drugs. 2011 Jul;72(4):536-44.

**99) PATERNAL DRINKING, INTIMATE RELATIONSHIP QUALITY, AND ALCOHOL CONSUMPTION IN PREGNANT UKRAINIAN WOMEN.**

Bakhireva LN, Wilsnack SC, Kristjanson A, Yevtushok L, Onishenko S, Wertelecki W, Chambers CD.
Department of Pediatrics, University of California, San Diego, La Jolla, 92093, USA.

**ABSTRACT**

**Objective:** Maternal alcohol consumption during pregnancy and fetal alcohol spectrum disorders (FASDs) represent a significant public health problem. The influence of the male partner's alcohol consumption patterns and the quality of the partner's intimate relationship might be important factors to consider in the design of successful FASD prevention programs.

**Method:** As part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders, 166 pregnant women in two regions in Ukraine participated in an in-person interview at an average gestational age of 18-19 weeks. Subjects were classified cross-sectionally as abstainers/light drinkers (n = 80), defined as low or no consumption of alcohol in the periconceptional period and none in the most recent 2 weeks of pregnancy; discontinuers (n = 43), defined as moderate to heavy alcohol use in the periconceptional period but none during the most recent 2 weeks of pregnancy; or continuing drinkers (n = 43), defined as continued moderate to heavy alcohol use within the most recent 2 weeks of pregnancy. Women also reported on their partner's drinking behavior and on the quality of their intimate relationship.

**Results:** Heavy paternal drinking was significantly associated with both continuing maternal drinking in the most recent 2 weeks (adjusted odds ratio [OR] = 34.1; 95% CI [5.9, 195.8]) and being a risky drinker only around conception (adjusted OR = 27.0; 95% CI [5.0, 147.7]). In addition, women who consumed alcohol during pregnancy had lower mean scores for satisfaction with partners' relationship and ability to discuss problems ($p < .05$) compared with light drinkers/abstainers.

**Conclusions:**

This study suggests that development of partner-based interventions, as opposed to those solely focused on maternal drinking, might be warranted as a strategy to prevent FASD.

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http://www.ncbi.nlm.nih.gov/pubmed/21683035

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PubMed, Acad Psychiatry. 2011 Jul-Aug;35(4):238-40.

**100) PSYCHIATRY TRAINEES' TRAINING AND EXPERIENCE IN FETAL ALCOHOL SPECTRUM DISORDERS**

Eyal R, O'Connor MJ.
Dept. of Psychiatry, UCLA, Los Angeles, CA. reyal@ucla.edu

**ABSTRACT**

**Background/Objective:** Alcohol is a teratogen. Fetal alcohol spectrum disorders (FASDs) affect about 1% of live births, causing severe impairment. Individuals affected by FASDs are overrepresented in psychiatric settings. This study reports on the education and experience of psychiatry trainees in approaching FASDs.

**Method:** Data were collected from psychiatry trainees throughout the country by use of a web-based questionnaire.

**Results:** A representative sample (N=308) of psychiatry trainees responded; 19% rate their education on FASDs as "good" or "excellent," and 89% report that they would like more education on FASDs: 6%, 15%, and 30%, endorsed the statement "It is safe to drink some alcohol" during the 1st, 2nd, and 3rd trimesters, respectively. Only 31% correctly report that individuals with an FASD are at equal risk for adverse outcomes as individuals with full-blown fetal alcohol syndrome.

**Conclusions:** Results reveal that training on FASDs is inadequate. Psychiatry trainees poorly understand the importance of abstinence throughout pregnancy. Trainees who report receiving supervision specifically addressing FASDs also report making the diagnosis much more frequently, suggesting that supervision in clinical settings is effective teaching. Results reveal that FASDs are underrecognized, resulting in missed opportunities for prevention and intervention.

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PubMed, Acta Med Iran. 2011 Jul;49(7):407-13.

**101) USING BIOCHEMICAL FINDINGS TO STUDY THE EFFECT OF SILYMARIN ON THE LIVER OF PREGNANT RAT THAT CONSUMED ETHANOL**

Ahmadi-Ashtiani H, Rastegar H, Javadi L.
Department of Biochemistry and Nutrition, Zanjan University of Medical Sciences, Iran.

**ABSTRACT**

In pregnancy period, there is high risk of hepatic diseases and alcohol consumption increases such risk. Some pregnant mothers are not able to quit the habit of drinking alcohol or they are unaware of its dangers. Finding a drug which is effective and efficient in reducing ethanol misuse consequences during pregnancy can assist the decrease of harmful effects of this habit. The purpose of the current research is to investigate the effects of oral administration of silymarin in preventing consequences of ethanol consumption on the liver during pregnancy, using the rat animal model as well as biochemical findings and clinical symptoms. 45 female rats were randomly divided into 3 groups, each composed of 15 rats. After the first day of pregnancy, the study was performed as follows. The first group received distilled water. The second group was given ethanol equivalent to 35% of their total required calorie. Furthermore, the third group received the same amount of ethanol plus 200 mg/kg silymarin. In order to evaluate liver's activity, biochemical analysis was performed at days 1, 7, 14, and 21, to

measure the amount of the enzymes ALT, AST, ALP, and bilirubin. The nutrition and clinical status of animal in the groups was studied and recorded 2 times daily. This study showed that silymarin's protective effects are expressed from the first day of treatment.

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PubMed, Alcohol Clin Exp Res. 2011 Jul;35(7):1321-30. doi: 10.1111/j.1530-0277.2011.01468.x.

**102) ETHANOL ALTERS BDNF-INDUCED RHO GTPASE ACTIVATION IN AXONAL GROWTH CONES.**

Lindsley TA, Shah SN, Ruggiero EA.
Center for Neuropharmacology & Neuroscience, Albany Medical College, 47 New Scotland Ave., Albany, NY 12208, USA. lindslt@mail.amc.edu

**ABSTRACT**

**Background:** The effects of ethanol on development of postmitotic neurons include altered neurite outgrowth and differentiation, which may contribute to neuropathology associated with fetal alcohol spectrum disorders. We previously reported that ethanol exposure alters axon growth dynamics in dissociated cultures of rat hippocampal pyramidal neurons. Given the important regulatory role of small Rho guanosine triphosphatases (GTPases) in cytoskeletal reorganization associated with axon growth, and reports that ethanol alters whole cell Rho GTPase activity in other cell types, this study explored the hypothesis that ethanol alters Rho GTPase activity specifically in axonal growth cones.

**Methods:** Fetal rat hippocampal pyramidal neurons were maintained in dissociated cultures for 1 day in control medium or medium containing 11 to 43 mM ethanol. Some cultures were also treated with brain-derived neurotrophic factor (BDNF), an activator of Rac1 and Cdc42 GTPases that promotes axon extension. Levels of active Rho GTPases in growth cones were measured using in situ binding assays for GTP-bound Rac1, Cdc42, and RhoA. Axon length, growth cone area, and growth cone surface expression of tyrosine kinase B (TrkB), the receptor for BDNF, were assessed by digital morphometry and immunocytochemistry.

**Results:** Although ethanol increased the surface area of growth cones, the levels of active Rho GTPases in axonal growth cones were not affected in the absence of exogenous BDNF. In contrast, ethanol exposure inhibited BDNF-induced Rac1/Cdc42 activation in a dose-dependent manner and increased RhoA activation at the highest concentration tested. Similar TrkB expression was observed on the surface of axonal growth cones of control and ethanol-treated neurons.

**Conclusions:** These results reveal an inhibitory effect of ethanol on growth cone signaling via small Rho GTPases during early stages of hippocampal development in vitro, and suggest a mechanism whereby ethanol may disrupt neurotrophic factor regulation of axon growth and guidance.

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PubMed, Am J Physiol Regul Integr Comp Physiol. 2011 Oct;301(4):R926-36. Epub 2011 Jun 29.

**103) DAILY ETHANOL EXPOSURE DURING LATE OVINE PREGNANCY: PHYSIOLOGICAL EFFECTS IN THE MOTHER AND FETUS IN THE APPARENT ABSENCE OF OVERT FETAL CEREBRAL DYSMORPHOLOGY**

Kenna K, De Matteo R, Hanita T, Rees S, Sozo F, Stokes V, Walker D, Bocking A, Brien J, Harding R.
Department of Anatomy and Developmental Biology, Monash University, Victoria, Australia.

**ABSTRACT**
High levels of ethanol (EtOH) consumption during pregnancy adversely affect fetal development; however, the effects of lower levels of exposure are less clear. Our objectives were to assess the effects of daily EtOH exposure (3.8 USA standard drinks) on fetal-maternal physiological variables and the fetal brain, particularly white matter. Pregnant ewes received daily intravenous infusions of EtOH (0.75 g/kg maternal body wt over 1 h, 8 fetuses) or saline (8 fetuses) from 95 to 133 days of gestational age (DGA; term ~145 DGA). Maternal and fetal arterial blood was sampled at 131-133 DGA. At necropsy (134 DGA) fetal brains were collected for analysis. Maternal and fetal plasma EtOH concentrations reached similar maximal concentration (~0.11 g/dl) and declined at the same rate. EtOH infusions produced mild reductions in fetal arterial oxygenation but there were no changes in maternal oxygenation, maternal and fetal Pa(CO(2)), or in fetal mean arterial pressure or heart rate. Following EtOH infusions, plasma lactate levels were elevated in ewes and fetuses, but arterial pH fell only in ewes. Fetal body and brain weights were similar between groups. In three of eight EtOH-exposed fetuses there were small subarachnoid hemorrhages in the cerebrum and cerebellum associated with focal cortical neuronal death and gliosis. Overall, there was no evidence of cystic lesions, inflammation, increased apoptosis, or white matter injury. We conclude that daily EtOH exposure during the third trimester-equivalent of ovine pregnancy has modest physiological effects on the fetus and no gross effects on fetal white matter development.

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PubMed, Matern Child Health J. 2011 Jun 28. [Epub ahead of print]

**104) FETAL ALCOHOL SPECTRUM DISORDERS: A POPULATION BASED STUDY OF PREMATURE MORTALITY RATES IN THE MOTHERS**

Li Q, Fisher WW, Peng CZ, Williams AD, Burd L.
North Dakota Fetal Alcohol Syndrome Center, University of North Dakota School of Medicine and Health Sciences, 501 N Columbia Road Stop 9037, Grand Forks, ND, 58202-9037, USA.

**ABSTRACT**
Fetal alcohol spectrum disorders (FASD) are associated with an increase in risk for mortality for people with an FASD and their siblings. In this study we examine mortality rates of birth mothers of children with FASD, using a retrospective case control methodology. We utilized the North Dakota FASD Registry to locate birth certificates for children with FASD which we used to identify birth mothers. We then searched for mothers' death certificates. We then compared the mortality rates of the birth mothers with an age matched control group comprised of all North Dakota women who were born and died in the same year as the birth mother. The birth mothers of children with FASD had a mortality rate of 15/304 = 4.93%; (95% CI 2.44-7.43%). The mortality rate for control mothers born in same years as the FASD mothers was 126/114,714 = 0.11% (95% CI 0.09-0.13%). Mothers of children with an FASD had a 44.82 fold increase in mortality risk and 87% of the deaths occurred in women under the age of 50. Three causes of death (cancer, injuries, and alcohol related disease)

accounted for 67% of the deaths in the mothers of children with FASD. A diagnosis of FASD is an important risk marker for premature death in the mothers of children diagnosed with an FASD. These women should be encouraged to enter substance abuse treatment.

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PubMed, Int J Environ Res Public Health. 2011 Jun;8(6):2331-51. Epub 2011 Jun 22.

**105) PREVALENCE OF CHILDREN WITH SEVERE FETAL ALCOHOL SPECTRUM DISORDERS IN COMMUNITIES NEAR ROME, ITALY: NEW ESTIMATED RATES ARE HIGHER THAN PREVIOUS ESTIMATES**

May PA, Fiorentino D, Coriale G, Kalberg WO, Hoyme HE, Aragón AS, Buckley D, Stellavato C, Gossage JP, Robinson LK, Jones KL, Manning M, Ceccanti M.
Center on Alcoholism, Substance Abuse, and Addictions (CASAA), The University of New Mexico, 2650 Yale SE, Albuquerque, NM 87106, USA. pmay@unm.edu

**ABSTRACT**
**Objective:** To determine the population-based epidemiology of fetal alcohol syndrome (FAS) and other fetal alcohol spectrum disorders (FASD) in towns representative of the general population of central Italy.

**Methods:** Slightly revised U.S. Institute of Medicine diagnostic methods were used among children in randomly-selected schools near Rome. Consented first grade children (n=976) were screened in Tier I for height, weight, or head circumference and all children≤10th centile on one of these measurements were included in the study. Also, teachers referred children for learning or behavioral problems. Children meeting either of these two criteria, along with randomly-selected controls, advanced to Tier II which began with a dysmorphology examination. Children with a possible FASD, and controls, advanced to Tier III for neurobehavioral testing, and their mothers were interviewed for maternal risks. Final diagnoses using indicators of dysmorphology, neurobehavior, and maternal risk were made in formally-structured, interdisciplinary case conferences.

**Results:** Case control comparisons of physical, neurobehavioral, and maternal risk variables are presented for 46 children with an FASD and 116 randomly-selected controls without a diagnosis on the FASD continuum. Rates of diagnoses within the FASD continuum are then estimated from these in-school data via three different methods. The range of rates of FAS produced by these methods is between 4.0 to 12.0 per 1,000; Partial FAS ranges from 18.1 to 46.3 per 1,000; and an FASD was found in 2.3% to 6.3% of the children.

**Conclusions:** These rates are substantially higher than previous estimates of FAS and overall FASD for the general populations of Western Europe and the U. S., and raise questions as to the total impact of FASD on mental deficit in mainstream populations of Western Europe and the United States where the majority are middle class and are not believed to be characterized by heavy episodic drinking.

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PubMed, Mol Pharmacol. 2011 Sep;80(3):446-57. Epub 2011 Jun 22.

**106) RESVERATROL RESTORES NRF2 LEVEL AND PREVENTS ETHANOL-INDUCED TOXIC EFFECTS IN THE CEREBELLUM OF A RODENT MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS**

Kumar A, Singh CK, Lavoie HA, Dipette DJ, Singh US.
Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, University of South Carolina, Columbia, South Carolina, USA.

**ABSTRACT**
In humans, ethanol exposure during pregnancy produces a wide range of abnormalities in infants collectively known as fetal alcohol spectrum disorders (FASD). Neuronal malformations in FASD manifest as postnatal behavioral and functional disturbances. The cerebellum is particularly sensitive to ethanol during development. In a rodent model of FASD, high doses of ethanol (blood ethanol concentration 80 mM) induces neuronal cell death in the cerebellum. However, information on potential agent(s) that may protect the cerebellum against the toxic effects of ethanol is lacking. Growing evidence suggests that a polyphenolic compound, resveratrol, has antioxidant and neuroprotective properties. Here we studied whether resveratrol (3,5,4'-trihydroxy-trans-stilbene), a phytoalexin found in red grapes and blueberries, protects the cerebellar granule neurons against ethanol-induced cell death. In the present study, we showed that administration of resveratrol (100 mg/kg) to postnatal day 7 rat pups prevents ethanol-induced apoptosis by scavenging reactive oxygen species in the external granule layer of the cerebellum and increases the survival of cerebellar granule cells. It restores ethanol-induced changes in the level of transcription factor nuclear factor-erythroid derived 2-like 2 (nfe2l2, also known as Nrf2) in the nucleus. This in turn retains the expression and activity of its downstream gene targets such as NADPH quinine oxidoreductase 1 and superoxide dismutase in cerebellum of ethanol-exposed pups. These studies indicate that resveratrol exhibits neuroprotective effects in cerebellum by acting at redox regulating proteins in a rodent model of FASD.

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PubMed, Hum Brain Mapp. 2011 Jun 20. doi: 10.1002/hbm.21313. [Epub ahead of print]

**107) UNDERSTANDING SPECIFIC EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON BRAIN STRUCTURE IN YOUNG ADULTS**

Chen X, Coles CD, Lynch ME, Hu X.
Biomedical Imaging Technology Center, Department of Biomedical Engineering, Emory University, Atlanta, Georgia. xiangchuan.chen@emory.edu

**ABSTRACT**
Prenatal alcohol exposure (PAE) is associated with various adverse effects on human brain and behavior. Recently, neuroimaging studies have begun to identify PAE effects on specific brain structures. Investigation of such specific PAE effects is important for understanding the teratogenic mechanism of PAE on human brain, which is critical for differentiating PAE from other disorders. In this structural MRI study with young adults, PAE effects on the volumes of automatically segmented cortical and subcortical regions of interest (ROIs) were evaluated both through a group difference approach and a parametric approach. In the group difference approach (comparing among two PAE and a control groups), a disproportionate PAE effect was found in several occipital and temporal

regions. This result is inconsistent with previous studies with child samples. Moreover, a gender difference in PAE effect was shown in some cortical ROIs. These findings suggest that sampling and gender may be important factors for interpreting specific PAE effects on human brain. With the parametric approach, it was demonstrated that the higher the PAE level, the smaller the entire brain, the lower the IQ. Several cortical and subcortical ROIs also exhibited a negative correlation between the PAE level and ROI volume. Furthermore, our data showed that the PAE effect on the brain could not be interpreted by the PAE effect on general physical growth until the young adult age. This study provides valuable insight into specific effects of PAE on human brain and suggests important implications for future studies in this field. Hum Brain Mapp, 2011.

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http://www.ncbi.nlm.nih.gov/pubmed/21692145

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PubMed, Alcohol Clin Exp Res. 2011 Jun 20. doi: 10.1111/j.1530-0277.2011.01572.x. [Epub ahead of print]

**108) ALCOHOL IN PREGNANCY: ATTITUDES, KNOWLEDGE, AND INFORMATION PRACTICE AMONG MIDWIVES IN DENMARK 2000 TO 2009**

Kesmodel US, Kesmodel PS.
From the Department of Obstetrics and Gynaecology (USK, PSK), Aarhus University Hospital, Skejby, Aarhus N, Denmark; School of Public Health, Department of Epidemiology (USK), Aarhus University, Aarhus C, Denmark; and Alcohol Treatment Centre, Social Services (PSK), Municipality of Aarhus, Aarhus C, Denmark.

**ABSTRACT**

**Background:** Most pregnant women in Denmark say they have not talked to their midwives about alcohol in pregnancy, and they have mostly been advised that some alcohol intake is all right. From 1999 to 2007, the Danish National Board of Health advised pregnant women that some alcohol intake was acceptable. Since 2007, the recommendation has been alcohol abstinence. The aim of this study was to describe the attitudes toward, knowledge about, and information practice concerning alcohol drinking in pregnancy among midwives in Denmark in 2000 and 2009 and how their answers related to the 2 different official recommendations at the time.

**Methods:** In 2000, we invited all midwives in the antenatal care center at Aarhus University Hospital. Ninety-four percent were interviewed about their attitudes toward and beliefs and knowledge about alcohol during pregnancy. Questions were also asked about information on alcohol provided to pregnant women. Identical questions were asked to all midwives (100%) in the antenatal care center in 2009. Results: In 2000, most midwives (69%) considered some alcohol intake in pregnancy acceptable, mostly on a weekly level, and only 28% advised abstinence. Binge drinking, on the other hand, was considered harmful by most. There was considerable inter-person variation in the participants' attitudes and what they recommended to pregnant women. In 2009, substantially more midwives (48%) considered abstinence to be best, and significantly, more midwives (61%) gave this advice to pregnant women. Participants had received information on alcohol mostly in a professional context. Their knowledge about the official recommendations about alcohol was good, but many did not inform about the official recommendation.

**Conclusions:** The attitudes toward and beliefs and knowledge about drinking in pregnancy among

midwives have changed along with a change in official policy. The change was mostly independent of personal characteristics of the midwives, including age, gender, and place of work.

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http://www.ncbi.nlm.nih.gov/pubmed/21689120

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PubMed, Community Ment Health J. 2011 Jun 18. [Epub ahead of print]

### 109) THE IMPACT OF FETAL ALCOHOL SPECTRUM DISORDERS ON FAMILIES: EVALUATION OF A FAMILY INTERVENTION PROGRAM

Leenaars LS, Denys K, Henneveld D, Rasmussen C.
Department of Educational Psychology, University of Alberta, 6-102 Education North, Edmonton, AB, T6G 2G5, Canada, leenaars@ualberta.ca

**ABSTRACT**
The main purpose of the present study was to conduct a preliminary evaluation of the coaching families (CF) program, which aids families and caregivers raising children with fetal alcohol spectrum disorders (FASD). Mentors in the program work with families to educate them about FASD, access resources, and advocate on their behalf. Retrospective data from 186 families were analyzed from pre- to post-program. As expected, among caregivers there was a significant decrease in needs and increase in goal attainment from pre- to post-program. Further, there was a significant decrease in caregiver stress from pre- to post-program. Families reported high overall satisfaction with the CF program. The limitations, directions for future research, and implications for service providers were also discussed.

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http://www.ncbi.nlm.nih.gov/pubmed/21687984

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ScienceDirect, doi:10.1016/j.neuroimage.2011.06.026
Received 13 January 2011; revised 8 June 2011; Accepted 9 June 2011. Available online 17 June 2011.

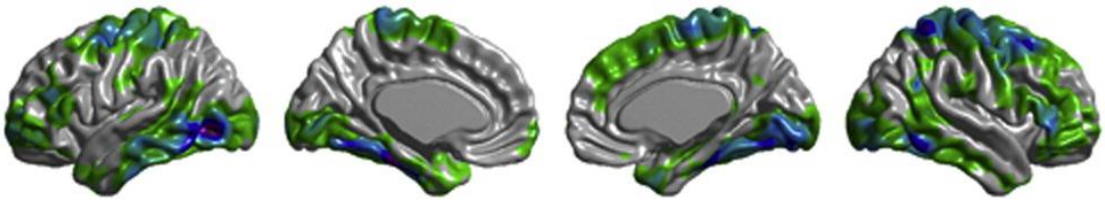
### 110) DEVELOPMENTAL CORTICAL THINNING IN FETAL ALCOHOL SPECTRUM DISORDERS

Dongming Zhou[a], Catherine Lebel[a], Claude Lepage[b], Carmen Rasmussen[c], Alan Evans[b], Katy Wyper[a], Jacqueline Pei[d], Gail Andrew[e], Ashleigh Massey[d], Donald Massey[d], Christian Beaulieu[a]
a Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada
b McConnell Brain Imaging Center, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada
c Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
d Department of Educational Psychology, University of Alberta, Edmonton, Alberta, Canada
e Glenrose Rehabilitation Hospital FASD Clinic, Edmonton, Alberta, Canada

**ABSTRACT**
Regional cortical thickness was evaluated using CIVET processing of 3D T1-weighted images (i) to compare the variation in cortical thickness between 33 participants with fetal alcohol spectrum disorders (FASD) aged 6–30 years (mean age 12.3 years) versus 33 age/sex/hand-matched controls, and (ii) to examine developmental changes in cortical thickness with age from children to young adults

in both groups. Significant cortical thinning was found in the participants with FASD in large areas of the bilateral middle frontal lobe, pre- and post- central areas, lateral and inferior temporal and occipital lobes compared to controls. No significant cortical thickness increases were observed for the FASD group. Cortical thinning with age in a linear model was observed in both groups, but the locations were different for each group. FASD participants showed thinning with age in the left middle frontal, bilateral precentral, bilateral precuneus and paracingulate, left inferior occipital and bilateral fusiform gyri; while controls showed decreases with age in the bilateral middle frontal gyrus, right inferior frontal gyrus, bilateral precuneus gyrus, and bilateral occipital gyrus. A battery of cognitive assessments of memory, attention, motor, and verbal abilities was conducted with many of the FASD participants, but no significant correlations were found between these cognitive scores and regional cortical thickness. Non-invasive measurements of cortical thickness in children to young adults with FASD have identified both key regions of cortex that may be more deleteriously affected by prenatal alcohol exposure as well as cortical changes with age that differ from normal developmental thinning.

Graphical abstract



**Research highlights**

► Prenatal alcohol exposure can result in brain injury and a diagnosis of FASD. ► Brain cortical thickness measured over developmental age span of 6–30 years. ► Regional bilateral decreases of cortical thickness were observed in FASD. ► Thinner cortex was observed in FASD over the entire age span. ► Cortical thinning with age was evident in both FASD and controls.

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http://www.sciencedirect.com/science/article/pii/S1053811911006446

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ScienceDirect, doi:10.1016/j.toxlet.2011.06.014
Received 3 May 2011; revised 9 June 2011; Accepted 10 June 2011. Available online 17 June 2011.

## 111) ACUTE EFFECTS OF ETHANOL ON THE TRANSFER OF NICOTINE AND TWO DIETARY CARCINOGENS IN HUMAN PLACENTAL PERFUSION

Jenni Veid[a, 1], Vesa Karttunen[a, 1], Kirsi Myöhänen[a], Päivi Myllynen[b], Seppo Auriola[c], Toivo Halonen[d], Kirsi Vähäkangas[a]
a Faculty of Health Sciences, School of Pharmacy/Toxicology, University of Eastern Finland, P.O. BOX 1627, FI-70211 Kuopio, Finland
b Institute of Biomedicine, Department of Pharmacology and Toxicology, P.O. BOX 5000, FI-90014 University of Oulu, Oulu, Finland
c Faculty of Health Sciences, School of Pharmacy/Pharmaceutical Chemistry, University of Eastern Finland, P.O. BOX 1627, FI-70211 Kuopio, Finland
d Eastern Finland Laboratory Centre (ISLAB), P.O. BOX 1700, FI-70211 Kuopio, Finland

**ABSTRACT**

Many mothers use, against instructions, alcohol during pregnancy. Simultaneously mothers are exposed to a wide range of other environmental chemicals. These chemicals may also harm the

developing fetus, because almost all toxic compounds can go through human placenta. Toxicokinetic effects of ethanol on the transfer of other environmental compounds through human placenta have not been studied before. It is known that ethanol has lytic properties and increases the permeability and fluidity of cell membranes. We studied the effects of ethanol on the transfer of three different environmental toxins: nicotine, PhIP (2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine) and NDMA (N-nitrosodimethylamine) in placental perfusion. We tested in human breast cancer adenocarcinoma cell line MCF-7 whether ethanol affects ABCG2/BCRP, which is also the major transporter in human placenta. We found that the transfer of ethanol is comparable to that of antipyrine, which points to passive diffusion as the transfer mechanism. Unexpectedly, ethanol had no statistically significant effect on the transfer of the other studied compounds. Neither did ethanol inhibit the function of ABCG2/BCRP. These experiments represent only the effects of acute exposure to ethanol and chronic exposure remains to be studied.

**Highlights**
• Transfer through perfused human placenta was used as a model of fetal exposure. • Ethanol did not increase the transplacental transfer of nicotine, NDMA or PhIP. • Ethanol transfer was similar to that of the passively diffusible antipyrine. • Ethanol did not inhibit the function of the efflux transporter ABCG2/BCRP *in vitro*.

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http://www.sciencedirect.com/science/article/pii/S0378427411012793

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PubMed, Alcohol Alcohol. 2011 Sep-Oct;46(5):514-22. Epub 2011 Jun 17.

**112) COMBINED PRE- AND POSTNATAL ETHANOL EXPOSURE IN RATS DISTURBS THE MYELINATION OF OPTIC AXONS**

Pons-Vázquez S, Gallego-Pinazo R, Galbis-Estrada C, Zanon-Moreno V, Garcia-Medina JJ, Vila-Bou V, Sanz-Solana P, Pinazo-Durán MD.
Ophthalmic Research Unit Santiago Grisolía, University Hospital Dr Peset, Av Gaspar Aguilar 90, 46017 Valencia, Spain. pons_she@gva.es

**ABSTRACT**
**Aims:** To analyse myelination and outgrowth of the optic axons in relation to the neuro-ophthalmological manifestations of ethanol (EtOH) abuse during pregnancy.

**Methods:** An experimental model of chronic EtOH exposure was developed in rats and their offspring by subjecting the dams to a liquid diet (35% of the daily total calories as either EtOH or maltose-dextrose nutritional controls (Con). Eyeballs and optic nerves were obtained at key developmental stages and processed for morphologic, immunocytochemical and immunoblotting procedures, using alternatively antibodies against myelin basic protein (MBP) or neurofilament (NF) protein, and image analysing.

**Results:** A significant delay in onset of optic axons myelination, as well as a significant reduction in optic nerve size ($P < 0.001$), optic axons number ($P < 0.001$), myelinated axons density ($P < 0.001$), number of myelin lamellae linked to axon diameter ($P < 0.001$) and optic axon cross-sectional area ($P < 0.001$) were detected in the global morphometric assessment of the EtOH nerves with respect to the Con. Expression of MBP and NF was noticeably reduced in the EtOH optic nerves when compared with the Con.

**Conclusion:** Disturbed myelination of optic axons, caused by EtOH abuse, strongly disrupts the optic

nerve development and the establishment of definitive retinal and optic nerve targets, and subsequently the visual patterns.

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http://www.ncbi.nlm.nih.gov/pubmed/21685480

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BMJ. 2011 Jun 17;342:d3762. doi: 10.1136/bmj.d3762.

**113) WOMEN TOLD THAT THEY MUST ABSTAIN FROM ALCOHOL IN PREGNANCY, IN CAMPAIGN FINANCED BY DRINKS INDUSTRY**

Mooney H.

**ABSTRACT**
Drinks giant Diageo is funding a training scheme that aims to teach midwives to advise expectant mothers of the risks of drinking alcohol during pregnancy.

The scheme, run by the National Organisation for Foetal Alcohol Syndrome (NOFAS-UK), hopes to reach 10 000 midwives and one million pregnant women over five years.

In its second year the project has already trained 800 midwives with funding from Diageo, producer of brands including Guinness, Johnnie Walker, and Smirnoff. The scheme is part of the government's drive to increase private investment in public health initiatives.

The advice given by the NOFAS differs from the Department of Health's. The organisation advises women to abstain entirely from alcohol during pregnancy and while trying to conceive, whereas the Department of Health says that, although women should avoid alcohol during pregnancy, "if they do choose to drink, to minimise the risk to the baby, they should not drink more than 1 or 2 …

**Read Full Article,**
http://www.bmj.com/content/342/bmj.d3762?view=long&pmid=21685439

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J Popul Ther Clin Pharmacol. 2011;18(2):e364-76. Epub 2011 Jun 15.

**114) LANGUAGE IMPAIRMENTS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS**

Wyper KR, Rasmussen CR.
Department of Educational Psychology, University of Alberta, Alberta, Canada.

**ABSTRACT**
**Background:** Fetal Alcohol Spectrum Disorder (FASD) is associated with a range of disabilities, including physical, behavioural, and cognitive deficits. One specific area of concern in children with FASD is the use and development of speech and language. Language deficits in FASD have been linked to learning problems and social difficulties.

**Objectives:** The current study sought to examine the language difficulties of children with FASD, and to identify areas of deficit that may be particularly pronounced among these children.

**Methods:** Fifty children, aged 5 to 13, (27 with FASD, 23 control children) were tested on the CREVT-2, the TOLD-P:3, and the TOLD-I:3.

**Results:** Children with FASD had significantly lower scores than control children on both receptive and expressive subtests of the CREVT-2. Younger children scored significantly lower than controls on the Relational Vocabulary and Sentence Imitation subtests of the TOLD-P:3, and older children were significantly delayed on the Word Ordering, Grammatic Comprehension, and Malapropisms subtests of the TOLD-I:3.

**Conclusions:** This study identified several areas of marked difficulty in children with FASD, adding to the current understanding of language development in this population. The results have implications for tailoring early interventions, and for providing evidence-based support to children prenatally exposed to alcohol.

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PubMed, Acta Paediatr. 2011 Nov;100(11):1481-8. doi: 10.1111/j.1651-2227.2011.02354.x. Epub 2011 Jun 10.

**115) RISK FACTORS FOR BEHAVIOURAL PROBLEMS IN FOETAL ALCOHOL SPECTRUM DISORDERS**

Fagerlund A, Autti-Rämö I, Hoyme HE, Mattson SN, Korkman M.
Folkhälsan Research Center, Helsinki, Finland. ase.fagerlund@folkhalsan.fi

**ABSTRACT**
**Aim:** To examine risk and protective factors associated with behavioural problems of children and adolescents following prenatal alcohol exposure.

**Methods:** A total of 73 children and adolescents with foetal alcohol spectrum disorders (FASD) were assessed for internalizing, externalizing and total behavioural problems using the Child Behavior Checklist. Linear regression models were used to determine the effects of diagnostic and environmental risk and protective factors on behaviour, while controlling for age, sex and IQ.

**Results:** Length of time spent in residential care was the most pervasive risk factor associated with internalizing, externalizing and total behavioural problems. A low dysmorphology score was related to more internalizing and total problems.

**Conclusions:** Children and adolescents prenatally exposed to alcohol faced greater risk of substantive behavioural problems (i) if they were less visibly alcohol affected and (ii) the longer time they had spent in residential care. The results underscore the clinical importance of appropriate services and care for less visibly affected children with FASD and highlight the need to attend to children with FASD being raised in institutions.

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http://www.ncbi.nlm.nih.gov/pubmed/21575054

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PubMed, J Neurosci Res. 2011 Oct;89(10):1676-84. doi: 10.1002/jnr.22689. Epub 2011 Jun 10.

**116) CYANIDIN-3-GLUCOSIDE AMELIORATES ETHANOL NEUROTOXICITY IN THE DEVELOPING BRAIN.**

Ke Z, Liu Y, Wang X, Fan Z, Chen G, Xu M, Bower KA, Frank JA, Ou X, Shi X, Luo J.
Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Kentucky 40536, USA.

**ABSTRACT**
Ethanol exposure induces neurodegeneration in the developing central nervous system (CNS). Fetal alcohol spectrum disorders (FASD) are caused by ethanol exposure during pregnancy and are the most common nonhereditary cause of mental retardation. It is important to identify agents that provide neuroprotection against ethanol neurotoxicity. Multiple mechanisms have been proposed for ethanol-induced neurodegeneration, and oxidative stress is one of the most important mechanisms. Recent evidence indicates that glycogen synthase kinase 3β (GSK3β) is a potential mediator of ethanol-mediated neuronal death. Cyanidin-3-glucoside (C3G), a member of the anthocyanin family, is a potent natural antioxidant. Our previous study suggested that C3G inhibited GSK3β activity in neurons. Using a third trimester equivalent mouse model of ethanol exposure, we tested the hypothesis that C3G can ameliorate ethanol-induced neuronal death in the developing brain. Intraperitoneal injection of C3G reduced ethanol-meditated caspase-3 activation, neurodegeneration, and microglial activation in the cerebral cortex of 7-day-old mice. C3G blocked ethanol-mediated GSK3β activation by inducing phosphorylation at serine 9 while reducing the phosphorylation at tyrosine 216. C3G also inhibited ethanol-stimulated expression of malondialdehyde (MDA) and p47phox, indicating that C3G alleviated ethanol-induced oxidative stress. These results provide important insight into the therapeutic potential of C3G.

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http://www.ncbi.nlm.nih.gov/pubmed/21671257

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PubMed, Alcohol Clin Exp Res. 2011 Nov;35(11):2063-74. doi: 10.1111/j.1530-0277.2011.01557.x. Epub 2011 Jun 8.

**117) EFFECTS OF EARLY POSTNATAL EXPOSURE TO ETHANOL ON RETINAL GANGLION CELL MORPHOLOGY AND NUMBERS OF NEURONS IN THE DORSOLATERAL GENICULATE IN MICE**

Dursun I, Jakubowska-Doğru E, van der List D, Liets LC, Coombs JL, Berman RF.
From the Department of Biological Sciences (ID, EJ-D), Middle East Technical University, Ankara, Turkey; Department of Neurobiology, Physiology, and Behavior (DvdL, LCL, JLC), UC Davis, Davis, California; and Center for Neuroscience, Department of Neurological Surgery (RFB), University of California Davis, Davis, California.

**ABSTRACT**
**Background:** The adverse effects of fetal and early postnatal ethanol intoxication on peripheral organs and the central nervous system are well documented. Ocular defects have also been reported in about 90% of children with fetal alcohol syndrome, including microphthalmia, loss of neurons in the retinal ganglion cell (RGC) layer, optic nerve hypoplasia, and dysmyelination. However, little is known about perinatal ethanol effects on retinal cell morphology. Examination of the potential toxic effects of alcohol on the neuron architecture is important because the changes in dendritic geometry and synapse distribution directly affect the organization and functions of neural circuits. Thus, in the present study, estimations of the numbers of neurons in the ganglion cell layer and dorsolateral

geniculate nucleus (dLGN), and a detailed analysis of RGC morphology were carried out in transgenic mice exposed to ethanol during the early postnatal period.

**Methods:** The study was carried out in male and female transgenic mice expressing yellow fluorescent protein (YFP) controlled by a Thy-1 (thymus cell antigen 1) regulator on a C57 background. Ethanol (3 g/kg/d) was administered to mouse pups by intragastric intubation throughout postnatal days (PDs) 3 to 20. Intubation control (IC) and untreated control (C) groups were included. Blood alcohol concentration was measured in separate groups of pups on PDs 3, 10, and 20 at 4 different time points, 1, 1.5, 2, and 3 hours after the second intubation. Numbers of neurons in the ganglion cell layer and in the dLGN were quantified on PD20 using unbiased stereological procedures. RGC morphology was imaged by confocal microscopy and analyzed using Neurolucida software.

**Results:** Binge-like ethanol exposure in mice during the early postnatal period from PDs 3 to 20 altered RGC morphology and resulted in a significant decrease in the numbers of neurons in the ganglion cell layer and in the dLGN. In the alcohol exposure group, out of 13 morphological parameters examined in RGCs, soma area was significantly reduced and dendritic tortuosity significantly increased. After neonatal exposure to ethanol, a decrease in total dendritic field area and an increase in the mean branch angle were also observed. Interestingly, RGC dendrite elongation and a decrease in the spine density were observed in the IC group, as compared to both ethanol-exposed and pure control subjects. There were no significant effects of alcohol exposure on total retinal area.

**Conclusions:** Early postnatal ethanol exposure affects development of the visual system, reducing the numbers of neurons in the ganglion cell layer and in the dLGN, and altering RGCs' morphology.

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http://www.ncbi.nlm.nih.gov/pubmed/21651582

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PubMed. Alcohol Clin Exp Res. 2011 Nov;35(11):1974-1984. doi: 10.1111/j.1530-0277.2011.01549.x. Epub 2011 Jun 7.

**118) LOCAL AND REGIONAL NETWORK FUNCTION IN BEHAVIORALLY RELEVANT CORTICAL CIRCUITS OF ADULT MICE FOLLOWING POSTNATAL ALCOHOL EXPOSURE**

Wilson DA, Peterson J, Basavaraj BS, Saito M.
From the Emotional Brain Institute (DAW, JP), Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York; Department of Child and Adolescent Psychiatry (DAW), New York University Langone Medical Center, New York, New York; Dominican College (JP), Orangeburg, New York; Division of Analytical Psychopharmacology (BSB), Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York; New York State Psychiatric Institute, Department of Psychiatry (BSB), College of Physicians & Surgeons, Columbia University, New York; Division of Neurochemistry (MS), Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York; and Department of Psychiatry (MS), New York University Langone Medical Center, New York, New York.

**ABSTRACT**
**Background:** Ethanol consumption during pregnancy can lead to fetal alcohol spectrum disorder (FASD), which consists of the complete spectrum of developmental deficits including neurological dysfunction. FASD is associated with a variety of neurobehavioral disturbances dependent on the age and duration of exposure. Ethanol exposure in neonatal rodents can also induce widespread apoptotic neurodegeneration and long-lasting behavioral abnormalities similar to FASD. The developmental stage of neonatal rodent brains that are at the peak of synaptogenesis is equivalent to the third

trimester of human gestation.
**Methods:** Male and female C57BL/6By mice were injected with ethanol (20%, 2.5 g/kg, 2 s.c. injections) or an equal volume of saline (controls) on postnatal day 7 (P7). Animals were allowed to mature and at 3 months were tested on an olfactory habituation task known to be dependent on piriform cortex function, a hippocampal-dependent object place memory task, and used for electrophysiological testing of spontaneous and odor-evoked local field potential (LFP) activity in the olfactory bulb, piriform cortex, and dorsal hippocampus.

**Results:** P7 ethanol induced widespread cell death within 1 day of exposure, with highest levels in the neocortex, intermediate levels in the dorsal hippocampus, and relatively low levels in the primary olfactory system. No impairment of odor investigation or odor habituation was detected in P7 ethanol-exposed 3-month-old mice compared to saline controls. However, hippocampal-dependent object place memory was significantly impaired in the P7 ethanol-treated adult mice. Odor-evoked LFP activity was enhanced throughout the olfacto-hippocampal pathway, primarily within the theta frequency band, although the hippocampus also showed elevated evoked delta frequency activity. In addition, functional coherence between the piriform cortex and olfactory bulb and between the piriform cortex and dorsal hippocampus was enhanced in the beta frequency range in P7 ethanol-treated adult mice compared to controls.

**Conclusions:** P7 ethanol induces an immediate wave of regionally selective cell death followed by long-lasting changes in local circuit and regional network function that are accompanied by changes in neurobehavioral performance. The results suggest that both the activity of local neural circuits within a brain region and the flow of information between brain regions can be modified by early alcohol exposure, which may contribute to long-lasting behavioral abnormalities known to rely on those circuits.

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http://www.ncbi.nlm.nih.gov/pubmed/21649667

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PubMed, BMC Pediatr. 2011 Jun 6;11:51.

**119) A SURVEY OF ITALIAN AND SPANISH NEONATOLOGISTS AND PAEDIATRICIANS REGARDING AWARENESS OF THE DIAGNOSIS OF FAS AND FASD AND MATERNAL ETHANOL USE DURING PREGNANCY**

Vagnarelli F, Palmi I, García-Algar O, Falcon M, Memo L, Tarani L, Spoletini R, Pacifici R, Mortali C, Pierantozzi A, Pichini S.
Arcispedale Santa Maria Nuova NICU, Reggio Emilia, Italy. federica.vagnarelli@asmn.re.it

**ABSTRACT**
**Background:** Ethanol is the most widely used drug in the world and a human teratogen whose consumption among women of childbearing age has been steadily increasing. There are no Italian or Spanish statistics on ethanol consumption during pregnancy nor any information regarding prevalence of fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorders (FASD). There is also a reasonable suspicion that these two diseases are underdiagnosed by professionals from the above-reported countries. The objectives of this study were: 1) to evaluate the experience, knowledge and confidence of Italian and Spanish neonatologists and paediatricians with respect to the diagnosis of FAS and FASD, and 2) to evaluate professionals awareness of maternal drinking patterns during pregnancy.

**Methods:** A multiple-choice anonymous questionnaire was e-mailed to Italian neonatologists

registered in the mailing list of the corresponding Society and administered to Italian and Spanish paediatricians during their National Congress.

**Results:** The response rate was 16% (63/400) for the Italian neonatologists of the National Society while a total of 152 Spanish and 41 Italian paediatricians agreed to complete the questionnaire during National Congress. Over 90% of the surveyed physicians declared that FAS is an identifiable syndrome and over 60% of them identified at least one of the most important features of FAS. Although over 60% Italian responders and around 80% Spanish responders were aware that ethanol use in pregnancy is dangerous, approximately 50% Italian responders and 40% Spanish ones allowed women to drink sometimes a glass of wine or beer during pregnancy.Neonatologists and paediatricians rated confidence in the ability to diagnosis FAS and FASD as low, with over 50% responders feeling they needed more information regarding FAS and FASD identification in newborn and child.

**Conclusions:** Italian and Spanish neonatologists and paediatricians do not feel confident about diagnosing FAS and FASD. More training is needed in order to accurately diagnose ethanol use during pregnancy and correctly inform pregnant women on the consequences on the newborn.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21645328

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Alcohol, Volume 45, Issue 5, Pages 441-449
Received 28 October 2010; received in revised form 4 February 2011; accepted 16 February 2011. published online 06 June 2011.

**120) MATERNAL EFFECTS ON ETHANOL TERATOGENESIS IN A CROSS BETWEEN A/J AND C57BL/6J MICE**

David Gilliam, Nate Valdez, Scott Branson, Ashley Dixon, Chris Downing

**ABSTRACT**

Genetic factors influence adverse pregnancy outcome in both humans and animal models. Animal research reveals that both the maternal and fetal genetic profiles are important for determining the risk of physical birth defects and prenatal mortality. Using a reciprocal-cross breeding design, we investigated whether the mother's genes may be more important than fetal genes in determining risk for ethanol teratogenesis. Examination of possible synergistic genetic effects on ethanol teratogenesis was made possible by using two mouse strains known to be susceptible to specific malformations. Inbred A/J (A) and C57BL/6J (B6) mice were mated to produce four fetal genotype groups: the true-bred AċA and B6ċB6 genotypes and the genetically identical AċB6 and B6ċA genotypes (the F1 genotype). Dams were administered either 5.8g/kg ethanol or an isocaloric amount of maltose–dextrin on day 9 of pregnancy. Fetuses were removed by laparotomy on gestation day 18, weighed, and assessed for digit, vertebral, and kidney malformations. Digit malformations in the genetically identical F1 ethanol-exposed litters showed a pattern consistent with a maternal genetic effect (AċB6 [2%] and B6ċA [30%]). In contrast, vertebral malformations were similar in all ethanol-exposed litters (AċA [26%], AċB6 [18%], B6ċA [22%], and B6ċB6 [33%]). The percentage of malformations did not differ between male and female fetuses, indicating sex-linked factors are not responsible for the maternal effect. Ethanol exposure decreased litter weights but did not affect litter mortality compared with maltose-exposed controls. This study supports the idea that genes influence malformation risk following in utero alcohol exposure. Specifically, maternal genes influence risk more than fetal genes

for some teratogenic outcomes. No evidence supported synergistic genetic effects on ethanol teratogenesis. This research supports the conclusion that uterine environment contributes to determining risk of Fetal Alcohol Spectrum Disorder.

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http://www.alcoholjournal.org/article/S0741-8329(11)00387-9/abstract

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PubMed, Neurotoxicol Teratol. 2011 Jun 1. [Epub ahead of print]

**121) EARLY EMBRYONIC ETHANOL EXPOSURE IMPAIRS SHOALING AND THE DOPAMINERGIC AND SEROTONINERGIC SYSTEMS IN ADULT ZEBRAFISH**

Buske C, Gerlai R.
Department of Cell & Systems Biology, Neuroscience, University of Toronto, Canada.

**ABSTRACT**
Fetal alcohol syndrome (FAS) is a devastating disorder accompanied by numerous morphological and behavioral abnormalities. Human FAS has been modeled in laboratory animals including the zebrafish. Recently, embryonic exposure to low doses of ethanol has been shown to impair behavior without any gross morphological alterations in zebrafish. The exposed zebrafish showed reduced responses to animated conspecific images. The effect of embryonic ethanol exposure, however, has not been investigated in a real shoal and the potential mechanisms underlying the behavioral impairment are also unknown. Here we show that a 2h long immersion in 0.25% and 0.50% (vol/vol) alcohol at 24h post fertilization significantly increases the distance among members of freely swimming groups of zebrafish when measured at 70days post fertilization. We also show that this impaired behavior is accompanied by reduced levels of dopamine, DOPAC, serotonin and 5HIAA as quantified by HPLC from whole brain extracts. Our results demonstrate that even very low concentrations of alcohol applied for a short period of time during the development of zebrafish can impair behavior and brain function. We argue that the observed behavioral impairment is not likely to be due to altered performance capabilities, e.g. motor function or perception, but possibly to social behavior itself. We also argue that our neurochemical data represent the first step towards understanding the mechanisms of this abnormality in zebrafish, which may lead to better modeling of, and ultimately perhaps better therapies for human FAS.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21658445

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PubMed, J Recept Signal Transduct Res. 2011 Jun;31(3):206-13.

**122) GABRB3 GENE EXPRESSION INCREASES UPON ETHANOL EXPOSURE IN HUMAN EMBRYONIC STEM CELLS**

Krishnamoorthy M, Gerwe BA, Scharer CD, Heimburg-Molinaro J, Gregory F, Nash RJ, Arumugham J, Usta SN, Eilertson CD, Stice SL, Nash RJ.
Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA.

**ABSTRACT**
Ionotropic receptors are the target for most mood-defining compounds. Chronic exposure to ethanol

(EtOH) alters receptor-mediated responses and the numbers of these channels and specific subunits; as well as induces anxiolytic, sedative, and anesthetic activity in the human brain. However, very little is known regarding the effects of EtOH on ionotropic receptor transcription during early human development (preimplantation). Using two separate human embryonic stem cell lines the study shows that low amounts of EtOH (20 mM) alters transcription of the ionotropic subunit GABRB3. Changes in ionotrophic receptor expression influence the central nervous system development and have been shown to produce brain abnormalities in animal models. These results suggest that low concentrations of EtOH can alter ionotropic receptor transcription during early human development (preimplantation), which may be a contributing factor to the neurological phenotypes seen in fetal alcohol spectrum disorder (FASD).

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http://www.ncbi.nlm.nih.gov/pubmed/21619448

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PubMed, J Womens Health (Larchmt). 2011 Jun;20(6):901-13.

**123) PREDICTORS OF DRINKING DURING PREGNANCY: A SYSTEMATIC REVIEW**

Skagerström J, Chang G, Nilsen P.
Department of Medical and Health Sciences, Division of Social Medicine and Public Health Science, Linköpings Universitet, Linköping, Sweden. janna.skagerstrom@liu.se

**ABSTRACT**
**Background:** Many pregnant women continue to drink alcohol despite clinical recommendations and public health campaigns about the risks associated with alcohol use during pregnancy. This review examines the predictors of prenatal alcohol use, with the long-term goal of developing more effective preventive efforts.

**Methods:** A literature search of several databases for relevant articles was undertaken. Studies were included if they occurred in the context of antenatal care, collected data during the woman's pregnancy (between 1999 and 2009), investigated predictors of any drinking, had a population-based orientation (e.g., did not focus only on high-risk drinkers), and were published in English in a scientific peer-reviewed journal between 1999 and 2009.

**Results:** Fourteen studies published between 2002 and 2009 fulfilled the inclusion criteria (United States, 4; Europe, 4; Australia and New Zealand, 3; Japan, 2; and Uganda, 1). The predictors of prenatal alcohol use most consistently identified were prepregnancy alcohol consumption and having been abused or exposed to violence. Less consistent predictors of drinking during pregnancy were high income/social class and positive dependence screen. Unemployment, marital status, and education level were examined in many studies but found to be predictive only infrequently.

**Conclusions:** Women's prepregnancy alcohol consumption (i.e., quantity and frequency of typical drinking) and exposure to abuse or violence were consistently associated with drinking during pregnancy. Antenatal care providers should assess these factors for improved detection of women at risk for alcohol-exposed pregnancies.

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http://www.ncbi.nlm.nih.gov/pubmed/21671775

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PubMed, J Dev Behav Pediatr. 2011 Jun;32(5):384-92.

**124) SLEEP AND SENSORY CHARACTERISTICS IN YOUNG CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER**

Wengel T, Hanlon-Dearman AC, Fjeldsted B.
University of Manitoba, Winnipeg, Canada.

**ABSTRACT**

**Background:** Fetal alcohol spectrum disorder (FASD) is a syndrome that results from prenatal alcohol exposure and is defined by significant neurobehavioral impairments. Sleep disruption has been recognized as a clinically important symptom of FASD that has multiple negative effects on the child's health, ability to function adaptively, as well as on family and caregivers. However, few studies have addressed and characterized the sleep problems in this population.

**Objective:** The objective of this study was to characterize sleep in FASD and describe the impact of sensory processing difficulties on sleep patterns in children with FASD.

**Methods:** Children with FASD were compared with age-matched typically developing children between 3 and 6 years of age. Sleep was assessed using actigraphy, a sleep log, and the Children's Sleep Habits Questionnaire. The Sensory Profile™, completed by caregivers, was used to evaluate the child's sensory processing abilities. Overall differences in sensory processing were correlated with actigraphic parameters measured in alcohol exposed and control groups.

**Results:** Data show that children with FASD have significantly more sleep disturbances than typically developing children, including increased bedtime resistance, shortened sleep duration, increased sleep anxiety, and increased night awakenings and parasomnias. Actigraphy reveals a significant difference between groups for sleep onset latency.

**Conclusions:** This study demonstrates that sensory processing deficits are widespread in children with FASD and that these deficits are associated with multiple sleep problems. Children with FASD should be screened for sleep-related disorders and would benefit from occupational therapy for sensory-based treatment aimed at sleep regulation and consolidation.

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http://www.ncbi.nlm.nih.gov/pubmed/21654404

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PubMed, Birth Defects Res C Embryo Today. 2011 Jun;93(2):115-33. doi: 10.1002/bdrc.20206.

**125) ZEBRAFISH EMBRYOS AND LARVAE: A NEW GENERATION OF DISEASE MODELS AND DRUG SCREENS**

Ali S, Champagne DL, Spaink HP, Richardson MK.
Institute of Biology, Leiden University, Sylvius Laboratory, The Netherlands.

**ABSTRACT**

Technological innovation has helped the zebrafish embryo gain ground as a disease model and an assay system for drug screening. Here, we review the use of zebrafish embryos and early larvae in applied biomedical research, using selected cases. We look at the use of zebrafish embryos as disease models, taking fetal alcohol syndrome and tuberculosis as examples. We discuss advances in imaging, in culture techniques (including microfluidics), and in drug delivery (including new techniques for the robotic injection of compounds into the egg). The use of zebrafish embryos in early stages of

drug safety-screening is discussed. So too are the new behavioral assays that are being adapted from rodent research for use in zebrafish embryos, and which may become relevant in validating the effects of neuroactive compounds such as anxiolytics and antidepressants. Readouts, such as morphological screening and cardiac function, are examined. There are several drawbacks in the zebrafish model. One is its very rapid development, which means that screening with zebrafish is analogous to "screening on a run-away train." Therefore, we argue that zebrafish embryos need to be precisely staged when used in acute assays, so as to ensure a consistent window of developmental exposure. We believe that zebrafish embryo screens can be used in the pre-regulatory phases of drug development, although more validation studies are needed to overcome industry scepticism. Finally, the zebrafish poses no challenge to the position of rodent models: it is complementary to them, especially in early stages of drug research.

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PubMed, Birth Defects Res A Clin Mol Teratol. 2011 Jul;91(7):623-30. doi: 10.1002/bdra.20823. Epub 2011 May 31.

**126) ASSOCIATIONS BETWEEN PERICONCEPTIONAL ALCOHOL CONSUMPTION AND CRANIOSYNOSTOSIS, OMPHALOCELE, AND GASTROSCHISIS**

Richardson S, Browne ML, Rasmussen SA, Druschel CM, Sun L, Jabs EW, Romitti PA; National Birth Defects Prevention Study.
Congenital Malformations Registry, Bureau of Environmental and Occupational Epidemiology, New York State Department of Health, Troy, USA. sdr06@health.state.ny.us

**ABSTRACT**

**Background:** Alcohol consumption during pregnancy is known to be associated with certain birth defects, but the risk of other birth defects is less certain. The authors examined associations between maternal alcohol consumption during pregnancy and craniosynostosis, omphalocele, and gastroschisis among participants in the National Birth Defects Prevention Study, a large, multicenter case-control study.

**Methods:** A total of 6622 control infants and 1768 infants with birth defects delivered from 1997-2005 were included in the present analysis. Maternal alcohol consumption was assessed as any periconceptional consumption (1 month prepregnancy through the third pregnancy month), and by quantity-frequency, duration, and beverage type. Alcohol consumption throughout pregnancy was explored for craniosynostosis since the period of development may extend beyond the first trimester. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression analysis. OR were adjusted for age, race/ethnicity, and state of residence at time of infant's birth. Gastroschisis OR were also adjusted for periconceptional smoking.

**Results:** Periconceptional alcohol consumption and craniosynostosis showed little evidence of an association (OR = 0.92; CI: 0.78-1.08), but alcohol consumption in the second (OR = 0.65; CI: 0.47-0.92) and third trimesters (OR = 0.68; CI: 0.49-0.95) was inversely associated with craniosynostosis. Periconceptional alcohol consumption was associated with omphalocele (OR = 1.50; CI: 1.15-1.96) and gastroschisis (OR = 1.40; CI: 1.17-1.67).

**Conclusions:** Results suggest that maternal periconceptional alcohol consumption is associated with omphalocele and gastroschisis, and second and third trimester alcohol consumption are inversely associated with craniosynostosis.

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Birth Defects Res A Clin Mol Teratol. 2011 Aug;91(8):703-15. doi: 10.1002/bdra.20820. Epub 2011 May 31.

**127) CELLULAR DNA METHYLATION PROGRAM DURING NEURULATION AND ITS ALTERATION BY ALCOHOL EXPOSURE**

Zhou FC, Chen Y, Love A.
Department of Anatomy & Cell Biology, Stark Neuroscience Research Institute, Indiana University School of Medicine, Indianapolis, IN 46202, USA. imce100@iupui.edu

**ABSTRACT**

**Background:** Epigenetic changes are believed to be among the earliest key regulators for cell fate and embryonic development. To support this premise, it is important to understand whether or not systemic epigenetic changes coordinate with the progression of development. We have demonstrated that DNA methylation is programmed when neural stem cells differentiate (Zhou et al.,2011). Here, we analyzed the DNA methylation events that occur during early neural tube development.

**Methods and Results:** Using immunocytochemistry, we demonstrated that the DNA methylation marks - 5-methylcytosine (5-MeC), DNA methylation binding domain 1 (MBD1), and DNA methytransferases 1 (DNMT1) were highly coordinated in temporal and spatial patterns that paralleled the progress of embryonic development. The above ontogenic program of DNA methylation was, however, subjected to environmental modification. Alcohol exposure during fetal development, which is known to cause fetal alcohol spectrum disorder, altered the density and distribution of the DNA methylation marks. The alcohol exposure (88 mM) over 6 or 44 hours at gestation day 8 (GD-8) to GD-10 altered timely DNA methylation and retarded embryonic growth. We further demonstrated that the direct inhibiting of DNA methylation with 5-aza-cytidine (5-AZA) resulted in similar growth retardation.

**Conclusions:** We identified a temporal and spatial cellular DNA methylation program after initial erasure, which parallels embryonic maturation. Alcohol delayed the cellular DNA methylation program and also retarded embryonic growth. Since direct inhibiting of DNA methylation resulted in similar retardation, alcohol thus can affect embryonic development through a epigenetic pathway.

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http://www.ncbi.nlm.nih.gov/pubmed/21630420

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PubMed, PLoS One. 2011;6(5):e19351. Epub 2011 May 31.

**128) ALCOHOL EXPOSURE DECREASES CREB BINDING PROTEIN EXPRESSION AND HISTONE ACETYLATION IN THE DEVELOPING CEREBELLUM**

Guo W, Crossey EL, Zhang L, Zucca S, George OL, Valenzuela CF, Zhao X.
Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, New Mexico, United States of America.

**ABSTRACT**

**Background:** Fetal alcohol exposure affects 1 in 100 children making it the leading cause of mental retardation in the US. It has long been known that alcohol affects cerebellum development and function. However, the underlying molecular mechanism is unclear.

**Methodology/Principal findings:** We demonstrate that CREB binding protein (CBP) is widely expressed in granule and Purkinje neurons of the developing cerebellar cortex of naïve rats. We also show that exposure to ethanol during the 3(rd) trimester-equivalent of human pregnancy reduces CBP levels. CBP is a histone acetyltransferase, a component of the epigenetic mechanism controlling neuronal gene expression. We further demonstrate that the acetylation of both histone H3 and H4 is reduced in the cerebellum of ethanol-treated rats.

**Conclusions/Significance:** These findings indicate that ethanol exposure decreases the expression and function of CBP in the developing cerebellum. This effect of ethanol may be responsible for the motor coordination deficits that characterize fetal alcohol spectrum disorders.

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PubMed, Birth Defects Res A Clin Mol Teratol. 2011 Jul;91(7):591-602. doi: 10.1002/bdra.20833. Epub 2011 May 31.

**129) CALCIUM-MEDIATED REPRESSION OF B-CATENIN AND ITS TRANSCRIPTIONAL SIGNALING MEDIATES NEURAL CREST CELL DEATH IN AN AVIAN MODEL OF FETAL ALCOHOL SYNDROME**

Flentke GR, Garic A, Amberger E, Hernandez M, Smith SM.
Department of Nutritional Sciences, University of Wisconsin-Madison, USA.

**ABSTRACT**

Fetal alcohol syndrome (FAS) is a common birth defect in many societies. Affected individuals have neurodevelopmental disabilities and a distinctive craniofacial dysmorphology. These latter deficits originate during early development from the ethanol-mediated apoptotic depletion of cranial facial progenitors, a population known as the neural crest. We showed previously that this apoptosis is caused because acute ethanol exposure activates G-protein-dependent intracellular calcium within cranial neural crest progenitors, and this calcium transient initiates the cell death. The dysregulated signals that reside downstream of ethanol's calcium transient and effect neural crest death are unknown. Here we show that ethanol's repression of the transcriptional effector β-catenin causes the neural crest losses. Clinically relevant ethanol concentrations (22-78 mM) rapidly deplete nuclear β-catenin from neural crest progenitors, with accompanying losses of β-catenin transcriptional activity and downstream genes that govern neural crest induction, expansion, and survival. Using forced expression studies, we show that β-catenin loss of function (via dominant-negative T cell transcription factor [TCF]) recapitulates ethanol's effects on neural crest apoptosis, whereas β-catenin gain-of-

function in ethanol's presence preserves neural crest survival. Blockade of ethanol's calcium transient using Bapta-AM normalizes β-catenin activity and prevents the neural crest losses, whereas ionomycin treatment is sufficient to destabilize β-catenin. We propose that ethanol's repression of β-catenin causes the neural crest losses in this model of FAS. β-Catenin is a novel target for ethanol's teratogenicity. β-Catenin/Wnt signals participate in many developmental events and its rapid and persistent dysregulation by ethanol may explain why the latter is such a potent teratogen.

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http://www.ncbi.nlm.nih.gov/pubmed/21630427

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Alcohol. 2011 May 26. [Epub ahead of print]

**130) PROCEEDINGS OF THE 2009 ANNUAL MEETING OF THE FETAL ALCOHOL SPECTRUM DISORDERS STUDY GROUP**

Zhou FC, Kane CJ, Smith SM.
Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA.

**ABSTRACT**
The annual meeting of the Fetal Alcohol Spectrum Disorders Study Group (FASDSG) was held on June 20, 2009 in San Diego, CA, as a satellite of the Research Society on Alcoholism Meeting. The FASDSG membership includes clinical, basic, and social scientists who meet to discuss recent advances and issues in Fetal Alcohol Spectrum Disorders research. The main theme of the meeting was "Epigenetics and Development." Two keynote speakers, Dr. Randy Jirtle and Dr. Michael Skinner, addressed the role of epigenetics and environmental inputs, including alcohol, during critical stages of development and their potential critical and long-lasting effects. Members of the FASDSG provided new findings through brief "FASt" data reports, and national agency representatives provided updates on activities and funding priorities. Scientific presentations were made by recipients of the Student Research Merit Award and Rosett Award.

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ScienceDirect, doi:10.1016/j.ijdevneu.2011.05.011
Received 23 December 2010; revised 12 May 2011; Accepted 25 May 2011. Available online 3 June 2011.

**131) ALCOHOL-INDUCED NEURONAL DEATH IN CENTRAL EXTENDED AMYGDALA AND PYRIFORM CORTEX DURING THE POSTNATAL PERIOD OF THE RAT**

V. Balaszczuk[a, b], C. Bender[a], G.L. Pereno[b, 1], C.A. Beltramino[a]
a Instituto de Investigación Médica Mercedes y Martín Ferreyra, Friuli 2434, 5016 Córdoba, Argentina
b Departamento de Biología Evolutiva Humana, Facultad de Psicología, Universidad Nacional de Córdoba, 5000 Córdoba, Argentina

**ABSTRACT**
Mothers who consume alcohol during pregnancy may cause a neurotoxic syndrome defined as fetal alcohol spectrum disorder (FASD) in their offspring. This disorder is characterized by reduction in

brain size, cognitive deficits and emotional/social disturbances. These alterations are thought to be caused by an alcohol-induced increase in apoptosis during neurodevelopment. Little is known about neuroapoptosis in the central extended amygdala and the pyriform cortex, which are key structures in emotional/social behaviors. The goal of this study was to determine the vulnerability of neuroapoptotic alcohol effects in those areas. Rats were administered alcohol (2.5 g/kg s.c. at 0 and 2 h) or saline on postnatal day (PND) 7, 15 and 20. The Amino-cupric-silver technique was used to evaluate neurodegeneration and immunohistochemistry to detect activated caspases 3–8 and 9 at 2 h, 4, 6, 8, 12 and 24 h after drug administration. We measured blood alcohol levels each hour, from 2 to 8 h post second administration of alcohol in each of the ages studied. Results showed alcohol induced apoptotic neurodegeneration in the central extended amygdala on PND 7 and 15, and pyriform cortex on PND 7, 15 and 20. These structures showed activation of caspase 3 and 9 but not of caspase 8 suggesting that alcohol-induced apoptosis could occur by the intrinsic pathway. The pharmacokinetic differences between ages did not associate with the neurodegeneration age dependence. In conclusion, these limbic areas are damaged by alcohol, and each one has their own window of vulnerability during the postnatal period. The possible implications in emotional/social features in FASD are discussed.

**Highlights**
► Alcohol-induced neuroapoptosis during postnatal period. ► Central extended amygdala and pyriform cortex are sensitivity to alcohol effect. ► Alcohol-induced apoptosis could occur by the intrinsic pathway. ► Ethanol pharmacokinetic is different on postnatal day 7, 15 and 20.

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ScienceDirect, doi:10.1016/j.drugalcdep.2011.05.024
Received 4 November 2010; revised 16 May 2011; Accepted 22 May 2011. Available online 20 June 2011.

## 132) ACUTE ADMINISTRATION OF VINPOCETINE, A PHOSPHODIESTERASE TYPE 1 INHIBITOR, AMELIORATES HYPERACTIVITY IN A MICE MODEL OF FETAL ALCOHOL SPECTRUM DISORDER

Fernanda Nunes[a], Kélvia Ferreira-Rosa[a], Maurício dos S. Pereira[b], Regina C. Kubrusly[b], Alex C. Manhães[a], Yael Abreu-Villaça[a], Cláudio C. Filgueiras[a]
a Laboratório de Neurofisiologia, Departamento de Ciências Fisiológicas, Instituto de Biologia Roberto Alcantara Gomes, Centro Biomédico, Universidade do Estado do Rio de Janeiro, Av. Prof. Manoel de Abreu 444, 5 andar, Vila Isabel, Rio de Janeiro, RJ, 20550-170, Brazil
b Laboratório de Neurofarmacologia, Departamento de Fisiologia e Farmacologia, Universidade Federal Fluminense, R. Ernani de Melo 101, São Domingos, Niterói, RJ, Brazil

**ABSTRACT**
**Background:** Maternal alcohol use during pregnancy causes a continuum of long-lasting disabilities in the offspring, commonly referred to as fetal alcohol spectrum disorder (FASD). Attention-deficit/hyperactivity disorder (ADHD) is possibly the most common behavioral problem in children with FASD and devising strategies that ameliorate this condition has great clinical relevance. Studies in rodent models of ADHD and FASD suggest that impairments in the cAMP signaling cascade contribute to the hyperactivity phenotype. In this work, we investigated whether the cAMP levels are affected in a long-lasting manner by ethanol exposure during the third trimester equivalent period of human gestation and whether the acute administration of the PDE1 inhibitor vinpocetine ameliorates the ethanol-induced hyperactivity.

**Methods:** From postnatal day (P) 2 to P8, Swiss mice either received ethanol (5 g/kg i.p.) or saline every other day. At P30, the animals either received vinpocetine (20 mg/kg or 10 mg/kg i.p.) or vehicle 4 h before being tested in the open field. After the test, frontal cerebral cortices and hippocampi were dissected and collected for assessment of cAMP levels.

**Results:** Early alcohol exposure significantly increased locomotor activity in the open field and reduced cAMP levels in the hippocampus. The acute treatment of ethanol-exposed animals with 20 mg/kg of vinpocetine restored both their locomotor activity and cAMP levels to control levels.

**Conclusions:** These data lend support to the idea that cAMP signaling system contribute to the hyperactivity induced by developmental alcohol exposure and provide evidence for the potential therapeutic use of vinpocetine in FASD.

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Alcohol Clin Exp Res. 2011 Sep;35(9):1686-93. doi: 10.1111/j.1530-0277.2011.01515.x. Epub 2011 May 20.

**133) ALCOHOL AND MATERNAL UTERINE VASCULAR ADAPTATIONS DURING PREGNANCY-PART I: EFFECTS OF CHRONIC IN VITRO BINGE-LIKE ALCOHOL ON UTERINE ENDOTHELIAL NITRIC OXIDE SYSTEM AND FUNCTION**

Ramadoss J, Jobe SO, Magness RR.
Department of Obstetrics and Gynecology, Perinatal Research Laboratories, University of Wisconsin, Madison, Wisconsin 53715, USA. ramadoss@wisc.edu

**ABSTRACT**
**Background:** Pregnancy-induced utero-placental growth, angiogenic remodeling, and enhanced vasodilation are all partly regulated by estradiol-17β-mediated activation of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production. However, very little is known about the effects of alcohol on these maternal utero-placental vascular adaptations during pregnancy and its potential role in the pathogenesis of fetal alcohol spectrum disorders (FASDs). In this study, we hypothesized that in vitro chronic binge-like alcohol will decrease uterine arterial endothelial eNOS expression and alter its multisite phosphorylation activity state via disruption of AKT signaling. To study the direct effects of alcohol on uterine vascular adaptations, we further investigated the effects of alcohol on estradiol-17β-induced uterine angiogenesis in vitro.

**Methods:** Uterine artery endothelial cells were isolated from pregnant ewes (gestational day 120 to 130; term = 147), fluorescence-activated cell sorted, validated, and maintained in culture to passage 4. To mimic maternal binge drinking patterns, cells were cultured in the absence or presence of a lower (LD) or higher dose (HD) of alcohol in a compensating sealed humidified chamber system equilibrated with aqueous alcohol for 3 hours on 3 consecutive days. Immunoblotting was performed to assess expression of NO system-associated proteins and eNOS multi-site phosphorylation. Following this treatment paradigm, control and binge alcohol-treated cells were passaged, grown for 2 days, and then treated with increasing concentrations of estradiol-17β (0.1, 1, 10, 100 nM) in the absence or presence of LD or HD alcohol to evaluate estradiol-17β-induced angiogenesis index using BrdU proliferation assay.

**Results:** LD and HD binge-like alcohol decreased uterine arterial eNOS expression ($p = 0.009$). eNOS multisite phosphorylation activation state was altered: P(635) eNOS was decreased ($p = 0.017$), P(1177) eNOS was not altered, and P(495) eNOS exhibited an inverse U-shaped dose-dependent relationship with alcohol. LD and HD alcohol decreased the major eNOS-associated protein cav-1 ($p < 0.001$). However, the commonly implicated AKT pathway did not correlate with eNOS posttranslational modifications. Assessment of uterine vascular adaptation via angiogenesis demonstrated that alcohol abrogated the dose-dependent proliferative effects of estradiol-17β and thus blunted angiogenesis.

**Conclusions:** Thus, the maternal uterine vasculature during pregnancy may be vulnerable to chronic binge-like alcohol. Altered eNOS multisite phosphorylation also suggests that alcohol produces specific effects at the level of posttranslational modifications critical for pregnancy-induced uterine vascular adaptations. Finally, the alcohol and estradiol-17β data suggest a negative impact of alcohol on estrogen actions on the uterine vasculature.

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http://www.ncbi.nlm.nih.gov/pubmed/21599719

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PubMed, PLoS One. 2011;6(5):e20037. Epub 2011 May 19.

**134) LARGE-SCALE ANALYSIS OF ACUTE ETHANOL EXPOSURE IN ZEBRAFISH DEVELOPMENT: A CRITICAL TIME WINDOW AND RESILIENCE**

Ali S, Champagne DL, Alia A, Richardson MK.
Institute of Biology, Leiden University, Sylvius Laboratory, Leiden, The Netherlands.

**ABSTRACT**

**Background:** In humans, ethanol exposure during pregnancy causes a spectrum of developmental defects (fetal alcohol syndrome or FAS). Individuals vary in phenotypic expression. Zebrafish embryos develop FAS-like features after ethanol exposure. In this study, we ask whether stage-specific effects of ethanol can be identified in the zebrafish, and if so, whether they allow the pinpointing of sensitive developmental mechanisms. We have therefore conducted the first large-scale (>1500 embryos) analysis of acute, stage-specific drug effects on zebrafish development, with a large panel of readouts.

**Methodology/Principal findings:** Zebrafish embryos were raised in 96-well plates. Range-finding indicated that 10% ethanol for 1 h was suitable for an acute exposure regime. High-resolution magic-angle spinning proton magnetic resonance spectroscopy showed that this produced a transient pulse of 0.86% concentration of ethanol in the embryo within the chorion. Survivors at 5 days postfertilisation were analysed. Phenotypes ranged from normal (resilient) to severely malformed. Ethanol exposure at early stages caused high mortality (≥88%). At later stages of exposure, mortality declined and malformations developed. Pharyngeal arch hypoplasia and behavioral impairment were most common after prim-6 and prim-16 exposure. By contrast, microphthalmia and growth retardation were stage-independent.

**Conclusions:** Our findings show that some ethanol effects are strongly stage-dependent. The phenotypes mimic key aspects of FAS including craniofacial abnormality, microphthalmia, growth retardation and behavioral impairment. We also identify a critical time window (prim-6 and prim-16) for

ethanol sensitivity. Finally, our identification of a wide phenotypic spectrum is reminiscent of human FAS, and may provide a useful model for studying disease resilience.

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PubMed, Birth Defects Res A Clin Mol Teratol. 2011 Jul;91(7):616-22. doi: 10.1002/bdra.20818. Epub 2011 May 17.

### 135) MATERNAL ALCOHOL DRINKING PATTERN DURING PREGNANCY AND THE RISK FOR AN OFFSPRING WITH AN ISOLATED CONGENITAL HEART DEFECT AND IN PARTICULAR A VENTRICULAR SEPTAL DEFECT OR AN ATRIAL SEPTAL DEFECT

Strandberg-Larsen K, Skov-Ettrup LS, Grønbaek M, Andersen AM, Olsen J, Tolstrup J.
Social Medicine Section of, Department of Public Health, University of Copenhagen, Denmark. ksla@sund.ku.dk

**ABSTRACT**
**Background:** This cohort study examines the possible association between maternal alcohol intake, including binge drinking, during pregnancy, and the subsequent risk of having a child with an isolated congenital heart defect and, more specifically, with the isolated form of ventricular septal defect (VSD) or of an atrial septal defect (ASD).

**Methods:** Participants were 80,346 pregnant women who were enrolled into the Danish National Birth Cohort in 1996-2002 and gave birth to a live-born singleton without any chromosome anomalies. Twice during pregnancy these women were asked about their intake of alcohol. Few (if any) women with an excessive/abusive intake of alcohol were enrolled into the Danish National Birth Cohort.

**Results:** Through linkage with the National Hospital Discharge Registry, we identified 477 infants with a diagnosis of isolated congenital heart defect registered at any time during their first 3½-years of life; they included 198 infants with a VSD and 145 with an ASD. Neither the number of episodes of binge drinking nor binge drinking during three different developmental periods was associated with VSD or ASD. Women drinking ½-1½, 2, and 3+ drinks of alcohol per week had adjusted prevalence ratios of delivering an infant with a VSD of 1.22 (95% CI = 0.90-1.66); 1.38 (95% CI = 0.83-2.28); and 1.10 (95% CI = 0.54-2.23), respectively. The test for trend was 0.29.

**Conclusions:** Prenatal exposure to low-to-moderate levels of alcohol on a weekly basis or occasional binge drinking during the early part of pregnancy was not statistical significantly associated with the prevalence of isolated VSD and ASD in offspring.

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PubMed, Alcohol Clin Exp Res. 2011 Aug;35(8):1404-17. doi: 10.1111/j.1530-0277.2011.01476.x. Epub 2011 May 16.

**136) EXTENSIVE DEEP GRAY MATTER VOLUME REDUCTIONS IN CHILDREN AND ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDERS**

Nardelli A, Lebel C, Rasmussen C, Andrew G, Beaulieu C.
Centre for Neuroscience, University of Alberta, Glenrose Rehabilitation Hospital, Edmonton, AB, Canada.

**ABSTRACT**

**Background:** The link between the numerous cognitive, motor, and behavioral difficulties of individuals with fetal alcohol spectrum disorders (FASD) and underlying specific structural brain injuries can be investigated using high-resolution imaging. Differential sensitivity of the brain's "relay" stations, namely the deep gray matter structures, may play a key factor given their multifaceted role in brain function. The purpose of our study was to analyze differences in deep gray matter volumes of children and adolescents with FASD relative to age/sex-matched controls and to examine whether any volume differences were consistent across the age range of neurodevelopment.

**Methods:** Children and adolescents (N = 28, 6 to 17 years) diagnosed with FASD and 56 age- and sex-matched healthy controls (i.e., 2 matched controls per FASD subject) underwent 3-dimensional T1-weighted MRI scans that were used for the automated volume measurement (FreeSurfer) of the intracranial space, total white matter, cortical gray matter, and 6 deep gray matter structures, namely the hippocampus, amygdala, thalamus, caudate, putamen, and globus pallidus, with left and right measured separately. Volumes were compared between FASD and controls, as well as changes with age.

**Results:** Significant reductions of volume in FASD were observed for the intracranial vault (7.6%), total white matter (8.6%), total cortical gray matter (7.8%), and total deep gray matter (13.1%). All 6 deep gray matter structures showed significant volume reductions bilaterally with the caudate (approximately 16%) and globus pallidus (approximately 18%) being most affected. The hippocampus, thalamus, and globus pallidus showed reductions in all 3 age subgroups (6 to 9, 10 to 13, and 14 to 17 years) but the caudate and putamen had smaller volumes for FASD only within the 2 youngest subgroups; the amygdala was only smaller for FASD in the 2 oldest subgroups.

**Conclusions:** Significant, but variable, volume reductions throughout the deep gray matter are observed over a wide age range of 6 to 17 years in FASD.

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http://www.ncbi.nlm.nih.gov/pubmed/21575012

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Psychiatry Research: Neuroimaging
ScienceDirect, doi:10.1016/j.pscychresns.2011.05.004
Received 22 October 2010; revised 28 April 2011; Accepted 15 May 2011. Available online 10 November 2011.

**137) DEFAULT MODE NETWORK DYSFUNCTION IN ADULTS WITH PRENATAL ALCOHOL EXPOSURE**

Priya Santhanam[a, 1], Claire D. Coles[b], Zhihao Li[a], Longchuan Li[a], Mary Ellen Lynch[b], Xiaoping Hu[a]
a Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta,

GA 30322, United States
b Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, United States

**ABSTRACT**
Prenatal alcohol exposure (PAE) is known to cause significant cognitive and attentional dysfunction. Given the relationship between default mode network (DMN) activity and task-related attentional modulation, it is possible that PAE affects activity of this network. In the present study, task-related deactivation as well as structural and resting state functional connectivity of the DMN were examined using diffusional tensor imaging and functional magnetic resonance imaging in non-dysmorphic and dysmorphic PAE populations and compared to healthy controls. The dysmorphic PAE group was found to have reduced DMN deactivation as compared to controls, indicating poorer attentional modulation during the cognitive task. Additionally, structural connectivity and baseline functional connectivity were lower in both PAE groups as compared to controls. Primarily the findings suggest that learning problems seen with PAE may be a combination of general attentional and specific cognitive deficits. A secondary implication is that DMN activity is affected to varying extents depending on the degree of PAE.

**Read Full Article,**
http://www.sciencedirect.com/science/article/pii/S092549271100196X

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Behavioural Brain Research
Volume 223, Issue 2, 1 October 2011, Pages 376-387
ScienceDirect, doi:10.1016/j.bbr.2011.05.005
Received 28 February 2011; revised 3 May 2011; Accepted 6 May 2011. Available online 14 May 2011.

**138) MATERNAL VOLUNTARY DRINKING IN C57BL/6J MICE: ADVANCING A MODEL FOR FETAL ALCOHOL SPECTRUM DISORDERS**

Morgan L. Kleiber[a, 1] , Elise Wright[b, 1, 2], Shiva M. Singh[a, b]
a Molecular Genetics Unit, Department of Biology, University of Western Ontario, London, Ontario, Canada N6A 5B7
b Neuroscience Program, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada N6A 5B7

**ABSTRACT**
Fetal alcohol spectrum disorders (FASD) remain the most common preventable cause of behavioural abnormalities and cognitive deficits, yet little is known about the biological mechanisms involved in FASD pathology. Maternal voluntary ethanol consumption in mice may be a useful model for establishing the biological basis of moderate ethanol exposure phenotypes, which make up the majority of FASD cases. We have employed a two-bottle choice paradigm of maternal ethanol consumption throughout gestation and the early postnatal period in C57BL/6J mice. We assessed the efficacy of this model to produce a range of FASD-relevant phenotypes and evaluated gene expression changes in the adult offspring. Results showed stable maternal consumption and lack of maternal care differences between ethanol-consuming and water-only dams. Ethanol-exposed offspring showed delays in neonatal reflex and coordination development. Further, ethanol-exposed adolescent mice showed decreased activity in a novel environment that appeared to be the result of novelty-induced anxiety, and acquisition learning deficits. Evaluation of the neurotransmitter-associated genes Gabra6, Glra1, and Grin2c revealed significant down-regulation of Glra1 and Grin2c in the brains of ethanol-exposed young adult males. These results suggest that this model is able to

produce a range of behavioural phenotypes consistent with prenatal ethanol exposure and may be used to evaluate resulting long-term genetic changes. Given the range of genetic resources available for inbred mouse strains, the model described here may prove to be a useful tool in evaluating the molecular basis of FASD.

**Highlights**
► Maternal voluntary ethanol consumption using high-drinking C57BL/6J mice is a promising model for human fetal alcohol spectrum disorders (FASD). ► We evaluated features of this model including maternal and offspring behaviour and adult offspring brain gene expression. ► Results showed moderate but consistent behavioural alterations as well as long-term gene expression changes in Glra1 and Grin2c. ► Results support the use of this model in evaluating both the behavioural and the genetic basis of FASD.

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PubMed, Eur J Paediatr Neurol. 2011 May 14. [Epub ahead of print]

**139) PERINATAL PHARMACOLOGY: APPLICATIONS FOR NEONATAL NEUROLOGY**
Smits A, Allegaert K.
Neonatal Intensive Care Unit, Division of Woman and Child, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.

**ABSTRACT**
The principles of clinical pharmacology also apply to neonates, but their characteristics warrant a tailored approach. We focus on aspects of both developmental pharmacokinetics (concentration/time relationship) and developmental pharmacodynamics (concentration/effect relationship) in neonates. We hereby aimed to link concepts used in clinical pharmacology with compound-specific observations (anti-epileptics, analgosedatives) in the field of neonatal neurology. Although in part anecdotal, we subsequently illustrate the relevance of developmental pharmacology in the field of neonatal neurology by a specific intervention (e.g. whole body cooling), specific clinical presentations (e.g. short and long term outcome following fetal exposure to antidepressive agents, the development of new biomarkers for fetal alcohol syndrome) and specific clinical needs (e.g. analgosedation in neonates, excitocytosis versus neuro-apoptosis/impaired synaptogenesis).

http://www.ncbi.nlm.nih.gov/pubmed/21576027

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PubMed, J Neurochem. 2011 Aug;118(4):646-57. doi: 10.1111/j.1471-4159.2011.07273.x. Epub 2011 May 13.

**140) CAMKII ACTIVATION IS A NOVEL EFFECTOR OF ALCOHOL'S NEUROTOXICITY IN NEURAL CREST STEM/PROGENITOR CELLS**
Garic A, Flentke GR, Amberger E, Hernandez M, Smith SM.
Department of Nutritional Sciences, University of Wisconsin-Madison, Madison, Wisconsin 53706, USA.

**ABSTRACT**
Prenatal ethanol exposure causes significant neurodevelopmental deficits through its induction of

apoptosis in neuronal progenitors including the neural crest. Using an established chick embryo model, we previously showed that clinically relevant ethanol concentrations cause neural crest apoptosis through mobilization of an intracellular calcium transient. How the calcium transient initiates this cell death is unknown. In this study, we identify CaMKII as the calcium target responsible for ethanol-induced apoptosis. Immunostaining revealed selective enrichment of activated phosphoCaMKII(Thr286) within ethanol-treated neural crest. CaMKII activation in response to ethanol was rapid (< 60 s) and robust, and CaMKII activity was increased 300% over control levels. Treatment with CaMKII-selective inhibitors but not those directed against CaMKIV or PKC completely prevented the cell death. Forced expression of dominant-negative CaMKII prevented ethanol's activation of CaMKII and prevented the ethanol-induced death, whereas constitutively active CaMKII in ethanol's absence significantly increased cell death to levels caused by ethanol treatment. In summary, CaMKII is the key signal that converts the ethanol-induced, short-lived Ca(i) (2+) transient into a long-lived cellular effector. This is the first identification of CaMKII as a critical mediator of ethanol-induced cell death. Because neural crest differentiates into several neuronal lineages, our findings offer novel insights into how ethanol disrupts early neurogenesis.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21496022

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J Popul Ther Clin Pharmacol. 2011;18(2):e261-72. Epub 2011 May 10.

**141) ALCOHOL CONSUMPTION DURING PREGNANCY AMONG WOMEN IN ISRAEL**

Senecky Y, Weiss N, Shalev SA, Peleg D, Inbar D, Chodick G, Nachum Z, Bar-Hamburger R, Shuper A.
Child Development and Rehabilitation Institute, Schneider Children's Medical Center of Israel, Petach Tikva, Israel. Senekimi@zahav.net.il

**ABSTRACT**

**Background:** Fetal alcohol spectrum disorder (FASD) is a range of disabilities caused by gestational exposure of the fetus to alcohol. Alcohol consumption in Israel has increased dramatically in the last decades. Our previous study revealed limited knowledge among Israeli medical professionals of the risks and potential long-term effects of FASD.

**Objectives:** To evaluate the awareness and knowledge of women regarding the current recommendations on alcohol consumption during pregnancy, evaluate how many of the women received information regarding alcohol consumption during pregnancy from medical professionals, and their personal drinking habits during pregnancy.

**Methods:** A cross-sectional sample of new mothers in 3 large hospitals in Israel were asked to complete an ad hoc questionnaire on aspects of alcohol consumption during pregnancy.

**Results:** A total of 3815 women of mean age 30.4 years participated in the study; 82% were Jewish. Alcohol consumption during pregnancy was reported by 14.1%, including more than 17% of the Jewish women, 11.1% of the Christian women, and none of the Muslim women. Rates were higher among nonsecular and younger women and first-time mothers. 71.6% of the sample claimed that women should not drink alcohol at all during pregnancy, and 21.4% thought that it was permissible if limited to 2 drinks per week. Seventy-five percent had received no formal information from medical professionals regarding alcohol consumption during pregnancy.

**Conclusions:** Alcohol consumption is frequent among pregnant women in Israel, especially young secular Jewish women with first pregnancies. Improved educational programs on the dangers of FASD are needed for both professionals and the general public.

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http://www.ncbi.nlm.nih.gov/pubmed/21576728

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PubMed, Alcohol Clin Exp Res. 2011 Sep;35(9):1644-61. doi: 10.1111/j.1530-0277.2011.01511.x. Epub 2011 May 9.

**142) ETHANOL-INDUCED MICROPHTHALMIA IS NOT MEDIATED BY CHANGES IN RETINOIC ACID OR SONIC HEDGEHOG SIGNALING DURING RETINAL NEUROGENESIS**

Kashyap B, Frey RA, Stenkamp DL.
Department of Biological Sciences, University of Idaho, Moscow, Idaho 83844-3015, USA.

**ABSTRACT**

**Background:** Microphthalmia (reduced eye size), generally accompanied by vision defects, is a hallmark of fetal alcohol spectrum disorder (FASD) in humans. In zebrafish, embryonic ethanol exposure over the time of retinal neurogenesis also results in microphthalmia. This microphthalmia is in part the consequence of reduced retinal cell differentiation, including photoreceptors. Here we pursue 2 signaling pathways implicated in other aspects of FASD pathogenesis: retinoic acid (RA) and Sonic hedgehog (Shh).

**Methods:** We evaluated markers for RA and Shh signaling within the eyes of embryos treated with ethanol during the period of retinal neurogenesis. We also performed rescue experiments using administration of exogenous RA and microinjection of cholesterol, which augments Shh signaling.

**Results:** Using sequential or co-treatments, RA did not rescue ethanol-induced microphthalmia at any concentration tested. In addition, RA itself caused microphthalmia, although the underlying mechanisms were distinct from those of ethanol. Interestingly, RA treatment appeared to recover photoreceptor differentiation in a concentration-dependent manner. This may be an independent effect of exogenous RA, as ethanol treatment alone did not alter RA signaling in the eye. Cholesterol injection also did not rescue ethanol-induced microphthalmia at any concentration tested, and ethanol treatments did not alter expression of shh, or of ptc-2, which is normally regulated by Shh signaling.

**Conclusions:** Together these findings indicate that, during the time of retinal neurogenesis, effects of ethanol on eye development are likely independent of the RA and Shh signaling pathways. These studies suggest that FASD intervention strategies based upon augmentation of RA or Shh signaling may not prevent ethanol-induced microphthalmia.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21554333

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PubMed, Alcohol Clin Exp Res. 2011 Jul;35(7):1201-3. doi: 10.1111/j.1530-0277.2011.01541.x. Epub 2011 May 9.

**143) COMMENTARY: WILL ANALYZING THE EPIGENOME YIELD COHESIVE PRINCIPLES OF ETHANOL TERATOLOGY?**

Miranda RC.
Department of Neuroscience & Experimental Therapeutics, Texas A&M Health Science Center (RCM), College of Medicine, College Station, TX, USA.

**ABSTRACT**
This commentary discusses the impact of the manuscript by Zhou et al., titled "Alcohol Alters DNA Methylation Patterns and Inhibits Neural Stem Cell Differentiation," published in the April 2011 issue of Alcoholism: Clinical and Experimental Research (volume 35, issue 4, pages 1-12). In this manuscript, the authors present intriguing evidence from a genome scale analysis of promoter DNA methylation patterns in a class of neural crest stem cells associated with dorsal root ganglia, showing that ethanol essentially prevents epigenetic programming associated with neural stem cell differentiation. This manuscript presents several interesting and novel pieces of data and raises important questions for future research. The implications of these data for our understanding of the etiology of fetal alcohol spectrum disorders are discussed.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21554338

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PubMed, Alcohol Clin Exp Res. 2011 Sep;35(9):1669-77. doi: 10.1111/j.1530-0277.2011.01513.x. Epub 2011 May 9.

**144) ASSOCIATION OF MODERATE ALCOHOL USE AND BINGE DRINKING DURING PREGNANCY WITH NEONATAL HEALTH**

Meyer-Leu Y, Lemola S, Daeppen JB, Deriaz O, Gerber S.
Department of Health Education, Midwifery Section, University of Applied Sciences Western Switzerland, Lausanne, Switzerland. ymeyer@hecvsante.ch

**ABSTRACT**
**Background:** Heavy drinking and smoking during pregnancy are known to have a negative impact on the unborn child. However, the impact of low-to-moderate alcohol consumption and binge drinking has been debated recently. The aim of this study was to examine the relationship of moderate prenatal drinking and binge drinking with birthweight, being small for gestational age (SGA) at birth, preterm birth, and neonatal asphyxia.

**Methods:** Moderate alcohol drinking, binge drinking, and several possible confounders were assessed in 1,258 pregnant women; information on neonatal health was obtained at birth.

**Results:** Results indicate that 30.8% of the women drank at low levels (<2 glasses/wk), 7.9% drank moderately (2 to 4 glasses/wk), and 0.9% showed higher levels of drinking (5 glasses/wk); 4.7% reported binge drinking (defined as 3 glasses/occasion). 6.4% of the children were SGA (<10th percentile of birthweight adjusted for gestational age), 4.6% were preterm (<37th week of gestation), and 13.0% showed asphyxia (arterial cord pH <7.10 and/or arterial cord lactate >6.35 mmol and/or Apgar score <7 at 5 minutes). When controlling for maternal age, citizenship, occupational status, parity, smoking, use of prescription/over-the-counter drugs, illicit drug use, and child gender moderate drinking was related to lower birthweight ($p < 0.01$), and moderate drinking and binge drinking were

associated with neonatal asphyxia at trend level (p = 0.06 and p = 0.09). Moderate drinking and binge drinking were not related to length of gestation.

**Conclusions:** In contrast to recent reviews in the field, our results assume that moderate drinking and binge drinking are risk factors for neonatal health.

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http://www.ncbi.nlm.nih.gov/pubmed/21554334

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PubMed, Neuropsychol Rev. 2011 Jun;21(2):204-23. Epub 2011 May 6.

**145) FROM RESEARCH TO PRACTICE: AN INTEGRATIVE FRAMEWORK FOR THE DEVELOPMENT OF INTERVENTIONS FOR CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS**

Kodituwakku PW, Kodituwakku EL.
University of New Mexico School of Medicine, Albuquerque, NM, USA. pkodituwakku@salud.unm.edu

**ABSTRACT**
Since fetal alcohol syndrome was first described over 35 years ago, considerable progress has been made in the delineation of the neurocognitive profile in children with prenatal alcohol exposure. Preclinical investigators have made impressive strides in elucidating the mechanisms of alcohol teratogenesis and in testing the effectiveness of pharmacological agents and dietary supplementation in the amelioration of alcohol-induced deficits. Despite these advances, only limited progress has been made in the development of evidence-based comprehensive interventions for functional impairment in alcohol-exposed children. Having performed a search in PubMed and PsycINFO using key words, interventions, treatment, fetal alcohol syndrome, prenatal alcohol exposure, and fetal alcohol spectrum disorders, we found only 12 papers on empirically-based interventions. Only two of these interventions had been replicated and none met the criteria of "well-established," as defined by Chambless and Hollon (Journal of Consulting and Clinical Psychology 66(1):7-18, 1998). There has been only limited cross-fertilization of ideas between preclinical and clinical research with regard to the development of interventions. Therefore, we propose a framework that allows integrating data from preclinical and clinical investigations to develop comprehensive intervention programs for children with fetal alcohol spectrum disorders. This framework underscores the importance of multi-level evaluations and interventions.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21544706

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PubMed, Neuroscience. 2011 May 5;181:196-205. Epub 2011 Mar 10.

**146) ETHANOL-INDUCED NEURODEGENERATION IN NRSF/REST NEURONAL CONDITIONAL KNOCKOUT MICE**

Cai L, Bian M, Liu M, Sheng Z, Suo H, Wang Z, Huang F, Fei J.
Laboratory of Molecular Cell Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China.

**ABSTRACT**
The transcription regulator, neuron-restrictive silencer factor (NRSF), also known as repressor

element-1 silencing transcription factor (REST), plays an important role in neurogenesis and various neuronal diseases such as ischaemia, epilepsy, and Huntington's disease. In these disease processes, neuronal loss is associated with abnormal expression and/or localization of NRSF. Previous studies have demonstrated that NRSF regulates the effect of ethanol on neuronal cells in vitro, however, the role of NRSF in ethanol-induced neuronal cell death remains unclear. We generated nrsf conditional knockout mice using the Cre-loxP system to disrupt neuronal expression of nrsf and its truncated forms. At postnatal day 6, ethanol significantly increased the expression of REST4, a neuron-specific truncated form of NRSF, in the brains of wild type mice, and this effect was diminished in nrsf conditional knockout mice. The apoptotic effect of ethanol was pronounced in multiple brain regions of nrsf conditional mutant mice. These results indicate that NRSF, specifically REST4, may protect the developing brain from ethanol, and provide new evidence that NRSF can be a therapeutic target in foetal alcohol syndrome (FAS).

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21396985

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PubMed, Neuropsychol Rev. 2011 Jun;21(2):148-66. Epub 2011 May 4.

**147) BIOBEHAVIORAL MARKERS OF ADVERSE EFFECT IN FETAL ALCOHOL SPECTRUM DISORDERS**

Jacobson SW, Jacobson JL, Stanton ME, Meintjes EM, Molteno CD.
Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI 48207, USA. sandra.jacobson@wayne.edu

**ABSTRACT**
Identification of children with fetal alcohol spectrum disorders (FASD) is difficult because information regarding prenatal exposure is often lacking, a large proportion of affected children do not exhibit facial anomalies, and no distinctive behavioral phenotype has been identified. Castellanos and Tannock have advocated going beyond descriptive symptom-based approaches to diagnosis to identify biomarkers derived from cognitive neuroscience. Classical eyeblink conditioning and magnitude comparison are particularly promising biobehavioral markers of FASD-eyeblink conditioning because a deficit in this elemental form of learning characterizes a very large proportion of alcohol-exposed children; magnitude comparison because it is a domain of higher order cognitive function that is among the most sensitive to fetal alcohol exposure. Because the neural circuitry mediating both these biobehavioral markers is well understood, they have considerable potential for advancing understanding of the pathophysiology of FASD, which can contribute to development of treatments targeted to the specific deficits that characterize this disorder.

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http://www.ncbi.nlm.nih.gov/pubmed/21541763

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PubMed, Hippocampus. 2011 May 3. doi: 10.1002/hipo.20925. [Epub ahead of print]

**148) CHOLINE SUPPLEMENTATION MITIGATES TRACE, BUT NOT DELAY, EYEBLINK CONDITIONING DEFICITS IN RATS EXPOSED TO ALCOHOL DURING DEVELOPMENT**

Thomas JD, Tran TD.
Department of Psychology, Center for Behavioral Teratology, San Diego State University, San Diego, California.

**ABSTRACT**
Children exposed to alcohol prenatally suffer from a range of physical, neuropathological, and behavioral alterations, referred to as fetal alcohol spectrum disorders (FASD). Both the cerebellum and hippocampus are affected by alcohol exposure during development, which may contribute to behavioral and cognitive deficits observed in children with FASD. Despite the known neuropathology associated with prenatal alcohol exposure, many pregnant women continue to drink (heavy drinkers, in particular), creating a need to identify effective treatments for their children who are adversely affected by alcohol. We previously reported that choline supplementation can mitigate alcohol's effects on cognitive development, specifically on tasks which depend on the functional integrity of the hippocampus. The present study examined whether choline supplementation could differentially mitigate alcohol's effects on trace eyeblink classical conditioning (ECC, a hippocampal-dependent task) and delay ECC (a cerebellar-dependent task). Long-Evans rats were exposed to 5.25 g/kg/day alcohol via gastric intubation from postnatal days (PD) 4-9, a period of brain development equivalent to late gestation in humans. A sham-intubated control group was included. From PD 10-30, subjects received subcutaneous injections of 100 mg/kg choline chloride or vehicle. Beginning on PD 32-34, subjects were trained on either delay or trace eyeblink conditioning. Performance of subjects exposed to alcohol was significantly impaired on both tasks, as indicated by significant reductions in percentage and amplitude of conditioned eyeblink responses, an effect that was attenuated by choline supplementation on the trace, but not delay conditioning task. Indeed, alcohol-exposed subjects treated with choline performed at control levels on the trace eyeblink conditioning task. There were no significant main or interactive effects of sex. These data indicate that choline supplementation can significantly reduce the severity of trace eyeblink conditioning deficits associated with early alcohol exposure, even when administered after the alcohol insult is complete. These findings have important implications for the treatment of fetal alcohol spectrum disorders.

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Drug and Alcohol Dependence
Volume 119, Issues 1-2, 1 December 2011, Pages 18-27
ScienceDirect, doi:10.1016/j.drugalcdep.2011.05.009
Received 24 September 2010; revised 2 May 2011; Accepted 3 May 2011. Available online 11 June 2011.

**149) MATERNAL RISK FACTORS PREDICTING CHILD PHYSICAL CHARACTERISTICS AND DYSMORPHOLOGY IN FETAL ALCOHOL SYNDROME AND PARTIAL FETAL ALCOHOL SYNDROME**

Philip A. May[a], Barbara G. Tabachnick[b], J. Phillip Gossage[a], Wendy O. Kalberg[a], Anna-Susan Marais[c], Luther K. Robinson[d], Melanie Manning[e], David Buckley[a], H. Eugene Hoyme[f]
a The University of New Mexico, Center on Alcoholism, Substance Abuse, and Addictions (CASAA), 2650 Yale SE, Albuquerque, NM 87106, United States
b California State University, Northridge, United States

c University of Stellenbosch, Faculty of Health Sciences, P.O. Box 10963, Tygerberg 7505, South Africa
d State University of New York, Buffalo, School of Medicine, Department of Pediatrics, 219 Bryant Street, Buffalo, NY 14222, United States
e Stanford University, School of Medicine, Department of Pediatrics 300 Pasteur Drive, H315 Stanford, CA 94305, United States
f The University of South Dakota, Sanford School of Medicine, Department of Pediatrics, 1305W. 18th Street, P.O. Box 5039, Sioux Falls, SD 57117-5039, United States

**ABSTRACT**
**Background:** Previous research in South Africa revealed very high rates of fetal alcohol syndrome (FAS), of 46–89 per 1000 among young children. Maternal and child data from studies in this community summarize the multiple predictors of FAS and partial fetal alcohol syndrome (PFAS).

**Method:** Sequential regression was employed to examine influences on child physical characteristics and dysmorphology from four categories of maternal traits: physical, demographic, childbearing, and drinking. Then, a structural equation model (SEM) was constructed to predict influences on child physical characteristics.

**Results:** Individual sequential regressions revealed that maternal drinking measures were the most powerful predictors of a child's physical anomalies ($R2 = .30$, $p < .001$), followed by maternal demographics ($R2 = .24$, $p < .001$), maternal physical characteristics ($R2 = .15$, $p < .001$), and childbearing variables ($R2 = .06$, $p < .001$). The SEM utilized both individual variables and the four composite categories of maternal traits to predict a set of child physical characteristics, including a total dysmorphology score. As predicted, drinking behavior is a relatively strong predictor of child physical characteristics ($\beta = 0.61$, $p < .001$), even when all other maternal risk variables are included; higher levels of drinking predict child physical anomalies.

**Conclusions:** Overall, the SEM model explains 62% of the variance in child physical anomalies. As expected, drinking variables explain the most variance. But this highly controlled estimation of multiple effects also reveals a significant contribution played by maternal demographics and, to a lesser degree, maternal physical and childbearing variables.

**Read Full Article,**
http://www.sciencedirect.com/science/article/pii/S0376871611002195

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PubMed, Neurotoxicol Teratol. 2011 Jul-Aug;33(4):444-50. Epub 2011 May 3.

**150) THE EFFECTS OF A SINGLE MEMANTINE TREATMENT ON BEHAVIORAL ALTERATIONS ASSOCIATED WITH BINGE ALCOHOL EXPOSURE IN NEONATAL RATS**

Idrus NM, McGough NN, Spinetta MJ, Thomas JD, Riley EP.
Center for Behavioral Teratology, Department of Psychology, San Diego State University, 6330 Alvarado Ct., Ste 100, San Diego, CA 92120, USA.

**ABSTRACT**
**Background:** The third trimester in human fetal development represents a critical time of brain maturation referred to as the "brain growth spurt". This period occurs in rats postnatally, and exposure to ethanol during this time can increase the risk of impairments on a variety of cognitive and motor tasks. It has been proposed that one potential mechanism for the teratogenic effects of ethanol is NMDA receptor-mediated excitotoxicity during periods of ethanol withdrawal. In neonatal rats,

antagonism of NMDA receptors during ethanol withdrawal, with drugs such as MK-801 and eliprodil, has been shown to mitigate some of the behavioral deficits induced by developmental ethanol exposure. The current study examined whether memantine, an NMDA receptor antagonist and a drug used clinically in Alzheimer's patients, would attenuate impairments associated with binge ethanol exposure in neonatal rats.

**Methods:** On postnatal day 6, rats were exposed to 6 g/kg ethanol via intubation with controls receiving an isocaloric maltose dextrin solution. Twenty-one hours following the ethanol binge, rats received intraperitoneal injections of memantine at 0, 10, 15, or 20 mg/kg. Ethanol's teratogenic effects were assessed using multiple behavioral tasks: open field activity, parallel bars and spatial discrimination reversal learning.

**Results:** Ethanol-treated rats were overactive in the open field and were impaired on both reversal learning and motor performance. Administration of 15 or 20 mg/kg memantine during withdrawal significantly attenuated ethanol's adverse effects on motor coordination, but did not significantly alter activity levels or improve the spatial learning deficits associated with neonatal alcohol exposure.

**Conclusion:** These results indicate that a single memantine administration during ethanol withdrawal can mitigate motor impairments but not spatial learning impairments or overactivity observed following a binge ethanol exposure during development in the rat.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21565269

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PubMed, West J Nurs Res. 2011 May 3. [Epub ahead of print]

**151) EFFECTS OF A MOTIVATIONAL INTERVIEWING INTERVENTION TO DECREASE PRENATAL ALCOHOL USE**

Osterman RL, Dyehouse J.
University of Cincinnati.

**ABSTRACT**
This study determined the effectiveness of motivational interviewing (MI) to decrease prenatal alcohol use, while examining mechanisms of behavior change based on self-determination theory that may have evoked decreases in drinking behaviors. In all, 67 pregnant women who reported previous-year alcohol use were randomly assigned to an MI intervention or comparison group, with 56 women completing all study procedures. Both groups were assessed at baseline and 4- to 6-week follow-up for alcohol use and mechanisms of behavior change (basic psychological needs satisfaction and autonomous motivation). Only the MI group received the intervention after baseline assessments. Although MI was not found effective in decreasing prenatal drinking behaviors in this study, nonspecific factors were identified, such as treatment structures, participant motivation for improvement, and provider qualities, which may have influenced these results. More research is needed to determine theory-based specific and nonspecific factors that drive effective nursing interventions to decrease alcohol use during pregnancy.

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http://www.ncbi.nlm.nih.gov/pubmed/21540353

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J Popul Ther Clin Pharmacol. 2011;18(2):e242-4. Epub 2011 May 2.

**152) UNDERSTANDING FETAL ALCOHOL SPECTRUM DISORDER--BRINGING SCHOOLS AND TEACHERS ON BOARD**

Koren G.
The Motherisk Program, Division of Clinical Pharmacology/Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada. gkoren@sickkids.ca

**ABSTRACT**
A new approach to the educational aspects of FASD will help educational experts to be better prepared for students affected by this challenging condition.

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http://www.ncbi.nlm.nih.gov/pubmed/21576726

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PubMed, J Ark Med Soc. 2011 May;107(12):260-2.

**153) FETAL ALCOHOL SPECTRUM DISORDERS: FLYING UNDER THE RADAR**

Eaton B, Gangluff D, Mengel M.

**ABSTRACT**
Alcohol exposure during pregnancy has been shown to result in a spectrum of birth defects known as Fetal Alcohol Spectrum Disorders (FASD) that can negatively impact a child's growth, development, cognition, behavior and physical appearance over his or her entire lifespan. FASD is not a diagnostic term, unlike Fetal Alcohol Syndrome (FAS), which is the most serious disorder within the spectrum. Despite warnings by the U.S. Surgeon General and others, childbearing age women continue to drink at high levels, even in pregnancy. As there is no cure for an FASD, preventive activities are currently the only successful approach to reduce the risk of an Alcohol-Exposed Pregnancy (AEP) through screening, education, or brief interventions of childbearing age women. The Midwest Region Fetal Alcohol Syndrome Training Center (MRFASTC) has established teams in 8 states in the Midwest, including Arkansas, with the goal of training health care professionals in FASD recognition, diagnosis, treatment, and prevention.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21667684

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PubMed, Health Res Policy Syst. 2011 May 14;9:18.

**154) COLLABORATING WITH CONSUMER AND COMMUNITY REPRESENTATIVES IN HEALTH AND MEDICAL RESEARCH IN AUSTRALIA: RESULTS FROM AN EVALUATION**

Payne JM, D'Antoine HA, France KE, McKenzie AE, Henley N, Bartu AE, Elliott EJ, Bower C.
Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Subiaco, Western Australia. janp@ichr.uwa.edu.au

**ABSTRACT**
**Objective:** To collaborate with consumer and community representatives in the Alcohol and Pregnancy Project from 2006-2008 http://www.ichr.uwa.edu.au/alcoholandpregnancy and evaluate

researchers' and consumer and community representatives' perceptions of the process, context and impact of consumer and community participation in the project.

**Methods:** We formed two reference groups and sought consumer and community representatives' perspectives on all aspects of the project over a three year period. We developed an evaluation framework and asked consumer and community representatives and researchers to complete a self-administered questionnaire at the end of the project.

**Results:** Fifteen researchers (93.8%) and seven (53.8%) consumer and community representatives completed a questionnaire. Most consumer and community representatives agreed that the process and context measures of their participation had been achieved. Both researchers and consumer and community representatives identified areas for improvement and offered suggestions how these could be improved for future research. Researchers thought consumer and community participation contributed to project outputs and outcomes by enhancing scientific and ethical standards, providing legitimacy and authority, and increasing the project's credibility and participation. They saw it was fundamental to the research process and acknowledged consumer and community representatives for their excellent contribution. Consumer and community representatives were able to directly influence decisions about the research. They thought that consumer and community participation had significant influence on the success of project outputs and outcomes.

**Conclusions:** Consumer and community participation is an essential component of good research practice and contributed to the Alcohol and Pregnancy Project by enhancing research processes, outputs and outcomes, and this participation was valued by community and consumer representatives and researchers. The National Health and Medical Research Council in Australia expects researchers to work in partnership and involve consumer and community representatives in health and medical research, and to evaluate community and consumer participation. It is important to demonstrate whether consumer and community participation makes a difference to health and medical research.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21569591

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PubMed, Paediatr Perinat Epidemiol. 2011 Jul;25(4):316-27. doi: 10.1111/j.1365-3016.2011.01197.x. Epub 2011 Apr 24.

**155) CHANGES IN HEALTH PROFESSIONALS' KNOWLEDGE, ATTITUDES AND PRACTICE FOLLOWING PROVISION OF EDUCATIONAL RESOURCES ABOUT PREVENTION OF PRENATAL ALCOHOL EXPOSURE AND FETAL ALCOHOL SPECTRUM DISORDER**

Payne J, France K, Henley N, D'Antoine H, Bartu A, O'Leary C, Elliott E, Bower C.
Telethon Institute for Child Health Research, University of Western Australia, Subiaco, WA, Australia. janp@ichr.uwa.edu.au

**ABSTRACT**
We provided health professionals in Western Australia (WA) with educational resources about prevention of prenatal alcohol exposure and fetal alcohol spectrum disorder and assessed changes in their knowledge, attitudes and practice concerning fetal alcohol syndrome (FAS) and alcohol consumption in pregnancy. Following our 2002 survey of health professionals in WA, we developed and distributed educational resources to 3348 health professionals in WA in 2007. Six months later we surveyed 1483 of these health professionals. Prevalence rate ratios [PRR] and 95% confidence intervals [CI] were calculated to compare 2007 results with results from the 2002 survey. Of the 1001 responding health professionals, 69.8% had seen the educational resources; of these 77.1% have

used them and 48.5% said the resources had assisted them to change their practice or their intention to change their practice. Compared with 2002, there was an increase in the proportion who knew all the essential features of FAS from 11.7% to 15.8% [PRR 1.35; 95% CI 1.09, 1.67] and had diagnosed FAS, from 4.8% to 7.3% [PRR 1.52; 95% CI 1.08, 2.13]. In 2007, 98.1% of health professionals stated they would advise pregnant women to consider not drinking at all or advise them that no alcohol in pregnancy is the safest choice. Health professionals surveyed in 2007 have increased their knowledge, changed their attitudes and practice about FAS, and altered the advice they give to pregnant women about alcohol consumption since our survey in 2002. It is essential that we build on this change and continue to support health professionals' knowledge, attitudes and practice about the prevention of prenatal alcohol exposure and fetal alcohol spectrum disorder. The educational resources for health professionals may be ordered as hard copies and downloaded from the internet http://www.ichr.uwa.edu.au/alcoholandpregnancy

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http://www.ncbi.nlm.nih.gov/pubmed/21649674

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PubMed, J Mol Histol. 2011 Jun;42(3):237-49. Epub 2011 Apr 23.

**156) THE EXPRESSION OF AKT AND ERK1/2 PROTEINS DECREASED IN DEXAMETHASONE-INDUCED INTRAUTERINE GROWTH RESTRICTED RAT PLACENTAL DEVELOPMENT**

Ozmen A, Unek G, Kipmen-Korgun D, Korgun ET.
Department of Histology and Embryology, Medical Faculty, Akdeniz University, 07070 Antalya, Turkey.

**ABSTRACT**
The placenta is a complicated tissue that lies between maternal and fetal compartments. Although the architecture of the human and rodent placentas differ a little in their details, their overall structures and the molecular mechanisms of placental developments are thought to be very similar. In rats, fetal-placental exposure to maternally administered glucocorticoids decreases birth weight and placental weight. The mechanism underlying the placental growth inhibitory effects of glucocorticoids have not been elucidated. Moreover it is still not determined that how Akt and ERK1/2 proteins related proliferation and apoptosis mechanisms are influenced by dexamethasone-induced IUGR (Intrauterine Growth Restriction) placentas. The aim of this study was to investigate the expression levels and spatio-temporal immunolocalizations of Akt, p-Akt, ERK1/2 and p-ERK1/2 proteins in normal and dexamethasone treated placental development in pregnant Wistar rats. Pregnant rats were subcutaneously injected with 100 µg/kg dexamethasone 21-acetate in 0.1 ml 10% ethanol on day 10 and 12 of gestation. Afterwards injection was continued as 200 µg/kg until they were killed on day 12 (injection started on day 10), 14, 16, 18 and 20 (injections started on day 12) of pregnancy. Placental and embryonal tissues were collected for immunohistochemistry and Western blot analysis. We found that maternal dexamethasone treatment led to a decrease in ERK1/2 and Akt activation during rat placental development. The decrease in Akt and ERK1/2 activations may result with cell survival inhibition or apoptosis stimulation. Hence, dexamethasone induced placental and embryonal developmental abnormalities could be associated with reduction of Akt and ERK1/2 activation.

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http://www.ncbi.nlm.nih.gov/pubmed/21512721

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PubMed, BMC Pregnancy Childbirth. 2011 Apr 11;11:27.

**157) PREVALENCE, PREDICTORS AND PERINATAL OUTCOMES OF PERI-CONCEPTIONAL ALCOHOL EXPOSURE--RETROSPECTIVE COHORT STUDY IN AN URBAN OBSTETRIC POPULATION IN IRELAND**

Mullally A, Cleary BJ, Barry J, Fahey TP, Murphy DJ.
Academic Department of Obstetrics & Gynaecology, Coombe Women and Infants University Hospital & Trinity College Dublin, Dublin 8, Republic of Ireland.

**ABSTRACT**

**Background:** Evidence-based advice on alcohol consumption is required for pregnant women and women planning a pregnancy. Our aim was to investigate the prevalence, predictors and perinatal outcomes associated with peri-conceptional alcohol consumption.

**Methods:** A cohort study of 61,241 women who booked for antenatal care and delivered in a large urban maternity hospital between 2000 and 2007. Self-reported alcohol consumption at the booking visit was categorised as low (0-5 units per week), moderate (6-20 units per week) and high (>20 units per week).

**Results:** Of the 81% of women who reported alcohol consumption during the peri-conceptional period, 71% reported low intake, 9.9% moderate intake and 0.2% high intake. Factors associated with moderate alcohol consumption included being in employment OR 4.47 (95% CI 4.17 to 4.80), Irish nationality OR 16.5 (95% CI 14.9 to 18.3), private health care OR 5.83 (95% CI 5.38 to 6.31) and smoking OR 1.86 (95% CI 1.73 to 2.01). Factors associated with high consumption included maternal age less than 25 years OR 2.70 (95% CI 1.86 to 3.91) and illicit drug use OR 6.46 (95% CI 3.32 to 12.60). High consumption was associated with very preterm birth (<32 weeks gestation) even after controlling for socio-demographic factors, adjusted OR 3.15 (95% CI 1.26-7.88). Only three cases of Fetal Alcohol Syndrome were recorded (0.05 per 1000 total births), one each in the low, moderate and high consumption groups.

**Conclusions:** Public Health campaigns need to emphasise the importance of peri-conceptional health and pre-pregnancy planning. Fetal Alcohol Syndrome is likely to be under-reported despite the high prevalence of alcohol consumption in this population.

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http://www.ncbi.nlm.nih.gov/pubmed/21481224

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PubMed, Paediatr Perinat Epidemiol. 2011 Jul;25(4):328-39. doi: 10.1111/j.1365-3016.2010.01179.x. Epub 2011 Apr 3.

**158) PATTERNS OF ALCOHOL CONSUMPTION AMONG PREGNANT AFRICAN-AMERICAN WOMEN IN WASHINGTON, DC, USA.**

Kiely M, Thornberry JS, Bhaskar B, Rodan MF.
Collaborative Studies Unit, Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD 20892-7510, USA. kielym@nih.gov

**ABSTRACT**

The objective of this paper is to describe the patterns and associated behaviours related to alcohol consumption among a selected sample of pregnant women seeking prenatal care in inner city

Washington DC. Women receiving prenatal care at one of nine sites completed an anonymous alcohol-screening questionnaire. Questions concerned the amount, type and pattern of alcohol consumption. Women were categorised as at no, low, moderate or high risk for alcohol consumption during pregnancy. For comparisons of risk levels of drinking, bivariate associations were examined using Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were also computed. Although 31% of current/recent drinkers stated that they continued to drink during pregnancy, responses to quantity/frequency questions revealed that 42% continued to do so. Women who were at high compared with moderate risk acknowledged that others were worried about their consumption [OR=4.0, 95% CI 1.5, 10.6], that they drank upon rising [OR=6.7, 95% CI 1.8, 26.9], had a need to reduce drinking [OR=3.2, 95% CI 1.3, 8.1] and in the past 5 years had had fractures [OR=4.2, 95% CI 1.0, 17.8] or a road traffic injury [OR=3.4, 95% CI 1.0, 12.2]. Women in the high/moderate compared with low-risk group were more likely to have been injured in a fight or assault [OR=2.7, 95% CI 1.3, 5.6]. This study validated the usefulness of our questionnaire in identifying women who were at risk for alcohol consumption during pregnancy across a range of consumption levels. Using our screening tool, women were willing to disclose their drinking habits. This low-cost method identifies women appropriate for targeting of interventions.

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http://www.ncbi.nlm.nih.gov/pubmed/21649675

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PubMed, Nihon Arukoru Yakubutsu Igakkai Zasshi. 2011 Apr;46(2):250-9.

**159) EFFECTS OF ETHANOL EXPOSURE ON SPATIAL LEARNING IN MICE DURING SYNAPTOGENESIS**

Furumiya J, Hashimoto Y.
Department of Legal Medicine, Kochi Medical School, Kochi University Kohasu, Oko-cho, Nankoku City, Kochi 783-8505, Japan.

**ABSTRACT**
**Background:** The effects of exposure to ethanol (EtOH) on spatial learning in mice during synaptogenesis and changes after maturation are not well understood. In this study, we used a water maze test to evaluate the effects of EtOH exposure on spatial learning during synaptogenesis period.

**Methods:** One-week-old pups from dams not exposed to EtOH during pregnancy were given 2 dorsal subcutaneous injections of 2.5 g/kg EtOH at a 2-h interval. At 8 h (n=6) and 24 h (n=5) after the first EtOH injection, the brains were perfused and fixed. The brain tissue sections were analyzed by TUNEL assay to detect DNA fragmentation and by immunohistochemistry to detect activated caspase-3. In addition, at 5 h (n=10), 8 h (n=5), and 24 h (n=7) after the first EtOH injection, blood and cerebral EtOH concentrations were measured by headspace gas chromatography. A water maze test was performed at age 7 weeks and 12 weeks.

**Results:** In neonatal EtOH exposure group, mice had a prolonged time to reach the platform compared to a control group. This trend was similar both trials of age 7 weeks and age 12 weeks. At 24 h after EtOH injection in the neonatal EtOH exposure group, the incidence of TUNEL and activated caspase-3 positive cells was 6.1 +/- 1.8% and 6.4 +/- 1.0%, respectively, in the cerebral cortex, 1.6 +/- 0.9% and 1.2 +/- 0.9%, respectively, in the hippocampus, and 11.0 +/- 4.4% and 16.3 +/- 7.8%, respectively, in the thalamus. In blood and cerebral tissue from mice treated with EtOH, as in the neonatal EtOH exposure group, EtOH remained at 0.93 +/- 0.79 mg/g and 0.96 +/- 0.78 mg/g, respectively, after 24 h.

**Conclusions:** The impairment in spatial learning due to EtOH exposure during the neonatal periods did not tend to improve after reaching maturity. Impairment in spatial learning after maturity in mice exposed to EtOH during synaptogenesis is likely due to apoptosis of brain neurons caused by EtOH.

**Link to the Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21702336

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ScienceDirect, doi:10.1016/j.alcohol.2010.12.004
Received 30 July 2010; revised 4 December 2010; Accepted 6 December 2010. Available online 2 March 2011

### 160) OPPOSITE EFFECTS OF ACUTE ETHANOL EXPOSURE ON GAP-43 AND BDNF EXPRESSION IN THE HIPPOCAMPUS VERSUS THE CEREBELLUM OF JUVENILE RATS

V.V. Kulkarny[1], N.E. Wiest[1], C.P. Marquez, S.C. Nixon, C.F. Valenzuela, N.I. Perrone-Bizzozero
Department of Neurosciences, University of New Mexico HSC, Albuquerque, NM 87131, USA

**ABSTRACT**
The adolescent brain is particularly vulnerable to the effects of alcohol, with intoxications at this developmental age often producing long-lasting effects. The present study addresses the effects of a single acute ethanol exposure on growth-associated protein-43 (GAP-43) and brain-derived neurotrophic factor (BDNF) gene expression in neurons in the cerebellum and hippocampus of adolescent rats. Male postnatal day 23 (P23) Sprague–Dawley rats were exposed to ethanol vapors for 2 h and after a recovery period of 2 h, the cerebellum and hippocampus were harvested and samples were taken for blood alcohol concentration (BAC) determinations. We found that this exposure resulted in a mean BAC of 174 mg/dL, which resembles levels in human adolescents after binge drinking. Analyses of total RNA and protein by quantitative reverse transcription PCR and western blotting, respectively, revealed that this single ethanol exposure significantly decreased the levels of GAP-43 mRNA and protein in the cerebellum but increased the levels of mRNA and protein in the hippocampus. BDNF mRNA and protein levels were also increased in the hippocampus but not in the cerebellum of these animals. In situ hybridizations revealed that GAP-43 and BDNF mRNA levels were primarily increased by alcohol exposure in hippocampal dentate granule cells and CA3 neurons. Overall, the reported alterations in the expression of the plasticity-associated genes GAP-43 and BDNF in juvenile rats are consistent with the known deleterious effects of binge drinking on motor coordination and cognitive function.

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http://www.sciencedirect.com/science/article/pii/S0741832911000176

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PubMed, Rev Neurol. 2011 Mar 1;52 Suppl 1:S53-7.

### 161) ALCOHOLIC FOETOPATHY: AN UPDATE

[Article in Spanish]
Martín Fernández-Mayoralas D, Fernández-Jaén A.
Unidad de Neurología Infantil.Hospital Quiron, Pozuelo de Alarcon, Madrid, Spain. dmfmayor@yahoo.es

**ABSTRACT**
**Introduction:** In recent years a great deal of attention has been given to the role of prenatal exposure

to alcohol in the production of a wide range of disorders known as foetal alcohol spectrum disorders (FASD). Foetal alcohol syndrome represents the classic syndrome and the most serious manifestation caused by the epigenetic changes induced by such exposure. It is considered to be the number one preventable cause of congenital defects and mental deficiency.

**Aim:** To update the body of knowledge on this group of disorders by reviewing the most important aspects in terms of the epidemiology, diagnostic criteria and treatment, with special emphasis on the associated cognitive and behavioural alterations.

**Development:** The worldwide prevalence of alcohol spectrum disorders could be around 1%. Today there are a number of diagnostic systems available for FASD. The most commonly used are the diagnostic criteria of the Institute of Medicine. The cognitive and behavioural alterations cover a wide range of disorders that are associated to the psychosocial environment in which the child develops. The executive functions are usually found to be affected and most patients associate attention deficit hyperactivity disorder. Few studies have been conducted on the effectiveness of treatments such as methylphenidate or atomoxetine in this population.

**Conclusions:** It is necessary to know the clinical, physical and cognitive manifestations of intrauterine exposure to alcohol. Likewise, randomised placebo-controlled randomised studies are needed to estimate the effectiveness of psychostimulants and atomoxetine in the treatment of these children.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21365604

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PubMed, Semin Pediatr Neurol. 2011 Mar;18(1):49-55.

**162) FETAL ALCOHOL SPECTRUM DISORDERS: GENE-ENVIRONMENT INTERACTIONS, PREDICTIVE BIOMARKERS, AND THE RELATIONSHIP BETWEEN STRUCTURAL ALTERATIONS IN THE BRAIN AND FUNCTIONAL OUTCOMES**

Reynolds JN, Weinberg J, Clarren S, Beaulieu C, Rasmussen C, Kobor M, Dube MP, Goldowitz D.
Department of Pharmacology and Toxicology, Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada. nazeem.muhajarine@usask.ca

**ABSTRACT**
Prenatal alcohol exposure is a major, preventable cause of behavioral and cognitive deficits in children. Despite extensive research, a unique neurobehavioral profile for children affected by prenatal alcohol exposure remains elusive. A fundamental question that must be addressed is how genetic and environmental factors interact with gestational alcohol exposure to produce neurobehavioral and neurobiological deficits in children. The core objectives of the NeuroDevNet team in fetal alcohol spectrum disorders is to create an integrated research program of basic and clinical investigations that will (1) identify genetic and epigenetic modifications that may be predictive of the neurobehavioral and neurobiological dysfunctions in offspring induced by gestational alcohol exposure and (2) determine the relationship between structural alterations in the brain induced by gestational alcohol exposure and functional outcomes in offspring. The overarching hypothesis to be tested is that neurobehavioral and neurobiological dysfunctions induced by gestational alcohol exposure are correlated with the genetic background of the affected child and/or epigenetic modifications in gene expression. The identification of genetic and/or epigenetic markers that are predictive of the severity of behavioral and

cognitive deficits in children affected by gestational alcohol exposure will have a profound impact on our ability to identify children at risk.

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PubMed, Semin Pediatr Neurol. 2011 Mar;18(1):21-5.

**163) EVIDENCE-BASED NEUROETHICS FOR NEURODEVELOPMENTAL DISORDERS**

Racine E, Bell E, Di Pietro NC, Wade L, Illes J.
Neuroethics Research Unit, Institut de recherches cliniques de Montréal, Montreal, Quebec, Canada. eric.racine@ircm.qc.ca

**ABSTRACT**
Many neurodevelopmental disorders affect early brain development in ways that are still poorly understood; yet, these disorders can place an enormous toll on patients, families, and society as a whole and affect all aspects of daily living for patients and their families. We describe a pragmatic, evidence-based framework for engaging in empiric ethics inquiry for a large consortium of researchers in neurodevelopmental disorders and provide relevant case studies of pragmatic neuroethics. The 3 neurodevelopmental disorders that are at the focus of our research, cerebral palsy (CP), autism spectrum disorder (ASD), and fetal alcohol spectrum disorder (FASD), bring unique and intersecting challenges of translating ethically research into clinical care for children and neonates. We identify and discuss challenges related to health care delivery in CP; neonatal neurological decision making; alternative therapies; and identity, integrity, and personhood.

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http://www.ncbi.nlm.nih.gov/pubmed/21575837

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PubMed, Alcohol Clin Exp Res. 2011 Jun;35(6):1081-91. doi: 10.1111/j.1530-0277.2011.01441.x. Epub 2011 Feb 17.

**164) ALCOHOL, SMOKING, AND DRUG USE AMONG INUIT WOMEN OF CHILDBEARING AGE DURING PREGNANCY AND THE RISK TO CHILDREN**

Muckle G, Laflamme D, Gagnon J, Boucher O, Jacobson JL, Jacobson SW.
Public Health Research Unit, CHUQ-Laval University Medical Research Center, Quebec City, QC, Canada. gina.muckle@psy.ulaval.ca

**ABSTRACT**
**Background:** Alcohol consumption during pregnancy, a known teratogen often associated with drug use and smoking is a well-known public health concern.

**Aim:** This study provides prevalence data for alcohol, smoking, and illicit drug use before, during, and after pregnancy among Inuit. Factors associated with alcohol use are also identified.

**Methods:** Two hundred and eight Inuit women from Arctic Quebec were interviewed at mid-pregnancy, and at 1 and 11 months postpartum to provide descriptive data on smoking, alcohol, and drug use during pregnancy, and the year before and after pregnancy. Sociodemographic and family

characteristics potentially associated with alcohol use were documented.

**Results:** Ninety-two percent of the women reported smoking and 61% reported drinking during pregnancy. Episodes of binging during pregnancy were reported by 62% of the alcohol users, which correspond to 38% of pregnant women. Thirty-six percent of the participants reported using marijuana during pregnancy. Alcohol use and binge drinking during pregnancy were more likely to be reported by women who lived in less crowded houses, had a better knowledge of a second language, drank alcohol more often and in larger amounts prior to pregnancy, and used illicit drugs. Binge drinkers were more likely to be single women and to have had fewer previous pregnancies. Postpartum distress and violence were more likely to be experienced by women who used alcohol during pregnancy. Binge drinking during pregnancy was best predicted by drinking habits before pregnancy, maternal symptoms of depression, the use of illicit drugs during pregnancy, and the number of young children living with the mother.

**Conclusions:** These results confirm that alcohol is a major risk factor to maternal and child health in this population, underscoring the need for culturally relevant and effective prevention programs.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21332531

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PubMed, Folia Neuropathol. 2011;49(1):47-55.

**165) DIFFERENTIAL EXPRESSION OF CALBINDIN D28K, CALRETININ AND PARVALBUMIN IN THE CEREBELLUM OF PUPS OF ETHANOL-TREATED FEMALE RATS**

Wierzba-Bobrowicz T, Lewandowska E, Stępień T, Szpak GM.
Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland. bobrow@ipin.edu.pl

**ABSTRACT**
Three calcium-binding proteins (CaBPs), calbindin D28k, calretinin and parvalbumin, were immunohistochemically examined in the cerebellum of ten-day-old rat pups of ethanol-treated dams. Dams were treated with ethanol during pregnancy and/or lactation. In the cerebellar cortex of the pups from control groups, Purkinje cells with their processes and Golgi cells were positive for calbindin D28k, whereas interneurons (Lugaro, Golgi and unipolar brush cells) and sometimes Purkinje cells were positive for calretinin. Parvalbumin immunoreactivity was observed in Golgi and basket cells, stellate cells and in some Purkinje cells. The number of positive cells and staining intensity for calbindin D28k and parvalbumin decreased in all experimental groups, whereas the immunoreaction for calretinin was visible only in interneurons and was more intense in experimental than in control groups. Calbindin D28k immunoreactivity in experimental groups was detected in some Purkinje cells and rarely in Golgi cells. The localization of very intense calretinin expression was visible mainly in unipolar brush cells. A parvalbumin-positive reaction was detected in single Purkinje cells and sometimes in basket cells. The results of the present study showed that immunoreactivity of the three calcium-binding proteins was found in the cells of the cerebellum of the ten-day-old pups from the control groups. In experimental groups of females treated with ethanol during pregnancy and/or lactation, we observed the most significant decrease in both the intensity and the number of immunoreactions of calbindin D28k and parvalbumin, but the intensity of the immunoreaction for calretinin was increased for interneurons. Ischaemic damage to Purkinje cells and loss of interneurons and Purkinje cells were also noted in these groups. A possible correlation between the duration of

ethanol intoxication, expression of calcium-binding proteins and pathological changes of cells in the cerebellar cortex of the pups of ethanol-treated dams is discussed.

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PubMed, Child Neuropsychol. 2011;17(3):290-309. doi: 10.1080/09297049.2010.544650.

**166) EXECUTIVE FUNCTION AND MEMORY IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER**

Pei J, Job J, Kully-Martens K, Rasmussen C.
Department of Educational Psychology, University of Alberta , Edmonton, Canada.

**ABSTRACT**
A complex relation exists between memory and executive functioning (EF), particularly when learning and recalling multifaceted or extensive information ( Moscovitch & Winocur, 2002 ). A common instrument for evaluating this relationship is the Rey-Osterrieth Complex Figure (ROCF; Rey, 1941 ; Osterrieth, 1944 ). The ROCF has proved particularly useful in pediatric research; however, little research has been conducted among children with Fetal Alcohol Spectrum Disorders (FASD). Seventy children (35 FASD, 35 control), aged 6 to 12 years, were tested using the ROCF. All participants with FASD had received a diagnosis according to the Canadian guidelines for FASD ( Chudley et al., 2005 ) using the 4-digit diagnostic code ( Astley, 2004 ). Significant group differences were revealed with children with FASD demonstrating substantial difficulties in organization, accuracy, and memory. Among children with FASD, a distinctive profile emerged, lending support to the argument that children with FASD experience deficits in EF and memory throughout their development. Information from the present study will not only help to improve understanding of functioning in this population but also provide insight into how to deal with EF and memory deficits in terms of testing, treatment, and intervention.

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http://www.ncbi.nlm.nih.gov/pubmed/21718218

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PubMed, Crit Rev Clin Lab Sci. 2011 Jan-Feb;48(1):19-47.

**167) MOLECULAR AND BEHAVIORAL ASPECTS OF THE ACTIONS OF ALCOHOL ON THE ADULT AND DEVELOPING BRAIN**

Alfonso-Loeches S, Guerri C.
Cell Pathology Laboratory, Prince Felipe Research Centre, Valencia, Spain.

**ABSTRACT**
The brain is one of the major target organs of alcohol actions. Alcohol abuse can lead to alterations in brain structure and functions and, in some cases, to neurodegeneration. Cognitive deficits and alcohol dependence are highly damaging consequences of alcohol abuse. Clinical and experimental studies have demonstrated that the developing brain is particularly vulnerable to alcohol, and that drinking during gestation can lead to a range of physical, learning and behavioral defects (fetal alcohol spectrum disorders), with the most dramatic presentation corresponding to fetal alcohol syndrome. Recent findings also indicate that adolescence is a stage of brain maturation and that heavy drinking

at this stage can have a negative impact on brain structure and functions causing important short- and long-term cognitive and behavioral consequences. The effects of alcohol on the brain are not uniform; some brain areas or cell populations are more vulnerable than others. The prefrontal cortex, the hippocampus, the cerebellum, the white matter and glial cells are particularly susceptible to the effects of ethanol. The molecular actions of alcohol on the brain are complex and involve numerous mechanisms and signaling pathways. Some of the mechanisms involved are common for the adult brain and for the developing brain, while others depend on the developmental stage. During brain ontogeny, alcohol causes irreversible alterations to the brain structure. It also impairs several molecular, neurochemical and cellular events taking place during normal brain development, including alterations in both gene expression regulation and the molecules involved in cell-cell interactions, interference with the mitogenic and growth factor response, enhancement of free radical formation and derangements of glial cell functions. However, in both adult and adolescent brains, alcohol damages specific brain areas through mechanisms involving excitotoxicity, free radical formation and neuroinflammatory damage resulting from activation of the innate immune system mediated by TLR4 receptors. Alcohol also acts on specific membrane proteins, such as neurotransmitter receptors (e.g. NMDA, GABA-A), ion channels (e.g. L-type $Ca^{2+}$ channels, GIRKs), and signaling pathways (e.g. PKA and PKC signaling). These effects might underlie the wide variety of behavioral effects induced by ethanol drinking. The neuroadaptive changes affecting neurotransmission systems which are more sensitive to the acute effects of alcohol occur after long-term alcohol consumption. Alcohol-induced maladaptations in the dopaminergic mesolimbic system, abnormal plastic changes in the reward-related brain areas and genetic and epigenetic factors may all contribute to alcohol reinforcement and alcohol addiction. This manuscript reviews the mechanisms by which ethanol impacts the adult and the developing brain, and causes both neural impairments and cognitive and behavioral dysfunctions. The identification and the understanding of the cellular and molecular mechanisms involved in ethanol toxicity might contribute to the development of treatments and/or therapeutic agents that could reduce or eliminate the deleterious effects of alcohol on the brain.

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http://www.ncbi.nlm.nih.gov/pubmed/21657944

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PubMed, Addiction. 2011 Jun;106(6):1037-45. doi: 10.1111/j.1360-0443.2010.03167.x. Epub 2010 Oct 18.

**168) RISKY SINGLE-OCCASION DRINKING: BINGEING IS NOT BINGEING**

Gmel G, Kuntsche E, Rehm J.
Alcohol Treatment Center, Lausanne University Hospital, Lausanne, Switzerland. gerhard.gmel@chuv.ch

**ABSTRACT**

**Aims:** To review the concept of binge drinking as a measure of risky single occasion drinking (RSOD), to illustrate its differential impact on selected health outcomes and to identify research gaps.

**Methods:** Narrative literature review with focus on conceptual and methodological differences, trajectories of RSOD and effects of RSOD on fetal outcomes, coronary heart disease (CHD) and injuries.

**Results:** Effects ascribed commonly to RSOD may often be the effects of an undifferentiated mixture of risky single occasions and regular heavy volume drinking, constituted by frequent, successive RSOD. This leads to the problem that additional risks due to RSOD are mis-specified and remain unidentified or underestimated in some cases, such as for injuries or CHD, but are probably

overstated for some chronic consequences or for effects of maternal drinking on newborns.

**Conclusion:** A stronger focus should be placed upon methods that can differentiate the effects of RSOD from those due to frequent occasions of heavy drinking that result in heavy volume drinking.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21564366

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PubMed, J Addict Res Ther. 2010 Sep 29;1(102). pii: 1000102.

**169) BIRTH OUTCOMES, LIFETIME ALCOHOL DEPENDENCE AND COGNITION IN MIDDLE ADULTHOOD**

Caspers KM, Arndt S.
Department of Epidemiology, University of Iowa, Iowa City, IA 52242, USA.

**ABSTRACT**
Prenatal exposure to alcohol is associated with cognitive abnormalities that persist throughout the lifespan and are also often a focus of studies examining cognitive outcomes associated with excessive alcohol use by an individual. This study examined the effect of birth outcomes consistent with fetal alcohol exposure on associations between lifetime alcohol dependence and cognition in middle adulthood. The sample was comprised of 315 adult adoptees ranging in age from 31 to 64 years (SD = 7.20). Facial morphology, pre-morbid cognition, and current cognition were assessed. Birth parent behaviors and birth outcomes (e.g., birthweight, gestational age) were obtained from adoption agency records. Lifetime alcohol dependence was determined from the Semi-Structured Assessment of the Genetics of Alcoholism - II. Univariate associations showed significantly poorer pre-morbid and current cognition when birth parent problems, short palpebral fissures, and thin upper lips were present. Lifetime alcohol dependence was associated with lower perceptional organization, processing speed and working memory. Multivariate analyses demonstrated continued significance suggesting unique contributions of each to cognition. Evaluating the possible role of fetal alcohol exposure within studies on alcoholism can only further improve the treatment and prevention of alcohol-related problems by isolating those cognitive outcomes uniquely attributable to an individual's consumption of alcohol.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/21643430

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Exp Toxicol Pathol. 2011 Nov;63(7-8):607-11. Epub 2010 Jun 7.

**170) ETHANOL-INDUCED INHIBITION OF FETAL HYPOTHALAMIC-PITUITARY-ADRENAL AXIS DUE TO PRENATAL OVEREXPOSURE TO MATERNAL GLUCOCORTICOID IN MICE**

Liang G, Chen M, Pan XL, Zheng J, Wang H.
Pharmacology Department of Basic Medical College, Wuhan University, Wuhan 430071, China.

**ABSTRACT**
Prenatal ethanol exposure has been well documented to be one of the etiological factors responsible for intrauterine growth retardation (IUGR). Previous studies have shown that chronic ethanol exposure during pregnancy elevated the basic level of corticosterone in fetus. However, the potential mechanisms behind them are still unclear. The aim of the present study was to investigate the effects

of prenatal ethanol exposure on maternal and fetal hypothalamic-pituitary-adrenal (HPA) axis as well as placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), and to clarify the mechanism of ethanol-induced IUGR. Pregnant mice were intragastricly administrated with ethanol at a dose of 6.4 g kg(-1) d(-1) from day 11 to 17 of gestation and parameters representing fetal growth and development were recorded either. The level of corticosterone in maternal serum was determined by ELISA kit. The mRNA expressions of steroidogenic acute regulatory protein (StAR) and cytochrome P450 cholesterol side chain cleavage (P450scc) both in maternal and fetal adrenal, and placental 11β-HSD-2 were detected by real-time quantitative PCR, respectively. The results showed that fetal body weight significantly decreased, and the incidence of IUGR was obviously increased after prenatal ethanol exposure. Maternal serum corticosterone level was elevated, and the expressions of StAR and P450scc were increased in maternal adrenal while decreased in fetal adrenal. The expression of placental 11β-HSD-2 was significantly reduced. These results suggest that prenatal ethanol exposure induces an inhibition of fetal HPA axis activity and IUGR occurs. The mechanism may be associated with ethanol-induced maternal HPA axis activation and high glucocorticoid condition, which impair the placental barrier, and lead to an overexposure of elevated maternal glucocorticoid to fetus, and eventually result in the inhibition of the fetal HPA axis.

**Read Full Article,**
http://www.ncbi.nlm.nih.gov/pubmed/20627497

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PubMed, J Addict Med. 2010 Jun;4(2):114-21.

**171) KNOWLEDGE, OPINIONS, AND PRACTICE PATTERNS OF OBSTETRICIAN-GYNECOLOGISTS REGARDING THEIR PATIENTS' USE OF ALCOHOL**

Anderson BL, Dang EP, Floyd RL, Sokol R, Mahoney J, Schulkin J.
Department of Research, American College of Obstetricians and Gynecologists, Washington, DC, USA. banderson@acog.org

**ABSTRACT**
**Objective:** To evaluate the evolution of fetal alcohol spectrum disorder prevention practices including awareness and use of recently published tools.

**Methods:** Fellows of the American College of Obstetricians and Gynecologists were asked about their knowledge, opinions, and practice regarding alcohol-related care. Eight hundred obstetrician-gynecologists (ob-gyns) were selected; 48.1% returned the survey.

**Results:** The majority (66.0%) indicated that occasional alcohol consumption is not safe during any period of pregnancy. There was no consensus when asked if alcohol's effect on fetal development is clear (46.9% thought it was clear and 45.9% did not). Most (82.2%) ask all pregnant patients about alcohol use only during patients' initial visit, whereas 10.6% ask during initial and subsequent visits. Most (78.5%) advise abstinence when pregnant women report alcohol use. When asked which validated alcohol risk screening tool they most commonly use with pregnant patients, 57.8% said they use no tool. Although 71.9% felt prepared to screen for risky or hazardous drinking, older ob-gyns indicated feeling significantly more unprepared than younger ob-gyns. "Patient denial or resistance to treatment" was the top issue affecting alcohol screening and "referral resources for patients with alcohol problems" was the resource needed most. Most ob-gyns were not aware of the National Institute on Alcohol Abuse and Alcoholism "Clinician's Guide" or the American College of Obstetricians and Gynecologists "Fetal Alcohol Spectrum Disorder Prevention Tool Kit."

**Conclusions:** There are few changes in the alcohol-related screening and treatment patterns of ob-

gyns since 1999; although perceived barriers and needs have changed. Interventions, including referral resources and continuing medical education training, are warranted.

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http://www.ncbi.nlm.nih.gov/pubmed/21769028

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## ARTICLE ABSTRACTS

Federal Legal Publications; The Journal of Psychiatry & Law
Season: 2011, Volume 39

### 1. ETHNIC AND CULTURAL FACTORS IN IDENTIFYING FETAL ALCOHOL SPECTRUM DISORDERS

By George W. Woods, M.D., Stephen Greenspan, PH.D., and Bhushan S. Agharkar, M.D.

**ABSTRACT**
A large percentage of those involved in the criminal justice system are poor and represent ethnic minorities, and many of them were born to mothers who drank during pregnancy. In this article, we review literature pertaining to physical, social, cognitive, and neurological deficits of individuals with Fetal Alcohol Spectrum Disorders (FASD), exploring the possibility that these deficits or their outward expression may be affected by cultural and ethnic influences. For the most part, the evidence suggests that the indicators of FASD are universal across all racial and cultural groups. These indicators are, however, often obscured in individuals from certain backgrounds, due to the salience of what might be termed "cultural overshadowing." This could be considered a form of unconscious or institutional discrimination, in that it denies criminal defendants from certain cultural backgrounds the opportunity to have courts take into account the possibility that their alleged or proven offenses were affected by serious brain-based impairments in reasoning and judgment. The law allows for consideration of these impairments in both sentencing and mitigation.

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https://www.federallegalpublications.com/journal-of-psychiatry-law/201109/jpl-20111-39-01-woods-ethnic-and-cultural-factors-identifying-fetal

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Federal Legal Publications; The Journal of Psychiatry & Law
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### 2. SUGGESTIBILITY AND FETAL ALCOHOL SPECTRUM DISORDERS: I'LL TELL YOU ANYTHING YOU WANT TO HEAR

By Natalie Novick Brown, PH.D., Gisli Gudjonsson, PH.D., and Pauk Connor, PH.D

**ABSTRACT**
This article reviews the role of suggestibility as a psychological vulnerability in people with FASD who are arrested and questioned by police. After a review of relevant literature on suggestibility and FASD, preliminary data are presented from a small pilot study on suggestibility involving defendants with FASD in the United States who were involved in either a pre-trial or post-conviction adjudication process. Results of that study suggest that persons with FASD may be highly suggestible in interrogative situations, which appears to stem from a combination of neurologically based tendencies to acquiesce to leading questions and change responses to questions as a function of negative feedback. Interrogative suggestibility found in the FASD population, which is likely due to central nervous system dysfunction, has broad forensic implications.

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https://www.federallegalpublications.com/journal-of-psychiatry-law/201110/jpl-2011-39-1-02-brown-suggestibility-and-fetal-alcohol-spectrum-di

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Federal Legal Publications; The Journal of Psychiatry & Law
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### 3. A JUDICIAL, PERSPECTIVE ON ISSUES IMPACTING THE TRIAL COURTS RELATED TO FETAL ALCOHOL SPECTRUM DISORDER

By Hon. Anthony Wartnik, J.D. and Hon. Susan Shepard Carlson, J.D.

**ABSTRACT**
This article explores issues that judges, prosecutors, defense counsel, treatment providers, and defendants face when a person who has, or may have, Fetal Alcohol Spectrum Disorders (FASD) is charged with a crime. The article is divided into three sections: the first section discusses basic legal concepts and how they relate to those in the criminal justice system who suffer from FASD; the second section examines case studies and lessons learned from the therapeutic drug court, a program of the King County Superior Court in Seattle, Washington; the final section presents case studies of serious felonies, and explores constitutional issues.

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Federal Legal Publications; The Journal of Psychiatry & Law
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### 4. FETAL ALCOHOL SPECTRUM DISORDERS AND VICTIMIZATION: IMPLICATIONS FOR FAMILIES, EDUCATORS, SOCIAL SERVICES, LAW ENFORCEMENT, AND THE JUDICIAL SYSTEM

By Karen Smith Thiel, J.D., PH.D., Nora Baladerian, PH.D., Katharine R. Boyce, J.D., Olegario Cantos VII, J.D., Leigh Ann Davis, M.S.S.W., M.P.A., Kathryn A. Kelly, B.A., Kathleen Tavenner Mitchell, M.H.S., AND James Stream, M.B.A.

**ABSTRACT**
Individuals with Fetal Alcohol Spectrum Disorders (FASD) are vulnerable to many forms of victimization. FASD is associated with cognitive deficits and a set of behaviors that may limit an individual's ability to recognize and report victimization experiences and provide testimony in judicial proceedings. Services must be established and provided to educate and train individuals with FASD, their family members, teachers, and social service workers to prevent victimization and report victimization when it occurs. Law enforcement and the judicial system also should develop systems to protect the rights of individuals with FASD who are victimized, especially when they appear as witnesses.

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https://www.federallegalpublications.com/journal-of-psychiatry-law/201110/jpl-2011-39-1-04-theil-fetal-alcohol-spectrum-disorders-and-victimi

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Federal Legal Publications; The Journal of Psychiatry & Law
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**5. THE CRIMINAL JUSTICE SYSTEM'S DISPARATE TREATMENT OF INDIVIDUALS WITH FETAL ALCOHOL SYNDROME DISORDERS IN CASES INVOLVING SEXUAL ACTIVITY**

By Jacqueline Mcmurtrie, J.D.

**ABSTRACT**
Individuals with Fetal Alcohol Spectrum Disorders (FASD) are treated differently by the criminal justice system in sex offense prosecutions, depending upon whether they are categorized as victims or perpetrators. The primary and secondary disabilities associated with prenatal alcohol exposure are often taken into consideration when assessing the capacity of a victim to consent to sexual activity, but generally not considered in determining whether a defendant had the mens rea to engage in criminal sexual conduct. This article traces the historical underpinnings of the mens rea requirement in criminal law and discusses its elimination in most prosecutions for statutory rape. The article recommends that additional research be conducted to determine the impact of prenatal alcohol exposure on an individual's capacity to consent to sexual activity. It suggests that fundamental principles of culpability require an examination of how FASD impacts an individual's capacity to engage in meaningful, responsible, decision making about sexual activity before criminal sanctions are imposed.

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https://www.federallegalpublications.com/journal-of-psychiatry-law/201110/jpl-2011-39-1-05-mcmurtrie-criminal-justice-system%E2%80%99s-disparate-trea

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Federal Legal Publications; The Journal of Psychiatry & Law
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**6. A COURT TEAM MODEL FOR CARE OF YOUNG CHILDREN IN FOSTER CARE: THE ROLE OF PRENATAL ALCOHOL EXPOSURE AND FETAL ALCOHOL SPECTRUM DISORDERS**

By Larry Burd, PH.D., Hon. Constance Cohen, J.D., Rizwan Shah, M.D., and Judy Norris, B.S.

**ABSTRACT**
Prenatal alcohol exposure (PAE) is common with about 80,000 women continuing to drink through all three trimesters of pregnancy each year. PAE is also associated with postnatal adversities, including abuse and neglect, which increase risk for foster care placement. Each day 700 children enter the foster care system. A diagnosis of Fetal Alcohol Spectrum Disorders (FASD) also increases the risk for foster care placement. Among children diagnosed with FASD 70% are or have been in foster care. FASD prevalence rates are increased 10- to 15-fold in foster care systems. Foster care is an important opportunity to detect FASD and provide services to infants and children with FASD. FASD is the third most common identifiable cause of mental retardation in the United States. We describe a court-team-based model of care developed to improve management of children with PAE or FASD entering foster care. The programmatic objectives include: enhancing detection of PAE; screening for FASD; increased consideration of FASD as a potential issue in treatment planning with foster parents; improved entry into treatment; and increased surveillance for parents with an FASD.

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https://www.federallegalpublications.com/journal-of-psychiatry-law/201110/jpl-2011-39-1-06-burd-court-team-model-care-of-young-children-foste

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Federal Legal Publications; The Journal of Psychiatry & Law
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## 7. LEGAL AND PSYCHOLOGICAL IMPLICATIONS OF NON-DISCLOSURE IN THE ADOPTION OF A CHILD WITH FETAL ALCOHOL SPECTRUM DISORDER

By Sharon James Williams, J.D., M.P.H., Daniel Dubovsky, M.S.W., and Jason Merritt, M.A.

**ABSTRACT**
Approximately 127,000 children were adopted in the United States in 2000 and the same number in 2001. When adoptions go well, the events that follow are mostly private family matters. On other occasions, families discover that they have adopted a child who is suffering from mental and/or physical ailments. In cases where the adoptive parents are not aware of the child's medical history, adoptions can have unfortunate endings, including adoption disruption, litigation, interfamily violence, and even death. This article focuses on the issues involved when a family discovers post-adoption that the child has Fetal Alcohol Spectrum Disorder (FASD). The article will first discuss the evolution of adoption and disclosure in the United States, then provide background on the nature of FASD and the difficulties of recognizing cases. The article will then focus on (a) the psychological impact on parents who have adopted a child who is found to have FASD and (b) the impact of disclosure upon state, national, and international law. The article concludes with recommendations for improving disclosure standards and reducing the risk of FASD going undetected and undisclosed in adoptive children.

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https://www.federallegalpublications.com/journal-of-psychiatry-law/201110/jpl-2011-39-1-07-williams-legal-and-psychological-implications-of-n

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## 8. FETAL ALCOHOL SPECTRUM DISORDERS: RESEARCH CHALLENGES AND OPPORTUNITIES

Kenneth R. Warren, Ph.D.; Brenda G. Hewitt; and Jennifer D. Thomas, Ph.D.

**ABSTRACT**
Although the adverse effects of prenatal alcohol exposure, which can result in a range of deficits collectively labeled fetal alcohol spectrum disorders (FASD), have long been known, challenges still remain in the identification and treatment of individuals with FASD. According to Dr. Kenneth R. Warren, Ms. Brenda G. Hewitt, and Dr. Jennifer D. Thomas, an important aspect of current FASD research is the development of tools to better identify individuals affected by prenatal alcohol exposure. Other efforts must focus on further elucidating the consequences of prenatal alcohol exposure, particularly neurodevelopmental deficits, and the mechanisms underlying alcohol's detrimental effects. Understanding these mechanisms, as well as genetic and socioeconomic factors contributing to the risk for FASD, will allow researchers and clinicians to develop more targeted prevention approaches as well as more effective treatment strategies.

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## 9. MATERNAL RISK FACTORS FOR FETAL ALCOHOL SPECTRUM DISORDERS: NOT AS SIMPLE AS IT MIGHT SEEM

Philip A. May, Ph.D., and J. Phillip Gossage, Ph.D.

**ABSTRACT**
Information about maternal drinking during pregnancy is vital for understanding the link between specific risk factors and a diagnosis along the continuum of fetal alcohol spectrum disorders (FASD); that information also can be the most difficult to obtain. Drs. Philip A. May and J. Phillip Gossage examine the importance of studying the drinking behaviors of women with children who have FASD. Risk factors such as the quantity, frequency, and timing of alcohol exposure are important but so are other factors, such as the mother's age; the number of prior pregnancies and number of children she has had; her body size, nutrition, and metabolism; as well as her socioeconomic status, spirituality, mental health, use of other drugs, and social relationships.

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## 10. COMBINATION DRUG USE AND RISK FOR FETAL HARM

Wei-Jung A. Chen, Ph.D., and Susan E. Maier, Ph.D.

**ABSTRACT**
It is well known that using alcohol, tobacco, and illicit drugs during pregnancy individually are hazardous to the developing fetus. When these are used in combination, however, the effects can be even more challenging and unpredictable. This short article by Drs. WeiJung A. Chen and Susan E. Maier describes the way drugs are absorbed, distributed, metabolized, and eliminated (i.e., pharmacokinetics) and how one drug can seriously and unpredictably alter the concentration, bioavailability (the rate of a drug entering the bloodstream), and net effect of the other drug.

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## 11. FOCUS ON: EPIGENETICS AND FETAL ALCOHOL SPECTRUM DISORDER

Michael S. Kobor, Ph.D., and Joanne Weinberg, Ph.D.

**ABSTRACT**
Epigenetics refers to stable but potentially reversible alterations in a cell's genetic information that result in changes in gene expression but do not involve changes in the underlying DNA sequence. Animal studies now suggest that epigenetic changes resulting from a mother's alcohol use may affect various stages of development and contribute to some of the abnormalities associated with fetal

alcohol spectrum disorders. Drs. Michael S. Kobor and Joanne Weinberg look at the ways in which alcohol exposure may induce epigenetic changes prior to and during pregnancy, affecting critical pathways that affect gene expression.

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**12. UNDERSTANDING THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE USING THREE-DIMENSIONAL FACIAL IMAGING**

Leah Wetherill, M.S., and Tatiana Foroud, Ph.D.

**ABSTRACT**
Although the facial features associated with fetal alcohol syndrome (FAS) can be distinct, some children with FAS may not be readily identified unless seen by a trained specialist. Moreover, subtle facial features may be present in people within the continuum of FASD. This brief article by Ms. Leah Wetherill and Dr. Tatiana Foroud examines a new threedimensional imaging tool for detecting subtle facial characteristics associated with prenatal alcohol exposure.

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**13. DISCRIMINATING THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE FROM OTHER BEHAVIORAL AND LEARNING DISORDERS**

Claire D. Coles, Ph.D.

**ABSTRACT**
Because fetal alcohol spectrum disorders (FASD) is not a medical diagnosis but rather a description of a spectrum of the consequences of prenatal alcohol exposure, it may be under recognized, especially in general clinical settings where children are referred for diagnosis and treatment of developmental and behavioral problems. This article by Dr. Claire D. Coles reviews the neurodevelopmental effects of prenatal alcohol exposure, including alterations in learning and memory, motor and sensory/motor skills, visual/spatial skills, and executive functioning and selfcontrol. Appropriate identification of the behavioral and developmental problems associated with FASD will allow for more targeted and effective interventions.

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## 14. THE QUEST FOR A NEUROBEHAVIORAL PROFILE OF HEAVY PRENATAL ALCOHOL EXPOSURE

Sarah N. Mattson, Ph.D., and Edward P. Riley, Ph.D.

**ABSTRACT**
Drinking heavily during pregnancy can have devastating results for the growing fetus, ranging from fullblown fetal alcohol syndrome (FAS), with its recognizable physical characteristics, to a variety of subtle neurobehavioral effects. In this short article, Drs. Sarah N. Mattson and Edward P. Riley describe the importance of developing a profile that takes into account the range of neurobehavioral effects found with heavy prenatal alcohol exposure. Such a profile would improve the identification and, consequently, the treatment of people with fetal alcohol spectrum disorders, even those who do not show the typical physical characteristics of FAS.

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## 15. FOCUS ON: BIOMARKERS OF FETAL ALCOHOL EXPOSURE AND FETAL ALCOHOL EFFECTS

Ludmila N. Bakhireva, M.D., Ph.D., M.P.H., and Daniel D. Savage, Ph.D.

**ABSTRACT**
Methods to screen for maternal drinking during pregnancy often can be inaccurate, and there are limitations of currently established biomarkers of alcohol consumption among pregnant women and alcohol exposure among newborns, making it difficult to accurately identify children with fetal alcohol spectrum disorders (FASD). Drs. Ludmila N. Bakhireva and Daniel D. Savage review the strengths and limitations of existing biomarkers and look at recent efforts to identify markers that can more accurately indicate the timing, duration, and level of prenatal alcohol exposure.

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## 16. BEHAVIORAL INTERVENTIONS FOR CHILDREN AND ADOLESCENTS WITH FETAL ALCOHOL SPECTRUM DISORDERS

Blair Paley, Ph.D., and Mary J. O'Connor, Ph.D.

**ABSTRACT**
Drinking during pregnancy can lead to a constellation of effects, termed fetal alcohol spectrum disorders (FASD), that range from intellectual and learning disabilities, poor executive function, and speech and language delays, to behavioral and emotional difficulties, poor social skills, and motor deficits. Drs. Blair Paley and Mary J. O'Connor examine the usefulness and the challenges associated with behavioral interventions in people with FASD. Such approaches include parentfocused

interventions, educational and cognitive interventions, and adaptive skills training. The article also reviews recent studies on the efficacy of behavioral approaches and highlights potentially fruitful directions for future research on the treatment of FASD.

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### 17. FETAL ALCOHOL SPECTRUM DISORDERS: EXPERIMENTAL TREATMENTS AND STRATEGIES FOR INTERVENTION

Nirelia M. Idrus, Ph.D., and Jennifer D. Thomas, Ph.D.

**ABSTRACT**
Drinking during pregnancy is known to cause a broad range of physical, neurological, and behavioral alterations, collectively known as fetal alcohol spectrum disorders (FASD), yet many women continue to drink. This has given rise to the need for experimental models to identify potential treatments for FASD. This article by Drs. Nirelia M. Idrus and Jennifer D. Thomas reviews different experimental treatments—such as pharmacological, nutritional, and environmental/ behavioral interventions—that can help mitigate some of the effects of prenatal alcohol exposure. Certain treatments target the underlying mechanisms that contribute to alcoholinduced damage, protecting against alcohol's teratogenic effects, whereas others may act to enhance plasticity in the central nervous system, either during alcohol exposure or long after alcohol exposure has ceased.

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### 18. PRENATAL ALCOHOL EXPOSURE AND MISCARRIAGE, STILLBIRTH, PRETERM DELIVERY, AND SUDDEN INFANT DEATH SYNDROME

Beth A. Bailey, Ph.D., and Robert J. Sokol, M.D.

**ABSTRACT**
A number of adverse pregnancy and birth outcomes have been linked to prenatal alcohol exposure. Studies suggest that drinking during pregnancy may increase the risk of miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. Drs. Beth A. Bailey and Robert J. Sokol review this research as well as the limitations of these studies. Establishing how combinations of alcohol's biological actions, as well as sociodemographic and other comorbid conditions, contribute to these adverse outcomes is an ongoing challenge.

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## 19. FOCUS ON: THE USE OF ANIMAL MODELS FOR THE STUDY OF FETAL ALCOHOL SPECTRUM DISORDERS

Shannon E. Wilson, D.V.M., Ph.D, and Timothy A. Cudd, D.V.M., Ph.D.

**ABSTRACT**
Studies in animals confirmed the relationship between prenatal alcohol exposure and neurodevelopmental disorders, which were first identified in human observational studies. Drs. Shannon E. Wilson and Timothy A. Cudd review the use of animal models in three areas of research: addressing basic questions about alcohol exposure during development; improving the identification of affected individuals; and developing approaches to reduce the impact of prenatal alcohol exposure. These animal model systems each provide specific strengths and together have helped to advance the research field of fetal alcohol spectrum disorders.

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## 20. FOCUS ON: MAGNETIC RESONANCE–BASED STUDIES OF FETAL ALCOHOL SPECTRUM DISORDERS IN ANIMAL MODELS

Shonagh K. O'Leary-Moore, Ph.D.; Scott E. Parnell, Ph.D.; Elizabeth A. Godin, Ph.D.; and Kathleen K. Sulik, Ph.D.

**ABSTRACT**
Magnetic resonance–based imaging technologies, including magnetic resonance imaging, diffusion tensor imaging, and magnetic resonance spectroscopy, are useful tools for studying the effects of alcohol on the developing brain and have important implications for clinical practice and research. Drs. Shonagh K. O'LearyMoore, Scott E. Parnell, Elizabeth A. Godin, and Kathleen K. Sulik show how these technologies are revealing the consequences of prenatal alcohol exposure in rodents, where alcohol exposure parameters, such as dose, timing and duration of alcohol, can be manipulated. The authors note that alcohol can induce neuropathology even at very early developmental stages, prior to the time when pregnancy typically is recognized in humans. Relating alcohol exposure parameters with developmental outcomes can improve diagnosis and prevention of FASD.

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## 21. FOCUS ON: NEUROTRANSMITTER SYSTEMS

C. Fernando Valenzuela, M.D., Ph.D.; Michael P. Puglia; and Stefano Zucca, M.Sc.

**ABSTRACT**
Prenatal alcohol exposure has been linked to abnormalities in the formation and refinement of developing brain circuits that are likely to be, in part, responsible for the persistent brain dysfunction

and behavioral effects that characterize fetal alcohol spectrum disorders (FASD). Dr. C. Fernando Valenzuela, Mr. Michael P. Puglia, and Mr. Stefano Zucca describe recent research using animal models of FASD to examine the effects of developmental ethanol exposure on γaminobutyric acid (GABA), glutamate, serotonin, and dopamine systems. The studies reviewed involve diverse animal models and examine both shortand longterm effects on brain chemistry and function.

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**22. FOCUS ON: STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITIES IN FETAL ALCOHOL SPECTRUM DISORDERS**

S. Christopher Nuñez, Ph.D.; Florence Roussotte; and Elizabeth R. Sowell, Ph.D.

**ABSTRACT**
Brain imaging studies of children and adolescents with fetal alcohol spectrum disorders (FASD) have detected differences in brain structure related to alcohol exposure in multiple brain systems and abnormalities in the white matter that connects these brain regions. Dr. S. Christopher Nuñez, Ms. Florence Roussotte, and Dr. Elizabeth Sowell review research on the relationships between these morphological differences and important cognitive functions, such as working memory, learning, and inhibitory control.

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Canada.com
By Mary Agnes Welch, Winnipeg Free Press; 4th November 2011

## A. SCREEN ALL PRISON INMATES FOR FETAL-ALCOHOL SYNDROME, DOCTOR URGES

A Winnipeg doctor is pushing to have all federal inmates screened for fetal-alcohol spectrum disorders so their sentences can be appropriately tailored for their disability.
Photograph by: Wayne Cuddington, The Ottawa Citizen

WINNIPEG — A Winnipeg doctor says he hopes all inmates will be screened for fetal alcohol spectrum disorder as a matter of course within the next five years, just in time for an expected spike in the country's prison population.

Dr. Albert Chudley, a top FASD expert, says a screening checklist first pioneered several years ago in Manitoba's Stony Mountain Institution is about to be tested again at an unnamed women's prison in Eastern Canada. It's already being evaluated at a prison in the Yukon.

If the tool works, if it helps pick out inmates who may suffer from FASD, Chudley hopes it will become standard procedure in every prison in the country in the next few years.

Speaking this week at a meeting of the Manitoba Criminal Justice Association, Chudley said proper screening could help reduce the number of repeat offenders by getting people with FASD the help they need before and after they're incarcerated.

It could finally count the number of people in prison with FASD. So far, researchers only have hints.

Chudley's research at Stony Mountain estimated that as many as 17 per cent of inmates have some level of brain damage caused by alcohol exposure in the womb. That research helped validate a short FASD checklist prison staff can use to find out about an inmate's behavioural patterns, history and the possibility his mother drank while pregnant. Most of the inmates screened by the checklist were ultimately diagnosed with FASD.

Thanks to new federal crime legislation, which includes mandatory minimum sentences for some drug offences, prisons and jails across Canada are expected to get even more crowded than they already are.

Chudley, along with provincial court Judge Mary Kate Harvie, told the group that crime and FASD are inextricably linked, and that the court and prison systems must start responding better.

Chudley, the head of the Winnipeg Regional Health Authority's genetics and metabolism program and a University of Manitoba professor, said people with FASD are easily led, can't see the consequences of their actions and are often victimized.

"They do the crime to please others, not necessarily themselves, and then they get tagged with it," said Chudley. Harvie has championed a relatively new court program in Manitoba that helps young offenders get an FASD diagnosis while in jail and then helps judges tailor a sentence to their disability.

So far, the program has assessed 133 offenders and diagnosed 94 with some form of FASD. Among the most recent 30 youths who were diagnosed, more than 70 per cent had IQs lower than 70, which means they have mild or moderate cognitive impairments.

**Link to the Article,**
http://www.canada.com/health/Screen+prison+inmates+fetal+alcohol+syndrome+doctor+urges/5657482/story.html

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Wayne State University – Public Relations
26th October 2011

## B. WAYNE STATE UNIVERSITY RECEIVES $655,500 GRANT FROM NIH TO DEVELOP A COMPUTER-DELIVERED INTERVENTION FOR ALCOHOL USE AMONG PREGNANT WOMEN

DETROIT - A team of researchers at Wayne State University's Parent Health Lab in the School of Medicine have received a three-year grant to develop a computer-delivered intervention for pregnant women at risk for alcohol use, which can lead to lifelong negative effects on the fetus. Prenatal exposure to alcohol affects attentional, cognitive, social and behavioral functioning and is a major cause of mental retardation. Infants born to African American women are at increased risk of adverse effects.
Screening, brief intervention, and referral for treatment ("SBIRT") approaches to alcohol use during pregnancy can be used by medical staff to identify and reduce alcohol use among pregnant women. SBIRT approaches are not often used, however, because of the amount of time, training, expertise and commitment required. Computer-delivered SBIRT approaches may offer an alternative approach

through the use of consistent screening and evidence-based brief interventions at a lower cost, without requiring significant time of medical staff.

With this in mind, the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health recently funded the "Healthy Pregnancy Study," which will help Steven Ondersma, Ph.D., associate professor of psychiatry and behavioral neurosciences, and colleagues develop and test a highly practical, high-reaching computer-delivered intervention to reduce alcohol use during pregnancy.

Ondersma's study will lay the groundwork for larger-scale investigations of computer-delivered SBIRT for alcohol use during pregnancy. Ondersma and his team will evaluate the utility of handheld mobile devices and an anonymous self-interview format in screening for at-risk drinking among patients at a prenatal clinic, along with sophisticated interactive intervention software. In addition, the study will examine the validity of the alcohol biomarker, Ethyl Glucuronide (EtG), to indicate alcohol exposure in study participants.

"If our study is successful, health care systems will have the ability to help far more at-risk women through this intervention than previously possible," said Ondersma. "In turn, it may also have a meaningful impact on reducing Fetal Alcohol Spectrum Disorders."

Wayne State University is one of the nation's pre-eminent public research universities in an urban setting. Through its multidisciplinary approach to research and education, and its ongoing collaboration with government, industry and other institutions, the university seeks to enhance economic growth and improve the quality of life in the city of Detroit, state of Michigan and throughout the world. For more information about research at Wayne State University, visit http://www.research.wayne.edu

Contact: Julie O'Connor
Voice: (313) 577-8845
Email: julie.oconnor@wayne.edu
Fax: (313) 577-3626

**Link to the Article,**
http://media.wayne.edu/2011/10/26/wayne-state-university-receives-655500-grant-from

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Allan Therapeutics Inc
September 28, 2011

## C. ALLON GRANTED IMPORTANT U.S. PATENT FOR PRECLINICAL COMPOUND AL-408

VANCOUVER, B.C. — Allon Therapeutics Inc. (TSX: NPC) announced today that it has been granted an important United States patent covering the composition of matter for the D-isomer of NAP (davunetide). The D-isomer of davunetide is known as AL-408 in the company's pipeline. This new patent strengthens Allon's intellectual property estate which includes 15 patent families, 58 issued patents and over 30 pending applications worldwide.

Previous pre-clinical studies have demonstrated that AL-408 shows potent neuroprotective effects in a number of in vitro and in vivo models of neurotoxicity. In an animal model of fetal alcohol syndrome, AL-408 increased survival and improved cognitive performance1. AL-408 has also shown potential neuroprotective activity in a preclinical model of amyotrophic lateral sclerosis (ALS)2.

Dr. Alistair Stewart, Allon's Vice President of Commercial Research, said this new U.S. patent provides protection for an important early-stage compound within the Company's product pipeline. "Allon's technology platform of neuroprotective peptides derived from naturally occurring brain proteins shows broad neuroprotective effects in a variety of diseases and conditions", explains Stewart. "AL-408 has shown some interesting early-stage research results in areas outside of neurodegenerative diseases, further diversifying and adding value to our product pipeline."

Allon's patent portfolio also includes issued patents and pending patent applications that provide protection around davunetide and its technology platform for treatment of neurodegenerative diseases, including progressive supranuclear palsy (PSP), Alzheimer's disease, and Parkinson's disease.

On August 12, 2011, the Company announced it had enrolled approximately 75% of the 300 patients specified in the protocol designed to assess efficacy and safety of davunetide (AL-108) in PSP patients. Enrollment began in the fourth quarter of 2010. The trial is being conducted under a Special Protocol Assessment (SPA) granted by the United States Food and Drug Administration (FDA), which ensures that the agreed clinical trial design meets the FDA's expectations for a pivotal study. This multi-national study is being conducted at leading medical institutions in the United States, Canada, the United Kingdom, France, Germany, and Australia. Details can be found at clinical trials.gov.

The patent granted by the United States Patent and Trademark Office covers the composition of matter for AL-408 that has the same amino acid sequence as davunetide but contains all D-amino acid isomers. Davunetide contains all L-isomers.

1 "Protective Peptides That Are Orally Active and Mechanistically Nonchiral", JPET 309: 1190–1197, 2004, Brenneman, D.E., et al.

2 "D-NAP provides neuroprotection in an ALS mouse model: evaluation of different administration schedules", J Mol Neurosci (2009) 39 (Suppl 1): S57 (abstract only), Jouroukhin Y. and Gozes I.

**About Allon**
Allon Therapeutics Inc. is a clinical-stage biotechnology company focused on bringing to market innovative central nervous system therapies. Allon's lead drug davunetide is proceeding in a pivotal Phase 2/3 clinical trial in an orphan indication, progressive supranuclear palsy (PSP), under a Special Protocol Assessment (SPA) with the U.S. Food and Drug Administration (FDA). This pivotal trial is based upon statistically significant human efficacy demonstrated in patients with amnestic mild cognitive impairment (a precursor to Alzheimer's disease) and cognitive impairment associated with schizophrenia, and in positive biomarker data.

The Company is listed on the Toronto Stock Exchange under the trading symbol "NPC".

**About Davunetide**
Allon is currently enrolling patients in a pivotal Phase 2/3 clinical trial evaluating davunetide as a potential treatment for progressive supranuclear palsy (PSP), a rapidly-progressing and fatal movement disorder with dementia which is often misdiagnosed as Parkinson's or Alzheimer's disease. Allon reached agreement on a SPA with the FDA, as well as Orphan Drug and Fast Track Status in the U.S. Similarly, Allon has Orphan Status for davunetide in the EU.

Davunetide is derived from a naturally occurring neuroprotective brain protein known as activity dependent neuroprotective protein (ADNP). Allon's human clinical and pre-clinical data suggest that davunetide works on microtubules, structures in the brain critical to communication between cells, and central to the tau pathway. Davunetide has shown statistically significant impacts on memory,

activities of daily living, and a biomarker of brain cell function and integrity. Allon has extensive intellectual property protecting davunetide.

**Forward Looking Statements**
Statements contained herein, other than those which are strictly statements of historical fact may include forward-looking information. Such statements will typically contain words such as “believes”, “may”, “plans”, “will”, “estimate”, “continue”, “anticipates”, “intends”, “expects”, and similar expressions. While forward-looking statements represent management’s outlook based on assumptions that management believes are reasonable, forward-looking statements by their nature are subject to known and unknown risks, uncertainties and other factors that may cause the actual results, events or developments to be materially different from any future results, events or developments expressed or implied by them. Such factors include, among others, the inherent uncertainty involved in scientific research and drug development, Allon’s early stage of development, lack of product revenues, its additional capital requirements, the risks associated with successful completion of clinical trials and the long lead-times and high costs associated with obtaining regulatory approval to market any product which Allon may eventually develop. Other risk factors include the limited protections afforded by intellectual property rights, rapid technology and product obsolescence in a highly competitive environment and Allon’s dependence on collaborative partners and contract research organizations. These factors can be reviewed in Allon’s public filings at www.sedar.com and should be considered carefully. Readers are cautioned not to place undue reliance on such forward-looking statements. Similarly, nothing in this press release is meant to promote a pharmaceutical product or make a regulated claim of efficacy.

**For further information please contact:**

Rick Smith
Allon Therapeutics Inc
Director, Investor Relations
(604) 742-2543
info@allontherapeutics.com
www.allontherapeutics.com

**Link to the Article,**
http://www.allontherapeutics.com/2011/09/allon-granted-important-u-s-patent-for-preclinical-compound-al-408/

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Press Release: Trimega Laboratories
Yahoo Finance
LONDON and CAPE TOWN, September 9, 2011 /PRNewswire/ --

## D. TRIMEGA LABORATORIES DEVELOPS WORLD'S FIRST COMMERCIAL TEST FOR FOETAL ALCOHOL SYNDROME IN SOUTH AFRICA

- Partnership with Cape Town's Tripelo to form part of UK-South Africa commitment to double bilateral trade by 2015

- Announcement coincides with World Foetal Alcohol Syndrome Day on 9 September

Trimega Laboratories, a leading substance misuse testing company, is implementing the world's first commercial project to diagnose and analyse Foetal Alcohol Syndrome (FAS) in new-born

babies.Headquartered in Manchester, UK, and founded and led by South African entrepreneur Avi Lasarow, Trimega has partnered with Tripelo, a forensic science company in Cape Town, to conduct the tests. Tripelo will start conducting tests in November 2011 and has already identified communities where the work will begin.South Africa has 4,000 new cases of FAS reported every year, one of the worst rates in the world.FAS is a pattern of mental and physical defects that can develop in a foetus when a mother drinks during pregnancy. When alcohol crosses the placental barrier it can stunt fetal growth, cause facial stigmata and damage neurons and brain structures.Early detection of FAS greatly increases a child's chance of surviving the more serious consequences of the condition.This initiative comes at a time when UK-South Africa trade relationships are entering a new phase. In June, the 9th UK-South Africa Bilateral Forum, hosted by Foreign Secretary William Hague, re-affirmed the commitment made during President Zuma's 2010 state visit to double bilateral trade between the countries by 2015. The UK Department for International Development committed £76 million between 2011 and 2015 to support the South African government with a range of development initiatives, including improving health.Marius Fransman, South Africa's Deputy Minister of International Relations and Cooperation, said: "The Trimega/Tripelo partnership is a great example of how the UK and South Africa can work together to share technology and expertise and provide a world-class initiative to fight a global problem."Through leveraging such partnerships we can create an enabling environment to overcome the systemic roots of poverty and under-development and in a practical way realise the strategic foreign policy objectives that touch the lives of the poor and vulnerable sectors of society."Bathabile Dlamini, the South African Minister of Social Development, said: "We are delighted that Trimega has partnered with Tripelo to help provide a solution to Foetal Alcohol Syndrome, which affects so many newborn babies in South Africa, and we look forward to Trimega transferring its technology to Tripelo in Cape Town."Dr. Zola Skweyiya, the High Commissioner of South Africa in the UK, said: "Trimega is a highly innovative biotechnology company that has already commericalised hair testing for evidence of alcohol abuse, and I am very proud that under the leadership of South African CEO, Avi Lasarow, the company has set-up such an important scientific partnership between the UK and South Africa."Avi Lasarow, CEO of Trimega Laboratories, said: "This is a real opportunity to make a positive difference in the lives of thousands of babies impacted by alcohol abuse. We are proud to now play our part in making a contribution to the welfare of children in South Africa and to furthering the research into Foetal Alcohol Syndrome."South Africa is already a very important country for Trimega: we have conducted several substance misuse projects in the country, and part of our customer services team operates in Johannesburg."Trimega's technology tests meconium, the first stool sample of a newborn infant, thus improving the chances of early detection. Professor Fritz Pragst, a member of Trimega's Scientific Board, is a leading research scientist on alcohol testing in meconium, and has successfully applied Trimega's technology at the Canadian Hospital for Sick Children.

**About Trimega Laboratories (http://www.trimegalabs.co.uk):** Established in London in 2005, Trimega Laboratories is well recognised for being a leader in the development of innovative techniques for testing for substances of abuse. Its core business is laboratory-based analysis of hair samples that provide accurate historical records of alcohol or drugs dependency over a one to 12 month period. In the UK, Trimega's core clients include: family law specialists, law courts, and social services. Trimega was the first to market with dual-marker hair alcohol testing (FAEE and EtG). Dual hair testing provides very accurate results: at its annual conference in March 2011, the Society of Hair Testing (SoHT) confirmed that dual testing on hair for alcohol misuse provides accuracy rates of over 94%, with less that 1% risk of a false positive, and 5.75% risk of a false negative. The SoHT's consensus was based on analysis of Trimega's data set of approximately 2,000 dual hair testing samples, the largest of its kind in the world.Other services offered by Trimega include: Roadside Testing for law enforcement, Hair Steroid Testing for athletes, and Hair Benzodiazepines Testing.Trimega won the title of Best Use of Technology in the 2008 Barclays-sponsored Startups Awards, and has been on the shortlist for the National Business Awards three years running. Trimega is also one of 25 companies to represent the UK in the 2011 European Business Awards.Trimega was responsible for the creation of a Hair Strand Scientific Advisory Board. Its purpose is to analyse the

fast growing database of information created from the 10,000 hair alcohol tests and 7,000 hair drug tests carried out on UK samples each year, of which Trimega is responsible for around 40%. The findings of the Board are shared with the Society of Hair Testing which will assist it in future decisions, particularly those relating to the setting of universal standards/guidelines.

**About Tripelo:** Tripelo was selected by Trimega Laboratories in 2011 as the South African company that will partner with Trimega to establish a national compliance laboratory for testing of ARV'S in hair together with Foetal Alcohol Syndrome and other identified substances. The company will work closely to establish a skills transfer programme and technology transfer between both countries as part of the bilateral trade initiatives between both countries.

**About World Foetal Alcohol Syndrome Day:** Every year on September 9th, International FASD Awareness Day is observed. Proclamations are issued in countries, states, provinces, and towns all around the world. Bells are rung at 9:09 a.m. in every time zone from New Zealand to Alaska. People all around the world gather for events to raise awareness about the dangers of drinking during pregnancy and the plight of individuals and families who struggle with Foetal Alcohol Spectrum Disorders (FASD). The first FAS Day was celebrated on 9/9/99. This day was chosen so that on the ninth day of the ninth month of the year, the world will remember that during the nine months of pregnancy a woman should abstain from alcohol. Anytime is a good time to raise awareness about Foetal Alcohol Spectrum Disorders (FASD).

**Link to the Article,**
http://finance.yahoo.com/news/Trimega-Laboratories-Develops-prnews-2367946672.html

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Jewish Tribune
Written by Rebeca Kuropatwa
Wednesday, 10 August 2011

## E. UNIVERSITIES TEAM UP FOR FETAL ALCOHOL SPECTRUM DISORDER RESEARCH

Winnipeg – The University of Manitoba has teamed up with Hebrew University of Jerusalem and the Manitoba government to support a new research collaboration to address fetal alcohol spectrum disorder (FASD).

To fund this initiative, the province will provide up to $750,000 from the Manitoba Research and Innovation Fund. During the next five years, the Manitoba government will match funds raised by the Canadian Friends of Hebrew University (CFHU) towards a new Canada-Israel FASD research consortium.

“We’re thrilled to see research, which began 12 years ago in Dr. Abraham Fainsod’s lab at Hebrew University, now be the focus of this collaboration with University of Manitoba researchers,” said Faith Kaplan, Winnipeg CFHU chapter president.

“FASD is a serious concern in communities around the world and we’re confident our research consortium will improve the understanding of what leads to children being born with it. Such collaboration is completely consistent with Hebrew University’s mission to improve the world.”

Fainsod’s new research suggests that Vitamin A could act almost like an antidote to the effects of alcohol on very early embryos during the critical development of the head and central nervous system – precisely when the most serious effects of FASD start.

“Scientifically, this is a very interesting story,” said Fainsod, a Hebrew University genetics and biochemistry professor. “If we can continue our research, we could do some good.”

The substance under scrutiny will be retinoic acid, a main biological form of Vitamin A and a critical element in cell development and revitalization (hence, why it is used in skin rejuvenating creams).

Alcohol prevents Vitamin A from being able to convert into retinoic acid, as both compete for one particular enzyme and the alcohol usually wins. Even more, as the body is busy processing alcohol, it stops making any new retinoic acid, interrupting normal head and brain cell development in embryos.

What Fainsod’s research suggests is that by adding more Vitamin A, rebalancing the alcohol and retinoic acid levels, brain defects caused by alcohol can be reversed or curbed.

Dr. Ab Chudley is Manitoba’s FASD expert, working in the field for decades, and is the U of M’s lead researcher.

“Alcohol affects many different parts of the brain, not just things like having small eyes and cranial or facial abnormalities,” said Dr. Chudley. “Many FASD-affected kids are impaired in the ability to learn and other critical functions.”

In early July, Dr. Chudley attended an Israel-Canada technology summit, where a delegation of scientists grappled with issues of neuroscience.

“At the summit, I visited Haifa, and one of my colleagues, another clinical geneticist, brought to my attention a study that she and her colleagues had done in Israel – looking at the proportion of Israeli women who were pregnant and who drank during the pregnancy. It was around 15 per cent.

“This came as a real surprise to me and others who never considered drinking to be an issue in Israel. I think, with the demographic change, with people from Europe coming to Israel, the culture has changed.”

Dr. Chudley said the FASD research is in its early stages, but if the animal studies go well, the next possibility would be to study it in humans in FASD-affected communities. From there, he anticipates “we might find that people of certain ethnic backgrounds are at greater risk of having FASD.”

As things stand, Dr. Chudley estimated the research time frame to be completed in five years.

“We hope to have most of the animal answers within the first or second year, and some of the genetic studies done by then,” he said. “When it comes to looking at intervention in a particular community that will, I hope, be more than five years down the road.”

Although Dr. Chudley said FASD prevention will likely result from the research, a cure is not anticipated, noting FASD-affected children have it as a life-long disability.

In Dr. Chudley’s view, “FASD is important globally, not only in Canada. Like Israel, we’re interested in this research from a science and biology perspective, as well as dealing with this public health issue.

“We haven’t been very effective in getting women to not drink while pregnant. The problem, sometimes, is that pregnancies aren’t planned. So, during critical periods of a baby’s development, a woman may not even know she’s pregnant and will still be drinking.

“Our aim is to perhaps improve the health of communities, enhancing and encouraging healthy living

and diet. Whether that will include a vitamin supplement remains to be seen."

**Link to the Article,**
http://www.jewishtribune.ca/TribuneV2/index.php?option=com_content&task=view&id=4609&Itemid=53

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Scott Kirk Special to the Reporter-News
Posted July 17, 2011 at 10:41 p.m.

## F. LIGHT DRINKING OK FOR MOMS-TO-BE, STUDY SAYS, BUT ABILENE DOCS DOUBTFUL

From the land Down Under comes a report that pregnant women may want to toast, literally. But some local medical professionals say moms-to-be should hold off on raising that glass.

A study by Australian researchers last June showed that among 2,300 children ages 2-14, the children of mothers who were moderate drinkers (two to six drinks per week) were better adjusted emotionally than the children of mothers who abstained during pregnancy.

Another study, reported by the Journal of the American Academy of Child and Adolescent Psychiatry, reported that of 11,500 children studied, the children born to light drinkers (one to two drinks per week) had higher cognitive scores in tests.

There are perhaps few pregnancy rules as sacrosanct as the one about avoiding alcohol, and these two studies appear to set that rule on its ear. Local doctors, however, advised caution.

"That study seems more like a psychological study rather than a medical study," said Edward Holt, an Abilene obstetrician. "I'm not saying it's a bad study, but it's not the Mayo Clinic, either."

Holt said the official position of the American College of Obstetricians and Gynecologists has not changed, nor did he expect it to change any time soon.
"The recommendation is no consumption of alcohol during pregnancy," he said.

Fetal alcohol syndrome — caused by imbibing large amounts of alcohol — is the biggest threat posed by alcohol consumption during pregnancy, Holt said. However, he said he still would suggest that pregnant women lay off the booze.

"I'd still recommend no alcohol," Holt said. "These studies are not definitive."

Nor is it likely there will be a definitive study on the effects of alcohol during pregnancy, said Abilene pediatrician Justin Smith.

"For one thing, it would be very difficult to find women who would be willing to be part of a controlled study on drinking during pregnancy," he said. "For another, when you do deal with problems that may be related to alcohol consumption during pregnancy, it's hard to get reliable data from mothers."

Like Holt, Smith said he would choose the safest option when advising pregnant women about drinking. "We have no idea of what the safe amount of drinking is," he said. "We'll err on the side of

caution and say no drinking."

As a pediatrician, Smith deals more often with infants than with pregnant women.

"I get a lot more questions about alcohol during breast-feeding than about alcohol during pregnancy," he said. "The rules about alcohol during breast-feeding are much looser. According to La Leche League, it's all right to have a glass of wine or a beer following a feeding. If you drink something harder, it's suggested that you do what they call 'pump and dump' before the next feeding."

The report in the psychiatric journal did not recommend that pregnant women should start drinking. It also noted factors that could cause alcohol-related problems, such as a certain version of a thyroid gene, Dio3, that is more susceptible to damage from alcohol.

The study from Australia suggested that women who had unplanned pregnancies and were light to moderate drinkers before they realized they were pregnant probably had little to worry about.

However, Holt suggested that pregnant women consult with their obstetrician about alcohol consumption and conduct Internet research on sites such as those of the American College of Obstetrician and Gynecologists (ACOG.org).

"The Mayo Clinic has a great website, also," he said.

Holt said that any decision about alcohol consumption during pregnancy needs to be made carefully.

"You have to remember it's a poison," he said.

**Link to the Article,**
http://www.reporternews.com/news/2011/jul/17/study-light-drinking-ok-for-moms-docs-doubtful/

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UNC Gillings School of Global Public Health
June 21, 2011

## G. NEW NUTRITION PROFESSOR BRINGS EXPERTISE IN FETAL ALCOHOL SPECTRUM DISORDERS


Dr. Philip May

A new nutrition professor at the University of North Carolina's Nutrition Research Institute (NRI) will expand the Institute's expertise and research in the field of fetal alcohol spectrum disorders (FASD). Philip A. May, PhD, was appointed research professor at UNC Gillings School of Global Public Health on April 1 and arrives at NRI this week.

FASDs are a group of physical, behavioral and cognitive conditions that can occur in a person whose mother drank alcohol during pregnancy. The disorders are preventable if the mother does not use alcohol while pregnant.

May earned a master's degree in sociology at Wake Forest University and a sociology doctorate from the University of Montana. His professional career has included service as a commissioned officer in

the U.S. Public Health Service. Most recently, he was professor of sociology and family and community medicine at the University of New Mexico at Albuquerque (UNM).

In addition to his appointment at UNC's public health school, May will maintain his role as Extraordinary Professor of Obstetrics and Gynecology on the health sciences faculty at The University of Stellenbosch, Tygerberg, in Cape Town, South Africa.

Widely recognized as a leader in the FASD research, May has received several prestigious awards for his work. Most recently, he was selected to deliver the University of New Mexico's 56th Annual Research Lecture, one of the highest honors that can be awarded to a UNM faculty member. His lecture, titled "Adventures in Public Health Research: Four Decades of Shoe-Leather Epidemiology and Prevention," shared key areas of his critical research, including suicide and alcohol epidemiology among a number of tribes of American Indians of the western states.

For the past four decades, May has led research on behavioral issues that directly relate to public health. He has conducted extensive research on the epidemiology of and risk factors for FASD, including alcohol use and abuse, and how FASD relates to mental health and deviance. May's specialty areas also extend to demography and medical sociology, focusing much of his research on community-wide prevention of the disorder.

At the NRI, May has begun a study designed to reveal the prevalence and specific characteristics of FASD. The project, recently funded by a grant from the National Institute on Alcohol Abuse and Alcoholism, part of the National Institutes of Health, includes studies in both the United States and South Africa. In the project, May will combine the knowledge gained in the United States and South Africa with the Institute's advancements in developing an individualized approach to nutrition.

"We have made great progress identifying the demographic and behavioral risk factors for FASD," May said. "Now we must look at individual risk factors and nutrient deficiencies - genetics and epigenetics may come into play."

May's work and experience will introduce a new facet to the research at the NRI and highlight the importance of epidemiological work in conjunction with established lab work.

"My lab is the community," May said. "It is important for behavioral, basic and clinical scientists to work together for a full understanding of the etiology and remediation of most of today's public health problems. Understanding how health problems are intertwined with particular lifestyles and influenced by unique social and cultural conditions advances translation of knowledge to effective intervention, prevention, and cures."

Steven Zeisel, MD, PhD, director of UNC Nutrition Research Institute, said he was pleased to welcome May to the NRI. "We expect that his significant perspective on fetal alcohol spectrum disorders will further broaden our reach in the nutrition science field," Zeisel said. "His work will create new discoveries for science and intervention opportunities for individuals."

More information about FASDs is available on the Centers for Disease Control and Prevention website.

**Link to the Article,**
http://www.sph.unc.edu/schoolwide_news/new_nutrition_professor_brings_expertise_in_fetal_alcohol_spectrum_disorders_19300_8289.html

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News.gather.com
by Elle Blake, June 23, 2011

## H. BABY DIES AFTER MUM BREASTFEEDS DRUNK

A mother who killed her baby after breastfeeding while drunk has warned others about the dangers of alcohol.

An inquest into the death of Naomi Rose found that mum Emma Hurst had fallen asleep while breastfeeding, after drinking a bottle of wine. Naomi's body was found by her father, Allen, 42.

Allen told the inquest that he found his daughter's body facing his wife, with his wife's breast laying on her face. He also noticed blood in his daughter's mouth.

Emma, 30, was originally arrested and charged with overlay, or suffocating a child while asleep, but pathologists couldn't find evidence which completely proved that this was how Naomi died. The charges were then dropped.

Emma told the inquest that she was nervous about a social services assessment, and had not eaten all day. She said she drank the bottle of wine just before giving Naomi her evening feed, at around 6pm. Emma, who has two other children, is then thought to have fallen asleep.

One of their neighbours, Sheila Bentley, told the inquest how she heard Allen shout "You've killed my baby!" and rushed around to help. Both Sheila and Emma tried to resuscitate Naomi, and she was taken to Royal Bolton Hospital by paramedics. Staff there could not revive her.

The shocking case has added to concerns over the UK's alcohol problem, with more and more expecting mothers admitting to drinking throughout their pregnancy, and ignoring the risks this poses for a baby. A lack of information is being blamed for this, and a course training midwives about the risk of alcohol is being announced, funded by a major alcohol company.

The Metro reported Emma speaking after the inquest, saying; "It is awful what has happened and I am not proud of my behaviour. No mother should be drinking at all. Since that day I have not taken one drip of alcohol. I should have been 100% sober and that is what I have to live with. I believe I have failed completely because I am her mum."

Her husband Allen added, "It has been a nightmare, but hopefully something good can come of this if it can help another child."

The coroner has now recorded a narrative verdict. Health chiefs have also reminded parents that the safest place for a baby for the first six months is a cot.

The case has caused widespread controversy. Details such as why the family were being assessed by social services have not been released, leading to people questioning how the couple were as parents previous to this incident. Whether you feel sorry for the family involved or feel they were responsible;

one thing is for sure - more education is definitely needed, to prevent tragedies like this from occurring again.

**Link to the Article,**
http://news.gather.com/viewArticle.action?articleId=281474979493571

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9News
22nd June 2011

## I. STUDY EXAMINES FETAL ALCOHOL EFFECTS - DRINKING DURING PREGNANCY CAN LEAD TO CHILDREN WHO, IN LATER LIFE, APPEAR BEFORE THE CRIMINAL COURTS

The Alcohol Education & Rehabilitation Foundation (AER Foundation) says fetal alcohol spectrum disorders (FASD) are the most common, preventable cause of disabilities and brain damage in children, triggered by exposure to alcohol during pregnancy.

AER Foundation chief executive Michael Thorn said people with FASD are often over-represented in the criminal justice system.

The foundation will fund an Australian first - a $60,000 research project aimed at raising the awareness of workers in criminal justice to this under-recognised disability.

Researchers will survey the knowledge, attitudes, practices and training deficits within Queensland criminal justice agencies when dealing with people suffering from FASD.

Led by the University of Queensland Centre for Clinical Research, those surveyed will include representatives from probation and parole services, correctional services, police, lawyers, judiciary, defence counsel and legal aid staff.

"It's unclear whether staff employed in criminal justice agencies are adequately equipped to deal with people with FASD," Mr Thorn said.

"In cases where FASD goes unidentified, defendants may be inappropriately dealt with by the justice process.

"Overall, the research outcomes will contribute to the development of appropriate rehabilitation, support and management strategies for FASD sufferers and their families."

A separate study based in Perth will look into how children and teenagers with FASD are treated by the criminal justice system.

Mr Thorn said avoiding alcohol during pregnancy is the best way to ensure children aren't born into a life of disability.

**Link to the Article,**
http://news.ninemsn.com.au/national/8264264/study-examines-fetal-alcohol-effects

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The Australian – News
June 20, 2011

## J. CLINIC TO TARGET BABY ALCOHOL DISORDERS - AUSTRALIA'S FIRST SCREENING AND DIAGNOSTIC SERVICE FOR CHILDREN WITH ALCOHOL-RELATED BIRTH DEFECTS COULD BE UP AND RUNNING BY THE END OF THE YEAR

The service is being set up by The Children's Hospital at Westmead in Sydney amid concerns that thousands of Australian children are suffering from fetal alcohol spectrum disorders (FASD).

The disorders are triggered in unborn babies exposed to alcohol consumed by their mothers and are the most common, preventable cause of disabilities and brain damage in children.

Experts fear that while physical signs of FASD such as smaller skulls are obvious to doctors, many associated neuro-developmental disorders are missed.

Elizabeth Elliott, Professor of Paediatrics and Child Health at the Children's Hospital said it was hard to know exactly how many children were affected by FASD because of a lack of research and diagnostic clinics.

However she estimates that at least two per cent of all Australian babies are born with FASD each year.

"That's likely a significant underestimate because doctors aren't recognising it and aren't asking women about alcohol use in pregnancy," she said.

"There's a lot of perceptions that making a diagnosis will stigmatise children and their families."

Prof Elliott said the clinic should be open later this year thanks to a $108,000 grant from the Alcohol Education and Rehabilitation Foundation.

It will ensure children suspected to have FASD are assessed, diagnosed and referred for treatment.

About 30 such clinics operate in the United States and Canada.

"We don't know the size of the problem but we know a lot of women are drinking at high-risk levels and that includes during pregnancy," Prof Elliott said.

"We have recently done a national survey suggesting 30 per cent of women did drink while they were pregnant and did so at high risk levels of five or more drinks on an average occasion.

"Many of those women were not aware of the potential harm of drinking alcohol during pregnancy.

"We have to get the message across that drinking alcohol when you are pregnant can damage the baby."

The Alcohol Education and Rehabilitation Foundation is funding the clinic along with six other projects targeting FASD as part of a $500,000 national campaign.

The foundation's chief executive Michael Thorn said FASD had been neglected for too long, with many sufferers having problems with learning, poor memory, coordination and communicating.

"If we don't do something about this now it will be too late for a generation of children who will be born into a life of disability as a result of their mother's drinking," he said.

Government guidelines for mums-to-be state that alcohol can harm the developing fetus or breastfeeding baby and recommend not drinking during pregnancy as the safest option.

**Link to the Article,**
http://www.theaustralian.com.au/news/breaking-news/clinic-to-target-baby-alcohol-disorders/story-fn3dxity-1226078614272

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Winnipeg Free Press
By: Carol Sanders
Posted: 06/18/2011

## K. STEMS CELLS, VITAMIN A EYED BY SCIENTISTS

Prof Dipak Sarkar

Stem cells and everyday vitamin A could be the keys to curbing or curing FASD. Scientists from New Jersey to Jerusalem are working on what may be two of the most promising breakthroughs since FASD was first given a name almost 40 years ago.

A Rutgers University professor thinks stem-cell research will lead to a cure in the next 15 years for some of the side-effects of fetal alcohol exposure -- including disease-related obesity, diabetes and a list of other health problems.

Prof. Dipak Sarkar's interest in alcohol research began in 1990, when he serendipitously observed the neuron-killing effect of a small dose of alcohol while working on neuronal development in lab rats.

The alcohol destroyed parts of the brain that maintain circadian rhythms and neurons that produce stress-relieving endorphins, he said.

Sarkar's research aims to use cell therapy to reverse some of that.

In 2009, his researchers found they could make endorphin cells in vitro from stem cells and put the stem cells in brains. They reprogrammed the body to replace the cells. The result was improved immune systems and lower stress levels.

"It's a major, major discovery," said the director of the endocrine program and biomedical division of the Center of Alcohol Studies by phone from New Jersey.

People with fetal alcohol spectrum disorder often try to relieve stress and feel better by using caffeine, nicotine, drugs or alcohol, but they end up feeling worse, he said. Using stem cells to put endorphins back in the brains of FASD patients isn't a cure-all, but it could help them feel and cope better, said Sarkar.

"In 15 years, we could really help these patients," he said.

Meanwhile, in Jerusalem, new research by an Israeli scientist suggests vitamin A could act as an antidote to the effects of alcohol on new embryos during the critical development of the head and

central nervous system. That's when the worst effects of FASD start.

Abraham Fainsod, a professor of genetics and biochemistry at the Hebrew University of Jerusalem, has been studying retinoic acid, one of the main biological forms of vitamin A and a critical element in cell development and revitalization.

Alcohol prevents the conversion of vitamin A to retinoic acid because both compete for one particular enzyme and the alcohol usually wins. While the body is processing alcohol, it's not making any new retinoic acid, which, in embryos, interrupts the normal development of the head and brain cells.

Fainsod's research suggests adding more vitamin A to the equation -- rebalancing the amount of alcohol and retinoic acid -- can reverse or curb brain defects caused by alcohol.

His research will benefit from a $750,000 grant from the Province of Manitoba to set up a joint consortium between scientists from the University of Manitoba and Fainsod's lab in Israel.

Vitamin A could one day be added to food the way folic acid was added to white flour to reduce birth defects such as spina bifida. But Fainsod is quick to say vitamin A should never be seen as a licence to drink while pregnant. Too much vitamin A can cause the same kinds of birth defects as alcohol, and scientists haven't yet figured out what the correct balance is.

Back in New Jersey, Sarkar sees a much broader spectrum of problems caused by alcohol than just a cognitive or brain disorder.

"FAS is not in one particular organ, and it has vast consequences," he said. "Alcohol given during fetal growth produces a major effect on the brain, the heart, the bones and metabolic system."

**Link to the Article,**
http://www.winnipegfreepress.com/opinion/fyi/stems-cells-vitamin-a-eyed-by-scientists-124123594.html

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Bulletin of the World Health Organization
June 2011

## L. FETAL ALCOHOL SYNDROME: DASHED HOPES, DAMAGED LIVES

Since the term was coined about 40 years ago, fetal alcohol syndrome has slowly become recognized as a public health issue. Alicestine October reports from South Africa's Western Cape province, which has the highest reported rate in the world.

Bulletin of the World Health Organization 2011;89:398–399. doi:10.2471/BLT.11.020611

"When I was pregnant with my son I drank a lot – mostly on weekends," says Marion Williams, a 45-year-old mother who lost two of her five children in childbirth.

Williams lives in one of South Africa's famous wine-growing areas in the Western Cape. She started drinking as a teenager and was taken out of school, she suspects, to work to buy wine for her parents.

Her third child was “born slow”, she says. She blames herself and her drinking for the disabilities he will live with for the rest of his life.

WHO/Alicestine October

Marion Williams at her home in the wine-growing area of Stellenbosch

“There is a lot he wants to do, but I must remind him he’s not like other kids: he can work with his hands and build cupboards but not a thinking and writing job,” she says, regretfully. “He asks me why I drank so much [while I was expecting him]. I don’t really have answers for him.”

Heavy drinking during pregnancy can lead to spontaneous abortion or a range of disabilities known as fetal alcohol spectrum disorders, of which fetal alcohol syndrome is the most severe.

Children with this condition are born with characteristic physical and mental defects, including short stature, and small head and brain.

There is no cure. Treatment is focused on mental health and medical services to manage the resulting lifelong disabilities that include learning difficulties, behavioural problems, language, delayed social or motor skills, impaired memory and attention deficits.


WHO/Alicestine October

Denis Viljoen stands in front of his campaign poster

“It is estimated that at least one million people in this country have fetal alcohol syndrome and approximately five million have partial fetal alcohol syndrome and [other] fetal alcohol spectrum disorders. It’s tragic because it’s completely preventable,” says researcher and human geneticist Denis Viljoen in Cape Town, the provincial capital of South Africa’s Western Cape.

“Fetal alcohol spectrum disorder is the most common birth defect in South Africa, by far more common than Down syndrome and neural-tube defects combined,” says Viljoen, who helped set up a nongovernmental organization (NGO) called the Foundation for Alcohol Related Research in 1997, after reaching the shocking conclusion that one in 10 of the children he saw at the genetics clinic at a hospital in Cape Town was affected.

“I saw then that fetal alcohol syndrome was much more common than people thought ... Public

awareness [in South Africa] started with our initial research," he says.

The NGO fights fetal alcohol syndrome on several fronts: it gathers scientific evidence to highlight the problem in the hope that government decision-makers will fund and initiate prevention programmes; it trains medical and social services staff to develop prevention programmes and it raises public awareness.

Based on his published work and ongoing research, Viljoen estimates that between 70 and 80 per 1000 babies born in the Western Cape have the syndrome – the highest known incidence in the world. And the problem is not just limited to the rural poor of the Western Cape. "We see an increasing number of children with fetal alcohol spectrum disorders from middle and higher socio-economic groups coming to our private practice," he says.

In developed countries, a recent surge in new cases is attributed to increased awareness and more doctors diagnosing the problem rather than a worsening of the problem. This is also the case in South Africa, Viljoen says.

There are no reliable global prevalence figures, but a 2005 study estimated a global incidence of 0.97 per 1000 live births based on research in the United States of America (USA).

Some governments run targeted prevention programmes, but in many countries this work is left largely to NGOs.

In the farming community where Williams lives, heavy drinking partly stems from the 400-year-old practice of giving slaves and their descendants alcohol in recompense and to keep them captive through addiction.

"Our work is largely confined to rural communities due to lack of funding to reach urban areas," says Francois Grobbelaar, who runs FASfacts, an NGO that works with farming communities to prevent fetal alcohol syndrome.

While the tot system, which was banned in the 1960s, entrenched a culture of alcohol abuse and still contributes to maternal drinking in the Western Cape, studies show that poor nutrition, ill health, stress and tobacco use also influence the severity of the effects of heavy maternal drinking. The communities most affected are often impoverished, poorly educated and socially deprived, such as indigenous populations in the Western Cape, who are partly of Khoisan descent, Aboriginals in Australia and Native Americans in the USA.

Awareness of the problem has grown ever since the term, fetal alcohol syndrome, was coined in 1973.

In the United Kingdom of Great Britain and Northern Ireland, NoFAS, an NGO, was set up in 2003 by the adoptive mother of a child with the syndrome and in 2007 the British Medical Association published a report on the problem calling on health professionals to step up efforts to prevent it.

In the Russian Federation, researchers from St Petersburg State University and Nizhny Novgorod State Pedagogical University have been working since 2003 on a project to prevent women from drinking during pregnancy. It is in collaboration with the University of Oklahoma Health Sciences Center and funded by the US National Institutes of Health and Centers for Disease Control and Prevention.

The project involves collecting data as an evidence base to develop prevention strategies, development of education materials for the public and doctors and a 20-site randomized trial to test a prevention intervention for women at risk. According to principal investigator Tatiana Balachova, the

clinical trial will be completed next year.

“You have to teach physicians and nurses how to talk to women in an effective way,” says Elena Varavikova, a leading researcher at the Federal Research Institute for Health Care in Moscow. “This should be included in their continuing medical education.” Doctors and other health-care professionals also need an incentive to do preventive work.

Funding for these activities should be covered by health insurers, she says.

“Our country has one of the highest levels of alcohol consumption with drinking among women on the rise, and recent studies found high rates of fetal alcohol syndrome in Russian orphanages. Now it is time to act,” says Varavikova, who is working on the project.

In South Africa’s Western Cape Province the syndrome is seen as part of the wider problem of alcohol abuse that carries a huge overall burden of disability due to injuries, often from interpersonal violence, and disease.

“We see that every Friday and Saturday night in our hospital trauma wards,” says Robert Macdonald, head of the substance abuse unit in the Western Cape Provincial Government. He hopes that the province’s Liquor Act, which comes into force this year, will reduce the alcohol supply by limiting access including closure of illegal shebeens (bars) and a ban on selling alcohol on credit. But he fears it will be difficult to police. “There are 37 000 illegal shebeens in the province and only a few hundred police officers available to enforce it.”

As Macdonald notes, the costs to society are high. “Fetal alcohol syndrome is also an issue because affected children require special-needs schooling and other forms of specialized care. It really has knock-on effects.” He adds that the Western Cape Department of Health is launching “Booza TV”, a television series this year to help educate people about alcohol abuse.

A study published in the American Medical Journal in 2004 estimated the social costs, including loss of productivity, lifelong costs of medical care and rehabilitation in the USA, at around US$ 4 billion in 1998.

Some children with fetal alcohol syndrome are not diagnosed because they are adopted or fostered and their new parents are not aware of their mother’s background of chronic alcohol abuse, campaigners say. Particularly in the case of fetal alcohol spectrum disorders other than fetal alcohol syndrome, they may look like other children, but their “difficult” behaviour may be misunderstood if they have not been diagnosed.

FASfacts runs fetal alcohol syndrome prevention campaigns for school pupils, other young people and adults. In addition, it works with bar owners by educating them not to sell alcohol to pregnant women and under-aged children. In one project, 100 pregnant women in high-risk communities are allocated mentors to support them and encourage them not to drink alcohol.

Viljoen says the Foundation for Alcohol Related Research’s training, prevention, research and awareness-raising work only receives “a little funding” from the departments of social development and agriculture and nothing from the health department of the Western Cape.

But despite these efforts, as long as alcohol is accessible, affordable and socially acceptable, prevention work will be an uphill struggle.

Given the addictive power of alcohol, some women still drink heavily during pregnancy despite receiving the right advice. Williams was advised to stop drinking while expecting her son: “I was hard-

headed and just kept on drinking."

It was only once Williams was expecting her youngest child that she managed to give up alcohol for good. The child "came out fine" and today her daughter is 12 years old and wants to be a teacher.

**Link to the Article,**
http://www.who.int/bulletin/volumes/89/6/11-020611/en/index.html

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# A DIFFERENTIAL APPROACH FOR EXAMINING THE BEHAVIORAL PHENOTYPE OF FETAL ALCOHOL SPECTRUM DISORDERS

*Kelly Nash[1,2], Gideon Koren[3], Joanne Rovet[1,3]*

*[1]Neuroscience and Mental Health Program, The Hospital for Sick Children, Toronto; [2]Ontario Institute for Studies in Education of the University of Toronto, Toronto; [3]Motherisk Program, The Hospital for Sick Children, Toronto, Ontario*

## ABSTRACT

### Background
In 2006, Nash and colleagues published results suggesting that individual items from the Child Behavior Checklist (CBCL) could be used as a screening tool that was highly sensitive in differentiating children with FASD from controls and children with Attention Deficit Hyperactivity Disorder (ADHD). Since many of the items referred to features of Oppositional Defiant/Conduct Disorder (ODD/CD), it was not clear whether the items reflected comorbidity with ODD/CD, or were unique to children with FASD.

### Objectives
The present study sought to replicate the results of our 2006 paper using a new and larger sample, which also includes a group of children diagnosed with ODD/CD.

### Methods
Retrospective psychological chart review was conducted on 56 children with FASD, 50 with ADHD, 60 with ODD/CD, and 50 normal control (NC) children. Receiver operating characteristic curve (ROC) analysis of CBCL items discriminating FASD from NC was used to compare FASD to the ADHD and ODD/CD groups.

### Results
ROC analyses showed scores of a) 3 or higher on 10 items differentiated FASD from NC with a sensitivity of 98%, specificity of 42% and b) 2 or higher on 5 items reflecting oppositional behaviors differentiated FASD from ADHD with a sensitivity of 89% and specificity of 42%.

### Conclusion
Our findings partially replicate the results of our 2006 study and additionally elucidate the behavioural differences between children with FASD and those with ODD/CD. The proposed screening tool is currently the only tool available that is empirically derived and able to differentiate children with FASD from children with clinically similar profiles.

**Key Words**: *Fetal alcohol spectrum disorder, screening, attention deficit hyperactivity disorder, oppositional defiant, conduct disorder*

Alcohol is a powerful teratogen with significant effects on the developing brain. The various conditions arising from prenatal alcohol exposure, such as Fetal Alcohol Syndrome (FAS) and Alcohol Related Neurodevelopmental Disorder (ARND), are known collectively as Fetal Alcohol Spectrum Disorders (FASD). Individuals with FASD often show a profile of reduced IQ[1,2], cognitive and learning disabilities[3] and severe behavior problems.[4] Attention problems are among the most prevalent[5-8] with approximately 70% of children with FASD having a clinically diagnosed attention disorder.[9] Indeed, attention deficit/hyperactivity disorder (ADHD) is 3 - 9 times higher in children with FASD than the

general population.[5] Moreover, children with FASD are also at high risk for other forms of psychopathology[9-11] with oppositional defiant/conduct disorder (ODD/CD) being the next most common to ADHD.[12,13]

Not surprisingly, children with FASD show many of the same behavior problems as children with ODD/CD, including deficits in moral development[14], lack of social judgment[5,15], and failure to learn from experience.[1] While studies using parent and teacher questionnaires also report attention and disruptive behavior problems[4], no study has directly compared the behavioral profiles of children with FASD to those with ODD/CD. Given that information regarding the specific profile of behavior disturbance in children with FASD is essential for a differential diagnosis, a comparison of the behavior problems between children with FASD and other psychopathologies is warranted. Indeed, many children with FASD are diagnosed with other psychopathological conditions such as ADHD or ODD/CD, which do not truly reflect the strengths and weaknesses unique to FASD and may affect treatment.[9]

A large proportion of individuals with FASD require extensive mental health services throughout their lifetime, therefore the costs associated with FASD are staggering. In Canada it is estimated that $344 million is spent annually on affected youth.[16] Given that incarceration and difficult-to-measure costs such as, lost productivity, alcoholism, and poor quality of life, are excluded from these estimates - the actual cost of FASD is likely much higher.[17] In view of an early landmark paper reporting that diagnosis at a young age was a significant factor in reducing these later secondary adverse outcomes, due to earlier entry into the mental health or special education system.[18] It is essential that children need to be identified earlier. Unfortunately, a large proportion of children with FASD fail to receive any diagnosis because skilled professionals and adequate mental health services are often lacking, especially if children reside in rural and remote areas, which represents an important public health concern.

Screening instruments are effective tools that can help expedite the diagnostic process by identifying children most in need of a comprehensive evaluation. To be effective, however, a screening tool must be sensitive and specific to the effects of prenatal alcohol exposure, easy to administer, applicable in a variety of contexts, and culturally appropriate.[19] Because children with FASD are often diagnosed and treated for a comorbid disorder rather than for FASD, the effects of the alcohol-related disorder is often overlooked and not treated. Therefore, to be able to differentially diagnose children on the FASD spectrum from those with other psychiatric disturbances of childhood is critical; however, techniques to do so are not readily available.

Pen-and-paper questionnaires that can be readily completed by parents and caregivers offer an effective method of FASD screening and so can serve as a first step to determine whether or not a child truly warrants being seen by a team of specialists required to conduct the necessary assessment. While such an approach has been effective in identifying other mental health disorders such as depression[20] and alcoholism[21], its suitability for children with FASD has only recently been considered.[22] As part of this effort, we developed a 10-item screening tool based on items from a standardized behavior problems questionnaire known as the Child Behavior Checklist (CBCL). We compared children with FASD to children with ADHD and typically developing children.[23] However, many of the items reflected features of ODD/CD. We were not certain whether the particular set of items comprising our tool reflected comorbidity with ODD/CD, or represented a unique and distinct feature of FASD. Consequently, a tool is required that accurately and reliably differentiates a diagnosis on the FASD spectrum from other childhood disorders, particularly ODD/CD.

To address these outstanding issues, we sought to: 1) replicate our 2006 paper using a larger and different sample of children with FASD, children with ADHD, and controls and 2) further determine the specificity of our screening tool by also comparing the FASD group with children with ODD/CD. Our ultimate goal was to construct a valid and reliable screening tool for FASD capable of differentiating children with FASD from other childhood psychopathologies including ODD/CD.

## METHODS

### Participants

The sample included 220 children aged 6 to 18 years, 56 with an FASD, 50 with ADHD, 60 with ODD/CD and 53 typically developing normal control (NC) children. The FASD group was recruited from the Motherisk Follow-up Clinic, which is located at The Hospital for Sick Children in Toronto. Children were brought to this clinic because their caregivers were concerned about whether the child's prenatal alcohol exposure was contributing to his or her presenting behavior problems.[24] In most cases seen our clinic, problematic drinking led to heavy prenatal alcohol exposure. In this clinic, an FAS or ARND diagnosis is based on the Canadian diagnostic guidelines[19], which were derived from the Washington 4-digit code[25] and IOM criteria[26], but designed to provide more specific criteria for behavioural characteristics. The Motherisk approach requires the children to have ARND as specified by the Canadian system, with or without the physical symptomatology. If the child presents with both significant facial and growth features the child is considered to have FAS.

Following detailed neuropsychological and speech language assessments, the psychological team assigns children scores based on their performance. A score of '4' requires an IQ below 70, and three significant areas of deficit, as specified by the Canadian Guidelines. A score of '3' requires and IQ above 70, with at least three significant areas of deficit; a score of '2' requires an IQ above 70 with at least 2 significant areas of deficit; and a score of '1' requires an IQ above 70 and no more than one significantly deficient area. A diagnosis of ARND requires a score above 3. To be diagnosed with FAS a child must present with the physical symptomotolgy, and have a score of 1 or above.

To be included in the FASD group, children had to have a documented history of prenatal exposure to alcohol and a diagnosis of ARND, as indicated by a score of 3 or 4, or FAS. Five children had a score of 4, and, also met criteria for FAS, while remaining children had a score of 3, and were diagnosed as ARND. While 100% of children in the FASD group were exposed to alcohol, 44.6% were additionally exposed to drugs (Table 1). Children were excluded if their exposure history was unconfirmed, their primary exposure was to a substance other than alcohol (e.g., cocaine, heroin, marijuana), or their score was 2 or below. As is importantly highlighted[27], several diagnostic centres use different nomenclature to refer to different diagnostic categories on the FASD spectrum. Therefore, in an effort to maintain consistency among different diagnostic centres, a score of 3 is similar to either an ARND or p/FAS diagnosis, while a score of 4 similar to an FAS diagnosis. 'Brain' scores of 1 and 2 are indicative of PAE, without meeting diagnostic criteria based on the Canadian guidelines.

The ADHD group consisted of 50 children recruited through a data pool of previous ADHD participants in our laboratory. All children had received an ADHD diagnosis using DSM-IV-TR criteria. All children had a previous diagnosis of ADHD, from a developmental pediatrician (MD), psychiatrist (MD), or clinical psychologist (PhD), at the time their parents completed the CBCL. Diagnosis was made using a combination of clinical interview, parent questionnaires, teacher questionnaires, and formal psychological testing. Any child with a history of prenatal drug or alcohol exposure, defined as > than 2 drinks during pregnancy, was excluded from this study, which was ascertained from family history forms, and interview records in the child's medical chart. At time of recruitment, 30 children were taking medications, 12 were not - medication status of the remaining eight children was not available.

The ODD/CD group comprised 60 children whose assessment records were ascertained through the Youthdale Treatment Centre who were attending as outpatients, between January 2004 and March 2006 and whose parents provided written consent for their child's clinical data to be used for research purposes. Only children with a confirmed primary diagnosis of ODD or CD, using DSM-IV-TR criteria were included. All children had a diagnosis of ODD/CD, from a developmental pediatrician (MD), psychiatrist (MD), or clinical psychologist (PhD) at the time their caregivers completed the CBCL. Diagnosis was made using a combination of clinical interview, parent questionnaires, teacher questionnaires, and formal psychological testing.

Excluded were children with a history of prenatal drug or alcohol exposure, which was ascertained from family history forms, and interview records in the child's medical chart. Approximately 30% of cases met this criteria and another 20% were excluded because we did not have sufficient validation of the child's prenatal exposure history. Thirty-one of the children had a co-morbid diagnosis of ADHD, 25 of whom were taking medication for their attention problems; 43 children were on medication for their behavior problems.

The NC group consisted of 53 previous control participants in other studies in our laboratory. Excluded were children with a history of prenatal drug or alcohol exposure, and a diagnosis of ADHD or ODD/CD. All procedures were approved by the Research Ethics Boards of both, The Hospital for Sick Children and Youthdale Treatment Centre.

**Procedures**

For all groups, information was obtained via retrospective chart review on maternal learning disabilities, paternal substance abuse, maternal psychiatric history, paternal psychiatric history, adoption or foster care, number of foster care placements, abuse, neglect, and socioeconomic status (SES; measured using the Hollingshead Four-Factor Index). From each child's chart, relevant CBCL data were extracted for each case using the items from our previous screener.[23]

**Data Analyses**

Analysis of variance (ANOVA) and chi-square tests were used to compare groups on demographic variables. As a first step, we compared endorsement rates for pairs of groups (FASD vs. NC, FASD vs. ADHD, FASD vs. ODD/CD) using the chi-square test. Receiver Operating Characteristic (ROC) curve analyses were then performed for different group pairs using the sum of items most strongly differentiating each pair. Area-under-the-curve (AUC) values were used to classify cases as being FASD or NC, FASD or ADHD, and FASD or ODD/CD based on the number of endorsed items and critical cutoff values. ROC analyses provide two important measures: 'sensitivity,' which measures the proportion of actual positives which are correctly identified as such (e.g. the percentage of exposed children who are correctly identified as having the condition), while 'specificity' measures the proportion of negatives which are correctly identified (e.g. the percentage of unexposed children who are correctly identified as not having the condition).

## RESULTS

**Demographic Information**

Table 1 presents the demographic data for the four groups and Table 2, detailed information for the FASD group. Most children in the FASD group were in foster care and had received more than one placement. Abuse and neglect were common and seen in 52% and 63% of FASD cases respectively. Groups differed significantly in gender [$\chi^2$ (3) = 9.7, $p < .03$] with the ADHD group having the highest male to female ratio (4:1), which reflects usual prevalence rates for ADHD in the general population. There was a significant effect of age, [$F$ (3, 210) = 27.0, $p < .01$] with children in the ODD/CD being significantly older than children in the FASD, ADHD and NC groups. There was also a significant effect of SES, [$F$ (3, 199) = 23.8, $p < .00$] reflected in children in the NC and ADHD having significantly higher SES than children in the FASD and ODD/CD groups. Lastly, children in the FASD group were significantly more likely to have been exposed to cigarettes compared to children with ADHD, ODD/CD and NC's [$\chi^2$ (3) = 97.5, $p < .00$].

**TABLE 1** Demographic Information

| | FASD (n=56) | ADHD (n=50) | ODD/CD (n=61) | NC (n=53) | p-value |
|---|---|---|---|---|---|
| | | | | | |
| **Age** | 10.87 (SD 2.75) | 9.36 (SD 1.70) | 12.90 (SD 1.59) | 9.81 (SD 2.41) | <.001 |
| Gender (% Male) | 62 | 82 | 59 | 54.7 | <.01 |
| **SES (%)**[1] | | | | | |
| High[2] | 26.8 | 46.0 | 27.1 | 83.3 | <.001 |
| Medium[3] | 41.1 | 30.0 | 49.2 | 16.7 | |
| Low[4] | 32.1 | 24.0 | 23.7 | 0 | |
| **Cigarette Exposure (%)** | | | | | |
| Yes | 41.1 | 8.0 | 8.2 | 3.8 | <.001 |
| No | 3.6 | 50.0 | 91.8 | 96.2 | |
| Unknown | 53.6 | 42.0 | 0 | 0 | |
| **Attention Meds (%)** | | | | | |
| Yes | 55.4 | 60.0 | 41.0 | 0 | <.001 |
| No | 44.6 | 24.0 | 59.0 | 100 | |
| Unknown | 0 | 2.0 | 0 | 0 | |
| **Psychiatric Meds (%)** | | | | | |
| Yes | 32.1 | 8.0 | 70.5 | 7.5 | <.001 |
| No | 53.6 | 54.0 | 29.5 | 92.5 | |
| Unknown | 14.3 | 62.0 | 0 | 0 | |

[1]SES data not available for all children; [2]SES = 1 or 2; [3]SES = 3; [4]SES = 4 or 5

**TABLE 2** Background Characteristics of Clinical Groups (%)

| **Family Status** | **FASD (n = 56)** | **ADHD (n = 50)** | **ODD/CD (n = 60)** | **p-value** |
|---|---|---|---|---|
| Foster | 67.8 | 0 | 42.6 | p < .000 |
| Adopted | 30.3 | 2.0 | 1.6 | p < .000 |
| Biological Parent | 2.0 | 98.0 | 65.8 | p < .000 |
| **Exposure History** | | | | |
| Alcohol Only | 16.1 | 0 | 0 | p < .000 |
| Alcohol and Drugs | 44.6 | 0 | 0 | p < .000 |
| Cigarettes | 8.0 | 8.0[1] | 8.2 | p < .000 |
| **Abuse History** | | | | |
| Abuse | 51.8 | 2.0 | 37.7 | p < .000 |
| Neglect | 62.5 | 2.0 | 1.6 | p < .000 |
| **Foster Care Placements** | | | | |
| 0 | 1.8 | 0 | 57.4 | p < .000 |
| 1 | 41.1 | 0 | 1.6 | p < .000 |
| >1 | 53.1 | 0 | 54.0 | p < .000 |

**Group Differences on Individual CBCL Items**

Findings from the Greenbaum (2000) study were used to select individual items from the CBCL questionnaire[28] to be studied presently. In that study, endorsement rates were defined accordingly: 1 if the item was endorsed as Somewhat True, 2 if the item was endorsed as Very True, or 0 if a child received a Not True rating. Using this approach, we also identified the same 12 items as having higher endorsement rates in FASD than NC:

- *"acts too young for his/her age"* [$\chi^2$ (1) = 15.7, $p < .01$],
- *"argues a lot"* [$\chi^2$ (1) = 34.0, $p < .01$],
- *"can't concentrate/pay attention for long"* [$\chi^2$ (1) = 58.0, $p < .01$],
- *"can't sit still, restless/hyperactive"* [$\chi^2$ (1) = 43.2, $p < .01$],
- *"cruelty, bullying, meanness to others"* [$\chi^2$ (1) = 16.5, $p < .01$],
- *"disobedient at home"* [$\chi^2$ (1) = 29.4, $p < .01$],
- *"doesn't seem to feel guilty after misbehaving"* [$\chi^2$ (1) = 14.4, $p < .01$],
- *"impulsive acts without thinking"* [$\chi^2$ (1) = 35.4, $p < .01$],
- *"showing off/clowning"* [$\chi^2$ (1) = 35.2, $p < .01$],
- *"steals at home"* [$\chi^2$ (1) = 24.5, $p < .01$],
- *"steals outside"* [$\chi^2$ (1) = 12.7, $p < .01$], and
- *"lying/cheating"* [$\chi^2$ (1) = 7.6, $p < .01$].

FASD also had significantly higher endorsement rates than ADHD for the following *five items:*

- *"acts young"* [$\chi^2$ (1) = 5.0, $p < .03$],
- *"cruelty bullying, meanness to others"* [$\chi^2$ (1) = 8.7, $p < .00$],
- *"doesn't seem to feel guilty after misbehaving"* [$\chi^2$ (1) = 17.7, $p < .00$],
- *"steals at home"* [$\chi^2$ (1) = 17.0, $p < .00$], and
- *"steals outside the home"* [$\chi^2$ (1) = 9.7, $p < .00$].

Groups did not differ on the following items:

- *"argues a lot"* [$\chi^2$ (1) = 0.82, $p = .37$],
- *"can't concentrate/pay attention for long"* [$\chi^2$ (1) = 1.6, $p = .21$],
- *"can't sit still; restless/hyperactive"* [$\chi^2$ (1) = 1.6, $p = .21$],
- *"disobedient at home"* [$\chi^2$ (1) = 1.7, $p = .19$],
- *"impulsive acts without thinking"* [$\chi^2$ (1) = 1.5, $p = .22$],
- *"showing off/clowning"* [$\chi^2$ (1) = 0.69, $p = .41$], and
- *"lying/cheating"* [$\chi^2$ (1) = 0.36, $p = .55$].

Children in the FASD group received a higher score than ODD/CD on only one item, namely "acts young" [$\chi^2$ (1) = 7.2, $p < .01$]. In contrast, ODD/CD were found to have higher endorsement rates than FASD on "cruelty, bullying, meanness to others" [$\chi^2$ (1) = 2.2, $p < .02$] and "steals at home" [$\chi^2$ (1) = 8.0, $p < .01$]. Groups did not differ on the following items:

- "*argues a lot"* [$\chi^2$ (1) = 1.2, $p = .27$],
- "*can't concentrate/pay attention for long"* [$\chi^2$ (1) = 0.26, $p = .01$],
- *"can't sit still, restless/hyperactive"* [$\chi^2$ (1) = 43.2, $p < .01$],
- *"disobedient at home"* [$\chi^2$ (1) = 29.4, $p < .61$],
- *"doesn't seem to feel guilty after misbehaving"* [$\chi^2$ (1) = 0.0, $p = .96$],
- *"impulsive acts without thinking"* [$\chi^2$ (1) = 0.47, $p = .49$],
- *"showing off/clowning"* [$\chi^2$ (1) = 0.01, $p = .91$],
- *"steals outside"* [$\chi^2$ (1) = 2.4, $p < .01$], and
- *"lying/cheating"* [$\chi^2$ (1) = 0.23, $p = .63$].

Descriptive statistics for all groups are presented in Table 3. In order to address the issue of comorbidity of ADHD in the ODD/CD group, additional chi square analyses were completed to the exclusion of the children with both ODD/CD and ADHD. Children with FASD continued to have significantly more endorsements on the item "acts young" [$\chi^2$ (1) = 13.5, p < .01], while children in the ODD/CD group had higher endorsement rates for being "disobedient at home" [$\chi^2$ (1) = 4.1, p < .05]. The previously significant items "cruelty, bullying, meanness to others" [$\chi^2$ (1) = 0.13, p = .72] and "steals at home" [$\chi^2$ (1) = 1.7, p = .19], were no longer significant. Descriptive statistics are presented in Table 4.

**TABLE 3** Endorsement Rates for Individual CBCL Items

| | **FASD (%)** | **ADHD (%)** | **ODD/CD (%)** | **NC (%)** | **FASD vs. ADHD** | **FASD vs. ODD/CD** | **FASD vs. NC** |
|---|---|---|---|---|---|---|---|
| Acts too young for his/her age | 80.4 | 64.0 | 60.7 | 24.5 | <.05 | <.05 | <.001 |
| Argues a lot | 94.6 | 90.0 | 98.3 | 34.0 | ns | ns | <.001 |
| Can't concentrate/pay attention for long | 92.9 | 98.0 | 95.1 | 24.5 | ns | ns | <.001 |
| Can't sit still/restless hyperactive | 83.9 | 92.0 | 83.6 | 24.5 | ns | ns | <.001 |
| Cruelty/bullying/meanness to others | 66.1 | 38.0 | 85.2 | 5.7 | <.01 | <.05 | <.001 |
| Disobedient at home | 87.5 | 78.0 | 98.3 | 24.5 | ns | <.05 | <.001 |
| Doesn't seem to feel guilty after misbehaving | 83.9 | 44.0 | 86.9 | 11.3 | <.001 | ns | <.001 |
| Impulsive acts without thinking | 94.6 | 88.0 | 95.1 | 30.2 | ns | ns | <.001 |
| Lying/cheating | 82.1 | 74.0 | 91.8 | 17.0 | ns | ns | <.001 |
| Showing off clowning | 86.4 | 74.0 | 75.4 | 26.4 | ns | ns | <.001 |
| Steals at home | 66.1 | 26.0 | 60.7 | 1.9 | <.001 | ns | <.001 |
| Steals outside the home | 46.4 | 18.0 | 44.2 | 1.9 | <.01 | ns | <.001 |

**TABLE 4** Endorsement Rates for Individual CBCL Items for the FASD group and ODD/CD Group Without a Comorbid ADHD Diagnosis Only

| | **FASD n = 56(%)** | **ODD/CD n = 31(%)** | ***p*-value** |
|---|---|---|---|
| Acts too young for his/her age | 80.4 | 45.0 | *p* <.01 |
| Argues a lot | 94.6 | 96.8 | *p* =.65 |
| Can't concentrate/pay attention for long | 92.9 | 93.5 | *p* =.98 |
| Can't sit still/restless hyperactive | 83.9 | 71.0 | *p* =.15 |
| Cruelty/bullying/meanness to others | 66.1 | 71.0 | *p* =.72 |
| Disobedient at home | 87.5 | 97.7 | *p* <.05 |
| Doesn't seem to feel guilty after misbehaving | 83.9 | 90.3 | *p* =.40 |
| Impulsive acts without thinking | 94.6 | 90.3 | *p* =.45 |
| Lying/cheating | 82.1 | 90.3 | *p* =.31 |
| Showing off clowning | 86.4 | 70.0 | *p* =.28 |
| Steals at home | 66.1 | 51.6 | *p* =.19 |
| Steals outside the home | 46.4 | 46.4 | *p* =.89 |

**Formulation of a Screening Tool**

To create the screening tool, our next step involved identifying specific items differentiating the various groups and then submitting them to ROC analyses. As shown in Figure 1, a comparison of FASD and NC groups indicated the largest Area Under the Curve (AUC) was achieved with .970 ($p < .001$); using a cutoff of 3 of 10 items, we were able to achieve sensitivity of 98% and specificity of 42%. It is important to note that although chi square analysis revealed 12 items to be significant, when submitted to a more rigorous statistical method designed for predicting group membership rather than measuring group differences, only 10 of those 12 items were significant, thus producing the largest area under the curve. When compared with ADHD, the largest AUC was achieved with .78 ($p < .001$); using a cutoff of 2 out of 5 items, we attained sensitivity of 89% and specificity of 54% (Figure 2). A comparable ROC analysis could not be conducted between FASD and ODD/CD groups because only one item differentiated them; however, information from the chi-square analyses of items differentiating groups were used in formulating the tool. Table 5 shows our 3-step screening tool approach.

**FIG. 1** ROC Curve Showing Items Most Strongly Discriminating Children with FASD from Controls

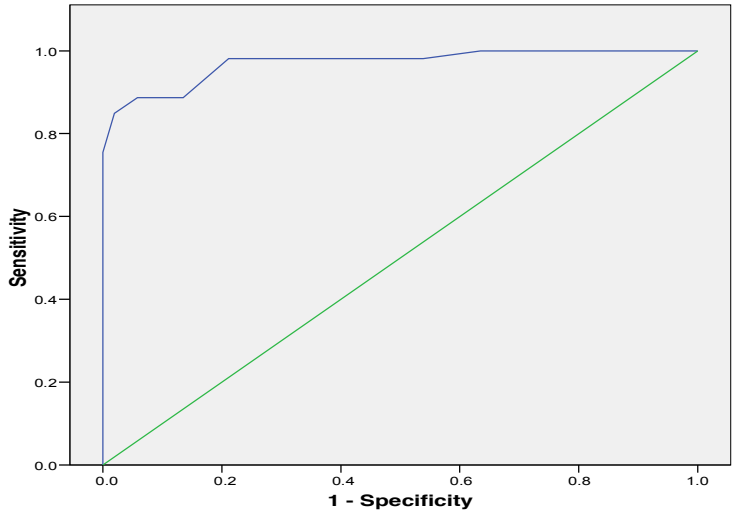
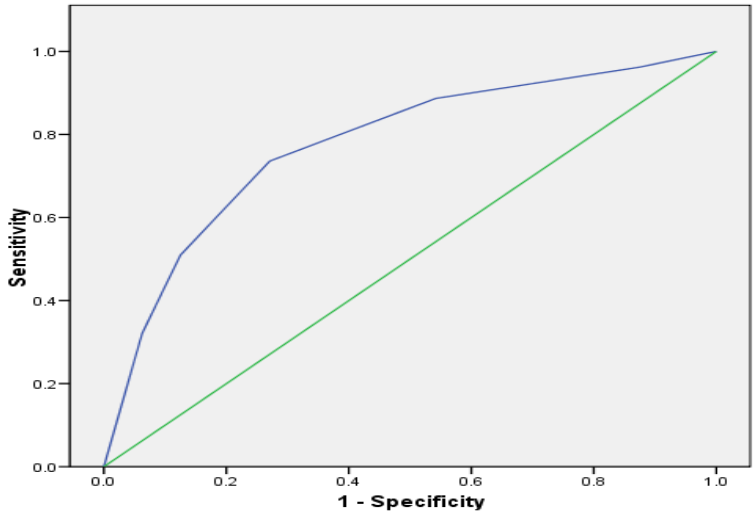



**FIG. 2** ROC Curve Showing Items Most Strongly Discriminating Children with FASD from ADHD



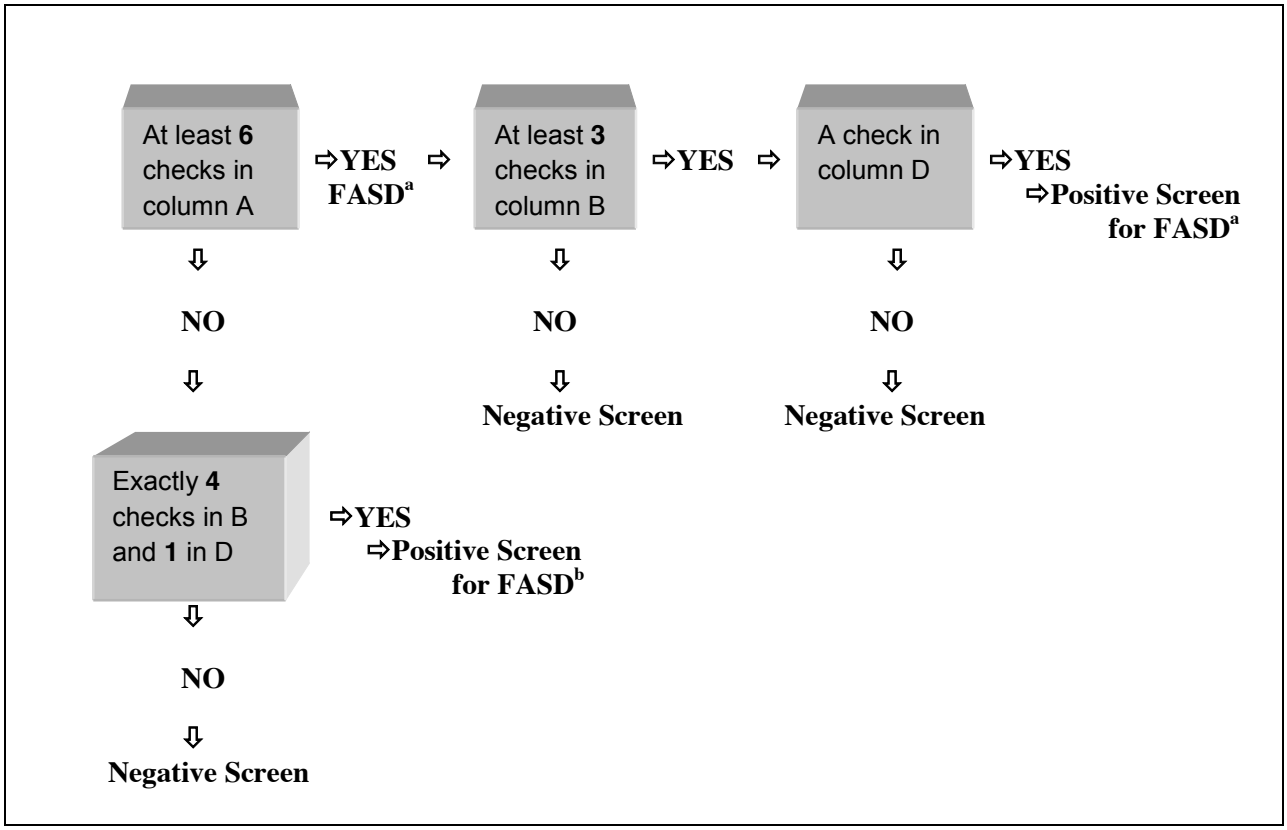
The Neurobehavioural Screening Tool (NST) form is designed to be administered for caregivers of children and youth suspected of having a Fetal Alcohol Spectrum Disorder based on behavioral observations. The caregiver should know the child well enough to be able to answer all questions contained in NST. The form should be administered to the respondent by a qualified health and social service professional, such as a social worker, law enforcement personnel, psychologist, or child and youth worker in the context of a clinical interview. The form should not be scored by the caregiver. The user should explain that the aim of the form is to gain a picture of the child's behaviour within the last 6 months (Table 5).

**TABLE 5** Neurobehavioural Screening Tool (NST): Guidelines and Scoring

| | | |
|---|---|---|
| **1)** Has your child been seen or accused of or thought to have act too young for his or her age? | **YES** | **NO** |
| **Place a checkmark ☑ in all columns if 'YES' was endorsed** | | |
| **2)** Has your child been seen or accused of or is thought to be disobedient at home? | **YES** | **NO** |
| **Place a checkmark ☑ in columns 'A' and 'C' if 'YES' was endorsed** | | |
| **3)** Has your child been seen or accused of or is thought to lie or cheat? | **YES** | **NO** |
| **4)** Has your child been seen or accused of/ or is thought to lack guilt after misbehaving? | **YES** | **NO** |
| **Place a checkmark ☑ in columns 'A' and 'C' for each 'YES'** | | |
| **5)** Has your child been seen or accused of or thought to have difficulty concentrating, and can't pay attention for long? | **YES** | **NO** |
| **6)** Has your child been seen or accused of or is thought to act impulsively and without thinking? | **YES** | **NO** |
| **7)** Has your child been seen or accused of or is thought to have difficulty sitting still is restless or hyperactive? | **YES** | **NO** |
| **Place a checkmark☑ in column 'A' for each 'YES' endorsed** | | |
| **8)** Has your child been seen or accused of or is thought to display acts of cruelty, bullying or mean? | **YES** | **NO** |
| **9)** Has your child been seen or accused of or is thought to steal items from home? | **YES** | **NO** |
| **10)** Has your child been seen or accused of or is thought to steal items outside of the home? | **YES** | **NO** |
| **Place a checkmark☑ in column 'B' for each 'YES' endorsed** | | |

| A | B | C | D |
|---|---|---|---|
| | | | |

**SCORING STEPS**
**The NST must be scored according to the following steps**




**Statistical Properties**

**Positive Screen (a):** Separates FASD from typically developing children with a 14% false positive rate and 18% false negative rate (sensitivity 86% & specificity 82%) and from children with ADHD with a 19% false positive rate and 28% false negative rate (sensitivity 81% & specificity 72%).

**Positive Screen (b):** Separates FASD, without ADHD symptoms, from typically developing children with a 30% false positive rate and a 20% false negative rate (sensitivity 70% & specificity 80%).

**Note:** If box 'D' is not checked this screener cannot separate FASD from ODD/CD.

## DISCUSSION

The present study, using a different sample of children, partially replicated the results of our previous findings[23]. Examination of individual item scores revealed that children with FASD differed from NC in behaviors reflecting immaturity, argumentativeness, inattention, and general disobedience. Although children with ADHD and ODD/CD showed many of the same behavior problems as children with FASD, children with ADHD were less likely than those with FASD to have behavior problems and act young; in contrast, children with ODD/CD were less likely than FASD to act young but were more cruel and disobedient at home.

Thus we were able to corroborate our previous findings in a different sample of children. Our present findings indicate that the same CBCL items from our previous study were highly discriminative of FASD and NC groups and that certain combinations of items differentiated children with FASD from unexposed children with ADHD and ODD/CD. This consistency, despite our using different children in each study, signifies these characteristics are consistent across different samples of children with FASD, validating this screening method. Also consistent with our previous work[23], we found that children with FASD exhibited poor attention and behavior suggestive of ADHD, but unlike ADHD displayed a greater lack of guilt after misbehaving, cruelty, tendency to act young for their age, and likelihood to steal. The latter finding supports previous research indicating poor social and moral development in children with FASD.[13,14,29,30]

The present study, which for the first time included an ODD/CD comparison group, serves to address the outstanding question from our previous work[23] concerning whether the items differentiating FASD from ADHD reflected comorbidity with ODD/CD or were unique to FASD. Our results now show that children with FASD are significantly more likely than ODD/CD to act young, while being somewhat less disobedient at home and cruel. This finding suggests children with FASD may have a distinct profile of behavior problems from that seen in ODD/CD. Our finding of greater immaturity in children with FASD than ODD/CD (as well as ADHD) is consistent with previous reports of arrested social development in this population.[31,32] However, future studies with a larger sample are needed to determine if additional behavioural differences exist between FASD and ODD/CD. As well as, determine the extent to which the greater social immaturity observed in FASD can be attributed to poor cognitive abilities.

Given the issue of comborbidity with ADHD in the ODD/CD group, an additional analysis was completed without the comorbid group. While the FASD group continued to show endorsements for "acts young," endorsements on cruelty, or stealing, no longer typified the ODD/CD group, which was instead rated as being significantly more disobedient at home. One reason for this change in items could reflect the fact that children meeting criteria for both ADHD and ODD/CD have more severe behavior problems overall.

The authors feel it is critical to highlight the fact that the NST is intended for screening purposes only and is not a diagnostic tool. It is essential that the rater of the NST be a caregiver who has known the child for at least 6 months, within the context of a home environment. The NST should be administered to the rater by a qualified health and social service professional, such as a social worker, law enforcement personnel, psychologist, or child and youth worker in the context of a clinical interview. Due to the sensitive nature of the screening process, and that the NST has only been validated for rating by caregivers, there is not yet an NST for use with other raters, who may also know the child well, such as teachers.

A number of limitations impede our having a full understanding of how prenatal alcohol exposure affects development, as is characteristic of most clinic-based research. First, because most children with FASD are not in the care of their biological mothers, exact information on dosage and timing of alcohol exposure was not available. Second, women who abuse alcohol typically smoke cigarettes. High rates of nicotine abuse alone have been shown to have negative postnatal consequences, while alcohol in combination with nicotine has been shown to increase these risks.[33,34] In the current study, we could not adequately control for this factor because a confirmed history of smoking was unavailable in many cases.

Several methodological limitations are also specific to the current study. Since data were collected retrospectively, certain background information was not available, particularly for the ADHD group. Finally, because the proposed screening tool is intended to be used as a screening instrument, variables important at the stage of diagnosis, such as age, family histories, and SES were not controlled for in the analyses.

## CONCLUSION

In summary, the present study identified a set of behavioral characteristics that distinguished children with FASD from children with two commonly associated childhood disorders, namely ADHD and ODD/CD. Clinicians and researchers working with children with FASD have long struggled to find appropriate interventions that meet the specific and diverse needs of this population, which may in part from the fact that the core disabilities of FASD are poorly understood. Our present work aimed at developing a screening tool, provided critical and unique information delineating the FASD profile from other psychopathological conditions and represents a critical step in alleviating this important public health concern.

Further information on the proposed screening tool as well as general screening for FASD can be found through the Canadian Association of Pediatric Health Centre's initiative for "Developing a National Screening Tool Kit for those Identified and Potentially Affected by FASD"(http://www.caphc.org/programs_fasd.html).

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**Corresponding Author:** kelly.nash@sickkids.ca

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# LANGUAGE IMPAIRMENTS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER

*Katherine R Wyper[1], Carmen R Rasmussen[2]*

*[1]Department of Educational Psychology, [2]Department of Pediatrics, University of Alberta, Alberta, Canada*

## ABSTRACT

### Background
Fetal Alcohol Spectrum Disorder (FASD) is associated with a range of disabilities, including physical, behavioural, and cognitive deficits. One specific area of concern in children with FASD is the use and development of speech and language. Language deficits in FASD have been linked to learning problems and social difficulties.

### Objectives
The current study sought to examine the language difficulties of children with FASD, and to identify areas of deficit that may be particularly pronounced among these children.

### Methods
Fifty children, aged 5 to 13, (27 with FASD, 23 control children) were tested on the CREVT-2, the TOLD-P:3, and the TOLD-I:3.

### Results
Children with FASD had significantly lower scores than control children on both receptive and expressive subtests of the CREVT-2. Younger children scored significantly lower than controls on the Relational Vocabulary and Sentence Imitation subtests of the TOLD-P:3, and older children were significantly delayed on the Word Ordering, Grammatic Comprehension, and Malapropisms subtests of the TOLD-I:3.

### Conclusions
This study identified several areas of marked difficulty in children with FASD, adding to the current understanding of language development in this population. The results have implications for tailoring early interventions, and for providing evidence-based support to children prenatally exposed to alcohol.

**Key Words**: *Fetal Alcohol Spectrum Disorder; language; communication*

Children with Fetal Alcohol Spectrum Disorder (FASD) display an array of physical, mental, cognitive, behavioural, and learning deficits.[1] Cognition is an area of particular concern, as children with FASD are shown to perform poorly on tasks of attention, intelligence, academic achievement, executive functioning, visual spatial ability, and memory. Another impairment that has been documented in children with FASD is a disrupted development and use of language.[2–5] In fact, Church and Kaltenbach[6] suggest that Fetal Alcohol Syndrome (FAS) may be one of the primary causes of hearing, speech, and language problems in children. Due to these impairments, individuals with FASD may struggle with social communication, particularly with respect to interpersonal language.[7] Many of these children display a limited use of interpersonal communication, especially in complex social interactions. Language impairments in FASD have also been associated with learning

difficulties,[8] difficulties initiating and maintaining conversation,[8] behaviour problems,[9] handling peer interactions and following social norms, social reasoning, and information processing.[10]

Although the evidence of language impairments in individuals with FASD is mixed, Mattson and Riley[5] indicate that, overall, the literature suggests significant speech and language delays in this population. Specifically, children with FASD may exhibit impairments in areas such as word articulation, naming ability, word comprehension, and both receptive and expressive language skills.[5] Some studies also suggest that children with FASD display a greater deficit on language-based measures of intelligence (Verbal IQ) than on visual or hands-on measures of intelligence (Performance IQ).[8,11–14] Moreover, deficits in verbal comprehension and spoken language,[15] language comprehension,[16] inappropriate use of pragmatic language,[3] poor linguistic understanding,[17] delayed language acquisition,[18] as well as delayed speech development, voice dysfunction, articulation disorders, and fluency and rate problems[9] have all been documented in children with prenatal alcohol exposure (PAE). Neuroimaging research in FASD has also reported functional impairment (as measured by functional magnetic resonance imaging (fMRI)) in multiple areas of the brain, including the temporal lobe, which is involved in language and learning (among other functions).[19]

As early as 1968, Lemoine, Harousseau, Borteyru, and Menuet[20] (as cited in Becker et al.[2]) reported speech and language impairments in children (n = 127) born to women with chronic alcoholism. Similar impairments were found in Iosub et al.'s study[9] of 45 individuals with FASD, where 80% were found to have delays in speech and language ability. Becker et al.[2] also found deficits in grammatical, semantic, and articulation ability, as well as poorer linguistic memory skills in children with FASD.

In 1991, Carney and Chermak[21] examined language development in ten children with FAS and 17 typically developing control children, between ages 4 and 12 years. Using the Test of Language Development – Primary (TOLD-P) and Test of Language Development – Intermediate (TOLD-I), Carney and Chermak[21] measured the phonologic, semantic, and syntactic elements of both receptive and expressive language in these children. Children with FAS displayed significant deficits on all but one subtest (*Word Articulation*) of the TOLD-P, and performed poorly on three (*Sentence Combining*, *Word Ordering*, and *Grammatical Comprehension*) out of five subtests on the TOLD-I as compared to controls. Carney and Chermak[21] suggest that older children with FAS experience deficits primarily with respect to the syntactic aspects of language, whereas younger children display more global language deficits. One explanation for this age-related difference is that as children age, their knowledge of vocabulary grows, but they still struggle to understand the grammatical and morphological aspects of language.[21]

More recently, Coggins et al.[3] examined communication deficits among a large sample (n = 393) of school-aged children with FASD. These children completed numerous standardized tests of language performance, which assessed their fundamental language skills, language comprehension, language development, overall language competence, and word knowledge. Nearly three-quarters of the children displayed significant language deficits, with 31% scoring in the mildly impaired range and 38% classified as moderately-to-severely impaired.[3] It is important to note, however, that many of these children had experienced adverse environmental conditions (e.g., abuse, neglect, unpredictable or negative caregiving, etc.), which may have confounded the effects of PAE alone.[3]

In another recent study, McGee, Bjorkquist, Riley, and Mattson[22] tested 25 children (aged 3 to 5 years) with *heavy* PAE (minimum of 4 drinks per occasion, once or more per week, or 14 drinks per week during pregnancy). They found that these children had significant deficits in both receptive and expressive language, and that expressive language was more severely impaired. Interestingly, McGee et al.[22] suggest that when general intellectual ability is taken into consideration, language is neither a strength nor a weakness in children with FASD (i.e., receptive and expressive language functioning is no more or less impaired than overall IQ). Nonetheless, they also note that language deficits have an impact on social communication and behavioural adjustment, and may lead to social rejection and problems later in life.[22]

Some of the factors believed to underlie the language deficits found in FASD include hearing impairments, dentofacial abnormalities, and overall cognitive impairment.[23] Children with FASD who have language impairments very often also have hearing disorders,[23] and central hearing deficits are hugely influential on language development, comprehension, and academic achievement. Dentofacial defects often require surgery and orthodontic intervention and influence speech production in individuals with FASD. Adnams et al.[24] suggest that a fundamental deficit in phonological awareness may also contribute to language and literacy problems in children with FASD.

Contrary to the vast body of research reporting language impairments in FASD, Greene, Ernhart, Martier, Sokol, and Ager[25] studied a group of over 250 children prenatally exposed to alcohol (without an FASD diagnosis) and found that language development was not related to alcohol exposure. Similarly, another study examining the relationship between prenatal exposure to teratogens (marijuana, cigarettes, and alcohol) and language development found no effect of alcohol on these abilities.[26] O'Leary, Zubrick, Taylor, Dixon, and Bower[27] also found that low levels of PAE were not related to language delays in later life. However, they noted a threefold (albeit nonsignificant) increase in risk of language delay in children of mothers who binge drank during late pregnancy.[27]

Several potential explanations for these contradictory findings exist. First, studies finding no effect of PAE on language difficulties may be explained by low levels of maternal alcohol consumption[26] and the use of less complex language measures,[28] whereas studies that report significant results employ tasks that also rely on phonological working memory.[29] The timing and pattern of drinking may also play a role in the degree of impairment, as heavy exposure in late pregnancy is associated with greater risk of language delay.[27] Also, Abkarian[30] suggests that even among children with PAE who have no documented or apparent problems with the use of verbal language (or cognitive functioning), there are often difficulties with comprehension and social communication ability. It has also been suggested that although children with FAS seem to have adequate social speech skills, the content of their speech is often irrelevant or off-topic.[30] Thus, while some children with PAE seem to have appropriate conversational skills on a superficial level, they may nonetheless struggle with higher-level linguistics. Furthermore, Hamilton[31] (as cited in Coggins et al.[7]) found that children with FAS were significantly more likely than controls to communicate using inappropriate responses during conversation. That is, children with FAS were less likely to elaborate on or extend the comments of their conversation partner. Finally, Coggins et al.[7] point out that when children with FASD are examined in less structured, more naturalistic environments (i.e., in social contexts and conversational narratives rather than standardized testing conditions), they display greater limitations than would be predicted based on their standardized test scores.

Although significant broad language impairments have been documented in both children and adults with FASD, there is a lack of data on the effect of PAE on specific linguistic processes.[28] Moreover, much attention has been devoted to understanding how well individuals with PAE understand and produce language, but no core deficit, profile, or consistent pattern of difficulties has yet been identified in this population.[3,5,7] Also, although deficits in both receptive and expressive language as well as language acquisition have been documented in children with FAS, less research has focused on the unique speech and language characteristics of these children.[32] Thus, the aim of the current study was to explore language abilities in children with FASD, and to add to the current understanding of the language profile in this population. Identifying a pattern of language deficits in children with FASD has diagnostic implications because language is one of the key neurobehavioural areas assessed in the diagnosis of FASD. Two broad, standardized measures of language were administered to identify the most severe areas of language deficit in children with FASD, with the ultimate goal of informing intervention research.

## METHODS

### Participants

Fifty children participated in this study: 27 children (10 females) with FASD, and 23 typically-developing control children (9 females).

All children with FASD had previously been medically diagnosed with an alcohol-related disorder falling under the umbrella term FASD (Neurobehavioural Disorder: Alcohol Exposed [NBD:AE], n = 13; Static Encephalopathy: Alcohol Exposed [SE: AE], n = 8; partial Fetal Alcohol Syndrome [pFAS], n = 1; Fetal Alcohol Syndrome [FAS], n = 2). Three participants had confirmed FASD, but a more specific diagnosis was not recorded in their clinical files. All children in the FASD group were recruited and diagnosed through the Glenrose Rehabilitation Hospital FASD clinic. They underwent an extensive multidisciplinary assessment according to the four-digit diagnostic code described by Astley.[33] Specifically, for brain dysfunction, a code of 1 indicated no evidence of brain damage, 2 indicated mild to moderate delay of dysfunction, and 3 indicated significant dysfunction. A brain code of 4 is given only to those with definite brain damage as indicated by structural evidence (e.g., microcephaly, structural abnormalities on MRI). Assignment of a brain code of 3 required significant impairment across three or more neurobehavioural domains (sensory/motor, communication, attention, intellectual, academic achievement, memory, executive functioning, adaptive functioning), whereas a brain code of 2 was assigned when current data did not support a ranking of 3 or 4 despite a strong history of significant cognitive and/or behavioural problems. For alcohol, a code of 1 indicates no risk, 2 unknown, 3 some risk, and 4 high risk. The clinic coordinator confirmed alcohol exposure prior to acceptance into the clinic, with scores of 3 and 4 seen as significant enough to lead to brain damage and thus acceptable for clinic admission. Confirmation of alcohol use was obtained from birth records, Child and Youth Services documentation, from the birth mother directly, or other reliable sources. Except for birth mother report, corroborative evidence of PAE was required. Rankings of growth deficiency and facial phenotype (where a code of 1 indicates unlikely, 2 possible, 3 probable, and 4 definite) were made by a developmental pediatrician. See Table 1 for a more comprehensive breakdown of diagnostic information for children with FASD.

**TABLE 1**

Breakdown of Diagnoses of Children With FASD (Astley[33])

| Score | Growth | Face* | Brain Function | Alcohol Exposure |
|---|---|---|---|---|
| 1 | 59.3% (16) | 40.7% (11) | 0% (0) | 0% (0) |
| 2 | 3.7% (1) | 29.6% (8) | 44.4% (12) | 0% (0) |
| 3 | 3.7% (1) | 3.7% (1) | 37.0% (10) | 33.3% (9) |
| 4 | 14.8% (4) | 3.7% (1) | 0% (0) | 48.1% (13) |

*Note:* Growth, Face, and Brain function scores: 1 = unlikely, 2 = possible, 3 = probable, 4 = definite. Alcohol exposure, Prenatal, and Postnatal scores: 1 = no risk, 2 = unknown risk, 3 = some risk, 4 = high risk.
*One participant had a cleft palate, thus a face score was unobtainable.

Additional data was obtained from the Glenrose FASD clinic database on potentially confounding variables, including exposure to other teratogens, comorbidities, number of placements, current placement, and IQ scores. Seven children in the FASD group had confirmed exposure (and one suspected exposure) to cocaine, one was exposed to heroine, six to tobacco, two to marijuana, two to "other" intravenous drugs, three to suspected/unspecified teratogens, eight unknown, and four were not exposed to any teratogens other than alcohol. Seven children had comorbid ADHD diagnoses (one with an ODD diagnosis as well), and two met the criteria for mental retardation. The average number of placements that children with FASD had experienced was 2.04 with a range of 1 to 4 (placement data was unavailable for three participants). Eleven children lived with biological family members (five with mother, one with father, four with grandparents, one with extended family), five were living in foster

placements, and eight had been permanently adopted. Fourteen children had been placed in their current homes between birth and 1 year of age, and seven between the ages of 1 to 4. Information regarding timing of placement was unavailable for six children. IQ scores were available for 20 children with FASD, with a mean of 85 (range 58-111).

Control children were recruited through colleagues, and none were diagnosed with FASD or any other neurobehavioural disorder (including ADHD and LD). Children with FASD ranged in age (in years-months) from 5-0 to 13-3, with a mean age of 9-0, and control children ranged in age from 5-0 to 13-3, with a mean age of 8-8. There was no significant difference in age between the two groups, ($F(1,46) = .32$, $p = .57$). All control participants resided in their biological parents' homes. Information regarding socioeconomic status (SES) was not available for either group.

**Procedure**

All children were tested on two measures of language ability: the Comprehensive Receptive and Expressive Vocabulary Test – Second Edition (CREVT-2[34]) and the Test of Language Development – Third Edition (TOLD-3[35]). There are two different versions of the TOLD-3 (primary and intermediate), designed for children of distinct younger and older age ranges. Thus children aged 5 through 8 years (12 FASD and 13 control) completed four subtests of the primary version of the TOLD-3 (TOLD-P:3[35]), and children aged 9 through 13 years (14 FASD and 10 control) completed four subtests of the intermediate version (TOLD-I:3[36]). All children completed the same version of the CREVT-2. These tests were consistently administered and scored by one research assistant. Children with FASD were tested as part of a more comprehensive cognitive battery, with the TOLD:3 and CREVT-2 administered at the end of the testing session. Control children were tested on language measures only, completing the TOLD:3 first, and the CREVT-2 second. Breaks were provided to all children as needed. Approval for this study was obtained from the Health Research Ethics Board at the University of Alberta.

**CREVT-2[34]**

***Receptive Vocabulary***

This task measures receptive oral vocabulary. The examiner reads a series of words, and the participant must point to a picture that best matches the word.

***Expressive Vocabulary***

This task measures expressive oral vocabulary. The examiner reads a series of words, and the participant is asked to describe their meanings.

**TOLD-P:3[35]**

***Relational Vocabulary***

This task measures participants' understanding and oral expression of the relationship between two words. Children must describe how two words are alike. For example, the examiner asks, "How are a pen and pencil alike?" and the child must respond with "they are writing tools," or some similar variation.

***Grammatic Understanding***

This syntactic task measures participants' comprehension of the meaning of sentences. The examiner reads a sentence, and the child must select one of three pictures that best matches the stimulus sentence.

***Sentence Imitation***

This task assesses participants' ability to produce correct sentences. The examiner reads a sentence and the child must imitate it exactly.

***Grammatic Completion***

This task measures a child's ability to recognize, use, and understand common English morphological forms, and focuses particularly on their knowledge of inflections. The examiner reads an incomplete sentence, and the child must finish the sentence by supplying the missing morphological form. For example, the examiner reads, "Carla has a dress. Denise has a dress. They have two _____" (pause), and the child must respond with "dresses."

**TOLD-I:3[36]**

***Word Ordering***

This task involves both listening and speaking skills, but focuses more on speaking ability, and measures syntactic ability. The examiner supplies the child with a string of randomly ordered words, and the child must rearrange the words to make a proper sentence. For example, when the examiner

reads "big, am, I," the child may respond with "I am big," or "am I big?"

***Generals***

This is primarily a speaking task, and measures semantic ability. The examiner reads three words, and the child must tell how they are alike. For example, the examiner reads "Mars, Venus, Pluto," and the child must state that they are all planets.

***Grammatic Comprehension***

This task mainly involves listening, and measures syntactic ability. It assesses a child's ability to recognize incorrect grammar in a spoken sentence. The examiner reads a series of sentences and the child is asked to identify whether they are correct or incorrect.

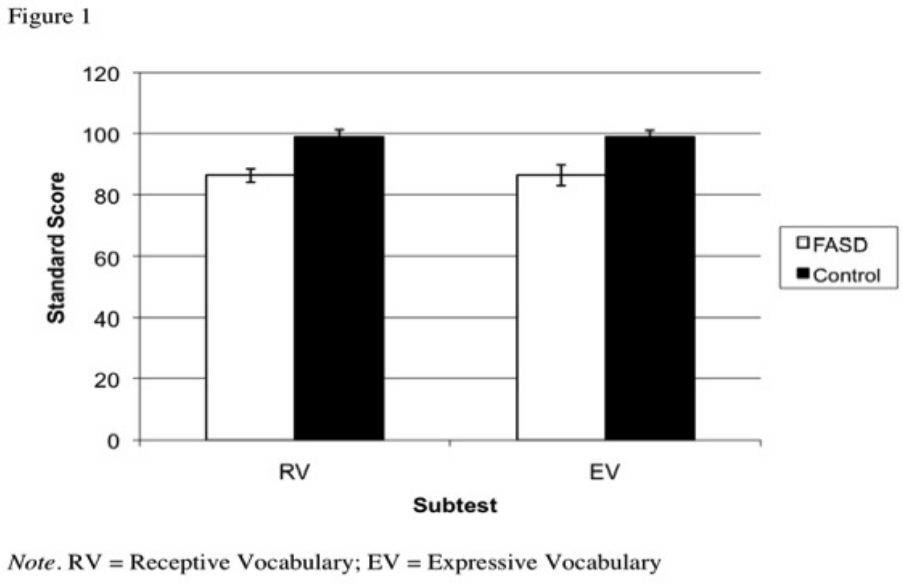
***Malapropisms***

This semantic task focuses primarily on receptive language skills. The examiner reads sentences that include malapropisms, which are words that sound appropriate, but are incorrect given the context of the sentence. The child must identify the malapropism, and provide the appropriate word. For example, when the examiner reads, "Mary had a little *ham*," the children must state that *ham* should be replaced with *lamb*.

## RESULTS

Mean scores and group comparisons are presented in Figure 1. Performance on the CREVT-2 was analyzed with a 2(Group: FASD, Control) x 2(Gender) x 2(Subtest: Expressive Vocabulary, Receptive Vocabulary) ANOVA with repeated measures on the last variable. Across all children, there was no significant difference between performance on the Receptive and Expressive subtests of the CREVT-2 $F(1, 43) = .036$ ($p > 0.05$), and there was no interaction between Group $F(1, 43) = .035$ ($p > 0.05$) or Gender $F(1, 43) = .991$ ($p > 0.05$). However, between-subject analysis revealed that there was a significant effect of Group, indicating that, overall, children with FASD had lower scores on the CREVT-2 than control children $F(1, 43) = 13.70$ ($p < 0.01$), $\eta p^2 = .24$. Because there was no effect of Gender in the CREVT-2 analysis, this variable was removed from all further analyses.

**FIG. 1** Mean scores and group comparisons among children with FASD and control children on the CREVT-2



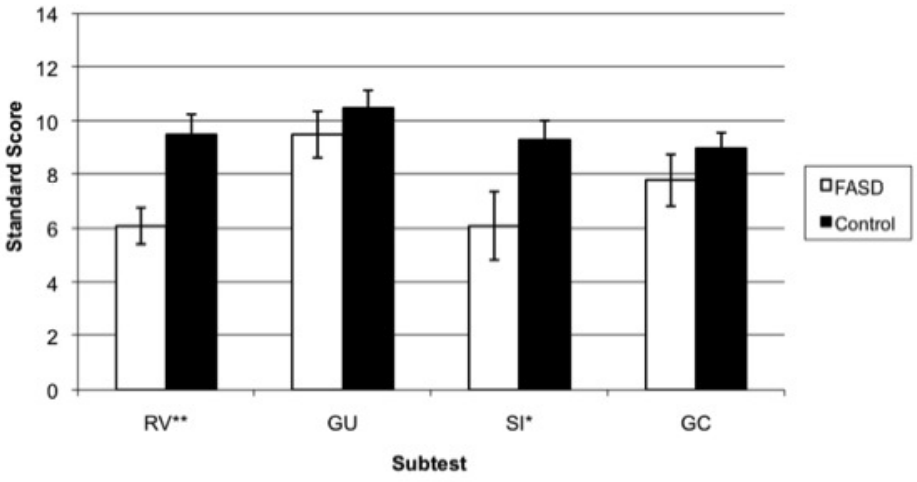

*Note*. RV = Receptive Vocabulary; EV = Expressive Vocabulary

Due to the different age ranges in the TOLD-3 measures, the sample sizes in the following analyses were approximately half of the entire sample. In the TOLD-P:3 analyses, there were 12 children with FASD and 13 control children, and in the TOLD-I:3, there were 14 children with FASD and 10 controls. Mean scores and group comparisons for the TOLD-P:3 are presented in Figure 2. To compare the effect of Group on the different TOLD-P:3 subtests, separate one-way between-subjects ANOVAs were performed. Children with FASD performed significantly poorer than control children on the Relational Vocabulary $F(1, 23) = 10.96$ ($p < 0.01$) and Sentence Imitation $F(1, 22) = 5.23$ ($p < 0.05$) subtests, but differences were not significant on Grammatic Understanding $F(1, 23) = 1.09$ ($p > 0.05$) or Grammatic Completion $F(1, 23) = 1.22$ ($p > 0.05$).

Mean scores and group comparisons for the TOLD-I:3 are presented in Figure 3. Separate one-way between-subjects ANOVAs were conducted again to compare the effect of Group on the different TOLD-I:3 subtests. Children with FASD performed significantly poorer than control children on the Word Ordering $F(1, 23) = 16.12$ ($p < 0.01$), Grammatic Comprehension $F(1, 23) = 24.77$ ($p < 0.01$), and Malapropisms $F(1, 23) = 20.63$ ($p < 0.01$) subtests, but differences were not significant on the Generals subtest $F(1, 23) = 1.70$ ($p > 0.05$).

**FIG. 2** Mean scores and group comparisons among children with FASD and control children on the TOLD-P:3

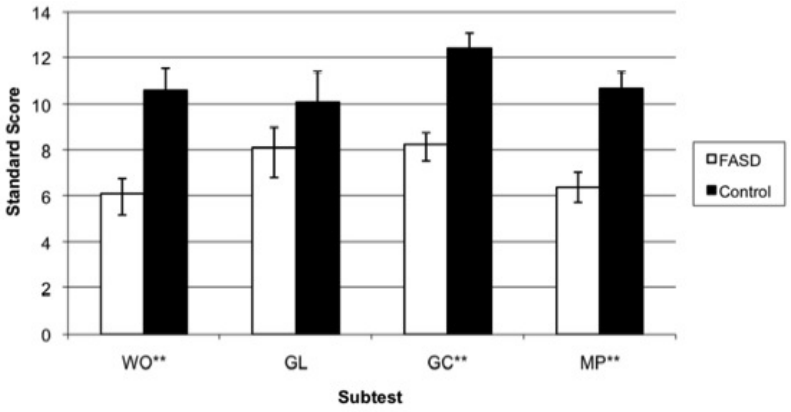
Figure 2




*Note*. *$p < 0.05$, **$p < 0.01$; RV = Relational Vocabulary; GU = Grammatic Understanding; SI = Sentence Imitation; GC = Grammatic Completion

**FIG. 3** Mean scores and group comparisons among children with FASD and control children on the TOLD-I:3

Figure 3




*Note*. *$p < 0.05$, **$p < 0.01$; WO = Word Ordering; GL = Generals; GC = Grammatic Comprehension; Malapropisms

To examine whether severity of FASD was related to severity of language impairment, two separate one-way ANOVAs were conducted. The first compared performance of children with a moderate diagnosis (Neurobehavioural Disorder: Alcohol Exposed) to performance of children with more severe diagnoses (Static Encephalopathy: Alcohol Exposed, partial Fetal Alcohol Syndrome, and Fetal Alcohol Syndrome). There was no significant difference between diagnostic groups on any language subtest (see Table 2 for a report of statistical values). A second ANOVA was conducted comparing children with a CNS code of 2 (indicating moderate dysfunction) and children with a CNS code of 3 (indicating severe dysfunction) based on Astley's[33] 4-digit code system. No significant differences were found between the two groups. Age was not correlated with any of the subtests administered except for the CREVT-2 Expressive Vocabulary subtest in control children only $r(20) = 0.51$.

To investigate whether home instability (i.e., multiple placements after birth) affected performance on language measures in children with FASD, we conducted a one-way ANOVA comparing scores of children who remained in one home after birth (biological or foster/adopted) and children who had experienced multiple placements. Due to small sample sizes for both TOLD:3 measures, we only analyzed scores on the CREVT-2 subtests. There was no significant difference between children with a single home placement and those with multiple placements on either of the CREVT-2 subtests, $F(1, 22) = 0.10$ ($p > 0.05$) and $F(1, 21) = 0.76$ ($p > 0.05$) for CREVT-2 Receptive vocabulary and Expressive vocabulary, respectively.

## DISCUSSION

Ample research has been conducted to examine language development in individuals prenatally exposed to alcohol, both with and without FASD diagnoses. Many of these individuals tend to be delayed in fundamental language skills and acquisition, comprehension, language and speech development, overall language competence, and knowledge of words.[3] Deficits range from lower levels of language functioning, such as word articulation, naming, and comprehension[5] to more

complex communication abilities, such as semantics, grammar, syntax, linguistic understanding and memory, and inappropriate use of pragmatic language.[2,3,17,21]

Despite the fact that such considerable language deficits have been documented in individuals with PAE, relatively little attention has been devoted to identifying unique patterns or profile of impairment in these individuals.[3,5,7,32] Thus, the aim of the current study was to ascertain what aspects of language are most significantly affected in children with FASD, and to identify a profile of language impairments. Children with FASD performed significantly poorer than control children on both the receptive and expressive subtests of the CREVT-2, indicating that these children struggle to match pictures to spoken words, and accurately describe the meanings of commonly used words. There was no difference in performance between the Receptive and Expressive subtests, suggesting that both components of oral vocabulary are impaired in children with FASD.

To examine whether there is a profile of language impairment in children with FASD, we compared FASD and control children on the subtests of the TOLD-3 (separately for the primary and intermediate versions). Children with FASD had significantly lower scores on two subtests of the TOLD-P:3– Relational Vocabulary and Sentence Imitation – but not Grammatic Understanding or Grammatic Completion, and on three subtests of the TOLD-I:3 – Word Ordering, Grammatic Comprehension, and Malapropisms – but not on Generals. This suggests that younger children with FASD struggle most with understanding and expressing the relationship between words and imitating spoken sentences. Yet they are not impaired in comprehending sentences or recognizing, using, and understanding common morphological forms. Older children seem to have the most difficulty with speaking and syntactic ability, recognizing and correcting incorrect grammar, and identifying and correcting malapropisms. Semantic ability in these older children appears to be unaffected. These results are slightly different than those reported by Carney and Chermak,[21] who suggest that younger children possess a more global deficit, whereas older children primarily have difficulty with the syntactic elements of language. That is, the results from this study may indicate that older children are impaired in more areas of functioning. This discrepancy may be due to the fact that Carney and Chermak's[21] sample size (n = 10) was slightly smaller than that of the current study (n = 24), and only included American Indian children, thus representing a very specific population. Their results may also have differed from the current study because they tested children with the most severe diagnosis in the FASD spectrum (FAS), whereas the diagnoses of children in this study ranged from NBD:AE to full FAS. Regardless, both Carney and Chermak's[21] and the current study suggest that children with FASD are significantly impaired in numerous areas of language development, particularly with regard to syntax.

Language difficulties are shown to have broad implications, as individuals with FASD tend to struggle with interpersonal language, peer interaction, appropriate conversation content, social reasoning, and information processing, especially as the complexity of social interaction increases.[7,8,10,30] Further, language deficits in individuals with FASD have been linked to learning and behaviour problems,[8,9] as well as "secondary disabilities" including difficulties with school and work, health problems, and legal issues.[7]

As described by Coggins et al.[7] and others, these language deficits have a long-lasting and profound impact on the lives of affected individuals, and are interconnected with a variety of factors. Research has also examined language within the context of social interaction. Results of these studies suggest that as the complexity of the social situation increases, children with FASD experience more difficulty using language appropriately.[7] As the demands of unstructured social interactions rise, the ability to use interpersonal language appropriately declines in children with FASD. This is an important finding, as such unstructured conditions are much more typical of everyday life than are the conditions of a standardized testing session. Simply having the necessary language does not suffice for competent communication; it is the ability to know *how* and *when* to use language that leads to success in social environments.

Coggins et al.[7] provide a thorough examination of the social implications of language

delays in FASD. They suggest that the pervasive neuropsychological deficits in individuals with FASD impair their ability to interact and communicate in social situations. Moreover, this impairment has been linked to "secondary disabilities" including mental health issues, legal problems, and difficulties with school or work.[7] As such, research that examines the specific language difficulties of individuals with FASD is important in designing interventions specifically tailored to this population.

A proper assessment of language ability may offer a significant clinical advantage for children with FASD, as the quality of narrative language skills in congruence with other abnormalities such as expressive language may be an indicator of PAE. Specifically, a distinct pattern of story-telling in social discourse may exist in children with FASD, regardless of their performance on a standardized expressive language task.[37] This suggests that, in addition to informing therapeutic intervention, language assessment may also have utility in the process of diagnosing FASD. For instance, children with FASD may display a particular pattern of pragmatic and semantic language deficits[37] which could inform the diagnostic process. Moreover, the existence of language and speech deficits in congruence with hearing dysfunction and craniofacial anomalies (e.g., cleft palate, cleft lip) may be important in the diagnostic process.[23] One factor to consider in the assessment of language and intelligence is hearing disorders, as they may impact the validity of language and intelligence measures.[23] Early evaluation and intervention for hearing, speech and language, and dentofacial dysfunction is critical, as receptive language, comprehension, language acquisition, and intellectual development may all be impaired by such deficits.[23]

Improperly identifying the neurodevelopmental deficits in children with FASD, and particularly those related to language, may lead to an underestimation of a child's need for school-based interventions.[38] As well, since unrecognized language deficits may result in poor development of coping strategies, leading to problem behaviours, there is a great need for schools and speech-language pathologists (SLPs) to increase their understanding of the neurobehavioural deficits in children with FASD (especially those who have experienced trauma), and tailor interventions to their specific needs.[38] Adopting a holistic and systemic perspective, which involves collaboration across disciplines, enables professionals to more effectively enhance the neurodevelopmental outcomes of children with FASD. Specifically, looking beyond the child to the familial and societal context in which he or she lives, as well as considering impairments beyond language ability (e.g., sensory and other cognitive deficits) is crucial in effectively meeting his or her needs and improving functioning.[39]

One example of a holistic intervention is the brain-behaviour based approach, whereby special attention is devoted to the child's unique difficulties, and aims to provide children with both physical and psychological safety in order to increase their ability to express their emotions and develop positive behaviours.[38] Another intervention was implemented by Adnams et al.[24] to ameliorate language deficits in children with FASD in South Africa. The intervention – Language Literacy Training (LLT) – is aimed at developing phonological awareness and other early literacy skills that contribute to efficacy in reading and spelling. The intervention was tested among three groups of children: children with FASD who received the intervention (LLT), children with FASD who did not receive the intervention (FASD-C), and control children without PAE who did not receive the intervention (NONEXP-C). The LLT group displayed significant relative gains over FASD-C on several language measures and caught up significantly to the NONEXP-C group on complex literacy skills.[24]

Another environmental factor that affects language development in children with FASD is early caregiving experiences. During an alcohol-affected child's first years of life, caregiving is suggested to have an especially important impact, not only on social and emotional development, but also on the neuropsychological functioning of the child (with concentration, attention, and language/speech problems being most significantly affected).[40] Specifically, placement in a long-term foster care setting and fewer traumatic experiences are associated with lower risk of problems in these areas.[40] Moreover, children who are exposed to alcohol in utero as

well as traumatic events in their early life have more severe neurodevelopmental impairments (including language deficits) than traumatized children without PAE.[38]

**Study Limitations**

One limitation in this study is that we were only able to match control children on age and gender, and therefore unable to examine explicitly how SES and other environmental issues, emotional problems such as depression and anxiety, other comorbidities such as ADHD or LDs, or pattern and timing of maternal drinking may impact the language abilities of children with FASD. An inherent difficulty in FASD research is that it is virtually impossible to control for post-natal and environmental factors that influence a child's development after birth, particularly for those with FASD. A second limitation of this study is that the measures we used to test language impairment do not represent the entire spectrum of abilities that contribute to communication. For instance, measures of hearing, working memory, problem solving, social perception, as well as complex measures that involve conversation or higher-level narratives would provide a more complete understanding of the context surrounding language disabilities in FASD. Lastly, because of the age division on the TOLD:3, our sample size for this measure was rather small. Age differences on the TOLD:3 must be interpreted with caution because this study was not longitudinal, thus further longitudinal research on language development in FASD is important. Although the results of the current study add to the overall understanding of language development in children with FASD, it is not possible to say whether the documented language deficits are due to diagnosis alone. Research using more specific and complex measures with a larger population with well controlled variables is warranted to identify a specific profile in these children.

## CONCLUSION

This study supports the literature suggesting significant language deficits in FASD. It demonstrates that children prenatally exposed to alcohol have problems with many of the basic language skills that are fundamental in cognitive, behavioural, and social development. As Adnams et al.[24] note, one of the reasons for the lack of systematically researched interventions for children with FASD is that there is no consensus on a specific neurobehavioural or cognitive profile. Therefore, the current study contributes in terms of identifying areas of deficit displayed by these children. Most importantly, it highlights areas that may be considered in designing interventions for improving basic language skills, which may have implications for the development of learning and behaviour, interpersonal communication, and social skills in individuals with FASD.

***Acknowledgments***

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**Corresponding Author:** carmen@ualberta.ca

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# Cognitive and behavioral effects of prenatal alcohol exposure

Piyadasa W Kodituwakku†, Judith M Segall[1] & Gregory K Beatty[2]
[1]Mind Research Network, Albuquerque, NM, USA
[2]Department of Psychology, University of New Mexico, Albuquerque, NM, USA
†Author for correspondence: Departments of Pediatrics & Neurosciences, Center for Development & Disability, University of New Mexico School of Medicine, 2300 Menaul NE, Albuquerque, NM 87107, USA
■ Tel.: + 1 505 272 1861 ■ Fax: + 1 505 272 3140 ■ pkodituwakku@salud.unm.edu

Children exposed to substantial amounts of alcohol prenatally are known to display a range of physical and cognitive anomalies, referred to as fetal alcohol spectrum disorders (FASDs). Animal models and neuroimaging studies of FASDs have consistently demonstrated that specific regions of the brain (e.g., midline structures) are more vulnerable to the teratogenic effects of alcohol than other regions. The main aim of this article is to assess whether findings from cognitive–behavioral studies of FASDs yield a profile that maps onto the pattern of damage revealed by neuroanatomical investigations. To achieve this aim, the findings from studies that have investigated elementary functions (e.g., associative learning), general functions (e.g., intellectual abilities), specific functions (e.g., language and memory) and behavior in children and adults with FASDs are examined. The cognitive–behavioral profile emerging from the data is defined as a generalized deficit in processing and integrating complex information. It is proposed that slow processing of information mainly contributes to this deficit. The clinical implications of the above characterization of the cognitive–behavioral profile in FASDs are discussed.

Since fetal alcohol syndrome (FAS) was first described approximately four decades ago [1,2], tremendous advances in our understanding of the teratogenic effects of alcohol have taken place. It is now known that children exposed to substantial amounts of alcohol during pregnancy exhibit a range of morphological and functional outcomes that are collectively referred to as fetal alcohol spectrum disorders (FASDs). On one end of the spectrum are those who display a characteristic pattern of malformations known as FAS. However, the majority of alcohol-exposed children have been found to show some or none of the dysmorphic features of FAS, but they do exhibit evidence of cognitive deficits and behavioral problems. The terms 'alcohol-related birth defects' and 'alcohol-related neurodevelopmental disorder' (ARND) are used to label specific clusters of minor physical anomalies and cognitive deficits in those who do not meet the diagnostic criteria of FAS [3]. Common to all individuals on the spectrum are the adverse outcomes of central nervous damage, which have been found to negatively impact not only affected individuals and their families, but also society in general [4].

The marked variability in the teratogenic effects of alcohol presents a formidable challenge to diagnosing individuals with prenatal alcohol exposure, particularly those with ARND. The diagnostic criteria of FAS, which are well established and have reliably been used across various ethnic groups, include pre- and/or post-growth restrictions, a characteristic pattern of malformations on the face and evidence of CNS dysfunction [5]. Children with FAS are small in stature, with their height and weight being below the tenth percentile. The characteristic pattern of facial anomalies includes the short palpebral fissures, smooth philtrum and thin vermillion border. CNS dysfunction is evidenced by microcephaly and cognitive–behavioral disabilities. Children with FAS may also exhibit birth defects involving other systems such as cardiac (e.g., atrial and ventricular septal defects), skeletal (e.g., clinodactaly), ocular (e.g., strabismus) and auditory (e.g., conductive hearing loss) systems [3]. Since the majority of individuals with prenatal alcohol exposure do not exhibit clinically discernable physical malformation, clinicians are faced with a challenging epistemological question: how does one know that observed neurodevelopmental problems in a child with prenatal alcohol exposure are indeed alcohol related? Particularly, clinicians find it difficult to distinguish children with ARND from other clinical groups such as attention deficit–hyperactivity disorder (ADHD) and conduct disorder [6,7].

Therefore, the question of whether alcohol-exposed children display a unique profile of cognitive skills and behavior has attracted considerable attention over the last 30 years, because identification of such a profile will aid in diagnosing ARND [8]. The identification of a unique pattern

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Future Neurology

Keywords
■ alcohol-related neurodevelopmental disorder ■ behavioral phenotype ■ cognitive phenotype ■ cognitive profile ■ fetal alcohol spectrum disorder ■ fetal alcohol syndrome

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of cognition and behavior in FASDs will also inform the development of intervention programs for alcohol-affected children.

## Delineation of cognitive & behavioral profiles in fetal alcohol spectrum disorders

Converging evidence from animal models and neuroimaging studies of FASDs has revealed that specific brain regions (e.g., hippocampus, caudate and cerebellum) are more vulnerable to the deleterious effects of alcohol than other regions [4]. As Figure 1 shows, anomalous brain development in children with prenatal alcohol exposure is moderated by genetic factors and the quality of postnatal experiences. In other terms, the trajectory of atypical brain development in children with FASDs is presumed to be determined by dynamic interactions between atypical brain hardware and the quality of postnatal experiences. Associated with atypical brain development are atypical trajectories of cognitive development. Atypical patterns of development have been observed both in elementary functions such as eyeblink conditioning (EBC) [9] and in complex functions such as memory [10,11] and executive control [12]. As Figure 1 depicts, deficits in complex neuropsychological functions lead to impairments in adaptive behavior and numerous social and legal problems referred to as secondary disabilities [13–17].

Accordingly, the task of delineating cognitive and behavioral profiles in children with FASDs boils down to answering three primary questions. First, do children with prenatal alcohol exposure display a unique profile of elementary functions? Second, do children with prenatal alcohol exposure display a unique profile of complex functions? Third, and do children with FASDs display a unique pattern of social and adaptive behavior?

In the study of cognitive–behavioral profiles of children with FASDs, researchers have often utilized the strategy of comparing alcohol-exposed children with those without prenatal alcohol exposure on selected test batteries designed to assess specific cognitive functions [18,19]. The choice of functions for investigation has often been guided by clinical impressions, as well as by data from animal and neuroimaging studies. Therefore, in the first section of this article we briefly review the literature on animal models of FASDs. In the second section, we summarize the findings from neuroimaging studies of children with FASDs. The third section reviews the literature on elementary functions such as EBC, and the fourth section focuses on complex functions such as executive control, memory and language. In the fifth section, we present a theoretical framework based on data from psychometrics, cognitive psychology and cognitive neuroscience to organize and interpret cognitive–behavioral findings on FASDs. The sixth section summarizes findings from studies of parent-rated behavior. In the seventh and final section, we present a summary of the findings and discuss future directions of research on neurobehavioral functioning in children with FASDs.

Given that the main aim of this article is to delineate cognitive and behavioral outcomes of prenatal alcohol exposure, only a brief overview of

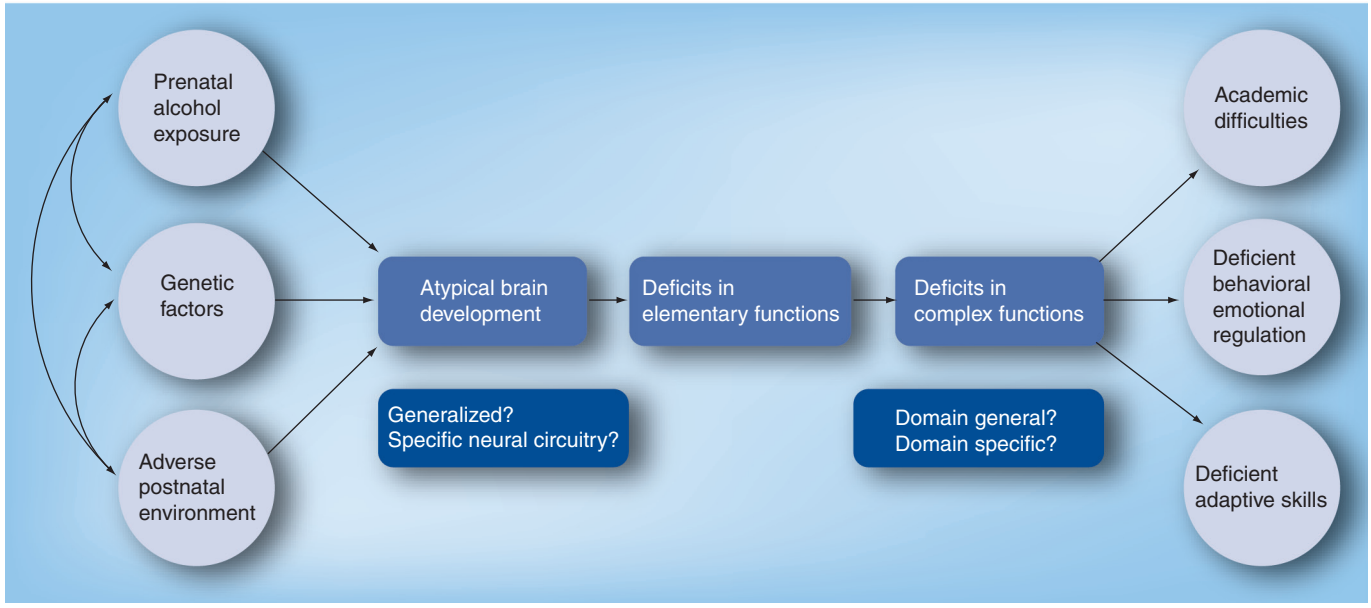


**Figure 1. Neuropsychological model of cognitive and behavioral outcomes of prenatal alcohol exposure.**
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the literature on animal models and neuroimaging studies of FASDs will be presented. The goal of this brief overview is to underscore two main findings that are relevant for human studies of FASDs: the specificity of alcohol's teratogenecity, and the plasticity of alcohol-exposed brains.

## Animal models of fetal alcohol spectrum disorders

Researchers have successfully created one or several morphological or behavioral characteristics of FASDs in a number of animal models including nonhuman primates, rodents (e.g., rats and mice), large animals (e.g., pigs) and simple animals (fish) [20]. Because animal models allow researchers to systematically manipulate the quantity, timing and frequency of exposure as well as genetic and environmental variables, these models have been used to demonstrate the specificity of alcohol's teratogenesis [21] in order to elucidate the mechanisms underlying the teratogenic effects [22] and to test the efficacy of behavioral and pharmacological interventions to reduce or ameliorate these effects [23,24].

In the early 1980s, researchers were successful in inducing the craniofacial malformations in animal models that resemble those seen in humans with FAS [21,25,26]. Sulik demonstrated that acute maternal alcohol administration at the gastrulation stages of embryonic development led to a range of malformation including microcephaly, short palpebral fissures and deficiencies in the philtral region [27]. Sulik also observed alcohol-induced deficiencies in the forebrain including the corpus callosum, basal ganglia, hippocampus and anterior cingulate [27]. These neuroanatomical findings have been confirmed and extended by magnetic resonance microscopic examination of mouse fetuses with acute alcohol exposure on gestational day 8 [28]. These investigators found volume reductions in every region that was examined, with the exception of the pituitary and septal regions. However, volume reductions were most pronounced in the olfactory bulb, hippocampus and cerebellum. Alcohol-induced birth defects, including growth restrictions, facial anomalies and defects in the CNS, have also been demonstrated in nonhuman primate models of FASDs [29,30].

Exposure to alcohol during later stages of brain development is known to produce specific patterns of anomalies. For example, exposure during epithelial cell proliferation and migration, which occurs from gestation day 12 to 21 in the rat and 7 to 21 weeks of gestation in the human, has been shown to disrupt the development of the cerebral cortex, as evidenced by decreased brain size [31], and the formation of specific structures (e.g., corpus callosum). Animal studies modeling alcohol exposure during the third trimester of human gestation have shown evidence of neuronal loss in multiple structures including the hippocampus and cerebellum [32,33]. In nonhuman primates, researchers have demonstrated alcohol-induced deficits in higher-level skills, such as object permanence [34].

Thus, animal studies of FASDs have demonstrated that specific regions of the brain are more vulnerable to the deleterious effects of alcohol. Animal models of FASDs have also considerably advanced our knowledge of the mechanisms underlying alcohol-induced damage in the developing brain. There is a growing body of literature showing that a number of mechanisms (e.g., disruption of glial development, oxidative stress and interruptions of neurotransmitters) contribute to alcohol-induced brain anomalies [22]. Recent studies of genetic and epigenetic influences on fetal development have provided fresh insights into the mechanisms of FASDs [35,36]. There is increasing evidence that ethanol exposure alters gene and miRNA expression in the fetal brain [37,38].

Furthermore, animal research has contributed considerably to our knowledge of potential behavioral strategies and pharmacological agents that can be used to ameliorate alcohol-induced deficits [23]. Investigators have obtained evidence that procedures such as neonatal handling [39,40], environmental enrichment [41] and rehabilitative training [42,43] produce behavioral changes in alcohol-exposed rodents. Neonatal handling, which is a well-established experimental procedure, usually involves separating pups from the dam for a brief period and stimulating them tactilely. While this procedure has been found to eliminate deficits in response inhibition [44] and reversal learning [39], it has been shown to be ineffective in the amelioration of spatial navigation deficits [45] or in the attenuation of the hypothalamic–pituitary–adrenal hyper-responsiveness associated with prenatal alcohol exposure [46]. Environmental enrichment typically involves the provision of increased opportunities for social interactions with conspecifics, enhancement of sensory experiences through increasing the variety and complexity of sensory input or the creation of an environment that promotes greater locomotor activity. A number of studies have documented that alcohol-exposed animals reared in enriched environments show a reduction

in alcohol-induced motor and learning deficits [41,47]. Klintosova *et al.* explored the efficacy of a structured motor training program in mitigating alcohol-induced motor deficits in an animal model of FASD [42,43]. The program involved performance of a series of complex motor tasks such as climbing ropes and rods, crossing narrow bridges and traversing beams. These investigators found that rehabilitative motor training ameliorated the alcohol-induced motor deficits and that these behavioral effects were associated with training-induced changes in cerebellar physiology and anatomy. Researchers have also employed animal models to evaluate the effects of pharmacological agents such as cognition-enhancing drugs on cognitive and behavioral deficits associated with prenatal alcohol exposure [48].

### *Neuroimaging studies*

The fact that microcephaly characterizes FAS naturally leads to the hypothesis that individuals with FAS may have pervasive brain damage. Consistent with this hypothesis, the early neuropathological studies of alcohol-exposed brains revealed evidence of widespread damage. Jones and Smith found various structural anomalies, including heterotopic cell clusters, enlarged lateral ventricles and agenesis of corpus callosum, in the brain of an infant with FAS who died 5 days after birth [5]. These findings were later confirmed by other neuropathological studies [49].

In view of the fact that the neuropathological findings are from the brains of children who had severe pathologies culminating in death, the question of whether these findings are of direct relevance to understating the brains of living individuals with FASDs can be raised [50]. However, recent advances in neuroimaging methodologies have allowed investigators to delineate structural and functional neuroanatomy in living individuals with FASDs. Consistent with the findings from animal models, neuroimaging studies of humans with FASDs have shown overall volumetric reductions and anomalies in specific regions of the brain, including the caudate and cerebellum [51]. Figure 2 illustrates microcephaly in an 18-year-old male diagnosed with FAS, who continues to show growth restrictions and facial anomalies. Compared with an age-matched normal control, the subject with FAS displays volumetric reductions in most regions of the brain. While numerous studies have documented global decreases in brain volume in individuals with FASDs [52,53], some have observed disproportionally greater reductions in some regions, particularly in the parietal region [53,54]. Using voxel-based morphometry, Sowell *et al.* also found that compared with controls, those with FASDs showed relative increases in the gray matter and decreases in the white matter in the perisylvian cortices of the temporal and parietal lobes [54].

A number of studies have reported abnormalities of the corpus callosum, ranging from microstructural anomalies in the posterior tracts [55] to partial or complete agenesis [56]. Bookstein and colleagues have reported that adults with prenatal alcohol exposure significantly differed from controls on morphometric indices of the corpus callosum, such as midline shape [57]. Using diffusion tensor imaging, a measure of tissue microstructural integrity, researchers have sought to determine whether specific regions of the corpus callosum (e.g., genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium) have been selectively damaged by alcohol teratogenecity. A number of studies have found abnormalities of the posterior corpus callosum of alcohol-exposed individuals, particularly in the isthmus [58] and in the lateral aspect of the splenium [59]. Others have observed differences in both the genu and splenium of the corpus callosum [52,60]. Several diffusion tensor imaging studies have reported evidence of anomalies in the white matter innervating a number of areas, including the bilateral medial and occipital lobes [61], lateral temporal lobes [59], basal ganglia and thalamus [52]. The white matter integrity has also been found to correlate with performances of children with FASDs on tests assessing visual–motor [59,62] and mathematical skills [63].

Some studies have suggested that the basal ganglia structures, particularly the caudate, are vulnerable to the effects of prenatal alcohol exposure [53,64]. Mattson *et al.* reported volumetric reductions in the caudate after controlling for reduced brain size [64]. Reduced size of the caudate nucleus can be seen in the image presented in Figure 2. Cortese *et al.* observed volumetric reductions as well as elevated metabolite ratios of *N*-acetyl-asparate (NAA):creatine, which is an index of neural function, in the caudate nucleus of alcohol-exposed children [65]. However, another group of investigators found that metabolite ratios NAA:creatine and NAA:choline were lower in alcohol-exposed children compared with controls in a number of regions including the parietal and frontal cortices, corpus callosum and thalamus [66]. Consistent with the findings from animal models, reductions in cerebellar volume in individuals with FASDs have also been reported [53]. Examination of regional

volumetric differences in the cerebellum has shown greater reductions in size of the anterior than in the posterior vermis [67].

Researchers have recently utilized functional MRI to investigate neural activation patterns in children with FASDs during performance of working memory, response inhibition and verbal learning tasks [68–71]. These studies have consistently shown that alcohol-exposed children exhibit blood oxygen level-dependent (BOLD) response patterns different from controls during task performance. Using functional MRI, we have obtained preliminary evidence that functional neural circuitries in alcohol-exposed children can be modified through practice. In a recent study, we recorded BOLD signals in alcohol-exposed children and controls during performance of simple and complex motor sequences. Simple sequences consisted of tapping a key five times with the index, middle or ring finger. In the complex condition, subjects were required to complete mixed tapping sequences (e.g., index, ring, middle, ring and index). Figure 3 shows differences in BOLD signals during nondominant hand performance of complex and simple sequences by a 16-year-old child with FAS, suggesting greater activation during the demanding condition. However, this difference in activation disappeared after practicing complex sequences for 8 weeks, suggesting neural plasticity of the motor system.

Although functional neural circuitries can be changed, convergent evidence from animal models and brain imaging studies shows that specific brain regions or specific neural circuitries are selectively affected in children and adults with FASDs. In view of these findings, it is reasonable to ask the question: do functions at elementary or higher order levels show selective impairments corresponding to selective anomalies in the brain?

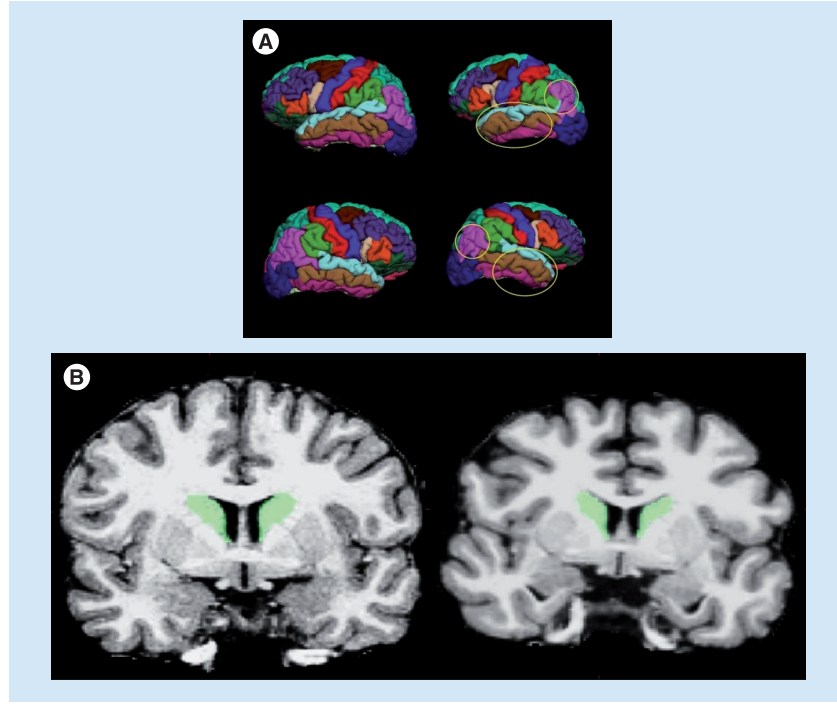


**Figure 2. Structural brain images of an 18-year-old male with fetal alcohol syndrome (right) and an age-matched normal control (left).** These images show volumetric differences in **(A)** the temporal and parietal lobes and **(B)** the caudate nucleus (green).

## Elementary functions

In this article, we use the term elementary to denote those functions that emerge early in development such as associative learning (e.g., EBC) and reflexive responses (e.g., prosaccades). Converging evidence from animal and human studies shows that the regions of the brain that mature early such as the brainstem and the cerebellum play a critical role in these elementary functions [72,73]. The delineation of brain function at an elementary level, which is comparable with the characterization of intermediate phenotypes or endophenotypes of neurogenetic disorders, has a number of advantages [74]. First, the study of the teratogenic effects on these functions allows for generalizing animal research to humans, since both animals and humans share numerous elementary processes (e.g., EBC and fear conditioning). Second, elementary functions can be more accurately mapped both spatially and temporally than complex functions in neuroimaging studies and hence may offer more accurate indices of alcohol's teratogenic effects. Third, given that elementary functions are often innate and less modifiable by cultural experience [75], the tests probing these functions may be suitable for crosscultural studies of FASDs. Fourth, being less modifiable by cultural experiences, elementary functions are expected to be closer to neuroanatomical and neurochemical variations associated with prenatal effects of alcohol and hence are better candidates for 'biomarkers' of alcohol's teratogenecity than complex functions.

In this article, we will briefly examine the effects of prenatal alcohol exposure on performance of three tasks that involve elementary learning and sensory–motor skills: EBC, prosaccades and orienting responses. Given that these tasks are known to be mediated by neural circuitries that mature early [73,76], they have been employed in the study of early markers of prenatal alcohol exposure in children.

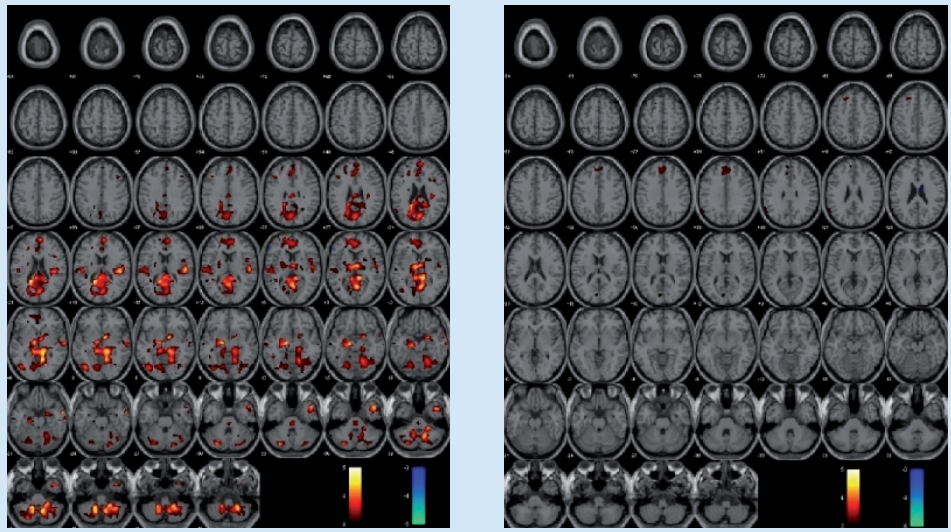

**Figure 3. Differences in blood oxygen level-dependent signals during pre- (left) and post-training (right) performance of complex motor sequences by a 16-year-old male with fetal alcohol syndrome.**

## Eyeblink conditioning

Eyeblink conditioning is a well-established paradigm of associative learning in which the eyeblink reflex is conditioned to a neutral stimulus (e.g., tone) that predicts an unconditioned stimulus (e.g., puff of air). It has been shown that EBC engages a neural circuitry involving the cerebellum and the hippocampus [77], which is highly sensitive to the effects of alcohol. Therefore, researchers have employed EBC as a biomarker of alcohol's teratogenecity in animal models [78,79]. These studies have demonstrated that alcohol-exposed animals show evidence of slow and impaired EBC, as indexed by later-onset or later-peaked conditioned responses. Coffin and colleagues compared children with FASDs, dyslexia, ADHD, and normal controls on EBC and found that those with FASDs and dyslexia showed deficits in the acquisition of conditioned responses compared with the other two groups [80]. Specifically, children with FASDs and dyslexia showed longer latencies and more timing errors in conditioned responses than the other two groups. Similarly, Jacobson *et al.* found that children with FASDs were markedly impaired at the acquisition of conditioned responses on an EBC task [9].

### *Prosaccades*

Saccades refer to rapid eye movements that shift the line of sight from one point of fixation to another in the visual field [81]. In the search for biomarkers of neuropsychiatric disorders, researchers have turned to the saccadic eye movement system because it is subserved by a well-delineated neural circuitry that comprises early-maturing (e.g., brainstem and cerebellum) as well as late-maturing (e.g., dorsolateral prefrontal cortex) regions of the brain [82]. The standard experimental procedure employed to investigate saccades involves requiring participants to look from a central fixation point towards a sudden onset target on the periphery (prosaccades) or to look away from the peripheral target towards its mirror image location (antisaccades). Numerous studies have demonstrated that a sudden onset stimulus captures our attention, generating a reflexive saccade toward it [83]. In sharp contrast, antisaccades require a deliberate effort to inhibit the prepotent ocular motor response of looking at the sudden onset stimulus. There is evidence that the saccadic network located in the brainstem and cerebellum controls the accuracy and velocity of prosaccades, whereas the programming of saccades involves additional regions including the frontal cortex [72]. Green *et al.* found that children with FASDs showed longer reaction times than controls during performance of prosaccades, suggesting a deficit in saccade initiation [84,85]. The investigators attributed the deficient initiation of responses to alcohol-induced damage to the structures that are critical for making saccade responses, including the parietal cortex and basal ganglia [84].

## Orienting responses

It is known that the vagus nerve responds rapidly to metabolic changes in the brain by regulating the heart's pacemaker [86]. When metabolic demands are low, vagal tone increases, lowering the heart's output. When metabolic demands increase, vagal tone decreases, signaling the heart to increase output [87]. Therefore, heart rate has proven to be a useful psychophysiological index of metabolic changes in the brain associated with the processing of internal or external stimuli [87]. Kable and Cole investigated encoding of auditory and visual stimuli in 6-month-old infants with prenatal alcohol exposure by assessing changes in heart rate (e.g., deceleration) [76]. They found that alcohol-exposed infants responded more slowly to stimuli (orienting responses), but showed higher levels of arousal compared with controls. However, the alcohol-exposed group did not differ from controls in sustaining deceleration responses, showing that the effect was specific to initiating them. The finding of slowness in orienting is in accordance with those reported by Jacobson, who compared cognitive impairments in infants resulting from exposure to three different teratogens: polychlorinated biphenyls (PCB), alcohol and cocaine [88]. The alcohol-exposed group was found to show slower rates of information processing compared with the other exposed group. However, compared with the PCB group, the alcohol-exposed group displayed relatively preserved recognition memory.

In summary, studies of elementary functions show that children with FASDs display impairments in the acquisition of conditioned responses in associative learning paradigms such as EBC. Children with FASDs have been observed to show slowness in the initiation of ocular motor responses in prosaccade tasks and orienting responses in visual and auditory encoding tasks. Compared with infants exposed to PCB and cocaine, those with prenatal alcohol exposure show slower rates of information processing. Thus, slowness of responding to novel stimuli, processing information and acquiring responses is the main finding from the aforementioned studies of elementary functions.

## Complex functions

We recently suggested that neurocognitive functioning in children with FASDs is characterized by a generalized deficit in the processing and integration of information, especially complex information [8,19]. In support of this hypothesis, evidence was drawn from three main areas of cognitive functioning: intellectual abilities, attention and information processing and specific domains of functioning such as language, visual perception, learning and memory, social cognition, number processing and motor skills.

### *Intellectual abilities*

Studies of intellectual functioning in children with FASDs have consistently shown that prenatal alcohol exposure is associated with diminished IQ scores, with average IQs ranging from borderline to low average ranges in this population [89,90]. Given that tests of intellectual functioning such as the Wechsler Intelligence Scale for Children (WISC) comprise measures of various domains such as verbal comprehension, perceptual organization, working memory and processing speed, IQ test results provide an insight into the broad landscape of cognitive skills. If prenatal alcohol exposure leads to selective damage to some functions, then one can expect an uneven profile of domain scores, particularly a discrepancy between verbal comprehension and perceptual organization. In a review of the literature covering both single case and group studies of intellectual functioning in FASDs, Mattson and Riley concluded that both verbal and nonverbal abilities in alcohol-exposed children were equally diminished [18]. Consistent with this pattern, Adnams *et al.* found that children with FASDs showed greater difficulty with intellectually more demanding subtests than with less demanding ones [91].

### *Attention & executive functions*

Considerable efforts have been devoted to the study of attention, including executive functions in children with FASDs, because prenatal alcohol exposure has been found to be associated with deficits in these areas [92–95]. Given that attention comprises multiple components, the focus of a number of studies has been on determining whether specific components are selectively compromised by prenatal alcohol exposure. Nanson and Hiscock found that children with FASDs were impaired on tests measuring an experimental model of attention [96] that comprises components such as the investment, organization and maintenance of effort and response inhibition [97]. Coles *et al.* compared children with FASDs and ADHD on a battery of tests assessing four components of attention: focus, sustain, encode and shift [95]. These investigators found that the FASD group exhibited greater difficulty in encode (i.e., digit recall) and shift (e.g., Wisconsin Card Sorting Test) components than in focus (i.e., digit symbol)

and sustain (i.e., continuous performance) components. The ADHD group displayed a distinct profile that was notable for greater difficulty with focus and sustain components than with the other components.

Some researchers have obtained evidence that the performance of alcohol-exposed children on tests of sustained attention varies by the modality of presentation (e.g., visual vs auditory). Coles *et al.* found that adolescents with FASDs were less efficient on a visual test of sustained attention, but performed as effectively as controls on an auditory test [98]. By contrast, Connor *et al.* found that alcohol-exposed adults displayed greater deficits in the auditory than the visual condition of a sustained attention task [94]. In a study of focused and shifting attention, Mattson *et al.* observed that children with FASDs showed performance impairments in both auditory and visual conditions, but that deficits in the visual condition were more pronounced [99].

The inconsistencies in these findings are attributable to the differences in task and subject characteristics across studies. While some studies have included children with heavy alcohol exposure [99], others have included those with moderate levels of exposure [93]. It is reasonable to expect that children with heavy prenatal alcohol exposure would display greater deficits in attention, involving both visual and auditory domains, than those with moderate levels of exposure. It has been reported that the amount of prenatal alcohol exposure is associated with attentional difficulties in the offspring [100]. Chiodo *et al.* found that maternal age moderated the effects of prenatal alcohol exposure on attention in children with FASDs, with those born to older mothers showing worse effects [101].

A consistent neurobehavioral finding in children with FASDs is that prenatal alcohol exposure is associated with deficits in executive functions, which refer to a range of abilities involving deliberate attention (or supervisory attention) including planning, set shifting, generation of novel responses (e.g., verbal and nonverbal fluency), maintenance of goal-directed behavior in the presence of interference and problem solving [102–104]. Underlying the aforementioned executive functions are working memory and response inhibition. Children with FASDs are deficient in cognitive planning, as assessed by look-ahead puzzles such as the Progressive Planning Test [105–107], the California Tower Task [103] and the Stockings of Cambridge [12]. These puzzles require participants to move a number of beads or discs from an initial position to a goal position under the constraints of specific rules. Because the moves are constrained by rules, the examinee must plan ahead before making a response. These investigations have consistently shown that children with FASDs solve fewer problems and violate task rules more often than typically developing controls on these tests. Children with FASDs have also been found to be deficient in nonverbal and verbal fluency [108] and multiple measures of concept formation [109]. There is evidence that prenatal alcohol exposure is associated with deficient performance on tests assessing extradimensional set shifting, such as the Wisconsin Card Sorting Test [95,105,110], and intradimensional set shifting, such as the Visual Discrimination Reversal Learning Test [106,111].

A number of studies have directly probed working memory and response inhibition, the two primary mechanisms underlying executive attention, in children with FASDs. There is evidence that children with FASDs are markedly impaired at the Visual Working Memory Test of the Cambridge Neuropsychological Tests Automated Battery (CANTAB) [12,106]. On this task, the FASD group made significantly more errors than the control group. Noland *et al.* reported that children exposed to alcohol performed less well than controls on a tapping inhibition task [112]. Prenatal alcohol exposure has also been observed to be associated with performance deficits in response inhibition tasks, such as the Stroop Task [94]. As noted previously, Green *et al.* demonstrated that the FASD group had increased saccade reaction times, greater intrasubject variability and more directional errors than the control group on a test measuring antisaccades, indicating deficient response inhibition [84,85].

In summary, children with prenatal alcohol exposure exhibit deficient performance on tests assessing different components of attention. There is also evidence that children with FASDs display greater difficulty with more complex tasks of executive functioning than with less complex ones. Aragon *et al.* reported that alcohol-exposed children succeeded in solving simple planning problems that could be solved using perceptual strategies, but demonstrated marked difficulty in solving those complex problems that involved holding and manipulating information in working memory [107]. Kodituwakku *et al.* found that children with FASDs had greater difficulty with

letter fluency than with category fluency [113]. The letter fluency task involved the examinee generating words beginning with specific letters under certain constraints, and hence is more demanding than the category fluency task, in which the examinee generated exemplars from a semantic category. Green *et al.* have also observed that children with FASDs performed worse than the control group on a number of tests assessing executive functions, with group differences becoming pronounced with increased task complexity [12].

### *Information processing*

The rate of information processing in children with prenatal alcohol exposure has been the subject of several studies. Jacobson found that infants exposed to alcohol processed information at a slower rate than comparison groups [88]. Roebuck *et al.* observed that alcohol-exposed children performed worse than controls on a task that involved interhemispheric transfer of information, making more errors with increased task complexity [114]. Burden *et al.* found that prenatal alcohol exposure was associated with slower processing of information, particularly on tasks that involved cognitive effort [115]. Green *et al.* also observed slower processing in alcohol-exposed children than controls on simple and choice reaction time tasks on the CANTAB [12]. Simmons *et al.* demonstrated that children with FASDs were slower than controls during response planning and response execution on a choice reaction time task [116]. Accordingly, converging evidence from a number of studies shows that prenatal alcohol exposure is associated with diminished efficiency in the processing of information, particularly complex information.

## Specific cognitive functions

Studies of FASDs focusing on specific cognitive functions such as memory and learning, language, visual perception, number processing and social cognition have produced results consistent with the deficient processing hypothesis [19]. As shown in the following sections, the converging data from the studies of specific functions indicate that children with FASDs perform less proficiently across the board relative to their typically developing peers when the task complexity is increased.

### *Learning & memory*

There is considerable evidence from animal models of FASDs that brain structures subserving learning and memory are specifically vulnerable to the teratogenic effects of alcohol [117]. As mentioned previously, neuroanatomical studies of the hippocampus in alcohol-exposed rodents have revealed a range of alterations including reduced numbers of neurons and lower dendritic spine density on pyramidal neurons, which are associated with learning and memory deficits. Inspired by the aforementioned findings, some investigators have sought to extend animal learning models to humans exposed to alcohol *in utero* [118,119]. Hamilton *et al.* demonstrated that children with FASDs were impaired in spatial learning and memory using a computerized (virtual) version of the water maze, a test that is sensitive to hippocampal functioning [118]. Uecker and Nadel also reported a study in which the Memory for Objects Task, a test that is sensitive to hippocampal functioning, was administered to children with FASDs [119]. Results showed that the FASD group demonstrated performance deficits at the delayed, but not at the immediate, recall trial. These investigators also observed that the FASD group was impaired at nonhippocampal visual tasks, indicating a generalized pattern of visual spatial difficulties.

Several investigators have sought to delineate the patterns of learning and memory in children with FASDs using standardized tests such as the Wide Range Assessment of Memory and Learning and the Children's Memory Scale [10,11]. Kaemingk *et al.* found that the FASD group showed deficient performance on both verbal and visual learning tasks, but was able to retain the limited information that they acquired [10]. Willford *et al.* found learning deficits in a large cohort of adolescents with prenatal alcohol exposure who did not have significant morphological anomalies [11]. Consistent with Kaemingk *et al.*'s findings, these investigators observed specific difficulty with encoding information in alcohol-affected children. Mattson and Roebuck have also found deficits in verbal and nonverbal learning in children with prenatal alcohol exposure, particularly in initial learning [120]. It should be noted that the efficiency of initial learning is dependent on multiple variables such as attention, motivation, and strategy application. Accordingly, children with FASDs seem to display deficits in the acquisition of both verbal and visual information, a finding that is commensurate with verbal and performance IQ deficits in these children. Coles *et al.* recently reported that memory deficits in alcohol-exposed individuals persist into adulthood [121].

### Language

Investigations into language skills in children with prenatal alcohol exposure have produced inconsistent results, primarily due to considerable variations in methodologies (e.g., retrospective or prospective), subject characteristics (e.g., age, ethnicity or amount of exposure) and task characteristics (e.g., standardized test batteries vs experimental probes) across studies. A number of prospective studies have investigated language development in large cohorts of children, mostly with low-to-moderate levels of prenatal alcohol exposure. Greene *et al.* evaluated receptive and expressive language skills in a cohort of children with prenatal alcohol exposure at 1, 2 and 3 years of age and found no association between alcohol exposure and language [122]. Similarly, Coles *et al.* found that language skills in children with prenatal alcohol exposure were relatively preserved in comparison with visual spatial skills [123]. While Fried *et al.* found an association between prenatal alcohol exposure and measures of language at 13 months, 2 years and 3 years of age but not at 4, 5 or 6 years of age in a cohort of children from Ottawa, Canada [124–126]. In another prospective study from Seattle, WA, USA, Streissguth *et al.* did not observe an association between language impairments and prenatal alcohol exposure at 7 years of age, but found deficits in phonological awareness in a dose–response fashion at 14 years of age [127]. The cohort members of the UK Millennium study who were born to light drinkers have been found to be unimpaired at verbal subtests from the British Ability Scale at 3 and 5 years of age [128,129].

In sharp contrast, the findings from retrospective studies show marked deficits in both expressive and receptive language, particularly in young children with substantial prenatal alcohol exposure [130]. Early reports based on small samples of children with FASDs documented a range of language difficulties, including deficits in prosody and social communication [131] and oral motor, articulatory and semantic problems [132], as well as impairments of syntactic skills [133]. Researchers have also obtained evidence that clinic-referred children with FASDs show deficits in vocabulary [105], naming [134] and fluency [108].

In view of the fact that the majority of children with FASDs studied in clinic-referred samples in North America are drawn from ethnic minorities, particularly American–Indian and African–American, the question of culture/race bias of the test instruments used to assess language in these groups has been raised [135]. Since researchers have attempted to match the clinical and control groups on ethnicity and socioeconomic status, this issue may not seriously threaten the internal validity of the findings. Another methodological issue is that the majority of participants in these studies often have histories of extreme life stressors negatively impacting language learning, as well as of experiencing limited language input. Considering the evidence that alcohol-exposed children with dysmorphia often have a variety of hearing disorders (e.g., delay in the maturation of the auditory system, congenital sensory neural hearing loss or central hearing loss) leading to language difficulties [136], the language deficits reported previously cannot be totally attributed to adverse life experiences. Furthermore, population-based epidemiological studies have provided evidence that children with substantial prenatal alcohol exposure who had not experienced significant life stressors also showed language deficits [113,137].

The pattern of test performance emerging from the studies of language in FASDs is that while younger children show global deficits, older children display deficits only in specific areas, such as syntax [133] and pragmatics or social communication [131,138,139]. Children with FASDs have been described as those who 'talk a lot, but say a little' [140]. Using tools such as narrative analysis, researchers have uncovered specific difficulties in pragmatics in older children with FASDs [141]. It should be noted that effective social communication requires complex cognitive skills including executive functions [138].

### Visual perception & visual construction

Despite the reports that children with FASDs have visual impairments and ocular abnormalities, relatively little is known about object recognition and motion perception in alcohol-affected children. Uecker and Nadel found that children with FASDs were relatively unimpaired at facial recognition, but were markedly impaired at tests assessing visual–motor integration such as the Beery Visual–Motor Integration and Clock Drawing tests [119]. Mattson *et al.* reported that children with FASDs had greater difficulty than controls in copying and recalling local features of hierarchical stimuli, such as a large letter 'D' (global) made up of small 'y' letters (local features) [142]. In a recent study of early stages of visual processing in children with FASDs, it was found that alcohol-affected children were slower than controls in letter recognition, which is consistent with the slow information processing reported by others in this population [Verney S *et al.*, Unpublished Data].

The aforementioned findings suggest that children with FASDs are unimpaired at simple perceptual tasks, but are impaired at tasks that require visual–motor integration. The FASD group may also be slower than controls in object recognition. The basis for the differential performance on global and local features is unknown.

### *Social cognition*

In view of the reports of poor social skills in children with FASDs, the question of whether impaired social cognition contributes to these deficits has attracted the attention of numerous investigators. Bishop *et al.* contrasted performances of children with autism and FASDs on the Autism Diagnostic Observation Schedule and found that the two groups exhibited distinctive patterns of impairments in social interaction and communication [143]. While children with FASDs did not have difficulty initiating social interactions and using nonverbal communication, they exhibited socially inappropriate behaviors and difficulty with peers. In other words, social deficits in children with FASDs appear to be associated with poor self-regulation rather than with an impairment of social sense. Schonfeld *et al.* have obtained evidence that deficient executive functions in children with FASDs were associated with reported deficits in social skills [14], which is consistent with the findings reported by Bishop *et al.* [143]. Rasmussen *et al.* found that children with FASDs showed performance deficits on tests assessing theory of mind, which is a building block of social skills, and that these deficits were associated with impaired executive functioning [144].

McGee *et al.* observed that children with FASDs were deficient in social information processing [145]. In this study, participants were required to view video vignettes depicting different social situations and then to respond to specific questions designed to tap social information processing. The results showed that children with FASDs had maladaptive processing patterns both in the generation and evaluation of responses in social situations. Greenbaum *et al.* compared children with FASDs and ADHD on a battery of tests assessing social cognition and emotional processing with a view to delineating unique profiles associated with the two disorders [146]. Results showed that the FASD group demonstrated weaker social cognition and facial affect identification than the ADHD and typically developing groups.

Thus, numerous investigators have documented that children with FASDs have deficits in social cognition and that these deficits contribute to their social problems. A number of researchers have found that deficient social cognition in children with FASDs is linked to impairments of higher-level processes, particularly executive control skills and intellectual disabilities. However, O'Connor *et al.* demonstrated that social skills deficits can be improved through training [147].

### *Number processing*

Some investigations into academic skills in children with FASDs have revealed that those with substantial prenatal alcohol exposure have greater difficulty with mathematics than with reading and spelling [110,148,149]. Howell *et al.* compared four groups of adolescents (FASDs with dysmorphia, FASDs without dysmorphia, learning disabled and typically developing) on a battery of tests assessing intellectual functioning and academic achievement [148]. While the learning disabled group performed poorly on all academic subjects, alcohol-affected youths showed significant deficits in mathematics. Goldschmidt *et al.* examined the association between prenatal alcohol exposure and academic achievement in a large cohort of children in a prospective study and found that exposure during the second trimester was related to mathematical skills in a linear dose–response fashion [149].

An important question that can be raised regarding the aforementioned findings concerns which defective cognitive processes contribute to the deficits in mathematical skills in children with FASDs. Kopera-Frye *et al.* compared performances of adolescents with FASDs and demographically matched controls on a battery of number processing tests including measures of number reading and writing, exact calculation, approximate calculation (selecting an approximate result for a calculation), number comparison and cognitive estimation [150]. The results showed greater difficulty with complex tasks, such as the cognitive estimation test, than with simple tasks, such as the number reading and writing.

Since the functional neuroanatomical circuitries associated with number processing have been well delineated [151,152], some have investigated differences in BOLD responses during performances of mathematical tasks by FASDs and control groups [153,154]. Santhanam *et al.* found that alcohol-exposed individuals with dysmorphia showed less activation in the

regions that are known to be associated with number processing, including the left superior and right inferior parietal regions and the medial frontal gyrus [154]. Meintjes *et al.* found that children with prenatal alcohol exposure recruited a broader range of brain regions than controls during number processing [153]. As mentioned previously, researchers have also documented an association between the integrity of the white matter and mathematical scores in children with FASDs [63].

However, the aforementioned neuropsychological and neuroimaging studies do not show that mathematical difficulties in children with FASDs remain static during development. Teachers often report that children with FASDs acquire the ability to carry out basic mathematical operations, even those used in elementary algebra, when they grow older. Therefore, difficulties in mathematics in this clinical group should be evaluated in a developmental framework.

### Motor functions

Convergent evidence from animal and human research shows that motor functions are vulnerable to the effects of prenatal alcohol exposure [42,155–162]. In their original clinical description of FAS, Jones *et al.* noted that alcohol-affected children had motor dysfunction, including tremulousness, weak grasp and poor hand–eye coordination [163].

Confirming the aforementioned clinical observations, a number of investigators have reported that children with FASDs display deficits in fine motor skills as measured by tests of finger dexterity such as finger tapping [160] and the Grooved Pegboard test [106,134]. There is also evidence that children with FASDs have a weaker bilateral strength of grip compared with age-matched controls [160]. In view of the fact that the cerebellum is sensitive to alcohol's teratogenecity, postural balance in children with FASDs has been the focus of some studies [158,159,161]. By systematically manipulating somatosensory and visual input, Roebuck *et al.* found that alcohol-exposed children were overly reliant on somatosensory feedback to maintain postural balance [158]. Children and adults with FASDs have also been found to show impaired performance on complex motor tasks such as tapping fingers in specific sequences [161].

Despite the difficulties with postural balance, children with prenatal alcohol exposure do not typically display deficits in gross motor behaviors such as running and jumping [91,157]. Although some fine motor deficits may diminish with practice, difficulties with complex motor tasks such as motor coordination persist into adulthood of alcohol-exposed individuals [161]. It should be noted that older children with FASDs show worse performance on fine motor tasks such as the Grooved Pegboard test only with the nondominant hand, perhaps due to hand difference in practice. As mentioned previously, we have obtained evidence for training-induced plasticity of the motor system in individuals with FASDs.

### Comparison of complex & simple tests

To test the hypothesis that children with FASDs show performance decrements with increased task complexity, Aragon *et al.* utilized a test battery comprised of simple and complex tasks from different domains of functioning [107]. Multidimensional scaling was used to test the accuracy of classifying neurocognitive tests into simple and complex groups. As predicted, complex tasks such as complex planning, letter fluency, logical memory and free recall discriminated alcohol-exposed children from controls, whereas simple tasks (e.g., simple planning, category fluency, simple spatial memory and recognition memory) did not. Recently, Mattson *et al.* reported the findings from an international study of neurocognitive functioning in children with FASDs, in which an extensive battery of tests was utilized [106]. Latent profile analysis yielded a two-class model that was successful at distinguishing alcohol-exposed children from controls with 92% accuracy. The tests discriminating between the two groups were the complex tests that involved executive functions.

### Theoretical framework

The theoretical framework that we use to interpret the aforementioned cognitive behavioral effects of prenatal alcohol exposure is based on convergent evidence from psychometrics, cognitive psychology and cognitive neuroscience. Using nonmetric scaling methods (e.g., the Radex model), Snow and colleagues obtained evidence for the complexity continuum of cognitive tests, with complex tests clustering together in a multidimensional space [164,165]. The complexity of a test is defined in terms of the number of elements that need to be manipulated to solve it. In this framework, complex tasks invoke executive attention to hold and manipulate multiple components for generating solutions. A close parallel to the complexity continuum is found in the results generated through the studies of fluid versus crystallized intelligence [166]. While

crystallized intelligence refers to the abilities depending on acquired knowledge or acculturation (e.g., general knowledge), fluid intelligence refers to the abilities involved in solving novel problems without the benefit of prior experience. The reasoning tasks designed to assess fluid intelligence such as the Raven Progressive Matrices Test typify complex tasks defined within the Radex model, because they involve simultaneously handling multiple elements. Computer simulation studies of performance on the Raven Matrices Test have confirmed that the ability to induce abstract relations and the ability to effectively manage a large number of goals in working memory are critical for solving complex problems on the test [167].

The theory of relational integration proposed by Halford to account for the processes involved in problem solving [168] accords with the notion of the complexity continuum. Halford defines the complexity of a problem in terms of the number of relations that need to be simultaneously considered to solve it [168]. A complex problem may involve considering 2D or 3D variations simultaneously and also integrating them. There is evidence that the efficiency of relational integration declines with age [169].

A number of investigators have examined BOLD signals during performance of tasks that varied in complexity in terms of the number of relations [170–172] and found that complex tasks recruit broadly distributed networks, including the prefrontal cortex. For example, three-relation Raven-type problems activated the bilateral frontal and left parietal, occipital and temporal regions [171]. Therefore, the ability to integrate multiple relationships is dependent on the integrity of cortico–cortical and cortico–subcortical connections. Dehaene *et al.* coined the term 'global workspace' to denote the neuronal processes involved in the performance of effortful tasks [173]. According to Dehaene *et al.*, distributed neurons with long-distance connectivity provide the neural basis for the global workspace [173].

We propose that children with FASDs have greater difficulty with tasks that involve processing of multiple relations or elements, and hence require executive attention. Performance of such tasks involves the global workspace proposed by Dehaene *et al.* [173]. We suggest that alcohol-induced reductions in the white matter volume and anomalies in the gray matter in specific regions of the brain [50] underpin the inefficiency in processing and integration of information, particularly complex information, in children with FASDs. The slowness in speed of processing and acquisition of responses is emerging as the hallmark of cognitive functioning in both infants and adults affected by prenatal alcohol exposure. It is reasonable to hypothesize that sluggish processing leads to generalized performance deficits in complex tasks [174] because the success in complex processing involves rapidly processing multiple elements and combining them.

There is a large body of literature that documents neurodevelopmental outcomes of exposure to other substances, such as cocaine, nicotine and marijuana [125,175,176]. While children exposed to these substances have been found to show deficits in some areas of functioning, such as language [177], working memory [178], and intellectual ability [179], they do not show deficits in processing and integration of multiple elements or relations to the same extent as children with FASDs. Although performance deficits on complex tasks such as verbal fluency and cognitive planning in FASDs remain significant after controlling for IQ [113], limited data are available on comparisons between FASDs and other clinical groups with comparable levels of intellectual disabilities on complex processing and integration tasks.

### Summary

Children with FASDs exhibit diminished intellectual functioning, with IQ scores that index verbal and visual spatial skills falling in the borderline to low average ranges. Alcohol-affected children have been shown to process information at a slower rate than their age peers. Slower processing has been observed even in infants with prenatal alcohol exposure. Children with FASDs demonstrate deficits in attention, particularly when deliberate effort or cognitive control is required. The results from the tests assessing specific areas of cognitive functioning (e.g., language, visual perception, memory and social cognition) show that when task demands increase, the performance of the FASD group declines at a faster rate than that of controls. As mentioned previously, these observations lead to the conclusion that children with FASDs have a generalized deficit in the processing and integration of information [19]. This deficit can be defined in terms of difficulty in handling multiple elements or multiple relations simultaneously and integrating them. In the next section, we turn to answering the second question that we raised at the outset: do children with FASDs display a unique pattern of parent- or teacher-rated behaviors?

### Parent- & teacher-rated behaviors

A number of investigators have examined behavioral data on children with FASDs, which are acquired through rating scales or interviews with caregivers, in order to determine whether there is a syndrome-specific profile of FASDs. Streissguth *et al*. administered a behavioral checklist to parents and caregivers of 472 individuals with prenatal alcohol exposure [140]. Results of this study helped the investigators identify 36 items from the checklist that were considered to be associated with the behavioral phenotype of FASDs. These included items such as 'overreacts', 'is unaware of consequences', 'talks a lot, but says a little', 'has difficulty completing tasks', 'shows poor judgment' and 'interrupts others'. Collectively, these items reflect a deficit in self-regulation and executive control. Consistent with this finding, Schonfeld *et al*. found that parent-reported executive control dysfunction was associated with deficient social skills in children with FASDs [14]. A methodological issue related to defining a behavioral phenotype in clinic-referred samples of children with FASDs concerns controlling for the confounding effects of environment. Having experienced multiple life stressors, children with FASDs seen in clinic settings often show numerous behavioral problems. Lynch *et al*. did not find an increased incidence of delinquency in a nonreferred sample of adolescents participating in a longitudinal study [180]. Therefore, the question of whether nonreferred children with FASDs who are living in stable home environments display a unique profile of behaviors has been raised. To answer this question, a questionnaire assessing disruptive behaviors was administered to a group of children with FASDs who were identified through a population-based epidemiological study conducted in Italy [181]. The results showed that teachers rated children with FASDs as having more inattentive behaviors than controls and that these inattentive behaviors were associated with academic problems in these children. Increased incidence of inattentive behaviors in the classroom can be interpreted in terms of slow information processing and diminished intellectual functioning. This is consistent with the finding that alcohol-exposed children are often rated as acting younger than their age [7].

A number of studies have documented that children with FASDs are deficient in adaptive skills that are essential for independent living, such as communication and socialization. Researchers have consistently found that children with FASDs score lower than typically developing controls across different domains of adaptive behavior functioning, as measured by scales such as the Vineland Adaptive Rating Scales [110]. A number of investigators have reported that children with FASDs show relatively greater deficits in socialization than in other domains as reported by caregivers [182], with social deficits becoming more pronounced when they reach adolescence [183]. It is reasonable to hypothesize that social demands during adolescence dramatically increase, since social interactions during this period of development involve the ability to coordinate a range of complex skills, such as reading nonverbal cues and understanding metaphorical language and humor. As mentioned previously, researchers have found that social skills in children with FASDs are associated with executive control skills. Crocker *et al.* found a distinct pattern of adaptive behavior deficits in children with FASDs compared with children with ADHD [184]. While both groups showed deficits in socialization and communication, the ADHD group, but not the FASD group, showed age-related gains in these areas.

A growing body of literature shows that the prevalence of psychiatric problems among alcohol-exposed children and adults is extremely high [13,185–188]. O'Connor and Paley found that approximately 87% of alcohol-exposed children with prenatal alcohol exposure met diagnostic criteria of a psychiatric disorder [185]. Sreissguth *et al.* reported that the lifespan prevalence of secondary disabilities including psychiatric problems was high in adolescents and young adults with prenatal alcohol exposure [13]. For example, approximately 50% of the Seattle longitudinal cohort had experienced confinement due to legal or psychiatric problems. Increased emotional and behavioral problems have also been observed in a European sample of young adults with prenatal alcohol exposure [16]. It is likely that interactions between alcohol-induced brain damage and life stressors lead to psychiatric and behavioral problems in this population.

In summary, children and adults with FASDs have been rated by caregivers as showing behavioral problems such as overreaction to situations, failure to anticipate consequences, impulsivity and psychiatric problems. The behavioral problems in alcohol-affected individuals appear to be related, in part, to executive control dysfunction. Children with FASDs have been rated by teachers as being inattentive. Inattentiveness could

be associated with slow information processing. Children affected by prenatal alcohol exposure have been observed to act younger than their age, which could be related to diminished intellectual functioning. Children with FASDs have consistently been found to have limited adaptive skills, particularly in the domain of social functioning. These difficulties are associated with their deficits in intellectual functioning and executive control [189]. Accordingly, parent/teacher-rated behavioral problems in children with FASDs are closely associated with a deficient capacity for processing and the integration of information. High prevalence rates of psychiatric problems can be attributable to complex interactions between alcohol-induced brain damage and life stressors.

## Conclusion

In this article, we reviewed findings from several lines of research on FASDs, including animal models, neuroimaging studies and neurocognitive/behavioral investigations. It is known that neuroanatomical and cognitive–behavioral outcomes in children with FASDs vary considerably depending on a wide range of factors, including the quantity, frequency and timing of exposure, genetic factors and postnatal experiences. Despite considerable variability in outcomes, the converging evidence from animal models and neuroimaging studies shows that specific regions of the brain are more vulnerable to the effects of alcohol than other regions. Particularly, the hippocampus, basal ganglia, cerebellum and corpus callosum have been found to be sensitive to the teratogenic effects of alcohol. In view of the finding that specific regions of the brain are vulnerable to alcohol, many researchers have hypothesized that children with FASDs are specifically impaired at functions subserved by these regions. The expectation of this type of neuroanatomically guided cognitive–behavioral research has been to identify a profile of 'damaged' and 'spared' skills.

However, the cognitive and behavioral data presented previously do not show an uneven profile made up of spared and damage skills. By contrast, children with FASDs show a generalized deficit in the processing and integration of information, particularly complex information. The studies targeting elementary functions, such as EBC, show children with FASDs are slow in the acquisition of conditioned responses. Researchers have found evidence of slower processing in children with FASDs at early stages of visual perception. Studies of intellectual functioning have revealed that children with FASDs are deficient in both verbal and visual spatial skills. On tests assessing specific functions such as language and memory, children with FASDs show performance decrements with increased task complexity. Deficits in adaptive behavior and behavioral problems in these children seem to be closely associated with deficient skills in executive functioning, slow processing of information and limitations of intellectual functioning.

The interpretation of a generalized pattern of processing difficulties in the presence of focal abnormalities of the brain poses a problem within an adult neuropsychological framework. We have argued elsewhere that this problem can be resolved by adopting a neurodevelopmental framework [19,190]. In a developing brain with neuroanatomical anomalies, so-called 'spared' regions may show atypical trajectories of development because of the processes of neural plasticity [191,192]. Given that multiple regions of the brain are damaged in children with prenatal alcohol exposure, a generalized pattern of processing difficulties can be expected. A developmental framework that emphasizes an interactive approach has already been successfully used in the study of children with prenatal alcohol exposure [193,194].

## Future perspective

The delineation of cognitive–behavioral difficulties within a neurodevelopmental framework has far-reaching implications for diagnosis and the development of interventions for alcohol-affected children. As noted previously, the central proposition of the neurodevelopmental framework is that cognitive functions in an individual change as a function of interactions between experiences and the brain hardware. Accordingly, the topography of cognitive skills and the underpinning neural circuitries are not expected to remain the same at two different ages of a given individual. In this section, we outline some ideas from a neurodevelopmental perspective that are relevant for future work on diagnosis and interventions for children with FASDs.

### Diagnosis

Unlike a genetic disorder resulting from mutation of a specific gene, FASDs constitute a heterogeneous group that varies considerably both in physical appearance and cognitive functioning. Since the majority of alcohol-affected children cannot be identified by

clinical dysmorphology evaluation, diagnosis of FASDs remains a formidable challenge for clinicians. The fact that cognitive functioning is influenced by a variety of factors, including postnatal life stressors [193] and genetic factors, neuropsychological data collected at one point in development are of limited value in making differential diagnoses.

In this article, we underscored the importance of assessing cognitive functioning at elementary and complex levels. As mentioned previously, assessment of elementary functions subserved by brain structures that mature and myelinate early may help identify biomarkers of alcohol's teratogenecity. Investigation into elementary functions such as sensory gating has proven to be a very useful strategy in understanding the etiology of schizophrenia. Similarly, we expect that exploration of elementary functions using behavioral probes and neuroimaging methods may allow early identification of children affected by prenatal alcohol exposure. Animal models of FASDs can be utilized to identify some elementary functions that are vulnerable to the teratogenic effects of alcohol. From a neurodevelopmental point of view, identification of elementary functions that are sensitive to alcohol will also help identify the building blocks of complex functions. Ultimately, delineation of complex functions will allow us to define the extent of disability and the development of intervention programs.

### Interventions

We recently outlined from a neurodevelopmental perspective some strategies for addressing cognitive and behavioral problems in children with FASDs [195]. Given that cognitive processes evolve through dynamic interactions between experiences and the brain's hardware, we defined behavioral therapies as the provision of experiences in a controlled manner to achieve desirable

## Executive summary

**Animal models**

- Animal models have demonstrated the specificity of alcohol's teratogenecity and elucidated the mechanisms of alcohol-induced brain damage.
- Animal models have also shown that specific regions of the brain are more vulnerable than others to the teratogenic effects of alcohol (midline structures).

**Neuroimaging studies**

- Structural and functional neuroimaging studies have identified abnormalities of specific regions of the brain in alcohol-affected children (e.g., cerebellum, corpus callosum, basal ganglia and parietal cortex).

**Elementary functions**

- Converging evidence from animal and human studies have revealed alcohol-induced deficits in associative learning (e.g., eyeblink conditioning), prosaccades and orienting responses.

**Complex cognitive functions**

- Children with fetal alcohol spectrum disorders (FASDs) process information at a slower rate than controls.
- Children with FASDs show deficits in intellectual functioning, with verbal and visual spatial skills both being equally diminished.
- Children with FASDs exhibit performance deficits on tests of executive functioning and attention.
- On tests assessing specific functions such as language and memory, alcohol-affected children show performance decrements with increased task complexity.
- This pattern of performance suggests a generalized deficit in the processing and integration of information, specifically complex information. Slow processing of information significantly contributes to this deficit.

**Effects of prenatal alcohol on behavior**

- On parent- and teacher-rated questionnaires, children with FASDs are often rated as 'acting young' and 'inattentive'.
- On measures of adaptive behavior, children with FASDs are rated as having social difficulties.
- These difficulties in behavior are associated with deficits in information processing, intellectual ability and executive functioning.

**Conclusion**

- The findings from neuroimaging and animal research and human neurobehavioral studies can be interpreted within a neurodevelopmental framework.

**Future perspective**

- The hypothesis that children with FASDs have a generalized deficit in the processing and integration of information has specific implications for the development of interventions and planning future research.
- In particular, we advocate the study of both elementary and complex functions and the use of process analysis and growth curve models in future research.
- The proposed neurodevelopmental framework allows for combining behavioral (experiential) and pharmacological approaches in the treatment of children with FASDs.

outcomes. The recommended strategies included social games targeting the development of executive control skills, repeated presentation of information using concrete examples and provision of information at a level that facilitates development (zone of proximal development).

The interactive perspective also emphasizes the importance of targeting neural and chemical structures directly. The target of a burgeoning area of research has been to develop cognition-enhancing drugs using animal models of FASDs. Researchers have obtained evidence that aniracetam, a cognitive enhancer, improved learning and memory in alcohol-exposed rodents [196]. Some investigators have explored the utility of ABT-239, a histamine H3-receptor antagonist, in the treatment of learning and memory deficits in alcohol-exposed animals [197,198]. Thomas *et al.* have found that both prenatal and postnatal choline supplementation is effective in the reduction of alcohol-induced cognitive deficits [199].

Since prenatal alcohol exposure is known to alter most neurotransmitters [200], some investigators have explored the efficacy of pharmacotherapy in the management of behavioral and emotional problems in children with FASDs [201–203]. Although psychostimulants are commonly being used to treat attentional difficulties in alcohol-affected children, this class of medications has been found to produce variable outcomes [202]. In a retrospective case series study, O'Malley *et al.* observed that alcohol-affected children responded better to dextroamphetamine (79%) than to methylphenidate (22%) [204]. Frankel *et al.* found that children who were prescribed neuroleptics benefitted more from a social skills training program than children who were prescribed psychostimulants [203]. There is a growing body of literature showing that genetic variability moderates responses to medication and behavioral interventions [205]. Therefore, we expect that clinicians will be able to optimally combine pharmacological agents and experiential therapies in the treatment of cognitive and behavioral deficits in children with FASDs by utilizing modern tools in genetics, neuropharmacology, behavioral sciences and neuroimaging in the near future.

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