INTRODUCTION

In 2014 Fetal* Alcohol Spectrum Disorder (FASD) hit the radar in the United Kingdom. FASD was debated in Parliament, the courts and the media. FASD was also addressed by David Cameron in Prime Minister's Questions. On the other side of the globe the Australian Government decided to make a commitment to and an investment in fetal alcohol research.

In this issue of the FETAL ALCOHOL FORUM we feature new innovative programmes from Japan to Italy, from the Netherlands to Reunion Island in the Indian Ocean.

There are also video links to the debate initiated by NOFAS-UK in the Houses of Parliament (click here) and experts responses to the recent court case challenging whether heavy drinking in pregnancy should be considered as a mother’s crime against her fetus. The Court of Appeal ruled that the fetus cannot be the victim of a crime. As controversial as the debate was, more importantly, it made people aware of the dangers of drinking alcohol in pregnancy.

For the 9th September (International FASD Day) the EUFASD Alliance with Fabrica of Benetton and the Local Health Authority of Treviso, Italy, launched the campaign Too Young To Drink. It was shared virally with 53 organisations in 27 countries. (Watch: Behind the Scenes: https://www.youtube.com/watch?v=5lAqHCo2XA; website: www.tooyoungtodrink.org).

New statistics in a Canadian study calculate the economic toll of FASD to be between 418 million and 1.08 billion Canadian dollars per annum due to loss of productivity in the work force.

I am fascinated by the original studies we have found for prevention, for care giver management, research re the ‘father factor’, research to reduce cell death and potentially reverse some of the teratogenic effects of prenatal alcohol. Also treatments for stress in adults with FASD, experiments to alter genetic signalling, small animal studies with Japanese rice fish, zebra fish and flies, ethanol inhalation research, new low level studies and new systematic reviews.

The universe of FASD is expanding. We are finding new constellations everyday.

If you have an FASD study or news you would like published in the next issue please send it to info@nofas-uk.org. We always appreciate your comments and valuable feedback. If you would like to be added to the FETAL ALCOHOL FORUM mailing list, please click here.

* fetal / fetus: International / medical spelling
Countries that have produced FASD Studies during the past 6 months:

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<tr>
<th>Country</th>
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You can download all issues of the FETAL ALCOHOL FORUM from our website: www.nofas-uk.org

This New Year we thank you all: scientists, health professionals, educators, families and everyone for being part of the NOFAS-UK extended FASD FAMILY.

Susan Fleisher  
Publisher

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Associate Editor
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   Raja A.S.Mukherjee  
   Lead Clinician and Consultant Psychiatrist  
   National FASD Specialist Behaviour Clinic  
   Surrey and Border’s Partnership NHS Foundation Trust  
   raja.mukherjee@sabp.nhs.uk  
   www.fasdclinic.com

It was in 2003 that my personal journey with FASD began. At that point in time as junior psychiatrist learning my way, I was slightly surprised to find no specialists working with this disorder. In other parts of the world, especially USA and Canada, these appeared to be common place. I have come to learn that is not necessarily true, yet isolated in the UK, that it is how it appeared.

Clinically, my own service began out of a research project to see individuals based on the model used in specialised tertiary neurodevelopmental clinics in the UK. Essentially a team of individuals who work together collaboratively to assess, diagnose and then develop recommendations regarding management for those individuals. The difficulty, in the absence of places to learn, is how to specialise and become an expert in this area. I was fortunate to have great support from across the Atlantic.

The presentations of individuals with FASD diagnoses, especially where the facial characteristics are absent, remain a challenge. In many parts of the world, at the time of starting the clinic, the process of evaluation and differentiation remained mainly through pattern recognition of features and gestalt. This meant that challenges existed where classic features were absent. Work conducted in Manchester, UK concluded that the process of ruling out different disorders that had similar profiles was essential and that a CGH micro array was one test that should be conducted in all as a minimum. This approach was adopted by our fledgling clinic when establishing itself properly in 2009.

It was also clear that in order to increase the confidence in diagnosis ruling out other teratogenic factors was also necessary. For example, other illicit drugs, medication, prematurity and postnatal insults were all thought to be important to rule out. The challenge here has always been the lack of information.

Consensus guidance regarding information to gather at different stages were produced in a meeting of professionals from across the UK, yet there remains a postcode lottery of practice. In some areas the information is gathered consistently and well, yet in others, the information is regularly absent.

It became apparent that in reality, whilst the clear cases could be diagnosed without wider testing, it was not possible where presentations were more subtle. It was considered vital to have a comprehensive approach that looked at wider profiling to be confident in the diagnosis. By 2011 our clinic was fully established as a tertiary level, nation service, being able to offer a comprehensive neurodevelopmental assessment, which diagnosed FASD, but also recognised the individuals function and wider needs.

By as far as possible identifying through comprehensive investigation background information, alongside thorough testing of cognition, communication, sensory profile, behaviour and function differentiation of the aetiological factors can for many cases be made. Some factors cannot be differentiated, for example cocaine use and alcohol, whereas heroin and alcohol can. This therefore is vital to complete properly.

The clinic is still however one of the few in the UK for children and the most specialist currently available for behaviour issues. It is also the only specialist adult clinic in the UK. Service models, if those affected are to be properly seen, diagnosed and supported need to be improved.

Diagram one represents the model of service delivery that has been proposed. This is a common model in a wider range of complex conditions. It is one that can be adopted also worldwide based on individual health systems but is
particularly relevant to the UK NHS structures. The challenge that remains in a financially challenged system is how to deliver this without new investment. Current healthcare strategy development in the UK is limited, due to challenges from funding reductions. It is however a model, that should it be implemented, would offer a rapid way in improving access, diagnosis and wider expertise. This would filter down from the national level to a local level. Ultimately by doing this, it would bring the expertise and knowledge up generally and also prevent the postcode lottery of diagnosis.

The lack of local knowledge has been highlighted now in several settings in the UK. Work conducted by Red Balloon Training as part of their needs evaluation project highlighted that GP, in all cases of those asked failed to know how to support affected individuals. This is consistent with wider published research that GPs and other health professionals often have heard of FASD but lacked the training or expertise to support and refer this group appropriately.

In secondary care, similar findings were found by our own research. This raised the question that if people lack the expertise to diagnose then families are likely to struggle. This too was seen in research conducted in adoptive families.

The recognition of FASD begins at the preconception stage. In UK a consensus document looking at pathways for service delivery was produced in 2013. It described proposed pathways for the recognition of alcohol consumption in pregnancy to the follow up and diagnosis of affected individuals. Unfortunately the ongoing postcode lottery of knowledge makes it a challenge to implement the recommendations. A whole system approach is required to allow change to happen. Unfortunately as this stands, the identified lack of information and knowledge is hindering this.

The UK has the potential to implement change and the structures to do this. The commitment and finance is currently lacking. Should this change, the benefits for those in the UK will be a model that can be adopted widely.

Diagram one: model of service delivery proposed in the UK
2. **A Pilot Study Exploring Parental Experiences and a Fetal Alcohol Spectrum Disorders (FASD) Education Program**

Barbara M. Burns¹, Lauren Davis² and Yasmin Senturias²,³

Yasmin Senturias, MD, FAAP
Academic Division Chief, Developmental and Behavioral Pediatrics Division
Carolinas Healthcare System
Adjunct Associate Professor of Pediatrics
University of North Carolina at Chapel Hill

Barbara M. Burns, Ph.D.
Professor and Director of Liberal Studies:
Pre-Teaching and Child Studies
Santa Clara University, Santa Clara, CA USA

Fetal Alcohol Spectrum Disorders (FASDs) are considered one of the leading causes of intellectual and developmental disabilities in the United States. (May and Gossage, 2001) Children diagnosed with an FASD have neurocognitive deficits that frequently result in behavioral problems. The role of caregivers for the child’s adaptation to his/her environment is important and a basic understanding of the neurodevelopmental reasons behind FASD symptoms may lead to more appropriate expectations about the child’s capability in various neurocognitive and developmental domains. However, programs that can be taken to scale in community groups have not been developed for caregivers and parents.

There is a paucity of empirically supported treatment options that alleviate the problems faced by children and families living with FASD (Grant et al., 2004; O’Malley & Streissguth, 2005; Premji, Benzies, Serrett, & Hayden, 2006). Current treatments for FASDs include medications to manage symptoms (including stimulants, antidepressants, neuroleptics, and antianxiety medications), behavior and education therapy, and parent training programs (Bertrand et al., 2004; 2009). Few programs have been specifically designed for families who are raising a child with a Fetal Alcohol Spectrum Disorder (Carmichael-Olson, Rudo-Stern & Gendler, 2011; Streissguth, 1997). The establishment of effective early intervention for FASDs would address an important educational and public health need (O’Malley & Streissguth, 2005; Premji et al., 2006).

To address this need and develop an education program for families with children diagnosed with FASD we wanted to address two critical questions. First, how can we better characterize the experience of parenting in a community sample of families who were raising a child diagnosed with a Fetal Alcohol Spectrum Disorder? Second, how can the design of an FASD Education Program heighten parents’ understanding of their child’s disability, provide them with techniques for working with their child to overcome social and educational barriers, and have lasting application to family life?

To begin to address these questions, we recruited families to participate in a one-day program in which parents completed a set of questionnaires before and after received educational training. One year later, parents again completed a subset of the questionnaires. The parents we interviewed had children between ages 2 and 11 years of age. The children recruited had previously been evaluated by trained clinicians and all met criteria for Alcohol Neurodevelopmental Disorder based on the Revised Institute of Medicine Criteria (Hoyme, 2005). Children had been adopted into their families or were under foster care. None of the parents interviewed were biological parents.

**Participants**

Thirty-one families participated in this study. These families were recruited through the Weisskopf Child Evaluation Center located at the University Of Louisville School Of Medicine in Louisville, Kentucky between 2010 to 2011. The children recruited had previously been evaluated by trained clinicians and all had an FASD diagnosis. The children in
these families ranged from 2 years to 11 years of age (24.3 months to 134.8 months, M = 83.79, SD = 28.6). Parents of 8 female and 23 male children participated in this study. The majority of these families had incomes ranging from $30,000 to $75,000. Two male and twenty-seven female caregivers (ages 25 to 61 years of age, M = 46.54, SD = 9.30) attended the sessions, and for two families both a male and female caregiver was present. Sixteen of these caregivers were adoptive or foster parents while the remaining fifteen were primary caregivers and relatives of one of the parents. This sample included no biological parents. The term parent here is used to refer to all caregivers. The mean education level for the parents was 13.85 years (SD = 2.60). Each family was given a small gas card to cover travel expenses and a small gift card as compensation for their participation and time. As compensation for time in completing the follow-up assessments, each family was given a second small gift card.

Human Subjects Approval

This study was approved by the University of Louisville Institutional Review Board. Informed consent was obtained from the legal guardian of the child participating prior to the collection of data.

Questions One: How Can We Better Characterize Parenting of Children Diagnosed with FASD?

Parent Characteristics. Stress in the parenting role was measured by the Parenting Stress Index, 3rd Edition (PSI, Abdin, 1995) which has three scales measuring anxiety and other emotional stressors brought about by parenting (Parenting Distress scale), satisfaction the parent derives from interaction with their child and how much their child meets their expectations (Parent-Child Dysfunction Interaction scale) and the child’s temperament and parent’s ability to tolerate their child in certain situations (Difficult Child scale). Parenting strategies were also measured using the Adult-Adolescent Parenting Inventory, 2nd Edition (AAPI; Bavelok & Keene, 1999); the Parenting Sense of Competence Scale (PSOC) includes sixteen items to measure parenting self-esteem divided into efficacy and satisfaction (Johnston & Mash, 1989); the Center for Epidemiologic Studies Short Depression Scale (CES-D; Radloff, 1977) to measure self reported symptoms associated with depression.

Characteristics of Children. The Eyberg Child Behavior Inventory (ECBI; Eyberg & Pincus, 1999) was used to obtain a measure of children’s behavior. This parent-report assessment measures the severity and frequency of conduct problems as rated by the parent (ECBI Intensity scale) and how problematic the conduct problems are as rated by the parent (ECBI Problem scale.

Findings: Not unexpectedly, we found that parents of children diagnosed with FASD were facing a great deal of stress associated with parenting. In over 77% of families, the scores on a total stress measure were higher than that of the norm. Additionally, almost 84% of parents had ratings greater than the norm on the difficult child scale. The assessment of children’s problem behaviors confirmed what has previously been reported in the literature regarding social-emotional and cognitive challenges associated with children diagnosed with FASD. Parents reported that their children were very challenging in day-to-day family life. Parents reported a great deal of problematic behaviors and the problems were intense. 90% of parents rated their children above the norm on a measure of problem intensity.

Question Two: How can we design an effective FASD parent education program?

FASD Parent Education Program: We set out to design a program that combined current scientific understanding of FASD and activities that provided parents with opportunities to view their child diagnosed with FASD from a new perspective of strengths and challenges. In our FASD Education Program, parents were given an overview of the current scientific understanding of FASD. Following this, they were given the opportunity to complete, in a group setting, a booklet entitled “All About Me”, developed by Ms. Laura Nagle from the Kentucky FASD Prevention Enhancement Site (See http://www.kyfasd.org/assets/downloads/AllAbout%20Me_FASD.pdf). Almost as soon as the “All About Me” booklet was distributed and parents were asked to fill in the first page of strengths of their child, parents started talking
to us about this experience as a novel and positive experience. It was apparent to all facilitators that parents enjoyed listing the strengths of their child and sharing them with the group.

The FASD facilitator underscored how useful it was to remember the many strengths of their children as it could help provide a more balanced perspective when they faced challenges in child rearing. The second page of the booklet focuses on the range of emotional responses of their child. The FASD facilitator introduced this page by talking about the importance of using individualized discipline methods. The core idea was that it is especially important for children diagnosed with FASD to learn self control and it is more helpful for parents to anticipate their child’s difficult emotions and tailor responses to their child in order to best help them regain control of themselves. The next section of the booklet lists some of the areas in which children with prenatal alcohol exposure can struggle, such as thinking abstractly, brain pace, learning from experience, and understanding cause and effect. Parents affirmed these challenges with examples. Suggestions are included in the booklet to address some of these challenges. Additional areas in which a child may struggle included rigid thinking, inability to read body language, poor memory, and problems in sensory integration. The FASD facilitator shared how occupational therapists often address sensory integration issues. Parents shared many stories of cutting tags out of their child’s clothes, being sure socks were inside out so the seam did not bother their child, etc., and a lively discussion emerged regarding how to make specific child accommodations at home and in school.

Making accommodations and adjustments in day-to-day life is the core message of the rest of the “All About Me” booklet. The FASD facilitator led a discussion on the use of concrete language; expecting to reteach things; providing external memory tools; speaking slowly and using fewer words; the importance of routine to their child; the need for extra supervision. The final section of the “All About Me” booklet focused on changing the home environment to help make it more individualized for the child’s strengths and challenges. The FASD facilitator suggested that some parents often express concern that making some of the suggested environmental changes or implementing some of the discussed techniques will end up enabling their child to perform poorly and help them learn to cope with the issues they face. The FASD facilitator shared that the FASD diagnosis is a partial explanation for some of their family struggles and hope for the best for their child is critical. The discussion of “All About Me” concluded with strong encouragement and support for parents to both encourage their child to be successful, and implement techniques to support their child in everyday struggles that may continue across childhood and youth development.

Findings and One Year Follow Up. An assessment and evaluation of the FASD education program was completed by all parents immediately following the session. This evaluation was overwhelmingly positive. 100% of parents (n = 30) reported that they found the education session to be useful. When asked if they felt the education session would have a positive impact on their relationship with their child, 100% of parents said “yes”. Parents reported that they learned a great deal and thought the material would be applicable in their family in daily activities. One calendar year later, each family was sent a parent survey to re-assess the utility of the FASD Parent Education Program. In the one-year follow up, parents were very positive about the program. Families reported that the education program had a positive impact on their relationship with their child, they applied the ideas in daily life and they would recommend this to others. More details about our study is available as an unpublished manuscript and can be requested from the corresponding author. (Burns, Davis and Senturias, unpublished manuscript)

Our follow up also included questionnaires on parenting stress and children’s behavior. We found no significant reductions in parenting stress but the second assessment of their child’s behavior one year after the education program using the age-adjusted Eyberg Child Behavior Inventory did show a significant reduction in intensity and problem behavior scores. While no conclusions regarding the impact of the actual FASD education program on parent views of children’s problem behaviors can be made, this pilot study suggests that our approach has potential to be used in an experimental study of the impact of FASD parent education on child behavior in this population.

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3. **Fetal Alcohol Spectrum Disorder (FASD): What Law Enforcement Professionals Need to Know**

   **Author:**

   Jerrod Brown MA, MS, MS, MS, is the treatment director for Pathways Counseling Center, Inc. Jerrod is also the founder and CEO of the American Institute for the Advancement of Forensic Studies (AIAFS).

   **Contributors:**

   Sarah E. Herrick, MA, LP, LPCC, CCFC, has worked with sexual abusers ranging in age from ten to elderly since 1991, in residential, community mental health, and prisons settings. Currently she is working with civilly committed sex offenders.

   Kathleen Bischel Beddow, MA, LMFT, is a Licensed Marriage and Family Therapist in private practice. She works with individuals and families experiencing relationship struggles and challenges from Autism Spectrum Disorders (ASD), Fetal Alcohol Spectrum Disorders (FASD), abuse, addiction, divorce or separation, mental illness symptoms and forensic experiences.

   Jeffrey Long-McGie, MA & MBA, is a Research Fellow at AIAFS, and currently training to become a licensed police officer.

   Judge Anthony (Tony) Wartnik, BA, JD, was a trial judge for 34 years in King County, Washington.
Tina Jay, AS, BSW, is an advocate for children as a Guardian Ad Litem since 1998, with a background in Early Childhood Education, a Bachelor’s Degree in Social Work, and currently pursuing a Master’s Degree in Forensic Mental Health.

Erv Winkauf, MA, is a retired 40-year law enforcement veteran with 19 years of teaching experience. He currently serves as chairperson of the Concordia University Criminal Justice Department in St. Paul.

Janina Wresh has 19 years of experience in law enforcement working in forensics crime laboratories, courts, and adult detention centers. She has served as a deputy sheriff, police officer, domestic abuse response specialist, crisis intervention specialist, and crime scene technician. Janina also serves as AIAFS’ Chief Operating Officer.

Fetal Alcohol Spectrum Disorder (FASD) is a continuum of pervasive conditions that are the result of prenatal alcohol exposure. These conditions can include intellectual deficits, interpersonal and social issues, and a host of adverse medical, as well as mental health complications. Contrary to popular belief, the large majority of individuals diagnosed with FASD do not have the facial features that are characteristic of a Fetal Alcohol Syndrome (FAS) diagnosis. The symptomatology of FASD can hinder the criminal justice process, thus it is important that law enforcement officers are trained and educated on the implications of FASD. The following considerations are provided to promote an increased understanding, appreciation, and communication across all criminal justice venues (e.g. arrest, investigative interview, trial process, incarceration, etc.)

**Adoption:** A high percentage of children in the adoption system have been exposed to alcohol prenatally. Many FASD-impacted children have experienced abuse and neglect early in life. These factors can lead to disrupted attachment patterns.

**Community Supervision:** Individuals with FASD often fail to comply with probation requirements. Traditional methods of community supervision rarely work for this population. Deficits in executive functioning, memory, and a high comorbidity of mental health and substance use concerns can all contribute to unintentionally violating conditions of probation.

**Confabulation:** Individuals with FASD may unintentionally provide inaccurate information to law enforcement officers due to their suggestibility and difficulties in conveying events in a logical sequence. In addition, they may experience cognitive deficits that make accurate retrieval of both short and long term memory difficult.

**Diagnostic Comorbidity:** Individuals with FASD may simultaneously be diagnosed with other major mental illnesses including Attention Deficit/Hyperactive Disorder, Reactive Attachment Disorder, Bipolar Disorder, Oppositional Defiant Disorder, and Conduct Disorder. These other diagnoses may pose their own unique challenges and should be thoroughly investigated.

**Family Violence:** Individuals with FASD often experienced a chaotic home life, as well as exposure to multiple forms of violence. Without proper supports and treatments, FASD-affected individuals are more likely to continue these cycles of abuse.

**Homelessness:** Without proper ongoing supports and services, individuals with FASD may end up homeless in adulthood. Executive functioning impairments that result in impulsivity, poor judgment, difficulties accessing risk, an inability to fully comprehend what drove past mistakes, deficits in recognition, limited financial skills, impaired social interactions, a lack of focus, and comorbid psychological illnesses may exacerbate the risk of homelessness.

**Incarceration:** Individuals with FASD present unique challenges in correctional settings. FASD-impacted persons are at an increased risk of experiencing victimization and exploitation by other inmates. FASD-related impairments may also impact one’s ability to comply with multi-step instructions and commands given by correctional staff.
Impulsivity: Individuals with FASD may “act before thinking” and not fully consider the consequences of waiving their right to an attorney, giving false statements, or other procedural decisions. FASD-impaired individuals can be extremely sensitive to disruptions, which may result in increased impulsive-type behaviors.

Procedural Incompetence: Individuals with FASD may have difficulty understanding their Miranda and Constitutional rights, participating in interrogative procedures, comprehending the adversarial trial process, and effectively assisting counsel in preparing a defense.

Sexual Offending: Inappropriate sexual behavior is a common problem for individuals with FASD. Poor understanding of social boundaries may also contribute to inappropriate and impulsive sexual behaviors. Additionally, individuals with FASD experience executive functioning deficits, emotional immaturity, and have a decreased understanding of cause and effect relationships. FASD-affected individuals also often have a poor understanding of social clues and demonstrate poor judgment. Thus, FASD must be considered when determining treatment and other intervention strategies.

Sleep: Individuals with FASD frequently experience profound sleep-related concerns. Chronic sleep problems can negatively impact emotional and physical health. Sleep-related deficits can also affect memory, mood, and motivation which can lead to an increase in anger, irritability, and impulsivity.

Substance Abuse: Individuals with FASD are at an increased risk to abuse illegal substances. Impaired judgment, poor impulsive control, and a high comorbidity of mental health conditions may be exacerbated by chemical abuse. Individuals with FASD are also more likely to be impacted by negative peer groups.

Suicide: Individuals with FASD have high rates of substance abuse, as well as high rates of depression. As such, FASD-impacted individuals are at an increased risk to threaten, attempt or commit suicide compared to persons without the condition. In addition to experiencing a history of traumatic experiences, individuals with FASD often struggle with other impairments that may impact overall quality of life.

Theft: Often the first crime an individual with FASD will commit is shoplifting. Compared to an individual without FASD, criminality generally starts at a younger age for a FASD-impacted youth, especially when lacking supports and services. Typically, youth with FASD have difficulty learning from consequences and may continue to engage in illegal activity on a regular basis.

Victimization: Individuals with FASD are vulnerable and commonly victimized. Financial exploitation is another concern impacting FASD-affected individuals. Additionally, it is common for FASD-impacted individuals to have experienced severe trauma (e.g. neglect, physical, psychological, and sexual abuse) early in life. These individuals may also struggle with the ability to recognize thoughts and feelings associated with trauma. This may lead to additional victimization, mental health problems, substance use, and believing what happened to them is normal, thus acting out that behavior on others.

Intervention Strategies: It is important for law enforcement professionals to employee strategies that are appropriate for individuals with FASD. D.E.A.R. is an acronym developed by our research team to assist officers with remembering suggested approaches that may increase positive outcomes for FASD-criminal justice involved individuals.

D.E.A.R.

DIRECT LANGUAGE

When interviewing an individual that is diagnosed with or suspected to have FASD, use simple and direct language. Be as concrete as possible, as this population has difficulties with abstract thinking. Explain things slowly to allow for more
time for the individual to process what they are being asked, and ask for the interviewee to explain your question back to you to ensure comprehension.

**ENGAGE SUPPORT SYSTEM**

When interviewing an individual that is diagnosed with or suspected to have FASD, be sure to ask whether they carry with them a card of a mentor, advocate, or case worker who can offer support and/or act as an interpreter. Given this population frequently does not understand the consequences of providing police with incriminating statements, avoid leading questions until a member of their support system is present.

**ACCOMMODATE NEEDS**

When interviewing an individual that is diagnosed with or suspected to have FASD, conduct the interview in a quiet place without distractions. Give the individual space and avoid physical confrontation. As this population usually functions at a lower developmental level than their chronological age; adapt your choice of words and your style of communication accordingly.

**REMAIN CALM**

When interviewing an individual that is diagnosed with or suspected to have FASD, do not rush, as this will cause stress and may result in the individual becoming overwhelmed. This population is characterized by an inability to manage their emotions and situations may escalate quickly. It is necessary to maintain a calm and collected demeanor with this population.

**FASD-Myths & Realities**

**Myth:** A small amount of alcohol will never harm an unborn child.  
**Reality:** In fact, women who consume only a small amount of alcohol are still putting their unborn child at risk for FASD.

**Myth:** FASD-impacted individuals will outgrow the disability.  
**Reality:** FASD is a lifelong disability that will never go away.

**Myth:** Only the poor have children with FASD.  
**Reality:** People from all types of backgrounds have children with FASD.

**Myth:** All Individuals with FASD have facial abnormalities.  
**Reality:** Most people with FASD do not have abnormal facial features.

**Myth:** Medical and healthcare professionals clearly understand the impact of FASD.  
**Reality:** Even today, many healthcare providers do not fully understand the harmful impact alcohol can have on the unborn child.

**Myth:** The criminal justice system is well equipped to deal with FASD.  
**Reality:** Many professionals within the criminal justice system have little to no training in the area of FASD, including identifying an individual impacted by FASD and how to engage and/or treat the individual.

**Myth:** FASD is less common than Autism Spectrum Disorders (ASD).  
**Reality:** FASD is more common than Autism Spectrum Disorders (ASD).

**Myth:** The educational system clearly understands the impact of FASD.  
**Reality:** Many children in the educational system with FASD fall through the cracks and are misdiagnosed or not diagnosed at all.
Myth: Individuals with FASD are untreatable and cannot improve functioning.

Realty: Effective treatment can help a person with FASD live a happy and productive life. The earlier the intervention, the better the outcome in minimizing the potential impacts of FASD.

Myth: It is not possible for an individual with FASD to complete school.

Realty: In fact, many individuals with FASD do complete school with the right type of support.

Myth: Individuals with FASD are not able to hold a job.

Realty: Many people with FASD are able to work and maintain employment.

Recommended Readings


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4. **FASD and Sleep-Related Disturbances with Children: Causes, Consequences, and Interventions**

**Authors:**

*Jerrod Brown*, MA, MS, MS, MS, is the Treatment Director for Pathways Counseling Center, Inc. Pathways’ focus is to provide programs and services that benefit individuals impacted by mental illness and addictions. Jerrod is also the founder and CEO of the American Institute for the Advancement of Forensic Studies (AIAFS) and lead developer and program director of an online graduate degree program in Forensic Mental Health from Concordia University, St. Paul, Minnesota. Email: Jerrod01234Brown@live.com

*Sarah E. Herrick*, MA, LP, LPCC, CCFC, has worked with sexual abusers ranging in age from ten to elderly since 1991, in residential, community mental health, and prisons settings. Currently, she is working with civilly committed sex offenders.

*Jeffrey Long-McGie*, MBA & MA, is a Research Fellow at the American Institute for the Advancement of Forensic Studies (AIAFS), and a criminal justice graduate student at St. Cloud State University.

*Judge Anthony (Tony) Wartnik*, BA, JD, was a trial judge for 34 years in King County, Washington. He chaired his court’s task force on protocols for determining competency of youth with organic brain damage and the Governor’s Advisory Panel of FAS/FAE.

**Contributors:**


**ABSTRACT**

Problems related to sleep are a common concern for the parents of young children with Fetal Alcohol Spectrum Disorder (FASD). Disrupted sleep patterns and other difficulties pertaining to sleep may adversely affect academic, behavioral, physical, emotional, and social functioning. Research suggests that children diagnosed with FASD are more likely to experience problems pertaining to initiating sleep, delayed sleep onset, bedtime resistance, maintaining sleep, restlessness during sleep, and chronic tiredness upon awakening from sleep. Hence, training in the early detection of sleep problems in this population and evidence-based interventions by professionals may prove beneficial for all aspects of public health. The present article briefly reviews the empirical literature in context to sleep-related disturbances and FASD.
Please note: The information in this article is neither a substitute nor a replacement for professional medical advice, diagnosis, or treatment. Consult your physician or another qualified healthcare professional if you have further questions regarding sleep health and education for you and/or your family members.

**FASD and Sleep-Related Disturbances: A General Introduction**

Sleep-related disturbances are common among children diagnosed with Fetal Alcohol Spectrum Disorder (FASD) (Hilakivi, Tuomisto, Hilakivi, Kianmaa, Hellevuo, & Hytyia, 1987; Ipsiroglu, McKellin, Carey, & Loock, 2013; Kelly, Day, & Streissguth, 2000; Rosett, Snyder, Sander, Lee, Cook, & Weiner, 1979; Scher, Richardson, Coble, Day, & Stoffer, 1988; Troese, Fukumizu, Sallinen, Gilles, Wellman, Paul, Brownd, & Hayes, 2008). In trials that have assessed clinically significant sleep disorders investigators have observed that 60% to 85% of the individuals with FASD are afflicted (Stade, Khuu, Bennett, Sandor, Stephens & Lanceta, 2008; Goril, 2011; Elgin, Bruaroy & Laegreid, 2007; Chen, Olson, Picciano, Starr & Owens, 2012). Recent estimates suggest that approximately 80% of children diagnosed with FASD experience sleep problems (Jan, Owens, Weiss, Johnson, Wasdell, & Freeman, 2008). Furthermore, these sleep disorders may be persistent into adulthood and may potentially negatively impact cognitive, behavioral issues and affective disorders (Volgin & Kubin, 2012; Volgin, 2012). High percentages of adult parents of children with FASD report their mothers drank when pregnant, a multi-generational pattern of FASD (Whitney, 2012). The FASD parent struggles with parenting limitations, including sleep disorders, which may contribute to the sleep and behavioral issues of their child with FASD. Limited research exists related to the causes, consequences, and solutions of FASD and sleep disturbances (Jan, Asante, Conry, Fast, Bax, & Ipsiroglu, 2010). Sleep-related problems in children with FASD can negatively impact behavioral, mental, and physical health, as well as cognitive functioning (Jan et al., 2010). The causes of sleep-related disturbances in children with FASD may range from environmental (e.g., family, neighborhood, school) to psychological (e.g., depression and anxiety) to biological (e.g., obesity and diabetes) and may enhance symptomology related to other comorbid conditions. Insomnia is the most commonly reported sleep-complaint observed in individuals with FASD (Ipsiroglu et al., 2013), including problems falling asleep, staying asleep, and waking up early (Jan et al., 2010). Sleep-wake concerns are frequently seen in children with FASD (Hanlon-Dearman, 2003; Ipsiroglu et al., 2013; Streissguth, 1997). Circadian rhythm abnormalities and frequent arousal during sleep can also present as consequences of prenatal alcohol exposure (Sakata-Haga, Dominguez, Sei, Fukui, Riley, & Thomas, 2006; Seia, Sakata-Hagab, Ohtab, Sawadab, Morita, & Fukui, 2003; Troese, et al., 2008). It should also be mentioned that alcohol exposure through breast milk may disrupt infant sleep-cycles (Menella & Garcia-Gomez, 2001).

**Comorbid Factors:** Although there appears to be a fairly clear connection between sleep-related disturbances and FASD, the reasons for this co-morbidity are largely unknown. Even subtle changes in the sleep patterns of children diagnosed with FASD may exacerbate symptomatology associated with comorbid mental health conditions (e.g., ADHD, anxiety, depression, and PTSD). Understanding the nature of the co-morbidity between sleep problems and FASD, in addition to the adoption of interventions based on this understanding, may improve the quality of life for these children and their families. Children with FASD can be difficult to calm, which may contribute to sleep-related difficulties (Brown, Tiede, Bickford, & Wentz, 2013b). Increased anxiety may play a role in sleep initiation and maintenance problems (Zhou, Wang & Zhu, 2010; Volgin & Kubin, 2012). The inability to self-sooth and regulate emotions are also common deficits associated with FASD (Westrupa, 2013). Animal studies involving FASD suggest that excessive levels of Orexin A and B (two highly conserved neuropeptide transmitters produced in the hypothalamus region that are critically involved in wakefulness) may mediate hyperactivity, sleep disorders, cognitive deficits and anxiety (Volgin, 2012). FASD-impacted children with insufficient sleep frequently experience an increase in daytime fatigue and hyperactivity (Hanlon-Dearman, 2003). Secondary conditions associated with FASD, such as ADHD, can contribute to increased sleep-related difficulties in this population (Chen et al., 2012). Emotional and social factors may also contribute to ongoing sleep issues in children with FASD (Jan et al., 2010). Additionally, sleep-related concerns in children with FASD could potentially lead to an increase in educational deficits (Tiede, 2013). It has been noted that racing thoughts are a common experience for children with FASD (Tiede, 2013), which may further exacerbate sleep problems for this group of individuals. Inadequate sleep has been found to further negatively impact adaptive functioning in FASD-affected children as well (Chen et al., 2012). Additionally, sleep disorders may function in a bidirectional manner as both the cause and effect of neuropsychiatric disorders such as depression and worsen conduct-disordered type behaviors (Baglioni, Battagliese, Feige, Spiegelhalder, Nissen, Voderholzer, 2011; Gregory & Sadeh, 2012; Shanahan, Copeland, Angold, Bondy & Costello, 2014). Information processing deficits among individuals with FASD are also common.
(Dubienski, 1996; Malbin, 2004; Page, 2001), and may possibly contribute to difficulties with learning new skills that target improving sleep practices.

**Healthcare Providers:** FASD and its relationship to sleep-related problems is an under-recognized issue among professionals (Bhatara, Loudenberg & Ellis, 2006; Chen et al., 2012 Green, Mihic, & Nikkel, 2009; Steinhausen, & Spohr, 1998). Frequently, healthcare providers are also unaware of the complexities associated with FASD and sleep-related concerns (Ipsiroglu et al., 2013). Pharmacological interventions may provide an option for the treatment of FASD-related sleep difficulties (Chen et al., 2012). Consultation with a healthcare provider who understands the complexities of FASD in relationship with sleep problems is recommended, especially when considering medications as a treatment option.

Caregiver and Family Impact: It is recommended that professionals emphasize the importance of sleep to caregivers of children with FASD. Children who experience impaired sleep cycles may inadvertently impact the quality of sleep of their caregivers (Meltzer & Mindell, 2007). FASD sleep-related problems often impact the entire family (Blakley, 2012), which may be further complicated by other secondary mental and medical health conditions. Children with FASD may be overly hyperactive and energized during bedtime routines (Brown et al., 2013b), thus contributing to ongoing issues of sleep initiation and caregiver fatigue. The routine of preparing a child with FASD for sleep can be an extremely challenging and a stressful task for the caregiver (Jan et al., 2010). Sleep deprivation in caregivers of children with FASD can also cause a decrease in patience and an increased in overall frustration (Brown, Clark, Wartnik, Tiede, & Terwey, 2013a; Hanlon-Dearm, 2003; Tiede, 2013). This may increase the propensity for caregivers to over-reactive to their children. Low frustration tolerance among caregivers and the child can easily escalate during bedtime routines and subsequently impact the child’s sleep quality throughout the entire sleep cycle (Brown et al., 2013b). It is important for caregivers of children with FASD to support not only other family members, but also incorporate self-care strategies into their daily lives (Brown & Bednar, 2004; Radford-Paz, 2013; Salmon, 2008).

**Intervention Strategies:** Improving sleep hygiene practices for children with FASD is a crucial first-step in managing sleep-related problems (Jan et al., 2010). Children with FASD often do not respond favorably to traditional sleep-improvement practices (Jan et al., 2010). Moreover, adapting to changes in routines, like modifications to bedtime schedules, can be difficult for individuals, especially children, with FASD (Dubienski, 1996; Malbin, 2004; Page, 2001). Sleep improvement strategies should be modified and tailored to meet the unique needs of children with FASD (Malhotra & Scott, 2011). Environmental accommodations, like providing shades on windows and white noise machines to mask traffic sounds, are other considerations to improve the sleep quality of children with FASD (Fjeldsted & Hanlon-Dearm, 2009). Consider limiting furniture and keeping the items in the bedroom to a minimum. A child with FASD may experience sensory overload if a bedroom is decorated with busy patterns and bold colors. Moreover, bright lights may also add to sensory overload. Fluorescent lights may also be problematic. As previously mentioned, treating children who are impacted by FASD and comorbid sleep problems with medications is an option. Implementing sleep hygiene strategies like developing bedtime rituals/routines, avoiding caffeine, decreasing water intake, and prohibiting electronic games prior to bedtime, may improve the overall quality of sleep for the child with FASD (Blakley, 2012). It is important to consider that treating sleep-related complaints in children with FASD may improve outcomes for other interventions (Jan et al., 2010). Finally, structure, consistency, and predictability in the child’s home environment has been found to be a protective factor against some of the secondary conditions associated with FASD (Clark, Lutke, Minnes, & Ouellette-Kuntz, 2004), which may also improve the quality of sleep for FASD-impacted children. Some caregivers of children with FASD have reported Melatonin supplements, similar to the applications used with other neurodevelopment disorders (Wasdell, Jan, Bomben, Freeman, Rietveld, Tai, Weiss, 2008), have shown some success. It is important to consult with a healthcare professional to determine if Melatonin supplements maybe an appropriate option.

**Trauma:** Individuals with FASD often experience comorbid trauma and sleep-related disorders (Tiede, 2013). FASD-impacted children who have experienced a history of trauma often present with additional challenges (Henry, Sloane, & Black-Pond, 2007), which may require expertise and training. Children with FASD who have experienced trauma frequently experience more profound deficits in language, learning, memory, and motor development compared to non-exposed adolescents (Henry et al., 2007), all of which can contribute to increased difficulties for caregivers and healthcare providers in treating sleep-related problems.

**Sleep Screening:** Screening for sleep-related problems in children with FASD is recommended (Chen et al., 2012). When screening for sleep-related problems in children with FASD, it is important to consider other possible contributing factors and consult with a healthcare professional to determine if Melatonin supplements maybe an appropriate option.

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medical health conditions that may be impacting sleep patterns (Blakley, 2012). Hence, seeking professional opinions is strongly encouraged.

**Bedtime Resistance:** Bedtime resistance is common among children with FASD (Brown et al., 2013b; Jan et al., 2010). Consistent and strict bedtime routines are recommended for children with FASD (Jan et al., 2010). This would also include weekend bedtime routines. Bedtime resistance maybe the result of secondary gains, developmentally-appropriate fears, exposure to past trauma, fear of the dark, previously unstructured bedtime routines, and/or sensory overload (Brown et al., 2013b). Quite, calm voices, repetitive directions, and picture cards may also be helpful at reducing bedtime resistance.

**Sensory Considerations:** An occupation therapy evaluation should be part of a multidisciplinary assessment when a child with FASD presents with severe sleep-related problems (Fjeldsted & Hanlon-Dearman, 2009) given sensory problems may contribute to sleep-related difficulties in children with FASD (Blakley, 2012). Occupation therapists can assist family members and caregivers with the creation of a bedroom environment that promotes a sense of peace and relaxation (Fjeldsted & Hanlon-Dearman, 2009), which is a necessary component for FASD-affected children who experience sleep-related issues. As such, it is important for caregivers to be aware of items in the bedroom that may contribute to sensory overload (Jan et al., 2010). Sensitivity to light is common among children with FASD (Jan et al., 2010). These sensory deficits may play a role in further exacerbating the quality of sleep for the FASD-impacted child (Wengel, Hanlon-Dearman & Fjeldsted, 2011; Jan et al., 2010). Olfactory sensitivity has been shown to play a possible role in sleep disruption (Clark, Li, Conry, Conry, & Loock, 2000). It has been noted that certain scents and textures have been found to contribute to increased sleep-related difficulties for children with FASD (Fjeldsted & Hanlon-Dearman, 2009). Caregivers should be aware of this sensitivity and identify potential sources of odor that may impact the olfactory senses for children with FASD. Additionally, reducing distractions and visual stimuli from the child’s bedroom may aid in the process of achieving improved sleep (Fjeldsted & Hanlon-Dearman, 2009). Children with FASD may be resistant to change in routines and rearranging of the bedroom, which may contribute to increased sensory problems. As it relates to auditory senses, children with FASD may be hypersensitive to sound (Brown et al., 2013b). Strategies implemented to help reduce noise and stimuli during bedtime hours may be worth consideration (Jan et al., 2010). During bedtime routines, excessive sounds should be minimized in order for the child to achieve optimal relaxation. Even dull persistent noises may promote aggravation and contribute to problems with the child falling and staying asleep (Brown et al., 2013b). The use of earplugs may be one strategy to consider when it is impossible to eliminate all sounds during hours of sleep (Brown et al., 2013b).

**Classrooms:** Teachers are often the first professionals to recognize and report academic and/or social behavior problems associated with sleep problems to parents, school psychologists, and physicians (Luginbuehl, Bradley-Klug, Ferron, Anderson, McDowell & Selim, 2008). Screening and intervention for pediatric sleep disorders within schools are not widely implemented and the benefits of integrating school personnel into the multidisciplinary sleep team has yet to be realized (Everhart, 2011). In the emerging studies on school-related sleep intervention strategies, formal sleep hygiene training and a program that used a cognitive-behavioral therapy framework showed evidence of success, with higher participation rates by adolescents in school compared to therapy outside of the school setting (Everhart, 2011). Sleep disorders, along with the global brain damage from FASD, bring challenges to the classroom, with the sleep disorder exacerbating the already difficult academic day for the FASD student. Children and adolescents with FASD often demonstrate higher order deficits that result in functioning at a younger age than their chronological age (Fast & Conry, 2004; Greenspan, 2008; Malbin, 2004; Popova, Lange, Bekmuradov, Mihic, & Rehm, 2011; Treit, Lebel, Baugh, Rasmussen, Andrew, & Beaulieu, 2013). Naps for five year-old children are a normal part of the day, but naps for chronologically older children with the brain function years younger, is often viewed as unacceptable. Practical strategies for daily success in the elementary classroom include increased and planned movement, physical activity in short bursts throughout the school day, shortened periods of focused activity, and a non-shaming, non-blaming provision for naps. In adolescent settings, the most effective strategy is the use of a non-shaming, non-blaming approach to minimize the stress on the already stressed FASD brain. Providing a quick screening tool to a school’s multi-disciplinary team, such as the Sleep Disorders Inventory for Students (Luginbuehl, Bradley-Klug, Ferron, Anderson, McDowell, Selim,2008), may enhance the overall understanding of the child’s behaviors in school. More research is needed to establish best practice for educators when presented with behaviors related to sleep disorders and FASD.

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Nutrition: Nutrition is another component to evaluate in children with FASD who experience sleep-related problems. Caregivers should consider consulting with a nutrition specialist/healthcare provider who understands the complexities of FASD. Improved nutritional habits, like a diet that includes all necessary food groups and providing snacks high in protein, low in sugars and without caffeine, may serve as a helpful intervention strategy when trying to improve sleep in children affected by prenatal alcohol exposure. It is important to consult with your healthcare provider prior to implementing special nutritional diets. It may prove beneficial to consult with nutritional experts to determine if the individual impacted by FASD suffers from food sensitivities or allergies which possibly impact sleep patterns.

Final Thoughts: Though sleeping problems may result in adverse outcomes for children diagnosed or suspected to be impacted by a FASD, when normal sleep patterns are restored, functioning may improve. In promoting preventative and intervention efforts, more research is needed, with a specific focus on the biopsychosocial causes and effects of sleep-related disturbances in children diagnosed with FASD. Such research may aid in the reduction of problems pertaining to falling and staying asleep, as well as could improve impaired academic performance across the lifespan. Integrating knowledge about the developmental processes into this discussion may be particularly beneficial in identifying factors that can contribute to sleep-related complaints for children at different cognitive and physical stages.

References


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APPENDIX A:

**FASD SLEEP IMPROVEMENT SUGGESTIONS**

*Please note: Consult with a qualified medical doctor or sleep specialist prior to the implementation of a sleep improvement program for your child with FASD.*

There are numerous strategies that families can utilize to improve the sleep of their child, which, in turn, may help the entire family sleep better. The following is a list of suggested techniques offered by sleep experts, as well as various caregivers, family members, and professionals who have regular contact with individuals impacted by FASD:

**Develop Bedtime Routines:**

- Consider a hot bath or shower before bed using lavender scents
- Use warm water to wash hands and face
- Provide yourself and the child time to relax and unwind prior to bedtime
- Avoid those activities that interfere with sleep health like videogames and/or television before bedtime
- Use picture cards that show the sequence of bedtime routines
- Be repetitious
- Exercise daily, however avoid exercising within an hour or two of bedtime
- During the day, find time for fun activities; yet stop at an hour or two before bedtime
- Reduce evening commitments so bedtime routines can become more consistent
- Place boundaries around the amount of time engaging in activities that are stressful prior to bedtime
- Reduce high conflict and stress from daily life
- Start bedtime process early, so as to not be rushed or feel stressed, which may raise cortisol levels and inhibit sleep.

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• Avoid naps after 3:00 pm
• Avoid large meals before bedtime
• Avoid shaming and blaming
• Consider rocking back and forth

Environmental Considerations:
• Ensure the bedroom is dark and set at a comfortable temperature
• Bright lights, busy patterns on the walls, and bold colors could induce sensory overloads
• Minimize furniture in the room
• Create a quiet, calm, relaxing, and comfortable bedtime environment
• If a child is scared, one can use a spray bottle to metaphorically spray away whatever they are fearful of (like “monster spray”).
• Invest in a comfortable mattress for your child
• Designate a stuffed animal to be the sleep protector if the child is fearful of something happening to them during the night
• Play soft music at bedtime
• Use of a weighted blanket should be explored
• Massage, body brushing, rocking is sometimes helpful
• Be cautious of adding too much stimulus; blankets/bed/pajamas with tags.
• Consider using laundry detergent and/or dryer sheets with lavender fragrances, unless the child is overly sensitive to scents. If that is the case, avoid scented laundry soaps and lotions.
• Use a machine or fan that produces white noise to drown out distracting sounds prior to and during sleep
• Remove TV's, video games, and/or computers from the room
• Use ear plugs if needed
• Consider using soft light bulbs

Nutritional Interventions:
• Reduce the amount of sugar consumed, especially before bedtime
• Avoid foods and beverages that may interfere with sleep, including drinks with caffeine and rich in carbohydrates

Caregiver Self-Care
• Caregivers should model appropriate sleep practices
• Avoid nicotine products
• Limit daily use of caffeine products

Specific Techniques to Explore
• Progressive Relaxation
• Guided imagery
• Massage, reflexology, somatics and yoga
• Counting your breathing
• Self-soothing techniques
• Mindfulness

Professional Consultations
• Seek out professionals familiar with FASD and sleep issues
• Nutritional experts and explore possible food sensitivities/allergies
• Consult about the use of medications to help improve sleep quality

Overall Comments and Encouragements
• Explore new ideas and approaches that may promote improved sleep
• Become committed and intentional about taking the necessary steps to improve sleep health for yourself and your child by searching out information and practicing the idea for at least 30 days

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Identify barriers to optimal sleep health, (like caffeine before bedtime, traffic noise, etc.)
Maintain a family sleep journal to determine what works well
Strive to achieve a deeper understanding of sleep health

5. The Importance of Screening for FASD in Criminal Justice Settings

Author:
Jerrod Brown, MA, MS, MS, MS, is the Treatment Director for Pathways Counseling Center, Inc. Pathways’ focus is to provide programs and services that benefit individuals impacted by mental illness and addictions. Jerrod is also the founder and CEO of the American Institute for the Advancement of Forensic Studies (AIAFS) and lead developer and program director of an online graduate degree program in Forensic Mental Health from Concordia University, St. Paul, Minnesota. Email: Jerrod01234Brown@live.com

What is the Problem?
Fetal Alcohol Spectrum Disorder (FASD) is a condition caused by the consumption of alcohol during pregnancy, resulting in irreversible brain damage. The developmental trajectory of individuals diagnosed with FASD include impaired social, educational, vocational, and cognitive skills. These impairments can lead individuals living with the challenges of FASD to be at an increased risk of becoming involved in the criminal justice system, with recent estimates suggesting that judges, correctional officers, law enforcement officers, and other professionals working within the system unknowingly interact with individuals diagnosed with FASD on a daily basis. Given recent survey evidence that criminal justice professionals often have a difficult time detecting FASD in their cases due to the invisible nature of the disorder, there is the need for regular screening of FASD in various criminal justice and legal settings. This is particularly true, as individuals diagnosed with FASD who are charged with criminal acts often have problems successfully navigating the legal and correctional systems (e.g., inability to exercise legal rights, waive rights, understand a plea, consult with legal counsel, understand the nature of adversarial court system, comply with conditions of release, and heavily influenced by peer pressure). Broadly, routine screening for FASD within criminal justice settings should assist in the following ways:

1. Routine screening for FASD may promote the use of a standardized, evidence-based metric of FASD signs and symptoms across mental health, correctional, and legal systems.

2. Screening for signs and symptoms of FASD will enable mental health, correctional, and legal professionals to communicate more effectively with individuals diagnosed with the disorder, especially through the subsequent use of prompts and language matched to their cognitive abilities.

3. Correctional and legal professionals need not rely solely on professionals with medical and mental health expertise to preliminarily screen for evidence of FASD.

4. Legal counsel will be able to better guide individuals with FASD through complex legal proceedings.

5. Judges will be able to make more informed sentencing decisions, including the use of diversion opportunities to promote treatment rather than incarceration.

6. Correctional and forensic mental health professionals will be better able to ethically obtain informed consent for both intra-institutional and community treatment.
7. Preventative measures (e.g., increased monitoring) can be put into place to reduce the likelihood of peer-victimization common with this population in correctional settings.

8. More effective reentry plans can be established by parole and probation boards to maximize the likelihood of individuals with FASD being able to adhere to the conditions of their release by matching them with available social services, ultimately reducing rates of recidivism and unnecessary use of state funds.

9. Researchers will be able to extract easy-to-analyze quantitative data from completed screening tools and run independent studies on the accuracy and reliability of the screening tool to grow its evidentiary support.

10. Early identification of FASD may help to minimize the detrimental effects of confabulation and false testimony during criminal investigations and court processes.

11. Predicting the efficacy of different treatment modalities will become easier for mental health and correctional professionals (especially those working with sexual offenders) due to a better understanding of the signs and symptoms of FASD.
1. **Fetal outcome after prenatal exposure to chemotherapy and mechanisms of teratogenicity compared to alcohol and smoking**

Vandenbroucke T¹, Verheecke M, Van Calsteren K, Han S, Claes L, Amant F
KU Leuven - University of Leuven, Department of Oncology, Herestraat 49, B-3000 Leuven, Belgium +32 16 34 42 52; +32 16 34 42 05; frederic.amant@uzleuven.be

**Abstract**

Introduction: The treatment of cancer during pregnancy is challenging because of the involvement of two individuals and the necessity of a multidisciplinary approach. An important concern is the potential impact of chemotherapy on the developing fetus. Areas covered: The authors review the available literature on neonatal and long-term outcome of children prenatally exposed to chemotherapy. Chemotherapy administered during first trimester of pregnancy results in increased congenital malformations (7.5 - 17% compared to 4.1 - 6.9% background risk), whereas normal rates are found during second or third trimester. Intrauterine growth restriction is seen in 7 - 21% (compared to 10%), but children develop normal weight and height on the long term. Children are born preterm in 67.1%, compared to 4% in general population. Normal intelligence, attention, memory and behavior are reported, although intelligence tends to decrease with prematurity. Global heart function remains normal, although small differences are seen in ejection fraction, fractional shortening and some diastolic parameters. No secondary cancers or fertility problems are encountered, but follow up periods are limited. Expert opinion: Most evidence is based on retrospective studies with small samples and limited follow up periods, methodology and lack of control groups. A large prospective case-control study with long-term follow up is needed in which confounding factors are well considered.

**Read Full Article,**

2. **Incidence and prevalence of fetal alcohol spectrum disorder by sex and age group in Alberta, Canada**

Thanh NX, Jonsson E, Salmon A, Sebastianski M

**Abstract**

ObjectivesTo estimate incidence and prevalence of FASD by sex and age in Alberta, Canada. MethodsWe included all patients recorded in the Alberta provincial health databases of inpatients, outpatients, and practitioner claims from 2003 to 2012. The number of people with FASD were calculated from available data on FAS (ICD-9 code 760.71; ICD-10 codes Q86.0 and P04.3) and estimated prevalence of FASD among individuals diagnosed with 21 FASD-related conditions (identified by a literature review) for which there are ICD codes, such as learning disability, mental retardation, and nervous system defects (Table 1). Fractions of FASD-related diagnoses that can be attributed to alcohol use during pregnancy were estimated by a systematic review. The incidence was measured as the number of new cases per 1000 births. The prevalence was measured as the number of cases per 1000 population in 2012. ResultsAnnually, 739 to 1884 people were born with FASD in Alberta establishing an incidence of 14.2 to 43.8 per 1000 births, depending on the length of follow-up. There were about 46,000 people living with FASD in Alberta 2012, including 6,000 FAS cases and 40,000 FASD-related cases. The prevalence of FASD was 11.7 (range 8.2 to 15.1) per 1000 population. The incidence and prevalence varied greatly by sex and age group. Generally, male and younger outnumbered female and older. Conclusion: This study suggests new incidence and prevalence of FASD, which are higher than what has been commonly used (1%), and its variations among sex and age groups.

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3. The Making of a Medical Disorder: Tracing the Emergence of Fetal Alcohol Spectrum Disorder in Alberta

Shankar I
Sociology, Mount Royal University, Calgary, Alberta, Canada.

Abstract
This article examines the processes through which health disorders become accepted as a public health concern, and the defining role played by social actors responsible for bringing such disorders to public attention. Such analysis provides us with a particular history of health disorders and the implications of this early history in the current conceptualization of such disorders within contemporary health programs and policies. This article traces the emergence and acceptance of fetal alcohol spectrum disorder (FASD) as a public health concern in Alberta and the ongoing tensions resulting from this early history. Specifically, the author examines the integral role of social workers and various government officials in getting FASD recognized as a health concern. This Alberta case study demonstrates the importance of investigating the sociopolitical context in which health disorders emerge and become accepted.

Read Full Article,

4. Fetal alcohol spectrum disorders among children in a Brazilian orphanage

Strömland K¹, Ventura LO, Mirzaei L, Fontes de Oliveira K, Marcelino Bandim J, Parente Ivo A, Brandt C
Institute of Neuroscience and Physiology, Department of Ophthalmology, University of Gothenburg, Gothenburg, Sweden.

Abstract
Background: The objective was to investigate the frequency of fetal alcohol spectrum disorders (FASD) and ophthalmologic anomalies in orphanage children in Brazil. Methods: A prospective study was performed on 94 children living in an orphanage in Brazil. The children were examined by a multidisciplinary team consisting of specialists in pediatrics, neurology, psychology, neuropsychiatry, and ophthalmology. Results: The main reasons for living in the orphanage, in 61% of the children, were negligence, child abuse, and abandonment. Of all the children studied, 50% had mothers with known alcohol abuse and 47% had one or more diagnoses of neurodevelopmental/behavioral and/or cognitive deficits. General developmental delay was found in 18%, intellectual disability in 3%, cognitive impairment in 27%, attention-deficit/hyperactivity disorder in 14%, and autism in 3%. Altogether 17% had FASD, comprising three children with fetal alcohol syndrome (FAS), six with partial FAS, and seven with alcohol-related neurodevelopmental disorder. 16% had ophthalmological findings such as poor vision, strabismus, and dysmorphology of the optic nerves. Twenty-eight children (30%) were adopted from the orphanage; of these, six had FASD (two FAS, three partial FAS, one alcohol-related neurodevelopmental disorder), five had attention-deficit/hyperactivity disorder, and eight had developmental delay. Conclusion: Nearly half of the children living in the orphanage had neurodevelopmental disorders and a considerable number showed signs of damage from prenatal alcohol exposure. A broader look at the problem of FASD in Brazil and other South American countries is desirable to document the burden of disease and provide data for targeting prevention efforts. Birth Defects Research (Part A), 2014. © 2014 Wiley Periodicals, Inc.

Read Full Article,
5. **Midwives’ knowledge, attitudes and practice about alcohol exposure and the risk of fetal alcohol spectrum disorder**


Telethon Kids Institute, The University of Western Australia, Perth, Australia

Child and Adolescent Health Service, Department of Health Western Australia, Perth, Australia

Janet M Payne, Email: ua.gro.sdiknohtelet@enyap.naj.

**Abstract**

**Background:** Midwives are an influential profession and a key group in informing women about alcohol consumption in pregnancy and its consequences. There are no current quantitative Australian data on midwives’ knowledge, attitudes and practice in relation to alcohol consumption during pregnancy and Fetal Alcohol Spectrum Disorder. We aimed to reduce this knowledge gap by understanding midwives’ perceptions of their practice in addressing alcohol consumption during pregnancy.

**Methods:** This cross-sectional study was conducted at 19 maternity sites across the seven health regions of country Western Australia. A questionnaire was designed following review of the literature and other relevant surveys. Midwifery managers of the maternity sites distributed questionnaires to all midwives working in their line of management. A total of 334 midwives were invited to participate in the research and (n=245, 73.4%) of these were eligible.

**Results:** The response fraction was (n=166, 67.8%). Nearly all (n=151, 93.2%) midwives asked pregnant women about their alcohol consumption during pregnancy and (n=164, 99.4%) offered advice about alcohol consumption in accordance with the Australian Alcohol Guideline, which states ‘For women who are pregnant or planning a pregnancy, not drinking is the safest option’. Nearly two thirds (n=104, 64.2%) of the midwives informed pregnant women about the effects of alcohol consumption in pregnancy, they did not always use the recommended AUDIT screening tool (n=66, 47.5%) to assess alcohol consumption during pregnancy, nor conduct brief intervention when indicated (n=107, 70.4%). Most midwives endorsed professional development about screening tools (n=145, 93.5%), brief intervention (n=144, 92.9%), and alcohol consumption during pregnancy and FASD (n=144, 92.9%).

**Conclusion:** Nearly all midwives in this study asked and advised about alcohol consumption in pregnancy and around two thirds provided information about the effects of alcohol in pregnancy. Our findings support the need for further professional development for midwives on screening and brief intervention. Policy should support midwives’ practice to screen for alcohol consumption in pregnancy and offer brief intervention when indicated.

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6. **Prevalence and characteristics of fetal alcohol spectrum disorders**

May PA1, Baete A2, Russo J3, Elliott AJ3, Blankenship J1, Kalberg WO4, Buckley D4, Brooks M4, Hasken J5, Abdul-Rahman O6, Adam MP7, Robinson LK8, Manning M9, Hoyme HE3

1Department of Nutrition, Gillings School of Global Public Health, Nutrition Research Institute, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Center on Alcoholism, Substance Abuse and Addictions (CASAA), The University of New Mexico, Albuquerque, New Mexico; Department of Pediatrics, Sanford School of Medicine, The University of South Dakota, Sioux Falls, South Dakota philip_may@unc.edu.

2Sanford Research, Sioux Falls, South Dakota;

3Sanford Research, Sioux Falls, South Dakota; Department of Pediatrics, Sanford School of Medicine, The University of South Dakota, Sioux Falls, South Dakota.
4Center on Alcoholism, Substance Abuse and Addictions (CASAA), The University of New Mexico, Albuquerque, New Mexico; 5Department of Nutrition, Gillings School of Global Public Health, Nutrition Research Institute, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; 6Department of Pediatrics, University of Mississippi, Jackson, Mississippi; 7Department of Pediatrics, University of Washington, Seattle, Washington; 8Dysmorphology and Clinical Genetics, State University of New York at Buffalo, Buffalo, New York; 9Departments of Pathology and Pediatrics, Stanford University, Stanford, California

Abstract

OBJECTIVES:
To determine the prevalence and characteristics of fetal alcohol spectrum disorders (FASD) among first grade students (6- to 7-year-olds) in a representative Midwestern US community.

METHODS:
From a consented sample of 70.5% of all first graders enrolled in public and private schools, an oversample of small children (≤25th percentile on height, weight, and head circumference) and randomly selected control candidates were examined for physical growth, development, dysmorphology, cognition, and behavior. The children’s mothers were interviewed for maternal risk.

RESULTS:
Total dysmorphology scores differentiate significantly fetal alcohol syndrome (FAS) and partial FAS (PFAS) from one another and from unexposed controls. Alcohol-related neurodevelopmental disorder (ARND) is not as clearly differentiated from controls. Children who had FASD performed, on average, significantly worse on 7 cognitive and behavioral tests and measures. The most predictive maternal risk variables in this community are late recognition of pregnancy, quantity of alcoholic drinks consumed 3 months before pregnancy, and quantity of drinking reported for the index child’s father. From the final multidisciplinary case findings, 3 techniques were used to estimate prevalence. FAS in this community likely ranges from 6 to 9 per 1000 children (midpoint, 7.5), PFAS from 11 to 17 per 1000 children (midpoint, 14), and the total rate of FASD is estimated at 24 to 48 per 1000 children, or 2.4% to 4.8% (midpoint, 3.6%).

CONCLUSIONS:
Children who have FASD are more prevalent among first graders in this Midwestern city than predicted by previous, popular estimates.

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7. Visual defects in a mouse model of fetal alcohol spectrum disorder

Lantz CL1, Pulimood NS2, Rodrigues-Junior WS3, Chen CK4, Manhaes AC5, Kalatsky VA6, Medina AE7
1Department of Anatomy, Virginia Commonwealth University, Richmond, VA, USA; Department of Biology, University of Maryland, College Park, MD, USA. 2Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA. 3Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA; Universidade Federal Fluminense, Niteroi, Brazil. 4Baylor College of Medicine, Houston, TX, USA. 5Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA; Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil. 6Enthought, Inc., Austin, TX, USA. 7Department of Anatomy, Virginia Commonwealth University, Richmond, VA, USA; Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA.

Abstract

www.nofas-uk.org 48
Alcohol consumption during pregnancy can lead to a multitude of neurological problems in offspring, varying from subtle behavioral changes to severe mental retardation. These alterations are collectively referred to as Fetal Alcohol Spectrum Disorders (FASD). Early alcohol exposure can strongly affect the visual system and children with FASD can exhibit an amblyopia-like pattern of visual acuity deficits even in the absence of optical and oculomotor disruption. Here, we test whether early alcohol exposure can lead to a disruption in visual acuity, using a model of FASD to mimic alcohol consumption in the last months of human gestation. To accomplish this, mice were exposed to ethanol (5 g/kg i.p.) or saline on postnatal days (P) 5, 7, and 9. Two to three weeks later we recorded visually evoked potentials to assess spatial frequency detection and contrast sensitivity, conducted electroretinography (ERG) to further assess visual function and imaged retinotopy using optical imaging of intrinsic signals. We observed that animals exposed to ethanol displayed spatial frequency acuity curves similar to controls. However, ethanol-treated animals showed a significant deficit in contrast sensitivity. Moreover, ERGs revealed a market decrease in both a- and b-waves amplitudes, and optical imaging suggest that both elevation and azimuth maps in ethanol-treated animals have a 10-20° greater map tilt compared to saline-treated controls. Overall, our findings suggest that binge alcohol drinking restricted to the last months of gestation in humans can lead to marked deficits in visual function.

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8. Fetal Alcohol Spectrum Disorders: Recent Neuroimaging Findings
Moore EM1, Migliorini R2, Infante MA3, Riley EP3
1Center for Behavioral Teratology, San Diego State University, San Diego, CA 92120.
2Center for Behavioral Teratology, San Diego State University, San Diego, CA 92120 ; SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA 92120.
3Center for Behavioral Teratology, San Diego State University, San Diego, CA 92120 ; Department of Psychology, San Diego State University, San Diego, CA 92182.

Abstract
Since the identification of Fetal Alcohol Syndrome over 40 years ago, much has been learned about the detrimental effects of prenatal alcohol exposure on the developing brain. This review highlights recent neuroimaging studies, within the context of previous work. Structural magnetic resonance imaging has described morphological differences in the brain and their relationships to cognitive deficits and measures of facial dysmorphology. Diffusion tensor imaging has elaborated on the relationship between white matter microstructure and behavior. Atypical neuromaturation across childhood and adolescence has been observed in longitudinal neuroimaging studies. Functional imaging has revealed differences in neural activation patterns underlying sensory processing, cognition and behavioral deficits. A recent functional connectivity analysis demonstrates reductions in global network efficiency. Despite this progress much remains unknown about the impact of prenatal alcohol exposure on the brain, and continued research efforts are essential.

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9. Addressing FASD in British Columbia, Canada: Analysis of Funding Proposals
George MA, Hardy C Canada

www.nofas-uk.org
Abstract
Background: Fetal Alcohol Spectrum Disorder is a preventable health issue affecting about 10% of the population. This research examined proposals submitted to a call for funding for projects to improve outcomes for people with fetal alcohol spectrum disorder (FASD).

Objectives: The aim was to use the proposals as proxy for perceptions of needs held by practitioners in British Columbia, Canada, where considerable FASD-related education and awareness exists.

Methods: Content analyses were conducted and Chi-square tests were used to test the relationship between proposal foci, community size and the submitting agency’s experience with FASD.

Results: Nine foci were found: Skill Development, Care, Training, Resource Development, Education, Transition, Peer Support, Research and Other. No statistically significant difference was found in proposal foci according to size of community, and only one focus, Research, was associated with agency experience. Proposals varied in intensity, timing, participants, and focus of change (people or environments).

Conclusions: Analysis of the proposals provides a unique view into perceptions regarding ways to improve outcomes for people with FASD.


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10. Productivity losses because of morbidity attributable to fetal alcohol spectrum disorder in Canada: a demographic approach

Easton B1, Burd L2, Sarnocinska-Hart A3, Rehm J4, Popova S5
1Social and Health Outcomes Research and Evaluation (SHORE), Massey University, Auckland, New Zealand.
2Department of Pediatrics, University of North Dakota School of Medicine, Grand Forks, North Dakota.
3Institute for Work and Health, Toronto, Ontario, Canada.
4Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada, Epidemiological Research Unit, Klinische Psychologie und Psychotherapie, Technische Universität Dresden, Dresden, Germany.
5Social and Epidemiological Research Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada, Factor-Inwentash Faculty of Social Work, University of Toronto, Toronto, Ontario, Canada.

Abstract
OBJECTIVE:
The purpose of this study was to estimate the productivity losses due to morbidity of individuals with fetal alcohol spectrum disorder (FASD).

METHOD:
A demographic approach was used. Population estimates were calculated using data for the most recent available year (i.e., 2011) on the population of Canada by provinces, the labor force, unemployment rate, and the average weekly wage, all of which were obtained from Statistics Canada. To estimate the number of FASD cases in Canada in 2011, the prevalence of FASD, obtained from the available epidemiological literature, was applied to the general population of Canada. Assumptions made on the level of impairment that would affect the ability of individuals with FASD to participate in the workforce or reduce their productivity were based on data obtained from the current epidemiological literature and experts’ opinions. To estimate the cost of FASD, a counterfactual scenario was used with an assumption that there is no one born with FASD in Canada.

RESULTS:
About 0.03% of the Canadian workforce experiences a loss of productivity because of FASD-attributable morbidity, which translates to aggregate losses ranging from $418 million Canadian dollars (CND) to $1.08 billion CND annually.

CONCLUSIONS:
FASD imposes a considerable economic toll on Canadian society and therefore requires more preventive efforts. (J. Stud. AlcoholDrugs, 75, 1011-1017, 2014).

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11. Fine motor skills in children with prenatal alcohol exposure or fetal alcohol spectrum disorder

Doney R1, Lucas BR, Jones T, Howat P, Sauer K, Elliott EJ
1School of Public Health, Curtin University, Perth, Australia; †Discipline of Paediatrics and Child Health, The Children's Hospitals Network (Westmead), University of Sydney Medical School, Sydney, Australia; The George Institute for Global Health, Sydney, Australia; Department of Health Professions, Faculty of Human Sciences, Macquarie University, Sydney, Australia; ‖Centre for Behavioural Research in Cancer Control, Curtin University, Perth, Australia.

Abstract

OBJECTIVE: Prenatal alcohol exposure (PAE) can cause fetal alcohol spectrum disorders (FASD) and associated neurodevelopmental impairments. It is uncertain which types of fine motor skills are most likely to be affected after PAE or which assessment tools are most appropriate to use in FASD diagnostic assessments. This systematic review examined which types of fine motor skills are impaired in children with PAE or FASD; which fine motor assessments are appropriate for FASD diagnosis; and whether fine motor impairments are evident at both "low" and "high" PAE levels.

METHODS: A systematic review of relevant databases was undertaken using key terms. Relevant studies were extracted using a standardized form, and methodological quality was rated using a critical appraisal tool.

RESULTS: Twenty-four studies met inclusion criteria. Complex fine motor skills, such as visual-motor integration, were more frequently impaired than basic fine motor skills, such as grip strength. Assessment tools that specifically assessed fine motor skills more consistently identified impairments than those which assessed fine motor skills as part of a generalized neurodevelopmental assessment. Fine motor impairments were associated with "moderate" to "high" PAE levels. Few studies reported fine motor skills of children with "low" PAE levels, so the effect of lower PAE levels on fine motor skills remains uncertain.

CONCLUSIONS: Comprehensive assessment of a range of fine motor skills in children with PAE is important to ensure an accurate FASD diagnosis and develop appropriate therapeutic interventions for children with PAE-related fine motor impairments.

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12. Cognitive and Adaptive Skill Profile Differences in Children With Attention-Deficit Hyperactivity Disorder With and Without Comorbid Fetal Alcohol Spectrum Disorder

Boseck JJ1, Davis AS, Cassady JC, Finch WH, Gelder BC
1a Department of Neuropsychology, Trinity Health, Minot, North Dakota

www.nofas-uk.org
**Abstract**

Children with fetal alcohol spectrum disorder (FASD) often present with comorbid attention-deficit hyperactivity disorder (ADHD), which can complicate diagnosis and treatment planning. This study investigated the cognitive and adaptive profiles of 81 children with ADHD/FASD and 147 children with ADHD. Multivariate analysis of variance and follow-up discriminant analysis indicated that the two groups had similar profiles on the Wechsler Intelligence Scale for Children-Fourth Edition and Vineland Adaptive Behavior Scales, although the children with comorbid ADHD/FASD demonstrated significantly more impairment in verbal ability, perceptual reasoning, working memory, processing speed, and overall adaptive skills. The results suggested that when compared with children with ADHD alone, children with ADHD/FASD exhibit significantly more impaired cognitive processing and adaptive skill deficits that are essential for school success and healthy social, behavioral, and emotional functioning. Research evaluating the profiles of these groups is likely to facilitate earlier and more accurate diagnosis and intervention.

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13. **Oxidative DNA damage in the in utero initiation of postnatal neurodevelopmental deficits by normal fetal and ethanol-enhanced oxidative stress in oxoguanine glycosylase 1 (ogg1) knockout mice**

Miller-Pinsler L1, Pinto DJ1, Wells PG2
1Department of Pharmacology and Toxicology, Faculty of Medicine.
2Department of Pharmacology and Toxicology, Faculty of Medicine; Division of Biomolecular Sciences, Faculty of Pharmacy, University of Toronto, Toronto, ON M5S 3M2, Canada. Electronic address: pg.wells@utoronto.ca.

**Abstract**

Studies in mice with deficient antioxidative enzymes have shown that physiological levels of reactive oxygen species (ROS) can adversely affect the developing embryo and fetus. Herein, DNA repair-deficient progeny of oxoguanine glycosylase 1 (ogg1) knockout mice lacking repair of the oxidative DNA lesion 8-oxo-2'-deoxyguanosine (8-oxodGuo) exhibited enhanced postnatal neurodevelopmental deficits, revealing the pathogenic potential of 8-oxodGuo initiated by physiological ROS production in fetal brain, and providing the first evidence of a pathological phenotype for ogg1 knockout mice. Moreover, when exposed in utero to ethanol (EtOH), ogg1 knockout progeny exhibited higher levels of 8-oxodGuo in fetal brain and more severe postnatal neurodevelopmental deficits than wild-type littermates, both of which were blocked by pretreatment with the free radical trapping agent phenylbutylnitrone. These results suggest ROS-initiated DNA oxidation, as distinct from altered signal transduction, contributes to neurodevelopmental deficits caused by in utero EtOH exposure, and fetal DNA repair is a determinant of risk.

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14. **Effects of Acute Prenatal Exposure to Ethanol on microRNA Expression are Ameliorated by Social Enrichment**

Ignacio C1, Mooney SM2, Middleton FA1
1Department of Neuroscience and Physiology, State University of New York Upstate Medical University, Syracuse, NY, USA; Department of Biochemistry and Molecular Biology, State University of New York Upstate Medical University, Syracuse, NY, USA; Developmental Exposure Alcohol Research Center (DEARC), Binghamton University, Binghamton, NY, USA.

www.nofas-uk.org
Abstract
Fetal alcohol spectrum disorders (FASDs) are associated with abnormal social behavior. These behavioral changes may resemble those seen in autism. Rats acutely exposed to ethanol on gestational day 12 show decreased social motivation at postnatal day 42. We previously showed that housing these ethanol-exposed rats with non-exposed controls normalized this deficit. The amygdala is critical for social behavior and regulates it, in part, through connections with the basal ganglia, particularly the ventral striatum. MicroRNAs (miRNAs) are short, hairpin-derived RNAs that repress mRNA expression. Many brain disorders, including FASD, show dysregulation of miRNAs. In this study, we tested if miRNA and mRNA networks are altered in the amygdala and ventral striatum as a consequence of prenatal ethanol exposure and show any evidence of reversal as a result of social enrichment. RNA samples from two different brain regions in 72 male and female adolescent rats were analyzed by RNA-Seq and microarray analysis. Several miRNAs showed significant changes due to prenatal ethanol exposure and/or social enrichment in one or both brain regions. The top predicted gene targets of these miRNAs were mapped and subjected to pathway enrichment analysis. Several miRNA changes caused by ethanol were reversed by social enrichment, including mir-204, mir-299a, miR-384-5p, mir-222-3p, miR-301b-3p, and mir-6239. Moreover, enriched gene networks incorporating the targets of these miRNAs also showed reversal. We also extended our previously published mRNA expression analysis by directly examining all annotated brain-related canonical pathways. The additional pathways that were most strongly affected at the mRNA level included p53, CREB, glutamate, and GABA signaling. Together, our data suggest a number of novel epigenetic mechanisms for social enrichment to reverse the effects of ethanol exposure through widespread influences on gene expression.


15. Fetal alcohol spectrum disorder: pathogenesis and mechanisms
Sulik KK
1Department of Cell Biology and Physiology and Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC, USA. Electronic address: mouse@med.unc.edu.

Abstract
This chapter provides an overview of animal model-based studies that have generated information critical to our understanding of the pathogenesis and mechanisms underlying alcohol-induced birth defects, in particular those involving the brain. Focus is placed on the developing organism itself, rather than the mother, placenta, or other extraembryonic tissues. Components of the cascades of alcohol-induced damage that are considered herein are excessive cell death, changes in the cell cycle and proliferation, cell migration, cell morphogenesis, and gene expression as well as free radical damage and interference with cell signaling. The roles played by one or more of these various factors in the genesis of structural and functional birth defects are dependent upon alcohol exposure patterns and dosage, the involved tissue, and the prenatal stage(s) at the time of exposure. Technologic advances and rapidly increasing knowledge in the fields of genetics, cell, developmental, and neurobiology are critical to accurately piecing together experimental evidence in refining our understanding of the genesis of alcohol-induced birth defects, to the planning and execution of future studies, and to applying the knowledge gained to diminish the severity or occurrence of fetal alcohol spectrum disorder.


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16. Neurobehavioral, neurologic, and neuroimaging characteristics of fetal alcohol spectrum disorders

Glass L1, Ware AL, Mattson SN2
1Center for Behavioral Teratology, San Diego State University, San Diego, CA, USA.
2Center for Behavioral Teratology, San Diego State University, San Diego, CA, USA. Electronic address: sarah.mattson@sdsu.edu.

Abstract
Alcohol consumption during pregnancy can have deleterious consequences for the fetus, including changes in central nervous system development leading to permanent neurologic alterations and cognitive and behavioral deficits. Individuals affected by prenatal alcohol exposure, including those with and without fetal alcohol syndrome, are identified under the umbrella of fetal alcohol spectrum disorders (FASD). While studies of humans and animal models confirm that even low to moderate levels of exposure can have detrimental effects, critical doses of such exposure have yet to be specified and the most clinically significant and consistent consequences occur following heavy exposure. These consequences are pervasive, devastating, and can result in long-term dysfunction. This chapter summarizes the neurobehavioral, neurologic, and neuroimaging characteristics of FASD, focusing primarily on clinical research of individuals with histories of heavy prenatal alcohol exposure, although studies of lower levels of exposure, particularly prospective, longitudinal studies, will be discussed where relevant.


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17. Excitatory Synaptic Function and Plasticity Is Persistently Altered in Ventral Tegmental Area Dopamine Neurons after Prenatal Ethanol Exposure

Hausknecht K1, Haj-Dahmane S1, Shen YL1, Vezina P2, Dlugos C3, Shen RY1
1Research Institute on Addictions, University at Buffalo, State University of New York, Buffalo, NY, USA.
2Department of Psychiatry and Behavioral Neurosciences, University of Chicago, Chicago, IL, USA.
3Department of Pathology and Anatomical Sciences, University at Buffalo, Buffalo, NY, USA.

Abstract
Prenatal ethanol exposure (PE) is one of the developmental factors leading to increased addiction propensity (risk). However, the neuronal mechanisms underlying this effect remain unknown. We examined whether increased excitatory synaptic transmission in ventral tegmental area (VTA) dopamine (DA) neurons, which is associated with drug addiction, is impacted by PE. Pregnant rats were exposed to ethanol (0 or 6 g/kg/day) via intragastric intubation from gestational day 8-20. Amphetamine self-administration, whole-cell recordings, and electron microscopy were performed in male offspring between 2-12-week-old. The results showed enhanced amphetamine self-administration in PE animals. In PE animals, we observed a persistent augmentation in calcium-permeable AMPA receptor (CP-AMPAR) expression, indicated by increased rectification and reduced decay time of AMPAR-mediated excitatory postsynaptic currents (AMPAR-EPSCs), enhanced depression of AMPAR-EPSCs by NASPM (a selective CP-AMPAR antagonist), and increased GluA3 subunits in VTA DA neuron dendrites. Increased CP-AMPAR expression in PE animals led to increased excitatory synaptic strength and the induction of CP-AMPAR-dependent long-term potentiation (LTP), an anti-Hebbian form of LTP. These observations suggest that, in PE animals, increased excitatory synaptic strength in VTA DA neurons might be susceptible to further strengthening even in the absence of impulse flow. The PE-induced persistent increase in CP-AMPAR expression, the resulting enhancement in excitatory synaptic strength, and CP-AMPAR-dependent LTP are similar to effects observed after repeated exposure to drugs of abuse, conditions known to increase addiction risk. Therefore, these mechanisms could be important neuronal substrates underlying PE-induced enhanced amphetamine self-administration and increased addiction risk in individuals with fetal alcohol spectrum disorders.

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18. Unilateral whisker clipping exacerbates ethanol-induced social and somatosensory behavioral deficits in a sex- and age-dependent manner

Wellmann KA1, Mooney SM2
1Department of Pediatrics, University of Maryland, Baltimore, MD 21201, United States. Electronic address: kwellmann@peds.umaryland.edu.
2Department of Pediatrics, University of Maryland, Baltimore, MD 21201, United States. Electronic address: smooney@peds.umaryland.edu.

Abstract
Prenatal exposure to ethanol results in sensory deficits and altered social interactions in animal and clinical populations. Sensory stimuli serve as important cues and shape sensory development; developmental exposure to ethanol or sensory impoverishment can impair somatosensory development, but their combined effects on behavioral outcomes are unknown. We hypothesized 1) that chronic prenatal ethanol exposure would disrupt social interaction and somatosensory performance during adolescence, 2) that a mild sensory impoverishment (neonatal unilateral whisker clipping; WC) would have a mildly impairing to sub-threshold effect on these behavioral outcomes, and 3) that the effect of ethanol would be exacerbated by WC. Long-Evans dams were fed a liquid diet containing ethanol or pair-fed with a non-ethanol diet on gestational days (G) 6-G21. Chow-fed control animals were also included. One male and female pup per litter underwent WC on postnatal day (P)1, P3, and P5. Controls were unclipped. Offspring underwent social interaction on P28 or P42, and gap-crossing (GC) on P31 or P42. Ethanol-exposed pups played less and crossed shorter gaps than control pups regardless of age or sex. WC further exacerbated ethanol-induced play fighting and GC deficits in all males but only in 28-day-old females. WC alone reduced sniffing in all males and in younger females. Thus, prenatal ethanol exposure induced deficits in social interaction and somatosensory performance during adolescence. Sensory impoverishment exacerbates ethanol's effect in 28-day-old male and female animals and in 42-day-old males, suggesting sex- and age-dependent changes in outcomes in ethanol-exposed offspring.

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19. The effects of alcohol on the developing brain

Zimatkin SM, bon' EI

Abstract
In the review the literature data on the effect of alcohol on the developing brain of human and animals are summarized. The information is presented on the neuroimaging, histological, cellular and molecular-genetic disturbances in the brain in fetal alcohol syndrome and following exposure to alcohol during the early postnatal period. The structural developmental abnormalities of the different parts of the brain, disorders of neurogenesis and neuronal apoptosis, changes in metabolism, receptors and secondary signals system of neurons are described. Prenatal alcohol exposure
causes significant, various long-term disturbances of the brain structures at the organ, tissue, cellular and subcellular level, which may lay in the basis of the observed neurological, behavioral and mental disorders.

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20. **An fMRI study of behavioral response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure**

Ware AL¹, Infante MA¹, O'Brien JW¹, Tapert SF³, Jones KL³, Riley EP¹, Mattson SN⁴
1Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120, USA.
2Department of Psychiatry, University of California, San Diego, San Diego, CA 92037, USA; VA San Diego Healthcare System, San Diego, CA 92161, USA.
3University of California, San Diego, School of Medicine, Department of Pediatrics, San Diego, CA 92093, USA.
4Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120, USA.
Electronic address: sarah.mattson@sdsu.edu.

**Abstract**

Heavy prenatal alcohol exposure results in a range of deficits, including both volumetric and functional changes in brain regions involved in response inhibition such as the prefrontal cortex and striatum. The current study examined blood oxygen level-dependent (BOLD) response during a stop signal task in adolescents (ages 13-16y) with histories of heavy prenatal alcohol exposure (AE, n=21) and controls (CON, n=21). Task performance was measured using percent correct inhibits during three difficulty conditions: easy, medium, and hard. Group differences in BOLD response relative to baseline motor responding were examined across all inhibition trials and for each difficulty condition separately. The contrast between hard and easy trials was analyzed to determine whether increasing task difficulty affected BOLD response. Groups had similar task performance and demographic characteristics, except for full scale IQ scores (AE<CON). The AE group demonstrated greater BOLD response in frontal, sensorimotor, striatal, and cingulate regions relative to controls, especially as task difficulty increased. When contrasting hard vs. easy inhibition trials, the AE group showed greater medial/superior frontal and cuneus BOLD response than controls. Results were unchanged after demographics and FAS diagnosis were statistically controlled. This was the first fMRI study to utilize a stop signal task, isolating fronto-striatal functioning, to assess response inhibition and the effects task difficulty in adolescents with prenatal alcohol exposure. Results suggest that heavy prenatal alcohol exposure disrupts neural function of this circuitry, resulting in immature cognitive processing and motor-association learning and neural compensation during response inhibition.

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21. **Third trimester-equivalent ethanol exposure is characterized by an acute cellular stress response and an ontogenetic disruption of genes critical for synaptic establishment and function in mice**

Kleiber ML¹, Laufer BI, Stringer RL, Singh SM
1Molecular Genetics Unit, Department of Biology, The University of Western Ontario, London, Ont., Canada.

**www.nofas-uk.org**
Abstract

The developing brain is remarkably sensitive to alcohol exposure, resulting in the wide range of cognitive and neurobehavioral characteristics categorized under the term fetal alcohol spectrum disorders (FASD). The brain is particularly susceptible to alcohol during synaptogenesis, a process that occurs heavily during the third trimester and is characterized by the establishment and pruning of neural circuitry; however, the molecular response of the brain to ethanol during synaptogenesis has not been documented. To model a binge-like exposure during the third-trimester neurodevelopmental equivalent, neonate mice were given a high (5 g/kg over 2 h) dose of ethanol at postnatal day 7. Acute transcript changes within the brain were assessed using expression arrays and analyzed for associations with gene ontology functional categories, canonical pathways, and gene network interactions. The short-term effect of ethanol was characterized by an acute stress response and a downregulation of energetically costly cellular processes. Further, alterations to a number of genes with roles in synaptic transmission and hormonal signaling, particularly those associated with the neuroendocrine development and function, were evident. Ethanol exposure during synaptogenesis was also associated with altered histone deacetylase and microRNA transcript levels, suggesting that abnormal epigenetic patterning may maintain some of the persistent molecular consequences of developmental ethanol exposure. The results shed insight into the sensitivity of the brain to ethanol during the third-trimester equivalent and outline how ethanol-induced alterations to genes associated with neural connectivity may contribute to FASD phenotypes.

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22. Chronic prenatal ethanol exposure alters expression of central and peripheral insulin signaling molecules in adult guinea pig offspring

Dobson CC1, Thevasundaram K1, Mongillo DL1, Winterborn A2, Holloway AC3, Brien JF4, Reynolds JN5
1Department of Biomedical and Molecular Sciences, Pharmacology and Toxicology Graduate Program, Queen's University, Kingston, ON, Canada K7L 3N6.
2Office of the University Veterinarian, Queen's University, Kingston, ON, Canada K7L 3N6.
3Department of Obstetrics and Gynecology, McMaster University, Hamilton, ON, Canada L8S 4K1.
4Department of Biomedical and Molecular Sciences, Pharmacology and Toxicology Graduate Program, Queen's University, Kingston, ON, Canada K7L 3N6; Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada K7L 3N6.
5Department of Biomedical and Molecular Sciences, Pharmacology and Toxicology Graduate Program, Queen's University, Kingston, ON, Canada K7L 3N6; Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada K7L 3N6. Electronic address: jnr@queensu.ca.

Abstract

Maternal ethanol consumption during pregnancy can produce a range of teratogenic outcomes in offspring. The mechanism of ethanol teratogenicity is multi-faceted, but may involve alterations in insulin and insulin-like growth factor (IGF) signaling pathways. These pathways are not only important for metabolism, but are also critically involved in neuronal survival and plasticity, and they can be altered by chronic prenatal ethanol exposure (CPEE). The objective of this study was to test the hypothesis that CPEE alters expression of insulin and IGF signaling molecules in the prefrontal cortex and liver of adult guinea pig offspring. Pregnant Dunkin-Hartley-strain guinea pigs received ethanol (4 g/kg maternal body weight/day) or isocaloric-sucrose/pair-feeding (nutritional control) throughout gestation. Fasting blood glucose concentration was measured in male and female offspring at postnatal day 150-200, followed by euthanasia, collection of prefrontal cortex and liver, and RNA extraction. IGF-1, IGF-1 receptor (IGF-1R), IGF-2, IGF-2 receptor (IGF-2R), insulin receptor substrate (IRS)-1, IRS-2, and insulin receptor (INSR) mRNA expression levels were measured in tissues using quantitative real-time PCR. The mean maternal blood ethanol concentration was 281 ± 15 mg/dL at 1 h after the second divided dose of ethanol on GD 57. CPEE resulted in increased liver weight in adult offspring, but
produced no difference in fasting blood glucose concentration compared with nutritional control. In the liver, CPEE decreased mRNA expression of IGF-1, IGF-1R, and IGF-2, and increased IRS-2 mRNA expression in male offspring only compared with nutritional control. Female CPEE offspring had decreased INSR hepatic mRNA expression compared with male CPEE offspring. In the prefrontal cortex, IRS-2 mRNA expression was increased in CPEE offspring compared with nutritional control. The data demonstrate that CPEE alters both central and peripheral expression of insulin and IGF signaling molecules at the mRNA level, which may be related to metabolic dysregulation in adult offspring. Furthermore, altered insulin and IGF signaling may be a mechanism of ethanol neurobehavioral teratogenicity.


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23. Early life ethanol exposure causes long-lasting disturbances in rat mesenchymal stem cells via epigenetic modifications

Leu YW¹, Chu PY², Chen CM³, Yeh KT⁴, Liu YM¹, Lee YH¹, Kuo ST⁵, Hsiao SH⁵
1Department of Life Science and Institute of Molecular Biology, National Chung Cheng University, Chia-Yi 621, Taiwan.
2Department of Pathology, Show Chwan Memorial Hospital, Changhua 500, Taiwan.
3Division of Neurosurgery, Changhua Christian Hospital, Changhua 500, Taiwan.
4Department of Pathology, Changhua Christian Hospital, Changhua 500, Taiwan.
5Department of Life Science and Institute of Molecular Biology, National Chung Cheng University, Chia-Yi 621, Taiwan.
Electronic address: bioshh@ccu.edu.tw.

Abstract

Fetal alcohol syndrome (FAS) is a birth defect due to maternal alcohol consumption during pregnancy. Because mesenchymal stem cells (MSCs) are the main somatic stem cells in adults and may contribute to tissue homeostasis and repair in adulthood, we investigated whether early life ethanol exposure affects MSCs and contributes to the propensity for disease onset in later life. Using a rodent model of FAS, we found that ethanol exposure (5.25g/kg/day) from postnatal days 4 to 9 in rat pups (mimic of human third trimester) caused long-term anomalies in bone marrow-derived MSCs. MSCs isolated from ethanol-exposed animals were prone to neural induction but resistant to osteogenic and adipogenic inductions compared to their age-matched controls. The altered differentiation may contribute to the severe trabecular bone loss seen in ethanol-exposed animals at 3 months of age as well as overt growth retardation. Expression of alkaline phosphatase, osteocalcin, aP2, and PPARγ were substantially inhibited, but BDNF was up-regulated in MSCs isolated from ethanol-exposed 3-month-old animals. Several signaling pathways were distorted in ethanol-exposed MSCs via altered trimethylation at histone 3 lysine 27. These results demonstrate that early life ethanol exposure can have long-term impacts in rat MSCs by both genetic and epigenetic mechanisms.


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24. A Practical Testing Battery to Measure Neurobehavioral Ability among Children with FASD

Kalberg WO¹, May PA², Blankenship J¹, Buckley D³, Gossage JP¹, Adnams CM³
1Center on Alcoholism, Substance Abuse and Addictions, The University of New Mexico, Albuquerque, New Mexico, USA.

www.nofas-uk.org
Abstract

AIMS:
To determine a brief, practical battery of tests that discriminate between children with a fetal alcohol spectrum disorder (FASD) and unexposed controls.

DESIGN:
Children received dysmorphology exams, a targeted battery of cognitive and behavioral tests, and their mothers were interviewed about maternal risk factors. Children diagnosed with an FASD and children unexposed to alcohol prenatally were compared on cognitive/behavioral test results.

SETTING:
A community in The Western Cape Province of South Africa.

PARTICIPANTS:
Sixty-one, first grade children with FASD and 52 matched normal controls.

MEASURES:
Statistical analyses of maternal drinking behavior and their child's test performance.

FINDINGS:
Self-reported maternal drinking patterns before during and after pregnancy were used to confirm prenatal exposures to alcohol in the group of children diagnosed with FASD. With this sample of children diagnosed with FASD and completely unexposed controls, the adverse effects of maternal drinking on children's performance are reported. Results of the battery of standardized cognitive and behavioral tests indicate highly significant differences (p ≤ .001) between groups on: intelligence, perceptual motor, planning, and logical, spatial, short term, long term, and working memory abilities. Furthermore, a binary logistical regression model of only 3 specific cognitive and behavioral tests, including Digit Span A+B (Wald = 4.10), Absurd Situation (Wald = 3.57), and Word Association (Wald = 4.30) correctly classified 79.1% of the child participants as FASD or controls.

CONCLUSIONS:
A brief, practical set of tests can discriminate children with and without FASD and provide useful information for interventions for affected children.

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Abstract

BACKGROUND:
Alcohol abuse during gestation may cause congenital heart diseases (CHDs). The underlying mechanisms of alcohol-induced cardiac deformities are still not clear. Recent studies suggest that histone modification may play a crucial role in this pathological process. Moreover, our previous studies reported that ethanol could induce histone3 lysine9 (H3K9) hyperacetylation and overexpression of heart development-related genes in vitro. The aim of this study was to investigate the effect of alcohol consumption during gestation on the imbalance of H3K9 acetylation and the alternation of the expression of heart development-related genes during cardiogenesis.

METHODS:
Pregnant mice were exposed to a single dose of alcohol (10 μl/g/d, 56% alcohol) by gavage every day in the morning from embryo day 7.5 (E7.5) to E15.5. Hematoxylin and eosin (H&E) staining was applied for observing the structure of the embryonic hearts. Western blotting and quantitative real-time polymerase chain reaction were used for detecting the level of H3K9 acetylation and gene expression. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) activities were detected by colorimetric assay and fluorometric assay.

RESULTS:
H&E staining of cardiac tissue showed abnormalities of embryonic hearts at E17.5. The level of H3K9 acetylation reached peak at E17.5 and decreased sharply to a low level at birth and maintained at low level afterward. Alcohol exposure increased H3K9 acetylation at E11.5, E14.5, E17.5, and E18.5, respectively (p < 0.05), and enhanced the expression of Gata4 in the embryonic hearts at E14.5 and E17.5, Mef2c at E14.5, and Nkx2.5 at E14.5 and E17.5, (p < 0.05) but not for Tbx5 (p > 0.05). On embryonic day 17.5, HAT activities of embryonic hearts increased significantly, however alcohol exposure did not alter HDAC activities.

CONCLUSIONS:
These data indicate a time course of H3K9 acetylation change during heart development and demonstrate that alcohol exposure in utero may induce an increase of HAT activities, which results in H3K9 hyperacetylation and an increase of the expression of heart development-related genes. These findings reveal a novel epigenetic mechanism that connects the alcohol consumption during the pregnancy and the development of CHD in the fetus.

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26. Gene-specific disruption of endocannabinoid receptor 1 (cnr1a) by ethanol probably leads to the development of fetal alcohol spectrum disorder (FASD) phenotypes in Japanese rice fish (Oryzias latipes) embryogenesis

Dasmahapatra AK1, Khan IA2
1National Center for Natural Product Research, University of Mississippi, University, MS, USA; Department of BioMolecular Sciences, Division of Pharmacology, University of Mississippi, University, MS, USA. Electronic address: asok@olemiss.edu.
2National Center for Natural Product Research, University of Mississippi, University, MS, USA

Abstract
Developmental ethanol exposure is able to induce Fetal Alcohol Spectrum Disorder (FASD) phenotypes in Japanese rice fish (Oryzias latipes) embryogenesis although the mechanisms are yet unknown. The present study was designed to investigate the probable roles played by cannabinoid (CB) receptors in FASD induction. Searching of public databases (GenBank, Ensembl) indicated that the Japanese rice fish genome includes three human ortholog CB receptor genes (cnr1a, cnr1b and cnr2) with substantial amino acid identities. Quantitative real-time PCR (qPCR) and whole mount in situ hybridization (WMISH) techniques were used to analyze the expression of these cnr genes during Japanese rice fish embryogenesis and also in response to developmental ethanol exposure. qPCR analyses showed that the expression of
all three CB receptor genes were developmentally regulated and only cnr2 mRNA showed maternal expression. The mRNA concentrations of these cnr genes were found to be enhanced after 3dpf and attained maximal levels either prior to or after hatching. Analysis by WMISH technique indicated that all three cnr genes were expressed in the head region of hatchlings. During development, ethanol selectively attenuated the expression of cnr1a mRNA only; the other two (cnr1b and cnr2) remained unaffected. Blocking of cnr1a by CB1 receptor antagonists rimonabant (10-20μM) or AM251 (0.2-1μM) 0-2dpf was unable to induce any FASD-related phenotypic features in embryos or in hatchlings. However, continuous exposure of the embryos (0-6dpf) to AM251 (1μM) was able to reduce the hatching efficiency of the embryos. Our data indicated that in Japanese rice fish, among these three cnrs, ethanol disrupted the expression of only cnr1a in a concentration-dependent manner that induced delay in hatching and might be responsible for the development of neurological disorders as observed in FASD phenotypes.

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27. Prenatal alcohol exposure alters p35, CDK5 and GSK3β in the medial frontal cortex and hippocampus of adolescent mice

Goggin SL, Caldwell KK, Cunningham LA, Allan AM  
1Department of Neuroscience, University of New Mexico School of Medicine, Albuquerque, NM 87131, United States

Abstract
Fetal alcohol spectrum disorders (FASDs) are the number one cause of preventable mental retardation. An estimated 2-5% of children are diagnosed as having a FASD. While it is known that children prenatally exposed to alcohol experience cognitive deficits and a higher incidence of psychiatric illness later in life, the pathways underlying these abnormalities remain uncertain. GSK3β and CDK5 are protein kinases that are converging points for a vast number of signaling cascades, including those controlling cellular processes critical to learning and memory. We investigated whether levels of GSK3β and CDK5 are affected by moderate prenatal alcohol exposure (PAE), specifically in the hippocampus and medial frontal cortex of the adolescent mouse. In the present work we utilized immunoblotting techniques to demonstrate that moderate PAE increased hippocampal p35 and β-catenin, and decreased total levels of GSK3β, while increasing GSK3β Ser9 and Tyr216 phosphorylation. Interestingly, different alterations were seen in the medial frontal cortex where p35 and CDK5 were decreased and increased total GSK3β was accompanied by reduced Tyr216 of the enzyme. These results suggest that kinase dysregulation during adolescence might be an important contributing factor to the effects of PAE on hippocampal and medial frontal cortical functioning; and by extension, that global modulation of these kinases may produce differing effects depending on brain region.

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28. Distinct neurobehavioral dysfunction based on the timing of developmental binge-like alcohol exposure

Sadrian B1, Lopez-Guzman M2, Wilson DA3, Saito M4  
1Department of Child and Adolescent Psychiatry, NYU School of Medicine, New York, NY, United States; Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, United States. Electronic address: Benjamin.Sadrian@nyumc.org.  
2Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, United States.
**Abstract**
Gestational exposure to alcohol can result in long-lasting behavioral deficiencies generally described as fetal alcohol spectrum disorder (FASD). FASD-modeled rodent studies of acute ethanol exposure typically select one developmental window to simulate a specific context equivalent of human embryogenesis, and study consequences of ethanol exposure within that particular developmental epoch. Exposure timing is likely a large determinant in the neurobehavioral consequence of early ethanol exposure, as each brain region is variably susceptible to ethanol cytotoxicity and has unique sensitive periods in their development. We made a parallel comparison of the long-term effects of single-day binge ethanol at either embryonic day 8 (E8) or postnatal day 7 (P7) in male and female mice, and here demonstrate the differential long-term impacts on neuroanatomy, behavior and in vivo electrophysiology of two systems with very different developmental trajectories. The significant long-term differences in odor-evoked activity, local circuit inhibition, and spontaneous coherence between brain regions in the olfactory-hippocampal pathway that were found as a result of developmental ethanol exposure, varied based on insult timing. Long-term effects on cell proliferation and interneuron cell density were also found to vary by insult timing as well as by region. Finally, spatial memory performance and object exploration were affected in P7-exposed mice, but not E8-exposed mice. Our physiology and behavioral results are conceptually coherent with the neuroanatomical data attained from these same mice. Our results recognize both variable and shared effects of ethanol exposure timing on long-term circuit function and their supported behavior.


29. **A comparison of the different animal models of fetal alcohol spectrum disorders and their use in studying complex behaviors**
Patten AR¹, Fontaine CJ¹, Christie BR²
¹Division of Medical Sciences, University of Victoria, Victoria, BC, Canada.
²Division of Medical Sciences, University of Victoria, Victoria, BC, Canada; Department of Biology, University of Victoria, Victoria, BC, Canada; Program in Neuroscience, The Brain Research Centre, University of British Columbia, Vancouver, BC, Canada; Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, BC, Canada

**Abstract**
Prenatal ethanol exposure (PNEE) has been linked to widespread impairments in brain structure and function. There are a number of animal models that are used to study the structural and functional deficits caused by PNEE, including, but not limited to invertebrates, fish, rodents, and non-human primates. Animal models enable a researcher to control important variables such as the route of ethanol administration, as well as the timing, frequency and amount of ethanol exposure. Each animal model and system of exposure has its place, depending on the research question being undertaken. In this review, we will examine the different routes of ethanol administration and the various animal models of fetal alcohol spectrum disorders (FASD) that are commonly used in research, emphasizing their strengths and limitations. We will also present an up-to-date summary on the effects of prenatal/neonatal ethanol exposure on behavior across the lifespan, focusing on learning and memory, olfaction, social, executive, and motor functions. Special emphasis will be placed where the various animal models best represent deficits observed in the human condition and offer a viable test bed to examine potential therapeutics for human beings with FASD.

Proceedings of the 2013 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group

Kable JA, Reynolds JN, Valenzuela CF, Medina AE
1 Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA. Electronic address: jkabl01@emory.edu.
2 Department of Biomedical and Molecular Sciences, Queens University, Kingston, Ontario, Canada.
3 University Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, USA.
4 Department of Pediatrics, University of Maryland, School of Medicine, Baltimore, MD, USA.

Abstract
The 2013 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) meeting was held in Orlando (Grand Cypress), FL with the theme "Developing Brain-Based Interventions for Individuals with Fetal Alcohol Spectrum Disorders." Children with fetal alcohol spectrum disorders have significant impairments in cognitive functioning and behavioral regulation skills, which lead to a lifetime of challenges for themselves and their families; thus, developing interventions that remediate or compensate for these deficits is of great importance. The conference included 2 keynote presentations, FAST data talks, award presentations, and updates by government agencies. In addition, a lively panel discussion addressed the challenges faced by FASDSG researchers in the translation of intervention strategies developed in preclinical studies to clinical trials and, ultimately, to clinical practice.

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5-methyltetrahydrofolate rescues alcohol-induced neural crest cell migration abnormalities

Shi Y, Li J, Chen C, Gong M, Chen Y, Liu Y, Chen J, Li T, Song W
Department of Clinical laboratory, Chongqing, China
Chongqing City Key Lab of Translational Medical Research in Cognitive Development and Learning and Memory Disorders, and Ministry of Education Key Lab of Child Development and Disorders, Children’s Hospital of Chongqing Medical University, Chongqing, 400014 China
Department of Biology, West Virginia University, Morgantown, WV USA
Townsend Family Laboratories, Department of Psychiatry, Brain Research Center, The University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC V6T 1Z3 Canada
Yu Shi, Email: c.udc.umqc@uyihsn.

Abstract
Background Alcohol is detrimental to early development. Fetal alcohol spectrum disorders (FASD) due to maternal alcohol abuse results in a series of developmental abnormalities including cranial facial dysmorphology, ocular anomalies, congenital heart defects, microcephaly and intellectual disabilities. Previous studies have been shown that ethanol exposure causes neural crest (NC) apoptosis and perturbation of neural crest migration. However, the underlying mechanism remains elusive. In this report we investigated the fetal effect of alcohol on the process of neural crest development in the Xenopus leavis.

Results Pre-gastrulation exposure of 2-4% alcohol induces apoptosis in Xenopus embryo whereas 1% alcohol specifically impairs neural crest migration without observing discernible apoptosis. Additionally, 1% alcohol treatment considerably increased the phenotype of small head (43.4% ± 2.4%, total embryo n=234), and 1.5% and 2.0% dramatically augment the deformation to 81.2% ± 6.5% (n=205) and 91.6% ± 3.0% (n=235), respectively (P<0.05). Significant accumulation of Homocysteine was caused by alcohol treatment in embryos and 5-methyltetrahydrofolate restores neural crest migration and alleviates homocysteine accumulation.
resulting in inhibition of the alcohol-induced neurocristopathies. Conclusions our study demonstrates that prenatal alcohol exposure causes neural crest cell migration abnormality and 5-methyltetrahydrofolate could be beneficial for treating FASD.

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32. **Neural crest development in fetal alcohol syndrome**

Smith SM¹, Garic A, Flentke GR, Berres ME

Department of Nutritional Sciences, University of Wisconsin-Madison, Madison, Wisconsin, 53706

**Abstract**

Fetal alcohol spectrum disorder (FASD) is a leading cause of neurodevelopmental disability. Some affected individuals possess distinctive craniofacial deficits, but many more lack overt facial changes. An understanding of the mechanisms underlying these deficits would inform their diagnostic utility. Our understanding of these mechanisms is challenged because ethanol lacks a single receptor when redirecting cellular activity. This review summarizes our current understanding of how ethanol alters neural crest development. Ample evidence shows that ethanol causes the "classic" fetalalcohol syndrome (FAS) face (short palpebral fissures, elongated upper lip, deficient philtrum) because it suppresses prechordal plate outgrowth, thereby reducing neuroectoderm and neural crest induction and causing holoprosencephaly. Prenatal alcohol exposure (PAE) at premigratory stages elicits a different facial appearance, indicating FASD may represent a spectrum of facial outcomes. PAE at this premigratory period initiates a calcium transient that activates CaMKII and destabilizes transcriptionally active β-catenin, thereby initiating apoptosis within neural crest populations. Contributing to neural crest vulnerability are their low antioxidant responses. Ethanol-treated neural crest produce reactive oxygen species and free radical scavengers attenuate their production and prevent apoptosis. Ethanol also significantly impairs neural crest migration, causing cytoskeletal rearrangements that destabilize focal adhesion formation; their directional migratory capacity is also lost. Genetic factors further modify vulnerability to ethanol-induced craniofacial dysmorphology and include genes important for neural crest development, including shh signaling, PDFGA, vangl2, and ribosomal biogenesis. Because facial and brain development are mechanistically and functionally linked, research into ethanol's effects on neural crest also informs our understanding of ethanol's CNS pathologies.

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33. **Exploring the complexity of intellectual disability in fetal alcohol spectrum disorders**

Chokroborty-Hoque A, Alberry B, Singh SM

Molecular Genetics Unit, Department of Biology, University of Western Ontario, London, ON, Canada

**Abstract**

Brain development in mammals is long lasting. It begins early during embryonic growth and is finalized in early adulthood. This progression represents a delicate choreography of molecular, cellular, and physiological processes initiated and directed by the fetal genotype in close interaction with environment. Not surprisingly, most aberrations in
brain functioning including intellectual disability (ID) are attributed to either gene(s), or environment or the interaction of the two. The ensuing complexity has made the assessment of this choreography, ever challenging. A model to assess this complexity has used a mouse model (C57BL/6J or B6) that is subjected to prenatal alcohol exposure. The resulting pups show learning and memory deficits similar to patients with fetal alcohol spectrum disorder (FASD), which is associated with life-long changes in gene expression. Interestingly, this change in gene expression underlies epigenetic processes including DNA methylation and miRNAs. This paradigm is applicable to ethanol exposure at different developmental times (binge at trimesters 1, 2, and 3 as well as continuous preference drinking (70%) of 10% alcohol by B6 females during pregnancy). The exposure leads to life-long changes in neural epigenetic marks, gene expression, and a variety of defects in neurodevelopment and CNS function. We argue that this cascade may be reversed postnatally via drugs, chemicals, and environment including maternal care. Such conclusions are supported by two sets of results. First, antipsychotic drugs that are used to treat ID including psychosis function via changes in DNA methylation, a major epigenetic mark. Second, post-natal environment may improve (with enriched environments) or worsen (with negative and maternal separation stress) the cognitive ability of pups that were prenatally exposed to ethanol as well as their matched controls. In this review, we will discuss operational epigenetic mechanisms involved in the development of intellectual ability/disability in response to alcohol during prenatal or post-natal development. In doing so, we will explore the potential of epigenetic manipulation in the treatment of FASD and related disorders implicated in ID.


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34. Ceramide is involved in alcohol-induced neural proliferation

Wang Z1, Deng T2, Deng J3, Deng J1, Gao X1, Shi Y3, Liu B3, Ma Z3, Jin H3
1Institute of Neurobiology, Henan University, Kaifeng 475004, Henan Province, China; Department of Anatomy, Basic Medical College, Zhengzhou University, Zhengzhou 450052, Henan Province, China.
2Department of Anatomy, Luohe Medical College, Luohe 462002, Henan Province, China.
3Institute of Neurobiology, Henan University, Kaifeng 475004, Henan Province, China.
4Department of Anatomy, Basic Medical College, Zhengzhou University, Zhengzhou 450052, Henan Province, China

Abstract

Prenatal alcohol exposure, especially during early pregnancy, can lead to fetal alcohol syndrome. The pharmacological and toxicological mechanisms of ethanol are related to the effects of ceramide. In this study, we established an alcohol exposure model in wild-type mice and in knockout mice for the key enzyme involved in ceramide metabolism, sphingomyelin synthase 2. This model received daily intragastric administration of 25% ethanol, and pups were used at postnatal days 0, 7, 14, 30 for experiments. Serology and immunofluorescence staining found that ethanol exposure dose-dependently reduced blood sphingomyelin levels in two genotypes of pups, and increased neural cell proliferation and the number of new neurons in the hippocampal dentate gyrus. Western blot analysis showed that the relative expression level of protein kinase C α increased in two notypes of pups after ethanol exposure. Compared with wild-type pups, the expression level of the important activator protein of the ceramide/ceramide-1-phosphate pathway, protein kinase C α, was reduced in the hippocampus of sphingomyelin synthase 2 knockouts. Our findings illustrate that ceramide is involved in alcohol-induced neural proliferation in the hippocampal dentate gyrus of pups after prenatal ethanol exposure, and the mechanism may be associated with increased pression of protein kinase C α activating the ceramide/ceramide-1-phosphate pathway.


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35. **Epigenetic regulation of the neural transcriptome and alcohol interference during development**

Resendiz M, Mason S, Lo CL, Zhou FC
1Stark Neuroscience Research Institute, Indianapolis, IN, USA; Indiana Alcohol Research Center, Indiana University School of Medicine, Indianapolis, IN, USA.
2Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA.
3Indiana Alcohol Research Center, Indiana University School of Medicine, Indianapolis, IN, USA; Department of Anatomy and Cell Biology, Indiana University School of Medicine, Indianapolis, IN, USA.
4Stark Neuroscience Research Institute, Indianapolis, IN, USA; Indiana Alcohol Research Center, Indiana University School of Medicine, Indianapolis, IN, USA.

**Abstract**

Alcohol intoxicated cells broadly alter their metabolites - among them methyl and acetic acid can alter the DNA and histone epigenetic codes. Together with the promiscuous effect of alcohol on enzyme activities (including DNA methyltransferases) and the downstream effect on microRNA and transposable elements, alcohol is well placed to affect intrinsic transcriptional programs of developing cells. Considering that the developmental consequences of early alcohol exposure so profoundly affect neural systems, it is not unfounded to reason that alcohol exploits transcriptional regulators to challenge canonical gene expression and in effect, intrinsic developmental pathways to achieve widespread damage in the developing nervous system. To fully evaluate the role of epigenetic regulation in alcohol-related developmental disease, it is important to first gather the targets of epigenetic players in neurodevelopmental models. Here, we attempt to review the cellular and genomic windows of opportunity for alcohol to act on intrinsic neurodevelopmental programs. We also discuss some established targets of fetal alcohol exposure and propose pathways for future study. Overall, this review hopes to illustrate the known epigenetic program and its alterations in normal brain stem cell development and further, aims to depict how alcohol, through neuroepigenetics, may lead to neurodevelopmental deficits observed in fetal alcohol spectrum disorders.


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36. **Prenatal xenobiotic exposure and intrauterine hypothalamus-pituitary-adrenal axis programming alteration**

1Department of Pharmacology, Basic Medical School of Wuhan University, Wuhan 430071, China.
2Department of Pharmacology, Basic Medical School of Wuhan University, Wuhan 430071, China; Hubei Provincial Key Laboratory of Developmentally Originated Disease, Wuhan 430071, China.
3Department of Pharmacology, Basic Medical School of Wuhan University, Wuhan 430071, China; Hubei Provincial Key Laboratory of Developmentally Originated Disease, Wuhan 430071, China. Electronic address: wanghui19@whu.edu.cn.

**Abstract**

The hypothalamic-pituitary-adrenal (HPA) axis is one of the most important neuroendocrine axes and plays an important role in stress defense responses before and after birth. Prenatal exposure to xenobiotics, including environmental toxins (such as smoke, sulfur dioxide and carbon monoxide), drugs (such as synthetic glucocorticoids), and foods and beverage categories (such as ethanol and caffeine), affects fetal development indirectly by changing the maternal status or damaging the placenta. Certain xenobiotics (such as caffeine, ethanol and dexamethasone) may also affect...
the fetus directly by crossing the placenta into the fetus due to their lipophilic properties and lower molecular weights. All of these factors probably result in intrauterine programming alteration of the HPA axis, which showed a low basal activity but hypersensitivity to chronic stress. These alterations will, therefore, increase the susceptibility to adult neuropsychiatric (such as depression and schizophrenia) and metabolic diseases (such as hypertension, diabetes and non-alcoholic fatty liver disease). The “over-exposure of fetuses to maternal glucocorticoids” may be the main initiation factor by which the fetal HPA axis programming is altered. Meantime, xenobiotics can directly induce abnormal epigenetic modifications and expression on the important fetal genes (such as hippocampal glucocorticoid receptor, adrenal steroidogenic acute regulatory protein, et al) or damage by in situ oxidative metabolism of fetal adrenals, which may also be contributed to the programming alteration of fetal HPA axis.

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37. Involvement of seven in absentia homolog-1 in ethanol-induced apoptosis in neural crest cells

Sun H¹, Chen X¹, Yuan F¹, Liu J¹, Zhao Y², Chen SY³
1Department of Cancer Biology and Pharmacology, University of Illinois College of Medicine, Peoria, IL 61605, United States.
2Ben May Department for Cancer Research, The University of Chicago, Chicago, IL 60637, United States.
3Department of Cancer Biology and Pharmacology, University of Illinois College of Medicine, Peoria, IL 61605, United States.
Electronic address: sychen@uic.edu.

Abstract
Ethanol-induced apoptosis in selected cell populations is a major component of pathogenesis underlying ethanol-induced teratogenesis. However, there is a fundamental gap in understanding how ethanol leads to apoptosis in embryos. In this study, we investigate the role of seven in absentia homolog-1 (Siah1) protein, an E3 ubiquitin ligase, in ethanol-induced apoptosis. Using an in vitro model of neural crest cell (NCC), JoMa1.3 cells, we found that exposure to 100mM ethanol resulted in a significant increase in Siah1 mRNA expression in NCCs, an ethanol-sensitive cell population implicated in Fetal Alcohol Spectrum Disorders (FASD). Treatment with 100mM ethanol for 24h also significantly increased the protein expression of Siah1 in JoMa1.3 cells. The nuclear translocation and accumulation of Siah1 was evidenced in the cells exposed to ethanol. In addition, we have found that the inhibition of Siah1 function with siRNA prevents ethanol-induced increase in Siah1 protein expression and nuclear translocation in NCCs. Down-regulation of Siah1 by siRNA also greatly diminished ethanol-induced cell death and caspase-3 activation, indicating that inhibition of Siah1 can attenuate ethanol-induced apoptosis. These results strongly suggest that Siah1 plays an important role in ethanol-induced apoptosis in NCCs.

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38. Attention, locomotor activity and developmental milestones in rats prenatally exposed to ethanol

Brys I¹, Pupe S², Bizarro L²
1Departamento de Psicologia do Desenvolvimento e da Personalidade, Instituto de Psicologia, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2600, Porto Alegre, RS 90035-003, Brazil. Electronic address: ivanibrys@gmail.com.
2Departamento de Psicologia do Desenvolvimento e da Personalidade, Instituto de Psicologia, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos 2600, Porto Alegre, RS 90035-003, Brazil.
Abstract

RATIONALE:
Decline of attentional performance as a function of time engaged on a task and hyperactivity are features shared by children and adults with fetal alcohol syndrome or attentional deficit and hyperactivity disorders.

OBJECTIVE:
To investigate the effects of prenatal exposure to two doses of ethanol on developmental milestones, locomotor activity and attention.

METHODS:
Wistar rats born from dams exposed to one of four maternal treatments during pregnancy were used: A35 - liquid diet with 35% ethanol-derived calories; A10 - liquid diet with 10% ethanol-derived calories; control - ethanol-free liquid diet; chow - laboratory chow and water.

RESULTS:
A35 performed worse in grip strength than control and chow (postnatal day - 14, p<0.05) but not in negative geotaxis (postnatal days 7-10); A35 also showed more locomotor activity than control and A10 (p<0.05). Regarding attention, acquisition of the five choice reaction time task was similar between groups, but, the percentage of omission errors from A35 group was greater than other groups at baseline parameters, at shorter (2s) and longer (7s) inter-trial intervals and at a shorter stimulus duration (0.5s) (p<0.05). The percentage of omissions was larger in A35 as the blocks progressed in sessions with either longer or shorter inter-trial intervals (group×block p<0.05). Animals from A10 group did not show any impairment in the tasks performed.

CONCLUSIONS:
Our study demonstrates that as well as developmental impairments, prenatal ethanol can produce deficits associated with an increase in attentional demand in rodents, analogous to those observed in fetal alcohol syndrome and attentional deficit and hyperactivity disorders.

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developed using T1-weighted images from 63 subjects that were imaged and manually labeled: 43 subjects were scanned once and were used for training models, and 20 subjects were imaged twice (with manual labeling applied to both runs) and used to assess reliability and validity. Intraclass correlation analysis shows that CATK is highly reliable (average test-retest ICCs of 0.96), and offers excellent agreement with the gold standard (average validity ICC of 0.87 against manual labels). Comparisons against an alternative atlas-based approach, SUIT (Spatially Unbiased Infratentorial Template), that registers images with a high-resolution template of the cerebellum, show that our AAM approach offers superior reliability and validity. Extensions of CATK to cerebellar hemisphere parcels are envisioned.

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40. Study protocol: Asking Questions about Alcohol in pregnancy (AQUA): a longitudinal cohort study of fetal effects of low to moderate alcohol exposure

Muggli E1, O'Leary C, Forster D, Anderson P, Lewis S, Nagle C, Craig JM, Donath S, Elliott E, Halliday J

1Murdoch Childrens Research Institute, The Royal Children's Hospital, Parkville, 3052, Victoria, Australia. evi.muggli@mcri.edu.au

Abstract

BACKGROUND:
Despite extensive research, a direct correlation between low to moderate prenatal alcohol exposure (PAE) and Fetal Alcohol Spectrum Disorders has been elusive. Conflicting results are attributed to a lack of accurate and detailed data on PAE and incomplete information on contributing factors. The public health effectiveness of policies recommending complete abstinence from alcohol during pregnancy is challenged by the high frequency of unplanned pregnancies, where many women consumed some alcohol prior to pregnancy recognition. There is a need for research evidence emphasizing timing and dosage of PAE and its effects on child development.

METHODS/DESIGN:
Asking QUESTions about AlcohOl (AQUA) is a longitudinal cohort aiming to clarify the complex effects of low to moderate PAE using specifically developed and tested questions incorporating dose, pattern and timing of exposure. From 2011, 2146 pregnant women completed a questionnaire at 8-18 weeks of pregnancy. Further prenatal data collection took place via a questionnaire at 26-28 weeks and 35 weeks gestation. Extensive information was obtained on a large number of risk factors to assist in understanding the heterogeneous nature of PAE effects. 1571 women (73%) completed all three pregnancy questionnaires. A biobank of DNA from maternal and infant buccal cells, placental biopsies and cord blood mononuclear cells will be used to examine epigenetic state at birth as well as genetic factors in the mother and child. Participants will be followed up at 12 and 24 months after birth to assess child health and measure infant behavioural and sensory difficulties, as well as family environment and parenting styles. A subgroup of the cohort will have 3D facial photography of their child at 12 months and a comprehensive developmental assessment (Bayley Scales of Infant & Toddler Development, Bayley-III) at two years of age.

DISCUSSION:
Using detailed, prospective methods of data collection, the AQUA study will comprehensively examine the effects of low to moderate alcohol consumption throughout pregnancy on child health and development, including the role of key mediators and confounders. These data will ultimately contribute to policy review and development, health professional education and information about alcohol consumption for pregnant women in the future.

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41. **A DTI-based tractography study of effects on brain structure associated with prenatal alcohol exposure in newborns**


Department of Human Biology, Faculty of Health Sciences, University of Cape Town, South Africa; MRC/UCT Medical Imaging Research Unit, Faculty of Health Sciences, University of Cape Town, South Africa; African Institute for Mathematical Sciences, Muizenberg, Western Cape, South Africa

**Abstract**

Prenatal alcohol exposure (PAE) is known to have severe, long-term consequences for brain and behavioral development already detectable in infancy and childhood. Resulting features of fetal alcohol spectrum disorders include cognitive and behavioral effects, as well as facial anomalies and growth deficits. Diffusion tensor imaging (DTI) and tractography were used to analyze white matter (WM) development in 11 newborns (age since conception <45 weeks) whose mothers were recruited during pregnancy. Comparisons were made with nine age-matched controls born to abstainers or light drinkers from the same Cape Coloured (mixed ancestry) community near Cape Town, South Africa. DTI parameters, T1 relaxation time, proton density and volumes were used to quantify and investigate group differences in WM in the newborn brains. Probabilistic tractography was used to estimate and to delineate similar tract locations among the subjects for transcallosal pathways, cortico-spinal projection fibers, and cortico-cortical association fibers. In each of these WM networks, the axial diffusivity was the parameter that showed the strongest association with maternal drinking. The strongest relations were observed in medial and inferior WM, regions in which the myelination process typically begins. In contrast to studies of older individuals with PAE, fractional anisotropy did not exhibit a consistent and significant relation with alcohol exposure. To our knowledge, this is the first DTI-tractography study of prenatally alcohol exposed newborns. Hum Brain Mapp, 2014. © 2014 Wiley Periodicals, Inc.

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42. **Role of microglia in regulation of ethanol neurotoxic action**

Chastain LG, Sarkar DK

Endocrinology Program, Department of Animal Sciences, Rutgers, The State University of New Jersey, New Brunswick, New Jersey, USA.

Endocrinology Program, Department of Animal Sciences, Rutgers, The State University of New Jersey, New Brunswick, New Jersey, USA. Electronic address: sarkar@aesop.rutgers.edu

**Abstract**

Exposure to alcohol, during development or adulthood, may result in damage to the nervous system, which underlies neurological and cognitive disruptions observed in patients with alcohol-related disorders, including fetal alcohol spectrum disorders (FASDs) and alcohol-use disorders (AUDs). Both clinical and preclinical evidence suggest microglia, the immune cells of the central nervous system, play a key role in modulating alcohol-induced neurotoxicity. Particularly, microglia are implicated in alcohol-induced neuroinflammation and in alcohol-induced increases in oxidative stress, which can lead to neuronal apoptosis. Recent studies also suggest a regenerative role for microglia in reestablishing homeostasis after alcohol exposure. These studies are summarized and reviewed in this chapter with emphasis on relevance to FASD and AUD.
Fetal alcohol spectrum disorders and neuroimmune changes

Drew PD¹, Kane CJ²
1Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.
2Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA. Electronic address: kanecynthiaj@uams.edu

Abstract
The behavioral consequences of fetal alcohol spectrum disorders (FASD) are serious and persist throughout life. The causative mechanisms underlying FASD are poorly understood. However, much has been learned about FASD from human structural and functional studies as well as from animal models, which have provided a greater understanding of the mechanisms underlying FASD. Using animal models of FASD, it has been recently discovered that ethanol induces neuroimmune activation in the developing brain. The resulting microglial activation, production of proinflammatory molecules, and alteration in expression of developmental genes are postulated to alter neuron survival and function and lead to long-term neuropathological and cognitive defects. It has also been discovered that microglial loss occurs, reducing microglia's ability to protect neurons and contribute to neuronal development. This is important, because emerging evidence demonstrates that microglial depletion during brain development leads to long-term neuropathological and cognitive defects. Interestingly, the behavioral consequences of microglial depletion and neuroimmune activation in the fetal brain are particularly relevant to FASD. This chapter reviews the neuropathological and behavioral abnormalities of FASD and delineates correlates in animal models. This serves as a foundation to discuss the role of the neuroimmune system in normal brain development, the consequences of microglial depletion and neuroinflammation, the evidence of ethanol induction of neuroinflammatory processes in animal models of FASD, and the development of anti-inflammatory therapies as a new strategy for prevention or treatment of FASD. Together, this knowledge provides a framework for discussion and further investigation of the role of neuroimmune processes in FASD.

Prenatal alcohol exposure reduces magnetic susceptibility contrast and anisotropy in the white matter of mouse brains

Cao W¹, Li W², Han H², O'Leary-Moore SK³, Sulik KK³, Allan Johnson G⁴, Liu C⁵
1Brain Imaging and Analysis Center, Duke University, Durham, NC, United States; Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.
2Brain Imaging and Analysis Center, Duke University, Durham, NC, United States.
3Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC, United States.
4Center for In Vivo Microscopy, Duke University, Durham, NC, United States.
5Brain Imaging and Analysis Center, Duke University, Durham, NC, United States; Department of Radiology, Duke University, Durham, NC, United States. Electronic address: chunlei.liu@duke.edu
Abstract
Prenatal alcohol exposure can result in long-term cognitive and behavioral deficits. Fetal alcohol spectrum disorder (FASD) refers to a range of permanent birth defects caused by prenatal alcohol exposure, and is the most common neurodevelopmental disorder in the US. Studies by autopsy and conventional structural MRI indicate that the midline structures of the brain are particularly vulnerable to prenatal alcohol exposure. Diffusion tensor imaging (DTI) has shown that abnormalities in brain white matter especially the corpus callosum are very common in FASD. Quantitative susceptibility mapping (QSM) is a novel technique that measures tissue's magnetic property. Such magnetic property is affected by tissue microstructure and molecular composition including that of myelin in the white matter. In this work, we studied three major white matter fiber bundles of a mouse model of FASD and compared it to control mice using both QSM and DTI. QSM revealed clear and significant abnormalities in anterior commissure, corpus callosum, and hippocampal commissure, which were likely due to reduced myelination. Our data also suggested that QSM may be even more sensitive than DTI for examining changes due to prenatal alcohol exposure. Although this is a preclinical study, the technique of QSM is readily translatable to human brain.

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46. A Qualitative Assessment of Program Characteristics for Preventing Secondary Conditions in Individuals with Fetal Alcohol Spectrum Disorders

Christie LM Patrenko¹, Naira Tahir¹, Erin C Mahoney¹, Nancy P Chin²
¹Mt. Hope Family Center, University of Rochester; ²Department of Public Health Sciences, University of Rochester School of Medicine and Dentistry, USA

BACKGROUND
Fetal alcohol spectrum disorders (FASD) are a major public health problem that affects 2 to 5 percent of the population. Individuals with FASD are at high risk for secondary conditions, such as mental health problems, school disruptions, and trouble with the law. Evidence-based intervention programs are needed to prevent and treat secondary conditions in this population.

OBJECTIVES
The purpose of this study was to identify intervention program characteristics for preventing secondary conditions in individuals with FASD from the perspectives of parents and service providers.

METHODS
This qualitative study utilized a phenomenological approach to identify program characteristics for preventing secondary conditions. Twenty-five parents of children (ages 3 to 33) with FASD and 18 service providers participated in focus groups or individual interviews. Data was systematically analyzed using a framework approach. Themes did not differ by participant type.

RESULTS
Participants emphasized five primary characteristics of intervention programs for individuals with FASD. Programs need to 1) be available to individuals across the lifespan, 2) have a prevention focus, 3) be individualized, 4) be comprehensive, and 5) be coordinated across systems and developmental stages. Participants discussed a variety of specific intervention strategies for each developmental stage and setting.

CONCLUSIONS
Program characteristics identified in this study are consistent with a positive behavior support framework. This framework is discussed in the context of research on existing interventions for individuals with FASD, and recommendations for future intervention development and evaluation are highlighted.

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47. Developmental Ethanol Exposure Leads to Dysregulation of Lipid Metabolism and Oxidative Stress in Drosophila

Logan-Garbsch T¹, Bortolazzo A², Luu P³, Ford A³, Do D³, Khodabakhshi P³, French RL⁴
¹San José State University; Stanford University;
²San José State University; University of Wisconsin-Madison;
³San José State University.
⁴San José State University rachael.french@sjsu.edu

Abstract
Ethanol exposure during development causes an array of developmental abnormalities, both physiological and behavioral. In mammals, these abnormalities are collectively known as Fetal Alcohol Effects (FAE)
or Fetal Alcohol Spectrum Disorder (FASD). We have established a Drosophila melanogaster model of FASD, and have previously shown that developmental ethanol exposure in flies leads to reduced expression of insulin like peptides (dILPs) and their receptor. In this work, we link that observation to dysregulation of fatty acid metabolism and lipid accumulation. Further, we show that developmental ethanol exposure in Drosophila causes oxidative stress, that this stress is a primary cause of the developmental lethality and delay associated with ethanol exposure, and, finally, that one of the mechanisms by which ethanol increases oxidative stress is through abnormal fatty acid metabolism. These data suggest a previously uncharacterized mechanism by which ethanol causes the symptoms associated with FASD.

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48. Identifying maternal risk factors associated with Fetal Alcohol Spectrum Disorders: a systematic review

Esper LH1, Furtado EF
1PAI-PAD Program for Assessment, Intervention and Prevention of Alcohol and Drugs in the Community, Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Sao Paulo, Brazil

Abstract
To identify the demographic, psychological, and social maternal risk factors associated with the development of Fetal Alcohol Spectrum Disorders (FASD). A bibliographic search was conducted in PubMed, SciELO, Lilacs, Web of Knowledge, and PsycINFO. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of the studies with case-control design. Articles were selected based on their relevance and presentation of data related to statistical comparisons of at least one or more demographic, psychological, or social maternal risk factors for FASD. 738 references were identified, of which 15 met the criteria to be included in the present review. Mothers of FASD children tend to: be older at the time of birth of the affected child, present lower educational level, have other family relatives with alcohol abuse, have other children with FASD, present a pattern of little prenatal care and a distinguishing pattern of alcohol consumption (alcohol use before and during pregnancy, failure to reduce alcohol use during pregnancy, and frequent episodes of binge drinking). Application of the NOS scale of methodological quality indicated that 8 studies (53 %) met the criterion for selection, 4 (27 %) were suitable for the criterion for comparability and only 4 studies were suitable for the exposition criterion. Mothers of FASD children have a distinctive pattern of drinking and accumulate several social risk factors. Maternal age at birth of the child seems to accentuate the risk. There are, however, few controlled studies that are adequate according to the NOS requirements for methodological quality. Fewer are based on the verification of a theoretical model. Clinicians should be aware of the relevance of preventive assessment of FASD risk mothers.

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49. Overweight and obesity among children and adolescents with fetal alcohol spectrum disorders

Fuglestad AJ1, Boys CJ, Chang PN, Miller BS, Eckerle JK, Deling L, Fink BA, Hoecker HL, Hickey MK, Jimenez-Vega JM, Wozniak JR
1Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota

www.nofas-uk.org
Abstract

BACKGROUND:
Because prenatal alcohol exposure is associated with growth deficiency, little attention has been paid to the potential for overweight and obesity in children with fetal alcohol spectrum disorders (FASD). This study examined the prevalence of overweight/obesity (body mass index [BMI]) in a large clinical sample of children with FASD.

METHODS:
Children, aged 2 to 19 years, who were evaluated for FASD at University Clinics, included 445 with an FASD diagnosis and 171 with No-FASD diagnosis. Prevalence of overweight/obesity (BMI ≥ 85 percentile) was compared to national and state prevalence. BMI was examined in relation to FASD diagnosis, gender, and age. Dietary intake data were examined for a young subsample (n = 42).

RESULTS:
Thirty-four percent with any FASD diagnosis were overweight or obese, which did not differ from the No-FASD group or U.S. prevalence. Underweight was prevalent in those with fetal alcohol syndrome (FAS) (17%). However, increased rates of overweight/obesity were seen in those with partial FAS (40%). Among adolescents, those with any FASD diagnosis had increased overweight/obesity (42%), particularly among females (50%). The rate in adolescent females with FASD (50%) was nearly 3 times higher than state prevalence for adolescent females (17 to 18%), p < 0.001. In the young subsample, those who were overweight/obese consumed more calories, protein, and total fat per day than those who were not overweight or obese.

CONCLUSIONS:
Rates of overweight/obesity are increased in children with partial FAS. In adolescents, rates are increased for any FASD diagnosis (particularly in females). Results are suggestive of possible metabolic/endocrine disruption in FASD—a hypothesis for which there is evidence from animal models. These data suggest that clinicians may consider prenatal alcohol exposure as a risk factor for metabolic/endocrine disruption, should evaluate diet as a risk in this population, and may need to target interventions to females prior to puberty to effect changes in overweight-related outcomes.


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50. Alterations of neocortical pyramidal neurons: turning points in the genesis of mental retardation

Granato A, De Giorgio A

1Department of Psychology, Catholic University, Milan, Italy

Abstract
Pyramidal neurons (PNs) represent the majority of neocortical cells and their involvement in cognitive functions is decisive. Therefore, they are the most obvious target of developmental disorders characterized by mental retardation. Genetic and non-genetic forms of intellectual disability share a few basic pathogenetic signatures that result in the anomalous function of PNs. Here, we review the key mechanisms impairing these neurons and their participation in the cortical network, with special focus on experimental models of fetal exposure to alcohol. Due to the heterogeneity of PNs, some alterations affect selectively a given cell population, which may also differ depending on the considered pathology. These specific features open new possibilities for the interpretation of cognitive defects observed in mental retardation syndromes, as well as for novel therapeutic interventions.


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51. Genomic factors that shape craniofacial outcome and neural crest vulnerability in FASD

Smith SM¹, Garic A¹, Berres ME², Flentke GR¹
¹Department of Nutritional Sciences, University of Wisconsin-Madison Madison, WI, USA.
²Department of Animal Sciences, University of Wisconsin-Madison Madison, WI, USA

Abstract

Prenatal alcohol exposure (PAE) causes distinctive facial characteristics in some pregnancies and not others; genetic factors may contribute to this differential vulnerability. Ethanol disrupts multiple events of neural crest development, including induction, survival, migration, and differentiation. Animal models and genomic approaches have substantially advanced our understanding of the mechanisms underlying these facial changes. PAE during gastrulation produces craniofacial changes corresponding with human fetal alcohol syndrome. These result because PAE reduces prechordal plate extension and suppresses sonic hedgehog, leading to holoprosencephaly and malpositioned facial primordia. Haploinsufficiency in sonic hedgehog signaling increases vulnerability to facial deficits and may influence some PAE pregnancies. In contrast, PAE during early neurogenesis produces facial hypoplasia, preceded by neural crest reductions due to significant apoptosis. Factors mediating this apoptosis include intracellular calcium mobilization, elevated reactive oxygen species, and loss of trophic support from β-catenin/calcium, sonic hedgehog, and mTOR signaling. Genome-wide SNP analysis links PDGFRA with facial outcomes in human PAE. Multiple genomic-level comparisons of ethanol-sensitive and -resistant early embryos, in both mouse and chick, independently identify common candidate genes that may potentially modify craniofacial vulnerability, including ribosomal proteins, proteosome, RNA splicing, and focal adhesion. In summary, research using animal models with genome-level differences in ethanol vulnerability, as well as targeted loss- and gain-of-function mutants, has clarified the mechanisms mediating craniofacial change in PAE. The findings additionally suggest that craniofacial deficits may represent a gene-ethanol interaction for some affected individuals. Genetic-level changes may prime individuals toward greater sensitivity or resistance to ethanol’s neurotoxicity.

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52. Alcohol use during pregnancy: considerations for Australian policy

McBride N
National Drug Research Institute, Health Sciences, Curtin University, Perth, Australia

Abstract

Although there is an extensive recorded history of concerns related to alcohol exposed pregnancies and possible outcomes of fetal alcohol spectrum disorder in recent scientific literature, Australia has only recently begun to accurately or systematically diagnose and record these conditions, or to provide comprehensive, coordinated, policy-guided funding, prevention, and treatment. This article discusses some considerations that can guide policy development within the Australian context including the social context and determinates of alcohol consumption during pregnancy and the need to consider the issue as one that goes beyond the decision making of individual women. The article also identifies the contribution of research to guide evidence-based policy development, including emerging evidence of epigenetics, and systematic reviews for prevention. Other policy considerations include costs, and the possibility of the prevention paradox applying to this field, with its associated impact on costs and focus of prevention.

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53. Use of novel inhalation kinetic studies to refine physiologically-based pharmacokinetic models for ethanol in non-pregnant and pregnant rats

Martin SA1, Oshiro WM, Evansky PA, Debn LL, Ledbetter AD, Ford J, Todd Krantz Q, LeFew WR, Beasley TE, El-Masri H, McLanahan ED, Boyes WK, Bushnell PJ
1Neurotoxicology Branch/Toxicity Assessment Division, Office of Research and Development (ORD), US Environmental Protection Agency, Research Triangle Park, NC, USA

Abstract

Ethanol (EtOH) exposure induces a variety of concentration-dependent neurological and developmental effects in the rat. Physiologically-based pharmacokinetic (PBPK) models have been used to predict the inhalation exposure concentrations (BEC) in the range associated with these effects. Previous laboratory reports often lacked sufficient detail to adequately simulate reported exposure scenarios associated with BECs in this range, or lacked data on the time-course of EtOH in target tissues (e.g. brain, liver, eye, fetus). To address these data gaps, inhalation studies were performed at 5000, 10,000, and 21,000 ppm (6 h/d) in non-pregnant female Long-Evans (LE) rats and at 21,000 ppm (6.33 h/d) for 12 d of gestation in pregnant LE rats to evaluate our previously published PBPK models at toxicologically-relevant blood and tissue concentrations. Additionally, nose-only and whole-body plethysmography studies were conducted to refine model descriptions of respiration and uptake within the respiratory tract. The resulting time-course and plethysmography data from these in vivo studies were compared to simulations from our previously published models, after which the models were recalibrated to improve descriptions of tissue dosimetry by accounting for dose-dependencies in pharmacokinetic behavior. Simulations using the recalibrated models reproduced these data from non-pregnant, pregnant, and fetal rats to within a factor of 2 or better across datasets, resulting in a suite of model structures suitable for simulation of a broad range of EtOH exposure scenarios.

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54. Hypothesis: genetic and epigenetic risk factors interact to modulate vulnerability and resilience to FASD

Tunc-Ozcan E, Sittig LJ, Harper KM, Graf EN, Redei EE
Department of Psychiatry and Behavioral Sciences, Northwestern University Chicago, IL, USA

Abstract

Fetal alcohol spectrum disorder (FASD) presents a collection of symptoms representing physiological and behavioral phenotypes caused by maternal alcohol consumption. Symptom severity is modified by genetic differences in fetal susceptibility and resistance as well as maternal genetic factors such as maternal alcohol sensitivity. Animal models demonstrate that both maternal and paternal genetics contribute to the variation in the fetus’ vulnerability to alcohol exposure. Maternal and paternal genetics define the variations in these phenotypes even without the effect of alcohol in utero, as most of these traits are polygenic, non-Mendelian, in their inheritance. In addition, the epigenetic alterations that instigate the alcohol induced neurodevelopmental deficits can interact with the polygenic inheritance of respective traits. Here, based on specific examples, we present the hypothesis that the principles of non-Mendelian inheritance, or “exceptions” to Mendelian genetics, can be the driving force behind the severity of the prenatal alcohol-exposed individual’s symptomology. One such exception is when maternal alleles lead to an altered intrauterine hormonal environment and, therefore, produce variations in the long-term consequences on the development of the alcohol-exposed fetus. Another exception is when epigenetic regulation of allele-specific gene expression generates disequilibrium between the maternal vs. paternal genetic contributions, and thereby, modifies the effect of

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prenatal alcohol exposure on the fetus. We propose that these situations in which one parent has an exaggerated influence over the offspring's vulnerability to prenatal alcohol are major contributing mechanisms responsible for the variations in the symptomology of FASD in the exposed generation and beyond.

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Srihartika V1, O’Leary C
1Centre for Population Health Research, Curtin University, Perth, Australia

Abstract
OBJECTIVE:
To examine fetal outcomes of mothers with an alcohol-related diagnosis

DESIGN:
Population-based cohort

SETTING:
Western Australia (WA)

POPULATION:
Births on the WA Midwives Notification System (1983-2007)

METHODS:
Infants of mothers with an alcohol-related diagnosis [International Classification of Disease (ICD), 9th/10th revisions] recorded on WA health data sets (non-Aboriginal n = 13 807; Aboriginal n = 9766) were identified through the WA data linkage system. A comparison cohort of infants born to mothers without an alcohol diagnosis was frequency matched on maternal age, year of birth of the offspring, and Aboriginal status (non-Aboriginal n = 40 148; Aboriginal n = 20 643)

MAIN OUTCOME MEASURES:
Poisson regression-generated adjusted relative risk (aRR) and 95% confidence intervals (95% CIs) for small for gestational age (SGA), preterm birth, and low-Apgar score, calculated separately for non-Aboriginal and Aboriginal infants of mothers with an alcohol diagnosis recorded during pregnancy and any alcohol diagnosis. Population-attributable fractions were calculated.

RESULTS:
The aRR for non-Aboriginal infants when a maternal alcohol diagnosis was recorded during pregnancy ranged from 1.79 (95% CI 1.42-2.16) for SGA to 2.57 (95% CI 1.69-4.27) for preterm birth <32 weeks of gestation, and for Aboriginal infants ranged from 2.69 (95% CI 2.28-3.16) to 1.99 (95% CI 1.40-2.84), respectively. The highest population-attributable fractions were for any alcohol diagnosis and for Aboriginal infants. For Aboriginal births, approximately 9% (95% CI 4.74-12.97) and 10.1% (95% CI 5.50-14.49) of moderate and very preterm births, respectively, and 24.4% (95% CI 13.5-21.2%) of SGAs were attributable to having a mother with any alcohol-related diagnosis.

CONCLUSIONS:
Mothers with an alcohol diagnosis are at increased risk of poor pregnancy outcomes. The public health impact of maternal alcohol-use disorders on fetal outcomes is significant.

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56. Advances in the development of novel antioxidant therapies as an approach for fetal alcohol syndrome prevention

Joya X1, Garcia-Algar O, Salat-Batlle J, Pujades C, Vall O
1Unitat de Recerca Infància i Entorn (URIE), Institut Hospital del Mar d’Investigacions Mèdiques (IMIM), Barcelona, Spain; Red de Salud Materno-Infantil y del Desarrollo (SAMID), Programa RETICS, Instituto Carlos III, Madrid, Spain

Abstract

Ethanol is the most common human teratogen, and its consumption during pregnancy can produce a wide range of abnormalities in infants known as fetal alcohol spectrum disorder (FASD). The major characteristics of FASD can be divided into: (i) growth retardation, (ii) craniofacial abnormalities, and (iii) central nervous system (CNS) dysfunction. FASD is the most common cause of nongenetic mental retardation in Western countries. Although the underlying molecular mechanisms of ethanol neurotoxicity are not completely determined, the induction of oxidative stress is believed to be one central process linked to the development of the disease. Currently, there is no known effective strategy for prevention (other than alcohol avoidance) or treatment. In the present review we will provide the state of art in the evidence for the use of antioxidants as a potential therapeutic strategy for the treatment using whole-embryo and culture cells models of FASD. We conclude that the imbalance of the intracellular redox state contributes to the pathogenesis observed in FASD models, and we suggest that antioxidant therapy can be considered a new efficient strategy to mitigate the effects of prenatal ethanol exposure.

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57. Impact of combined prenatal ethanol and prenatal stress exposures on markers of activity-dependent synaptic plasticity in rat dentate gyrus

Staples MC1, Porch MW1, Savage DD2
1Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA. 2Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, USA. Electronic address: DSavage@salud.unm.edu

Abstract

Prenatal ethanol exposure and prenatal stress can each cause long-lasting deficits in hippocampal synaptic plasticity and disrupt learning and memory processes. However, the mechanisms underlying these perturbations following a learning event are still poorly understood. We examined the effects of prenatal ethanol exposure and prenatal stress exposure, either alone or in combination, on the cytosolic expression of activity-regulated cytoskeletal (ARC) protein and the synaptosomal expression of AMPA-glutamate receptor subunits (GluA1 and GluA2) in dentate gyrus of female adult offspring under baseline conditions and after 2-trial trace conditioning (TTTC). Surprisingly, baseline cytoplasmic ARC expression was significantly elevated in both prenatal treatment groups. In contrast, synaptosomal GluA1 receptor subunit expression was decreased in both prenatal treatment groups. GluA2 subunit expression was elevated in the prenatal stress group. TTTC did not alter ARC levels compared to an unpaired behavioral control (UPC) group in any of the 4 prenatal treatment groups. In contrast, TTTC significantly elevated both synaptosomal GluA1 and GluA2 subunit expression relative to the UPC group in control offspring, an effect that was not observed in any of the other 3 prenatal treatment groups. Given ARC’s role in regulating synaptosomal AMPA receptors, these results suggest that

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prenatal ethanol-induced or prenatal stress exposure-induced increases in baseline ARC levels could contribute to reductions in both baseline and activity-dependent changes in AMPA receptors in a manner that diminishes the role of AMPA receptors in dentate gyrus synaptic plasticity and hippocampal-sensitive learning.

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58. **Consuming non-alcoholic beer and other beverages during pregnancy and breastfeeding**

Adiong JP, Kim E, Koren G, Bozzo P
College of Family Physicians of Canada

**Abstract**

**QUESTION:**
An increasing number of my patients are asking about the safety of consuming non-alcoholic beer and other alcohol-free versions of alcoholic beverages during pregnancy and breastfeeding, as they believe that these drinks might be a "safer" alternative to regular alcoholic beverages. What are Motherisk’s recommendations regarding these products?

**ANSWER:**
Such drinks might contain higher alcohol levels than what is indicated on their labels. As there is no known safe level of alcohol intake in pregnancy, abstinence from non-alcoholic beverages would eliminate any risk of fetal alcohol spectrum disorder. Although it is likely that moderate intake of non-alcoholic beverages would pose no harm to breastfed infants, briefly delaying breastfeeding after consumption of such drinks would ensure that the infant is not exposed to alcohol.

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59. **Simplified gyral pattern in severe developmental microcephalies? New insights from allometric modeling for spatial and spectral analysis of gyrification**

Germanaud D1, Lefèvre J2, Fischer C3, Bintner M4, Curie A5, des Portes V5, Eliez S6, Elmaleh-Bergès M7, Lamblin D8, Passemard S9, Operto G10, Schaer M10, Verloes A11, Toro R12, Mangin JF13, Hertz-Pannier L13
1INSERM, UMR 1129, F-75015 Paris, France; CEA, NeuroSpin, UNIAC'T, UNIPEDIA, F-91191 Gif sur Yvette, France; AP-HP, Hôpital Robert Debré, Service de Neuropédiatrie et Pathologie Métabolique, F-75019 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, Faculté de Médecine Paris Diderot, F-75010 Paris, France. Electronic address: david.germanaud@rdb.aphp.fr.
2Aix-Marseille Université, CNRS, LSIS lab, UMR 7296, F-13397 Marseille, France.
3CEA, NeuroSpin, UNATI, LNAO, F-91191 Gif sur Yvette, France.

**4Groupe Hospitalier Sud-Réunion, Pôle de Radiologie, Service de Neuroradiologie, F-97410 Saint-Pierre, La Réunion, France.**
5SHL, Hôpital Femme Mère Enfant, Centre de Référence "Déficiences Intellectuelles de Causes Rares", F-69677 Bron, France; Université Lyon 1, Université de Lyon, Faculté de médecine Lyon Sud - Charles Mérieux, F-69008 Lyon, France; CNRS, Université Lyon 1, Université de Lyon, L2C2, Institut des Sciences Cognitives, UMR 5304, F-69675 Bron, France.
6Office Médico-Pédagogique, Department of Psychiatry, University of Geneva School of Medicine, Geneva, Switzerland.
7AP-HP, Hôpital Robert Debré, Service d’Imagerie Pédiatrique, F-75019 Paris, France.
8Fondation Père Favron, IMS Charles Isautier, CAMPs, F-97450 Saint-Louis, La Réunion, France.
9Univ Paris Diderot, Sorbonne Paris Cité, Faculté de Médecine Paris Diderot, F-75010 Paris, France; INSERM, UMR 1141, F-75019 Paris, France; AP-HP, Hôpital Robert Debré, Service de Génétique Clinique, F-75019 Paris, France.

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The strong positive-allometric relationship between brain size, cortical extension and gyrification complexity, recently highlighted in the general population, could be modified by brain developmental disorders. Indeed, in case of brain growth insufficiency, the pathophysiological relevance of the "simplified gyral pattern" phenotype is strongly disputed since almost no genotype-phenotype correlations have been found in primary microcephalies. Using surface scaling analysis and newly-developed spectral analysis of gyrification (Spangy), we tested whether the gyral simplification in groups of severe microcephalies related to ASPM, PQBP1 or fetal-alcohol-syndrome could be fully explained by brain size reduction according to the allometric scaling law established in typically-developing control groups, or whether an additional disease effect was to be suspected. We found the surface area reductions to be fully explained by scaling effect, leading to predictable folding intensities measured by gyrification indices. As for folding pattern assessed by spectral analysis, scaling effect also accounted for the majority of the variations, but an additional negative or positive disease effect was to be suspected. We found the surface area reductions to be fully explained by scaling effect, leading to predictable folding intensities measured by gyrification indices. As for folding pattern assessed by spectral analysis, scaling effect also accounted for the majority of the variations, but an additional negative or positive disease effect was found in the case of ASPM and PQBP1-linked microcephalies, respectively. Our results point out the necessity of taking allometric scaling into account when studying the gyrification variability in pathological conditions. They also show that the quantitative analysis of gyrification complexity through spectral analysis can enable distinguishing between even (predictable, non-specific) and uneven (unpredictable, maybe disease-specific) gyral simplifications.
relative to the saline treated group. Increased acetylation of H3K9 and increased mRNA expression of Gata4, α-MHC, cTnT were observed in these hearts. Treatment with the pan-histone acetylase inhibitor, anacardic acid, reduced the binding of P300, PCAF to the Gata4 promoter and reversed H3K9 hyperacetylation in the presence of ethanol. Interestingly, anacardic acid attenuated over-expression of Gata4, α-MHC and cTnT in fetal mouse hearts exposed to ethanol.

**CONCLUSIONS:**
Our results suggest that P300 and PCAF may be critical regulatory factors that mediate Gata4 over-expression induced by ethanol exposure. Alternatively, P300, PCAF and Gata4 may coordinate over-expression of cardiac downstream genes in mouse hearts exposed to ethanol. Anacardic acid may thus protect against ethanol-induced Gata4, α-MHC, cTnT over-expression by inhibiting the binding of P300 and PCAF to the promoter region of these genes.

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Abstract
Functional magnetic resonance imaging (fMRI) reveals brain activation abnormalities during visuo-spatial attention and working memory among those with fetal alcohol spectrum disorders (FASD) in cross-sectional reports, but little is known about how activation changes over time during development within FASD or typically developing children. We studied 30 controls and 31 individuals with FASD over 2 years (7-14 years at first participation) with a total of 122 scans, as part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders. Despite comparable performance, there were significant group differences in visuo-spatial activation over time bilaterally in frontal, parietal, and temporal regions. Controls showed an increase in signal intensity in these multiple regions whereas FASD participants showed a decrease in brain activation. Effects were also found in 2 small independent samples from the USA, corroborating the findings from the larger group. Results suggest that the long-lasting effect of prenatal alcohol may impact the maturation of visuo-spatial attention and differentiate those with FASD from controls. Based on this first longitudinal fMRI study in FASD children, our novel findings suggest a possible neural mechanism for attention deficits common among individuals with FASD.

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PubMed, Genom Data, 2014 Dec 1;2:139-143.

63. Molecular effect of ethanol during neural differentiation of human embryonic stem cells in vitro
Kim JJ1, Duan L2, Tu TG1, Elie O1, Kim Y1, Mathiyakom N1, Elashoff D2, Kim Y3
1 Laboratory of Stem Cell and Cancer Epigenetic Research, UCLA School of Dentistry, Los Angeles, CA, USA.
2 Department of Biostatistics and Medicine, UCLA School of Public Health, Los Angeles, CA, USA.
3 Laboratory of Stem Cell and Cancer Epigenetic Research, UCLA School of Dentistry, Los Angeles, CA, USA; Division of Oral Biology and Medicine, UCLA School of Dentistry, Los Angeles, CA, USA; Center for Oral and Head/Neck Oncology Research Center, Los Angeles, CA, USA; UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; UCLA Broad Stem Cell Research Center, Los Angeles, CA, USA

Abstract
Potential teratogenic effects of ethanol on fetal development have been documented. Especially studies have demonstrated deleterious effect of ethanol exposure on neuronal development in animal models and on the maintenance and differentiation of neuronal precursor cells derived from stem cells. To better understand molecular effect of ethanol on the process of neural differentiation, we have performed gene expression microarray analysis on human embryonic stem cells being directed to neural rosettes and neural precursor cells in the presence of ethanol treatment. Here we provide detailed experimental methods, analysis and information associated with our data deposited into Gene Expression Omnibus (GEO) under GSE56906. Our data provide scientific insight on potential molecular effects of fetal alcohol exposure on neural differentiation of early embryo development.

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64. Prenatal Ethanol Exposure Up-Regulates the Cholesterol Transporters ATP-Binding Cassette A1 and G1 and Reduces Cholesterol Levels in the Developing Rat Brain

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Zhou C1, Chen J1, Zhang X2, Costa LG3, Guizzetti M4
1Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA.
2Department of Psychiatry, College of Medicine, University of Illinois at Chicago, Chicago, IL, USA Jesse Brown VA Medical Center, Chicago, IL, USA.
3Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA Department of Neuroscience, University of Parma, Parma, Italy.
4Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA Department of Psychiatry, College of Medicine, University of Illinois at Chicago, Chicago, IL, USA Jesse Brown VA Medical Center, Chicago, IL, USA mguizzetti@psych.uic.edu

Abstract

AIMS: Cholesterol plays a pivotal role in many aspects of brain development; reduced cholesterol levels during brain development, as a consequence of genetic defects in cholesterol biosynthesis, leads to severe brain damage, including microcephaly and mental retardation, both of which are also hallmarks of the fetal alcohol syndrome. We had previously shown that ethanol up-regulates the levels of two cholesterol transporters, ABCA1 (ATP binding cassette-A1) and ABCG1, leading to increased cholesterol efflux and decreased cholesterol content in astrocytes in vitro. In the present study we investigated whether similar effects could be seen in vivo.

METHODS: Pregnant Sprague-Dawley rats were fed liquid diets containing 36% of the calories from ethanol from gestational day (GD) 6 to GD 21. A pair-fed control groups and an ad libitum control group were included in the study. ABCA1 and ABCG1 protein expression and cholesterol and phospholipid levels were measured in the neocortex of female and male fetuses at GD 21.

RESULTS: Body weights were decreased in female fetuses as a consequence of ethanol treatments. ABCA1 and ABCG1 protein levels were increased, and cholesterol levels were decreased, in the neocortex of ethanol-exposed female, but not male, fetuses. Levels of phospholipids were unchanged. Control female fetuses fed ad libitum displayed an up-regulation of ABCA1 and a decrease in cholesterol content compared with pair-fed controls, suggesting that a compensatory up-regulation of cholesterol levels may occur during food restriction.

CONCLUSION: Maternal ethanol consumption may affect fetal brain development by increasing cholesterol transporters’ expression and reducing brain cholesterol levels.

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65. Caregivers’ management of schooling for their children with fetal alcohol spectrum disorder

Swart S1, Hall WA2, McKee WT2, Ford L2
1University of British Columbia, Vancouver, British Columbia, Canada suretha@mail.ubc.ca.
2University of British Columbia, Vancouver, British Columbia, Canada.

Abstract

In this article we describe a grounded theory study of how caregivers of school-aged children with fetal alcohol spectrum disorder (FASD) managed their children's schooling. We completed 30 interviews with 17 caregivers residing in a western Canadian province, as well as document analysis and 25 hours of participant observation. We used constant comparative analysis to construct our substantive theory: intertwining to fit in. The core variable is an iterative cycle caregivers used to resolve their main concerns: preventing their children from failing academically and in social interactions and preventing
themselves from being regarded as unacceptable parents. To intertwine to fit in, caregivers used two strategies: orchestrating schooling and keeping up appearances. They also regulated their relationships with their children. "Intertwining to fit in" contributes to the literature on attachment and parenting and extends explanations about caregivers' advocacy for their children with FASD. The theory has implications for school personnel and practitioners, as well as researchers.


66. Low-dose maternal alcohol consumption: effects in the hearts of offspring in early life and adulthood

Nguyen VB1, Probyn ME2, Campbell F3, Yin KV1, Samuel CS3, Zimanyi MA1, Bertram JF1, Black MJ1, Moritz KM2
1Department of Anatomy and Developmental Biology, Monash University, Melbourne, Victoria, Australia.
2School of Biomedical Sciences, University of Queensland, Brisbane, Queensland, Australia.
3Department of Pharmacology, Monash University, Melbourne, Victoria, Australia

Abstract
High alcohol consumption during pregnancy leads to deleterious effects on fetal cardiac structure and it also affects cardiomyocyte growth and maturation. This study aimed to determine whether low levels of maternal alcohol consumption are also detrimental to cardiomyocyte and cardiac growth in the early life of offspring and whether cardiac structure and function in adulthood is affected. Pregnant Sprague-Dawley rat dams were fed a control or 6% (volume/volume) liquid-based ethanol supplemented (isocaloric) diet throughout gestation. At embryonic day 20, the expression of genes involved in cardiac development was analyzed using Real-time PCR. At postnatal day 30, cardiomyocyte number, size, and nuclearity in the left ventricle (LV) were determined stereologically. In 8-month-old offspring, LV fibrosis and cardiac function (by echocardiography) were examined. Maternal ethanol consumption did not alter gene expression of the cardiac growth factors in the fetus or cardiomyocyte number in weanling offspring. However, at 8 months, there were significant increases in LV anterior and posterior wall thickness during diastole in ethanol-exposed offspring (P = 0.037 and P = 0.024, respectively), indicative of left ventricular hypertrophy; this was accompanied by a significant increase in fibrosis. Additionally, maximal aortic flow velocity was significantly decreased in ethanol-exposed offspring (P = 0.035). In conclusion, although there were no detectable early-life differences in cardiac and cardiomyocyte growth in animals exposed to a chronic low dose of ethanol during gestation, there were clearly deleterious outcomes by adulthood. This suggests that even relatively low doses of alcohol consumed during pregnancy can be detrimental to long-term cardiac health in the offspring.


67. Incidence of prenatal alcohol exposure in Prince Edward Island: a population-based descriptive study

Bryanton J1, Gareri J2, Boswall D3, McCarthy MJ1, Fraser B4, Walsh D5, Freeman B5, Koren G2, Bigsby K4
1School of Nursing, University of Prince Edward Island, Charlottetown, PEI.
2Motherisk Program, The Hospital for Sick Children, Toronto, Ont.; Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ont.
3PEI Reproductive Care Program, Charlottetown, PEI.
4Queen Elizabeth Hospital, Charlottetown, PEI.
5Prince County Hospital, Summerside, PEI

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Abstract

BACKGROUND:
Fetal alcohol spectrum disorder (FASD) is a leading preventable cause of neurodevelopmental disability in North America. The stigma associated with alcohol use and abuse during pregnancy makes it difficult to obtain information on prenatal alcohol use through self-reporting. We assessed the incidence of prenatal alcohol exposure in Prince Edward Island to facilitate future public health initiatives addressing FASD.

METHODS:
Prenatal alcohol exposure was examined via population-based collection of meconium and analysis of fatty acid ethyl esters (FAEEs). Fatty acid ethyl esters are nonoxidative metabolites of ethanol that are produced in the fetus. Meconium FAEE concentrations of 2.0 nmol/g or greater are indicative of frequent prenatal alcohol exposure during the last 2 trimesters of pregnancy. Samples were collected from 1307 neonates between Nov. 8, 2010, and Nov. 8, 2011, in hospitals in PEI, or from those born to mothers who resided in PEI but gave birth in Halifax, Nova Scotia. Samples were frozen and shipped for analysis. Fatty acid ethyl esters were analyzed by gas chromatography-mass spectrometry and quantified by means of deuterated internal standards.

RESULTS:
Of the 1307 samples collected, 1271 samples were successfully analyzed. Positive results for FAEEs were obtained in 3.1% (n = 39) of samples collected within the first 24 hours after birth.

INTERPRETATION:
Not all neonates exposed to heavy prenatal alcohol in utero will exhibit FASD; based on current estimates of predictive value for disease by exposure, our findings suggest that 1.3% of neonates born in PEI during this 1-year period will have FASD. In its application to an entire provincial birth cohort, this study successfully implemented a public health-centred approach for evaluating population-based risk of FASD, with implications for practice across Canada.

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68. Bovine Brain: An in vitro Translational Model in Developmental Neuroscience and Neurodegenerative Research
Peruffo A, Cozzi B
Department of Comparative Biomedicine and Food Science, University of Padova, Padova, Italy

Abstract
Animal models provide convenient and clinically relevant tools in the research on neurodegenerative diseases. Studies on developmental disorders extensively rely on the use of laboratory rodents. The present mini-review proposes an alternative translational model based on the use of fetal bovine brain tissue. The bovine (Bos taurus) possesses a large and highly gyrencephalic brain and the long gestation period (41 weeks) is comparable to human pregnancy (38-40 weeks). Primary cultures obtained from fetal bovine brain constitute a validated in vitro model that allows examinations of neurons and/or glial cells under controlled and reproducible conditions. Physiological processes can be also studied on cultured bovine neural cells incubated with specific substrates or by electrically coupled electrolyte-oxide-semiconductor capacitors that permit direct recording from neuronal cells. Bovine neural cells and specific in vitro cell culture could be an alternative in comparative neuroscience and in neurodegenerative research, useful for studying development of normal
and altered circuitry in a long gestation mammalian species. Use of bovine tissues would promote a substantial reduction in the use of laboratory animals.

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69. Fetal alcohol programming of hypothalamic proopiomelanocortin system by epigenetic mechanisms and later life vulnerability to stress

Bekdash R1, Zhang C, Sarkar D

1Endocrinology Program, Department of Animal Sciences, Rutgers, The State University of New Jersey, New Brunswick, New Jersey; Neuroscience Graduate Program, The State University of New Jersey, New Brunswick, New Jersey

Abstract

Hypothalamic proopiomelanocortin (POMC) neurons, one of the major regulators of the hypothalamic-pituitary-adrenal (HPA) axis, immune functions, and energy homeostasis, are vulnerable to the adverse effects of fetal alcohol exposure (FAE). These effects are manifested in POMC neurons by a decrease in Pomc gene expression, a decrement in the levels of its derived peptide β-endorphin and a dysregulation of the stress response in the adult offspring. The HPA axis is a major neuroendocrine system with pivotal physiological functions and mode of regulation. This system has been shown to be perturbed by prenatal alcohol exposure. It has been demonstrated that the perturbation of the HPA axis by FAE is long-lasting and is linked to molecular, neurophysiological, and behavioral changes in exposed individuals. Recently, we showed that the dysregulation of the POMC system function by FAE is induced by epigenetic mechanisms such as hypermethylation of Pomc gene promoter and an alteration in histone marks in POMC neurons. This developmental programming of the POMC system by FAE altered the transcriptome in POMC neurons and induced a hyperresponse to stress in adulthood. These long-lasting epigenetic changes influenced subsequent generations via the male germline. We also demonstrated that the epigenetic programming of the POMC system by FAE was reversed in adulthood with the application of the inhibitors of DNA methylation or histone modifications. Thus, prenatal environmental influences, such as alcohol exposure, could epigenetically modulate POMC neuronal circuits and function to shape adult behavioral patterns. Identifying specific epigenetic factors in hypothalamic POMC neurons that are modulated by fetal alcohol and target Pomc gene could be potentially useful for the development of new therapeutic approaches to treat stress-related diseases in patients with fetal alcohol spectrum disorders.

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70. MiR-153 targets the nuclear factor-1 family and protects against teratogenic effects of ethanol exposure in fetalneural stem cells

Tsai PC1, Bake S1, Balaraman S1, Rawlings J1, Holgate RR1, Dubois D1, Miranda RC2

1Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M Health Science Center, Bryan, TX 77807-3260, USA.
2Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M Health Science Center, Bryan, TX 77807-3260, USA miranda@medicine.tamhsc.edu
Abstract

Ethanol exposure during pregnancy is an established cause of birth defects, including neurodevelopmental defects. Most adult neurons are produced during the second trimester-equivalent period. The fetal neural stem cells (NSCs) that generate these neurons are an important but poorly understood target for teratogenesis. A cohort of miRNAs, including miR-153, may serve as mediators of teratogenesis. We previously showed that ethanol decreased, while nicotine increased miR-153 expression in NSCs. To understand the role of miR-153 in the etiology of teratology, we first screened fetal cortical NSCs cultured ex vivo, by microarray and quantitative RT-PCR analyses, to identify cell-signaling miRNAs and gene networks as important miR-153 targets. Moreover, miR-153 over-expression prevented neuronal differentiation without altering neuroepithelial cell survival or proliferation. Analysis of 3'UTRs and in utero over-expression of pre-miR-153 in fetal mouse brain identified Nfia (nuclear factor-1A) and its paralog, Nfib, as direct targets of miR-153. In utero ethanol exposure resulted in a predicted expansion of Nfia and Nfib expression in the fetal telencephalon. In turn, miR-153 over-expression prevented, and partly reversed, the effects of ethanol exposure on miR-153 target transcripts. Varenicline, a partial nicotinic acetylcholine receptor agonist that, like nicotine, induces miR-153 expression, also prevented and reversed the effects of ethanol exposure. These data collectively provide evidence for a role for miR-153 in preventing premature NSC differentiation. Moreover, they provide the first evidence in a preclinical model that direct or pharmacological manipulation of miRNAs have the potential to prevent or even reverse effects of a teratogen like ethanol on fetal development.

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71. Nutrition Implications for Fetal Alcohol Spectrum Disorder

Young JK1, Giesbrecht HE1, Eskin MN1, Aliani M1, Suh M2
1Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, Manitoba, Canada.
2Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, Manitoba, Canada miyoung.suh@umanitoba.ca

Abstract

Prenatal alcohol exposure produces a multitude of detrimental alcohol-induced defects in children collectively known as fetal alcohol spectrum disorder (FASD). Children with FASD often exhibit delayed or abnormal mental, neural, and physical growth. Socioeconomic status, race, genetics, parity, gravidity, age, smoking, and alcohol consumption patterns are all factors that may influence FASD. Optimal maternal nutritional status is of utmost importance for proper fetal development, yet is often altered with alcohol consumption. It is critical to determine a means to resolve and reduce the physical and neurological malformations that develop in the fetus as a result of prenatal alcohol exposure. Because there is a lack of information on the role of nutrients and prenatal nutrition interventions for FASD, the focus of this review is to provide an overview of nutrients (vitamin A, docosahexaenoic acid, folic acid, zinc, choline, vitamin E, and selenium) that may prevent or alleviate the development of FASD. Results from various nutrient supplementation studies in animal models and FASD-related research conducted in humans provide insight into the plausibility of prenatal nutrition interventions for FASD. Further research is necessary to confirm positive results, to determine optimal amounts of nutrients needed in supplementation, and to investigate the collective effects of multiple-nutrient supplementation.

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72. **Automated cerebellar segmentation: Validation and application to detect smaller volumes in children prenatally exposed to alcohol**

Cardenas VA\(^1\), Price M\(^1\), Infante MA\(^2\), Moore EM\(^2\), Mattson SN\(^3\), Riley EP\(^3\), Fein G\(^1\)

1Neurobehavioral Research, Inc., Ala Moana Pacific Center, 1585 Kapiolani Blvd., Suite 1030, Honolulu, HI 96814, USA.
2Center for Behavioral Teratology, San Diego State University, San Diego, CA 92120, USA.
3Center for Behavioral Teratology, San Diego State University, San Diego, CA 92120, USA; Department of Psychology, San Diego State University, San Diego, CA 92182, USA

**Abstract**

**OBJECTIVE:** To validate an automated cerebellar segmentation method based on active shape and appearance modeling and then segment the cerebellum on images acquired from adolescents with histories of prenatal alcohol exposure (PAE) and non-exposed controls (NC).

**METHODS:** Automated segmentations of the total cerebellum, right and left cerebellar hemispheres, and three vermal lobes (anterior, lobules I-V; superior posterior, lobules VI-VII; inferior posterior, lobules VIII-X) were compared to expert manual labelings on 20 subjects, studied twice, that were not used for model training. The method was also used to segment the cerebellum on 11 PAE and 9 NC adolescents.

**RESULTS:** The test-retest intraclass correlation coefficients (ICCs) of the automated method were greater than 0.94 for all cerebellar volume and mid-sagittal vermal area measures, comparable or better than the test-retest ICCs for manual measurement (all ICCs $>0.92$). The ICCs computed on all four cerebellar measurements (manual and automated measures on the repeat scans) to compare comparability were above 0.97 for non-vermis parcels, and above 0.89 for vermis parcels. When applied to patients, the automated method detected smaller cerebellar volumes and mid-sagittal areas in the PAE group compared to controls ($p < 0.05$ for all regions except the superior posterior lobe, consistent with prior studies).

**DISCUSSION:** These results demonstrate excellent reliability and validity of automated cerebellar volume and mid-sagittal area measurements, compared to manual measurements. These data also illustrate that this new technology for automatically delineating the cerebellum leads to conclusions regarding the effects of prenatal alcohol exposure on the cerebellum consistent with prior studies that used labor intensive manual delineation, even with a very small sample.

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73. **Factors influencing women's decisions to drink alcohol during pregnancy: findings of a qualitative study with implications for health communication**

Cardenas VA\(^1\), Price M\(^1\), Infante MA\(^2\), Moore EM\(^2\), Mattson SN\(^3\), Riley EP\(^3\), Fein G\(^1\)

1Postdoctoral Research Fellow, The University of Queensland, UQ Centre for Clinical Research, Royal Brisbane and Women’s Hospital Site, Herston, Queensland 4029, Australia. c.meurk@uq.edu.au

**Abstract**

**BACKGROUND:** Despite Australian guidelines advising abstinence from alcohol during pregnancy, a relatively high number of Australian women continue to drink alcohol while pregnant. While some call for greater advocacy of the need for abstinence, others have expressed concern that abstinence messages may be harmful to pregnant women and their unborn babies due to the anxiety they could provoke. We present findings on women's deliberations over drinking alcohol during pregnancy,
particularly their emotional dimensions, to inform debates about public health messages and practitioner-patient discussions regarding alcohol use during pregnancy.

METHODS:
Semi-structured face-to-face interviews were conducted with 40 women in their homes. Our sample comprised women aged 34-39, drawn from the Australian Longitudinal Study on Women’s Health, living in the Greater Brisbane Area who were pregnant, or had recently given birth, in 2009. An inductive qualitative framework analysis approach was used to identify and interpret themes explaining why pregnant women choose to drink or not.

RESULTS:
Women generally described drinking small amounts of alcohol during pregnancy as being a low risk activity and talked about the importance of alcohol to their social lives as a reason for continuing to drink or finding abstinence a burden; sensitisation to the judgements of others was not widespread. Women predominantly assessed the risk of their drinking in terms of the kinds of alcoholic beverages consumed rather than alcohol content. In reflecting on the advice they recalled receiving, women described their healthcare practitioners as being relaxed about the risks of alcohol consumption.

CONCLUSIONS:
The significance of alcohol to women’s identity appeared to be an important reason for continued alcohol use during pregnancy among otherwise risk averse women. Anxiety about alcohol consumption during pregnancy was not widespread. However, obstetricians were an important mediator of this. Health messages that dispel the notion that wine is a “healthy” choice of alcoholic beverage, that provide women with strategies to help them avoid drinking, that advise the broader public not to pressure women to drink if they do not want to, and educate women about the effects of ethanol on maternal and fetal bodies, should be considered.


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74. Prenatal alcohol exposure and adolescent stress - unmasking persistent attentional deficits in rats

Comeau WL1, Winstanley CA, Weinberg J

1Department of Cellular and Physiological Sciences, University of British Columbia, 2350 Health Sciences Mall, Vancouver, BC, V6T 1Z3, Canada

Abstract
Prenatal alcohol exposure (PAE) can produce a myriad of deficits. Unfortunately, affected individuals may also be exposed to the stress of an adverse home environment, contributing to deficits of attentional processes that are the hallmark of optimal executive function. Male offspring of ad-libitum-fed Control (Con), Pairfed (PF), and PAE dams were randomly assigned to either a 5-day period of variable chronic mild stress (CMS) or no CMS in adolescence. In adulthood, rats were trained in a non-match to sample task (T-maze), followed by extensive assessment in the five-choice serial reaction time task. Once rats acquired the five-choice serial reaction time task (stable accuracy), they were tested in three challenge conditions: (i) increased sustained attention, (ii) selective attention and, (iii) varying doses of d-amphetamine, an indirect dopamine and norepinephrine agonist. At birth and throughout the study, PAE offspring showed reduced body weight. Moreover, although PAE animals were similar to Con animals in task acquisition, they were progressively less proficient with transitions to shorter stimulus durations (decreased accuracy and increased omissions). Five days of adolescent CMS increased basal corticosterone levels in adolescence and disrupted cognitive performance in adulthood. Further, CMS augmented PAE-related disturbances in acquisition and, to a lesser extent, also disrupted attentional processes in Con and PF animals. Following task acquisition, challenges unmasked persistent attentional difficulties resulting from both PAE and adolescent CMS. In conclusion, PAE, adolescent CMS, and their interaction produced unique behavioural profiles that suggest vulnerability in select neurobiological processes at different stages of development.
75. A tensor-based morphometry analysis of regional differences in brain volume in relation to prenatal alcohol exposure

Meintjes EM\(^1\), Narr KL\(^2\), der Kouwe AJ\(^3\), Molteno CD\(^4\), Pirnia T\(^2\), Gutman B\(^5\), Woods RP\(^2\), Thompson PM\(^5\), Jacobson JL\(^6\), Jacobson SW\(^6\)

\(^1\)Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town 7925, South Africa; MRC/UCT Medical Imaging Research Unit, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town 7925, South Africa.
\(^2\)Department of Neurology, Geffen School of Medicine, University of California Los Angeles (UCLA), 710 Westwood Plaza, Los Angeles, CA 90095, USA.
\(^3\)Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Room 2301, Building 149, 13th Street, Charlestown, MA 02129, USA; Department of Radiology, Harvard Medical School, 23 Shattuck Street, Boston, MA 02115, USA.
\(^4\)Department of Psychiatry and Mental Health, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925, Cape Town, South Africa.
\(^5\)Imaging Genetics Center, University of Southern California, 4676 Admiralty Way, Marina del Rey, CA 90292, USA.
\(^6\)Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town 7925, South Africa; Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, 3901 Chrysler Drive, Suite 2-C, Detroit, MI 48201, USA.

Abstract

Reductions in brain volumes represent a neurobiological signature of fetal alcohol spectrum disorders (FASD). Less clear is how regional brain tissue reductions differ after normalizing for brain size differences linked with FASD and whether these profiles can predict the degree of prenatal exposure to alcohol. To examine associations of regional brain tissue excesses/deficits with degree of prenatal alcohol exposure and diagnosis with and without correction for overall brain volume, tensor-based morphometry (TBM) methods were applied to structural imaging data from a well-characterized, demographically homogeneous sample of children diagnosed with FASD (n = 39, 9.6-11.0 years) and controls (n = 16, 9.5-11.0 years). Degree of prenatal alcohol exposure was significantly associated with regionally pervasive brain tissue reductions in: (1) the thalamus, midbrain, and ventromedial frontal lobe, (2) the superior cerebellum and inferior occipital lobe, (3) the dorsolateral frontal cortex, and (4) the precuneus and superior parietal lobule. When overall brain size was factored out of the analysis on a subject-by-subject basis, no regions showed significant associations with alcohol exposure. FASD diagnosis was associated with a similar deformation pattern, but few of the regions survived FDR correction. In data-driven independent component analyses (ICA) regional brain tissue deformations successfully distinguished individuals based on extent of prenatal alcohol exposure and to a lesser degree, diagnosis. The greater sensitivity of the continuous measure of alcohol exposure compared with the categorical diagnosis across diverse brain regions underscores the dose dependence of these effects. The ICA results illustrate that profiles of brain tissue alterations may be a useful indicator of prenatal alcohol exposure when reliable historical data are not available and facial features are not apparent.

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76. **Construction of vapor chambers used to expose mice to alcohol during the equivalent of all three trimesters of human development**

Morton RA¹, Diaz MR², Topper LA², Valenzuela CF²

¹Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center; ramorton@salud.unm.edu.
²Department of Neurosciences, School of Medicine, University of New Mexico Health Sciences Center.

**Abstract**

Exposure to alcohol during development can result in a constellation of morphological and behavioral abnormalities that are collectively known as Fetal Alcohol Spectrum Disorders (FASDs). At the most severe end of the spectrum is Fetal Alcohol Syndrome (FAS), characterized by growth retardation, craniofacial dysmorphology, and neurobehavioral deficits. Studies with animal models, including rodents, have elucidated many molecular and cellular mechanisms involved in the pathophysiology of FASDs. Ethanol administration to pregnant rodents has been used to model human exposure during the first and second trimesters of pregnancy. Third trimester ethanol consumption in humans has been modeled using neonatal rodents. However, few rodent studies have characterized the effect of ethanol exposure during the equivalent to all three trimesters of human pregnancy, a pattern of exposure that is common in pregnant women. Here, we show how to build vapor chambers from readily obtainable materials that can each accommodate up to six standard mouse cages. We describe a vapor chamber paradigm that can be used to model exposure to ethanol, with minimal handling, during all three trimesters. Our studies demonstrate that pregnant dams developed significant metabolic tolerance to ethanol. However, neonatal mice did not develop metabolic tolerance and the number of fetuses, fetus weight, placenta weight, number of pups/litter, number of dead pups/litter, and pup weight were not significantly affected by ethanol exposure. An important advantage of this paradigm is its applicability to studies with genetically modified mice. Additionally, this paradigm minimizes handling of animals, a major confound in fetal alcohol research.

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77. **A qualitative assessment of program characteristics for preventing secondary conditions in individuals with fetal alcohol spectrum disorders**

Patrenko CL, Tahir N, Mahoney EC, Chin NP

¹Mt. Hope Family Center, University of Rochester
²Department of Public Health Sciences, University of Rochester School of Medicine and Dentistry

Address correspondence to: Christie L. M. Petrenko, Ph.D., Mt. Hope Family Center, University of Rochester, 187 Edinburgh St., Rochester, NY 14618, USA. Phone: 585-275-2991 x 241. Fax: 585-454-2972. Email: Christie.petrenko@rochester.edu

**Abstract**

**BACKGROUND:**

Fetal alcohol spectrum disorders (FASD) are a major public health problem that affects 2 to 5 percent of the population. Individuals with FASD are at high risk for secondary conditions, such as mental health problems, school disruptions, and trouble with the law. Evidence-based intervention programs are needed to prevent and treat secondary conditions in this population.

**OBJECTIVES:**

The purpose of this study was to identify intervention program characteristics for preventing secondary conditions in individuals with FASD from the perspectives of parents and service providers.

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METHODS:
This qualitative study utilized a phenomenological approach to identify program characteristics for preventing secondary conditions. Twenty-five parents of children (ages 3 to 33) with FASD and 18 service providers participated in focus groups or individual interviews. Data was systematically analyzed using a framework approach. Themes did not differ by participant type.

RESULTS:
Participants emphasized five primary characteristics of intervention programs for individuals with FASD. Programs need to 1) be available to individuals across the lifespan, 2) have a prevention focus, 3) be individualized, 4) be comprehensive, and 5) be coordinated across systems and developmental stages. Participants discussed a variety of specific intervention strategies for each developmental stage and setting.

CONCLUSIONS:
Program characteristics identified in this study are consistent with a positive behavior support framework. This framework is discussed in the context of research on existing interventions for individuals with FASD, and recommendations for future intervention development and evaluation are highlighted.

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78. Prenatal alcohol exposure increases postnatal acceptability of nicotine odor and taste in adolescent rats
Mantella NM1, Youngentob SL2
1Department of Psychiatry and Behavioral Sciences, State University of New York Upstate Medical University, Syracuse, New York, United States of America.
2Department of Psychiatry and Behavioral Sciences, State University of New York Upstate Medical University, Syracuse, New York, United States of America; State University of New York Developmental Exposure Alcohol Research Center, Syracuse & Binghamton, New York, United States of America.

Abstract
Human studies indicate that alcohol exposure during gestation not only increases the chance for later alcohol abuse, but also nicotine dependence. The flavor attributes of both alcohol and nicotine can be important determinants of their initial acceptance and they both share the component chemosensory qualities of an aversive odor, bitter taste and oral irritation. There is a growing body of evidence demonstrating epigenetic chemosensory mechanisms through which fetal alcohol exposure increases adolescent alcohol acceptance, in part, by decreasing the aversion to alcohol's bitter and oral irritation qualities, as well as its odor. Given that alcohol and nicotine have noteworthy chemosensory qualities in common, we investigated whether fetal exposure to alcohol increased the acceptability of nicotine's odor and taste in adolescent rats. Study rats were alcohol-exposed during fetal development via the dams' liquid diet. Control animals received ad lib access to an iso-caloric, iso-nutritive diet throughout gestation. Odorant-induced innate behavioral responses to nicotine odor (Experiment 1) or orosensory-mediated responses to nicotine solutions (Experiment 2) were obtained, using whole-body plethysmography and brief access lick tests, respectively. Compared to controls, rats exposed tofetal alcohol showed an enhanced nicotine odor response that was paralleled by increased oral acceptability of nicotine. Given the common aversive component qualities imbued in the flavor profiles of both drugs, our findings demonstrate that like postnatal alcohol avidity, fetal alcohol exposure also influences nicotine acceptance, at a minimum, by decreasing the aversion of both its smell and taste. Moreover, they highlight potential chemosensory-based mechanism(s) by which fetal alcohol exposure increases the later initial risk for nicotine use, thereby contributing to the co-morbid expression with enhanced alcohol avidity. Where common chemosensory mechanisms are at play, our results suggest broader implications related to the consequence of fetal exposure with one substance of abuse and initial acceptability of others.
79. **Heat shock factor 2 is a stress-responsive mediator of neuronal migration defects in models of fetal alcohol syndrome**


1CNRS UMR7216 Épigénétique et Destin Cellulaire, Paris Cedex 13, France Univ Paris Diderot Sorbonne Paris Cité, Paris Cedex 13, France ED 387 iViv UPMC Univ Paris 06, Paris, France Univ Paris Diderot, Paris Cedex 13, France.

2CNRS UMR7216 Épigénétique et Destin Cellulaire, Paris Cedex 13, France Univ Paris Diderot Sorbonne Paris Cité, Paris Cedex 13, France.

3INSERM U1141, Hôpital Robert Debré, Paris, France Faculté de Médecine Denis Diderot, Univ Paris Diderot Sorbonne Paris Cité, Paris, France.

4INSERM UMR 866, Dijon, France Faculty of Medicine and Pharmacy, Univ Burgundy, Dijon, France.

5Carol Davila University of Medicine and Pharmacy Fundeni Hospital, Bucharest, Romania.

6Department of Neurobiology and Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, CT, USA.

7Laboratoire de Biologie du Développement de Villefranche-sur-mer, Observatoire Océanologique, CNRS, Villefranche-sur-mer, France Sorbonne Universités UPMC Univ Paris 06, Villefranche-sur-mer, France.

8CNRS UMR7216 Épigénétique et Destin Cellulaire, Paris Cedex 13, France Univ Paris Diderot Sorbonne Paris Cité, Paris Cedex 13, France. valerie.mezger@univ-paris-diderot.fr

**Abstract**

Fetal alcohol spectrum disorder (FASD) is a frequent cause of mental retardation. However, the molecular mechanisms underlying brain development defects induced by maternal alcohol consumption during pregnancy are unclear. We used normal and Hsf2-deficient mice and cell systems to uncover a pivotal role for heat shock factor 2 (HSF2) in radial neuronal migration defects in the cortex, a hallmark of fetal alcohol exposure. Upon fetal alcohol exposure, HSF2 is essential for the triggering of HSF1 activation, which is accompanied by distinctive post-translational modifications, and HSF2 steers the formation of atypical alcohol-specific HSF1-HSF2 heterocomplexes. This perturbs the in vivo binding of HSF2 to heat shock elements (HSEs) in genes that control neuronal migration in normal conditions, such as p35 or the MAPs (microtubule-associated proteins, such as Dclk1 and Dcx), and alters their expression. In the absence of HSF2, migration defects as well as alterations in gene expression are reduced. Thus, HSF2, as a sensor for alcohol stress in the fetal brain, acts as a mediator of the neuronal migration defects associated with FASD.

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Abstract
Objective: Prenatal smoking, alcohol use, and obesity have significant effects on maternal and fetal health. However, not much is known about the genetic contributions to these risk factors among pregnant women. We evaluate the associations between several candidate genes and smoking, alcohol use, pre-pregnancy body weight, and weight gain during pregnancy in a sample of pregnant women. Methods: The study analyzes a sample of about 1900 mothers from the Danish National Birth Cohort. We test the association between 1450 SNPs in/near 117 genes/loci and various risk factor measures. Results: Only a few SNPs in FTO were significantly associated with pre-pregnancy obesity and body mass index (4 and 2 SNPs, respectively) after SNP-level correction for multiple testing. A few loci were significantly related to various smoking measures (any smoking, quitting and cigarette number) with gene/locus-level correction for multiple testing, but not after SNP-level correction. Similarly, some loci were significant for the alcohol measures at the gene/locus-level but not at SNP-level correction. Conclusion: The study suggests that the majority of the evaluated candidate genes may not play an important role in influencing these risk factors among pregnant women, highlighting the importance of other genetic factors and non-genetic contributors to their etiology.

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81. Developmental age strengthens barriers to ethanol accumulation in zebrafish

Lovely CB1, Nobles RD2, Eberhart JK3
1Molecular Biosciences, University of Texas at Austin, Austin, TX 78713, USA; Waggoner Center for Alcohol & Addiction Research, University of Texas at Austin, Austin, TX 78713, USA. Electronic address: benlovely@austin.utexas.edu.
2Ophthalmology and Visual Science, University of Texas Health Science Center at Houston, Houston, TX 77030, USA.
3Molecular Biosciences, University of Texas at Austin, Austin, TX 78713, USA; Waggoner Center for Alcohol & Addiction Research, University of Texas at Austin, Austin, TX 78713, USA

Abstract
Fetal Alcohol Spectrum Disorders (FASD) describes a wide range of phenotypic defects affecting facial and neurological development associated with ethanol teratogenicity. It affects approximately 1 in 100 children born in the United States each year. Genetic predisposition along with timing and dosage of ethanol exposure are critical in understanding the prevalence and variability of FASD. The zebrafish attributes of external fertilization, genetic tractability, and high fecundity make it a powerful tool for FASD studies. However, a lack of consensus of ethanol treatment paradigms has limited the interpretation of these various studies. Here we address this concern by examining ethanol tissue concentrations across timing and genetic background. We utilize headspace gas chromatography to determine ethanol concentration in the AB, fli1:EGFP, and Tu backgrounds. In addition, we treated these embryos with ethanol over two different developmental time windows, 6-24 h post fertilization (hpf) and 24-48 hpf. Our analysis demonstrates that embryos rapidly equilibrate to a sub-media level of ethanol. Embryos then maintain this level of ethanol for the duration of exposure. The ethanol tissue concentration level is independent of genetic background, but is timing-dependent. Embryos exposed from 6 to 24 hpf were 2.7-4.2-fold lower than media levels, while embryos were 5.7-6.2-fold lower at 48 hpf. This suggests that embryos strengthen one or more barriers to ethanol as they develop. In addition, both the embryo and, to a lesser extent, the chorion, surrounding the embryo are barriers to ethanol. Overall, this work will help tighten ethanol treatment regimens and strengthen zebrafish as a model of FASD.

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82. Executive functioning deficits in preschool children with Fetal Alcohol Spectrum Disorders

Fuglestad AJ, Whitley ML, Carlson SM, Boys CJ, Eckerle JK, Fink BA, Wozniak JR

Abstract

Executive function (EF) deficit is a hallmark of Fetal Alcohol Spectrum Disorders (FASD), but the vast majority of available evidence comes from school-age children and adolescents. Very little is known about EF during the critical developmental period prior to 6 years of age in FASD. We evaluated EF in 39 children with FASD (3.0-5.5 years) and a comparison group of 50 age-matched, nonexposed controls. Measures included the EF Scale for Early Childhood and a Delay of Gratification task. Compared to age-matched controls, preschool children with FASD had impairments on the EF Scale and showed more impulsivity on the Delay of Gratification task. To confirm the EF Scale finding, FASD group performance was compared to a separate normative dataset (N = 1,400). Those with FASD performed below normal (M = -0.57, SD = 0.92). Within the FASD group, IQ was correlated with the EF Scale (partial r = .60, p = .001) and Delay of Gratification (partial r = .58, p = .005). EF Scale performance did not differ significantly across levels of FASD severity (fetal alcohol syndrome [FAS], partial FAS, or alcohol-related neurobehavioral disorder [ARND]). However, compared to normative data, those with FAS had the largest deficits (M = -0.91 SD from the mean, SE = 0.23), followed by partial FAS (M = -0.66 SD from the mean, SE = 0.26), then ARND (M = -0.36 SD from the mean, SE = 0.20). These novel data show that EF deficits manifest well before the age of 6 years in children with FASD, that they occur across the spectrum, and that EF may be most impaired in children with more severe forms of FASD and/or lower IQs.

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83. Improving executive functioning in children with fetal alcohol spectrum disorders

Nash K, Stevens S, Greenbaum R, Weiner J, Koren G, Rovet J

Abstract

An extensive body of literature has documented executive function (EF) impairments in children with fetal alcohol spectrum disorders (FASD); however, few studies have aimed specifically at improving EF. One treatment program that shows promise for children with FASD is the Alert Program for Self-Regulation®, which is a 12-week treatment specifically designed to target self-regulation, a component of EF. The present study sought to examine if Alert would produce improvements in self-regulation that would generalize to other aspects of EF, behavior, and social skills in children with FASD. Twenty-five children aged 8-12 years diagnosed with an FASD were assigned in alternating sequence to either an immediate treatment (TXT) or a delayed treatment control (DTC) group. Both groups received a comprehensive evaluation of EF at baseline and upon completing therapy (TXT), or after a 12- to 14-week interval from baseline (DTC). Parents also completed questionnaires assessing EF and behavior at both time points. For the TXT group only, parent questionnaires were readministered at 6-month follow-up. At the 12-week follow-up, the TXT group displayed significant improvements in inhibitory control and social cognition. Parents of children in the TXT group reported improved behavioral and emotional regulation, as well as reduced externalizing behavior problems. These behavioral improvements along with further improved parent-rated inhibitory control was maintained at the 6-month follow-up. The EF disabilities in children with FASD can be remediated through a targeted treatment approach aimed at facilitating self-regulation skills.
84. Fetal alcohol spectrum disorder: development of consensus referral criteria for specialist diagnostic assessment in Australia

¹Telethon Kids Institute, The University of Western Australia, Perth, Australia. rochelle.watkins@telethonkids.org.au

Abstract

BACKGROUND:
Fetal alcohol spectrum disorder (FASD) is known to be under-recognised in Australia. The use of standard methods to identify when to refer individuals who may have FASD for specialist assessment could help improve the identification of this disorder. The purpose of this study was to develop referral criteria for use in Australia.

METHOD:
An online survey about FASD screening and diagnosis in Australia, which included 23 statements describing criteria for referral for fetal alcohol syndrome (FAS) and FASD based on published recommendations for referral in North America, was sent to 139 health professionals who had expertise or involvement in FASD screening or diagnosis. Survey findings and published criteria for referral were subsequently reviewed by a panel of 14 investigators at a consensus development workshop where criteria for referral were developed.

RESULTS:
Among the 139 health professionals who were sent the survey, 103 (74%) responded, and 90 (65%) responded to the statements on criteria for referral. Over 80% of respondents agreed that referral for specialist evaluation should occur when there is evidence of significant prenatal alcohol exposure, defined as 7 or more standard drinks per week and at least 3 standard drinks on any one day, and more than 70% agreed with 13 of the 16 statements that described criteria for referral other than prenatal alcohol exposure. Workshop participants recommended five independent criteria for referral: confirmed significant prenatal alcohol exposure; microcephaly and confirmed prenatal alcohol exposure; 2 or more significant central nervous system (CNS) abnormalities and confirmed prenatal alcohol exposure; 3 characteristic FAS facial anomalies; and 1 characteristic FAS facial anomaly, growth deficit and 1 or more CNS abnormalities.

CONCLUSION:
Referral criteria recommended for use in Australia are similar to those recommended in North America. There is a need to develop resources to raise awareness of these criteria among health professionals and evaluate their feasibility, acceptability and capacity to improve the identification of FASD in Australia.

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85. "It’s better for me to drink, at least the stress is going away": perspectives on alcohol use during pregnancy among South African women attending drinking establishments

Watt MH¹, Eaton LA², Choi KW³, Velloza J⁴, Kalichman SC⁵, Skinner D⁶, Sikkema KJ⁷
¹Duke University, Duke Global Health Institute, Durham, NC 27708, USA. Electronic address: melissa.watt@duke.edu.

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Abstract
The Western Cape of South Africa has one of the highest rates of fetal alcohol spectrum disorders (FASD) globally. Reducing alcohol use during pregnancy is a pressing public health priority for this region, but insight into the experiences of women who drink during pregnancy is lacking. Convenience sampling in alcohol-serving venues was used to identify women who were currently pregnant (n = 12) or recently post-partum (n = 12) and reported drinking during the pregnancy period. In-depth qualitative interviews were conducted between April and August 2013. Interviews explored drinking narratives, with textual data analyzed for themes related to factors that contributed to drinking during pregnancy. All but one woman reported her pregnancy as unplanned. The majority sustained or increased drinking after pregnancy recognition, with patterns typically including multiple days of binge drinking per week. Analysis of the textual data revealed five primary factors that contributed to drinking during pregnancy: 1) women used alcohol as a strategy to cope with stressors and negative emotions, including those associated with pregnancy; 2) women drank as a way to retain social connection, often during a difficult period of life transition; 3) social norms in women's peer groups supported drinking during pregnancy; 4) women lacked attachment to the pregnancy or were resistant to motherhood; and 5) women were driven physiologically by alcohol addiction. Our data suggest that alcohol-serving settings are important sites to identify and target women at risk of drinking during pregnancy. Intervention approaches to reduce alcohol use during pregnancy should include counseling and contraception to prevent unwanted pregnancies, mental health and coping interventions targeting pregnant women, peer-based interventions to change norms around perinatal drinking, and treatment for alcohol dependence during pregnancy. Our findings suggest that innovative interventions that go beyond the boundaries of the health care system are urgently needed to address FASD in this region.

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pregnant women and women intending a pregnancy, there is an urgent need for wider implementation of prevention programs and policy approaches that can reduce the risk for this serious public health problem.

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87. Fetal alcohol spectrum disorders and cognitive functions of young children

Bakoyiannis I, Gkioka E, Pergialiotis V, Mastroleon I, Prodromidou A, Vlachos GD, Perrea D.
Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, Athens University, Medical School, 15B Ag. Thoma str, 115 27, Athens, Greece, pergialiotis@yahoo.com

Abstract
Abstract Fetal alcohol spectrum disorder (FASD) is one of the main causes of mental retardation worldwide. Nearly 1% of children in North America are affected from antenatal exposure to ethanol. Its economic burden in industrialized countries is increasing. It is estimated that, in the United States, 4.0 billion dollars are annually expended in the treatment and rehabilitation of these patients. As a pathologic entity, they present with a broad symptomatology. Fetal alcohol syndrome (FAS) is the most readily recognized clinical manifestation of these disorders. Various factors seem to contribute in the pathogenesis of FASD-related cognitive disorders. During the last 20 years, several potential pretranslational and posttranslational factors have been extensively studied in various experimental animal models. Research has specifically focused on several neurotransmitters, insulin resistance, alterations of the hypothalamic-pituitary-adrenal (HPA) axis, abnormal glycosylation of several proteins, oxidative stress, nutritional antioxidants, and various epigenetic factors. The purpose of the present review is to summarize the clinical manifestations of this disorder during childhood and adolescence and to summarize the possible pathophysiologic and epigenetic pathways that have been implicated in the pathophysiology of FASD.

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88. Fetal Alcohol Spectrum Disorder and the Neurobehavioural Screening Tool: Evaluating the Effect of Maternal Depression

Kevin Haynes1,2; Irena Nulman1,2,3; Gideon Koren1,2,3
1The Hospital for Sick Children, Motherisk Program, Toronto, Canada
2The Hospital for Sick Children, Child Health Evaluative Sciences, Toronto, Canada
3The University of Toronto, Department of Pediatrics, Toronto, Canada

Background
The behaviour of children diagnosed with a Fetal Alcohol Spectrum Disorder (FASD) is characterized by very complex and pervasive neurobehavioural effects. In contrast to children exhibiting the full facial dysmorphology who are relatively easy to assess and diagnose, those children presenting with Alcohol Related Neurodevelopmental Disorder (ARND) are much more challenging to diagnose due to poor specificity of the brain dysfunction; hence identifying the neurodevelopmental phenotype of FASD is extremely challenging. In 2006 the Neurobehavioral Screening Tool (NST)
was developed, which derived from a selection of 10 questions from the Child Behavior Checklist (CBCL) developed by Achenbach. The NST is an official screening tool in the FASD toolkit of the Public Health Agency of Canada, and has been shown to identify a phenotypical neurobehavioral pattern in children affected by FASD with high sensitivity and specificity. A challenge in the interpretation of screening results has been ascertaining the potential influence of maternal psychiatric morbidity. The most common psychiatric morbidity among mothers who consume alcohol in excess during pregnancy is depression.

Objective
The purpose of this study was to examine the influence of maternal depression, evidenced by clinical diagnosis, and use of antidepressant drugs, on the typical behavioural presentation displayed by children diagnosed with an FASD.

Methods
Endorsement rates of NST items among children diagnosed with an FASD reported in three previous studies (n=134) and the typically developing healthy control children from these studies (n=112) were compared with the prospectively collected results of children born to and reared by mothers suffering from clinical depression (n=49) and additional typically developing healthy control children (n=22).

Results
In this study, none of the children born to the mothers suffering from clinical depression screened positive on the NST, however a significant number of these caregivers reported that their child was hyperactive. The mother’s level of depression as indicated by her CES-D score was also shown to correlate with the child’s conduct, namely, lying/cheating and disobedience at home.

Conclusion
These results indicate that the sensitivity and specificity of the NST are not significantly affected by maternal depression, however endorsement rates of items measuring impulse control, oppositional behaviours and conduct may be influenced. Further studies are needed to examine the potential effects of other maternal psychopathologies on endorsement rates.

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89. Incidence and Prevalence of Fetal Alcohol Spectrum Disorder by Sex and Age Group in Alberta, Canada
Nguyen Xuan Thanh1, Egon Jonsson2, Amy Salmon3, Meghan Sebastianski4
1School of Public Health, University of Alberta, and Institute of Health Economics, Edmonton, AB, Canada; 2Dept. of Medicine, University of Alberta, Dept. of Community Health Sciences, University of Calgary, and Institute of Health Economics, Edmonton, AB, Canada; 3School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, and Institute of Health Economics, Edmonton, AB, Canada; 4Dept. of Medicine, University of Alberta, Edmonton, AB, Canada

Objectives
To estimate incidence and prevalence of FASD by sex and age in Alberta, Canada.

Methods
We included all patients recorded in the Alberta provincial health databases of inpatients, outpatients, and practitioner claims from 2003 to 2012. The number of people with FASD were calculated from available data on FAS (ICD-9 code 760.71; ICD-10 codes Q86.0 and P04.3) and estimated prevalence of FASD among individuals diagnosed with 21 FASD-related conditions (identified by a literature review) for which there are ICD codes, such as learning disability, mental retardation, and nervous system defects (Table 1). Fractions of FASD-related diagnoses that can be attributed to alcohol use during pregnancy were estimated by a systematic review. The incidence was measured as the number of new cases per 1000 births. The prevalence was measured as the number of cases per 1000 population in 2012.
Results
Annually, 739 to 1884 people were born with FASD in Alberta establishing an incidence of 14.2 to 43.8 per 1000 births, depending on the length of follow-up. There were about 46,000 people living with FASD in Alberta 2012, including 6,000 FAS cases and 40,000 FASD-related cases. The prevalence of FASD was 11.7 (range 8.2 to 15.1) per 1000 population. The incidence and prevalence varied greatly by sex and age group. Generally, male and younger outnumbered female and older.

Conclusion
This study suggests new incidence and prevalence of FASD, which are higher than what has been commonly used (1%), and its variations among sex and age groups.

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90. Frequent Behavioural Challenges in Children with Fetal Alcohol Spectrum Disorder: A Needs-Based Assessment Reported by Caregivers and Clinicians

Courtney R. Green1,2, Jessica Roane3, Amy Hewitt1,2 Nazeem Muhajarine4, Christopher Mushquash5, Andre Sourander6, Patricia Lingley-Pottie5,7, Patrick McGrath5,7, James N. Reynolds1,2
1Centre for Neuroscience Studies, and 2Department of Biomedical and Molecular Sciences, Queen’s University, Kingston, Ontario, Canada; 3IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada; 4Department of Community Health and Epidemiology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; 5Department of Psychology, and Northern Ontario School of Medicine, Human Sciences Division, Lakehead University, Thunder Bay, Ontario, Canada; 6Department of Child Psychiatry, University of Turku, Turku, Finland; 7Strongest Families Institute, Halifax, Nova Scotia, Canada

Objective
Despite substantial research characterizing the brain injury, a significant gap still exists in providing timely and effective care for children with Fetal Alcohol Spectrum Disorder (FASD). The objective of this study was to conduct a needs assessment that could help inform intervention programs and appropriate strategies to manage challenging behaviours targeted to families impacted by FASD.

Methods
Sixty caregivers and 26 clinicians from across Canada completed a semi-structured telephone interview.

Results
Caregivers reported that the most challenging behaviour categories were “Externalizing Behaviours”, “Cognitive Difficulties”, and “Social Difficulties/Maladjustment”, whereas the most successful parenting strategies were “Parental Reflection”, “Routine/Structure/Consistency”, and “Environmental Modification”. Clinicians reported that “Insufficient Support/Knowledge from Health and Social Professionals and Agencies” and “Behavioural Difficulties/Challenges” were the most common concerns from caregivers of children with FASD.

Conclusions
The number and extent of challenges reported make it evident that there are many unmet needs that compromise the quality of life for these caregivers, their children, and their families. These data will be used to inform the development of an intervention program that will provide a family-centered approach to training, education, and support for children with FASD and their families.

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91. Costs of Health Services Utilization of People with Fetal Alcohol Spectrum Disorder by Sex and Age Group in Alberta, Canada

Nguyen Xuan Thanh1,2, Egon Jonsson1,2,3
1Institute of Health Economics, Edmonton, Canada; 2University of Alberta, Edmonton, Canada; 3University of Calgary, Calgary, Canada

Objectives
To estimate the annual health services utilization (HSU) cost per person with FASD by sex and age; the lifetime HSU cost per person with FASD by sex, and the annual HSU cost of FASD for Alberta by sex.

Methods
The HSU costs of FASD including physician, outpatient, and inpatient services were described by sex and age. The costs per person-year were estimated by multiplying the average number of hospitalizations, outpatient visits, and physician visits per person-year by the average cost of each service. The annual HSU cost of FASD for Alberta was estimated by multiplying the annual HSU cost per person with FASD by the number of people living with FASD in Alberta in 2012. The lifetime HSU cost per person with FASD was estimated by sex for several lifespans ranging from 10 to 70 years.

Results
The annual cost of HSU for people with FASD in Alberta was $259 million, of which FAS accounted for 26%. The annual HSU cost per person with FAS and FASD were $6,200 and $5,600, respectively. The incremental annual HSU cost per person with FAS is $4,100 and with FASD is $3,400 as compared to the general population. The lifetime (70 years) HSU cost per person with FAS was $506,000 and with FASD was $245,000. Males had higher HSU costs than females. HSU costs of FAS and FASD varied greatly by age group.

Conclusion
The findings suggest that FASD is a public health issue in Alberta and can be used for economic evaluations of FASD intervention and/or prevention in the province.

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92. Educating students with FASD: linking policy, research and practice

Julie A. Millar1, Janet Thompson1, Dorothy Schwab2, Ana Hanlon-Dearman3,4, Deborah Goodman5, Gal Koren6 and Paul Masotti7
1Winnipeg School Division, Canada; 2Manitoba FASD Centre, Canada; 3University of Manitoba, Canada; 4Children’s Hospital of Winnipeg, Canada; 5Research and Program Evaluation Child Welfare Institute, Children’s Aid Society of Toronto, Canada; 6The Motherisk Program, The Hospital for Sick Children, Canada; 7Department of Community Health Sciences, University of Manitoba, Canada

Fetal alcohol spectrum disorder (FASD) is a prevalent neurodevelopmental disability with significant implications for learning and behaviour. International research suggests that the prevalence of FASD in school-aged children is 2.3–6.3%. In this paper, we address the questions: (1) what is FASD; (2) what is the prevalence of FASD in schools; (3) what is the impact of FASD; and (4) why develop special FASD education strategies and programmes? We summarise the 18-year history of Winnipeg School Division’s development of its FASD Programme of services, describe the specialised FASD classrooms and then present the results from a consensus-generating workshop comprised of 36 FASD education professionals, with over 209 years of collective FASD education programme experience, who were asked to identify and reach consensus on best strategies and lessons learned in FASD education programmes. We then suggest that effectively educating children with FASD is critical to get right if positive educational outcomes are to be realised.
93. Neurobehavioral, neurologic, and neuroimaging characteristics of fetal alcohol spectrum disorders
Leila Glass, Ashley L. Ware, Sarah N. Mattson  USA

Abstract
Alcohol consumption during pregnancy can have deleterious consequences for the fetus, including changes in central nervous system development leading to permanent neurologic alterations and cognitive and behavioral deficits. Individuals affected by prenatal alcohol exposure, including those with and without fetal alcohol syndrome, are identified under the umbrella of fetal alcohol spectrum disorders (FASD). While studies of humans and animal models confirm that even low to moderate levels of exposure can have detrimental effects, critical doses of such exposure have yet to be specified and the most clinically significant and consistent consequences occur following heavy exposure. These consequences are pervasive, devastating, and can result in long-term dysfunction. This chapter summarizes the neurobehavioral, neurologic, and neuroimaging characteristics of FASD, focusing primarily on clinical research of individuals with histories of heavy prenatal alcohol exposure, although studies of lower levels of exposure, particularly prospective, longitudinal studies, will be discussed where relevant.

Read Full Article,
http://www.researchgate.net/publication/268632754_Educating_students_with_FASD_linking_policy_research_and_practice
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94. Fetal Alcohol Spectrum Disorders and Neuroimmune Changes
Paul D. Drew, Cynthia J.M. Kane
1Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.
2Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA. Electronic address: kanecynthiaj@uams.edu.

Abstract
The behavioral consequences of fetal alcohol spectrum disorders (FASD) are serious and persist throughout life. The causative mechanisms underlying FASD are poorly understood. However, much has been learned about FASD from human structural and functional studies as well as from animal models, which have provided a greater understanding of the mechanisms underlying FASD. Using animal models of FASD, it has been recently discovered that ethanol induces neuroimmune activation in the developing brain. The resulting microglial activation, production of proinflammatory molecules, and alteration in expression of developmental genes are postulated to alter neuron survival and function and lead to long-term neuropathological and cognitive defects. It has also been discovered that microglial loss occurs, reducing microglia's ability to protect neurons and contribute to neuronal development. This is important, because emerging evidence demonstrates that microglial depletion during brain development leads to long-term neuropathological and cognitive defects. Interestingly, the behavioral consequences of microglial depletion and neuroimmune activation in the fetal brain are particularly relevant to FASD. This chapter reviews the neuropathological and behavioral abnormalities of FASD and delineates correlates in animal models. This serves as a foundation to discuss the role of the neuroimmune system in normal brain development, the consequences of microglial depletion and neuroinflammation, the evidence of
ethanol induction of neuroinflammatory processes in animal models of FASD, and the development of anti-inflammatory therapies as a new strategy for prevention or treatment of FASD. Together, this knowledge provides a framework for discussion and further investigation of the role of neuroimmune processes in FASD.

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95. **Fetal alcohol spectrum disorder: pathogenesis and mechanisms**

Kathleen K. Sulik

Department of Cell Biology and Physiology and Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC, USA. Electronic address: mouse@med.unc.edu

**Abstract**

This chapter provides an overview of animal model-based studies that have generated information critical to our understanding of the pathogenesis and mechanisms underlying alcohol-induced birth defects, in particular those involving the brain. Focus is placed on the developing organism itself, rather than the mother, placenta, or other extraembryonic tissues. Components of the cascades of alcohol-induced damage that are considered herein are excessive cell death, changes in the cell cycle and proliferation, cell migration, cell morphogenesis, and gene expression as well as free radical damage and interference with cell signaling. The roles played by one or more of these various factors in the genesis of structural and functional birth defects are dependent upon alcohol exposure patterns and dosage, the involved tissue, and the prenatal stage(s) at the time of exposure. Technologic advances and rapidly increasing knowledge in the fields of genetics, cell, developmental, and neurobiology are critical to accurately piecing together experimental evidence in refining our understanding of the genesis of alcohol-induced birth defects, to the planning and execution of future studies, and to applying the knowledge gained to diminish the severity or occurrence of fetal alcohol spectrum disorder.

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96. **Response inhibition deficits in children with Fetal Alcohol Spectrum Disorder: Relationship between diffusion tensor imaging of the corpus callosum and eye movement control**

Angelina Paolozza, Sarah Treit, Christian Beaulieu, James N. Reynolds

Centre for Neuroscience Studies, Queen's University, Kingston, ON K7L 3N6, Canada

Department of Biomedical and Molecular Sciences, Queen's University, Kingston, ON K7L 3N6, Canada

Centre for Neuroscience, University of Alberta, Edmonton, AB T6G-2E1, Canada

Department of Biomedical Engineering, University of Alberta, Edmonton, AB T5G 0B7, Canada

James N. Reynolds: jnr@queensu.ca

Corresponding author at: Botterell Hall, .18 Stuart Street, Queen's University, Kingston, ON K7L 3N6, Canada. Tel.: + 1 613 533 6946; fax: + 1 613 533 6840. Email: jnr@queensu.ca

**Abstract**

Response inhibition is the ability to suppress irrelevant impulses to enable goal-directed behavior. The underlying neural mechanisms of inhibition deficits are not clearly understood, but may be related to white matter connectivity, which can be assessed using diffusion tensor imaging (DTI). The goal of this study was to investigate the relationship between response inhibition during the performance of saccadic eye movement tasks and DTI measures of the corpus callosum in children with or without Fetal Alcohol Spectrum Disorder (FASD). Participants included 43 children with an FASD
diagnosis (12.3 ± 3.1 years old) and 35 typically developing children (12.5 ± 3.0 years old) both aged 7–18, assessed at three sites across Canada. Response inhibition was measured by direction errors in an antisaccade task and timing errors in a delayed memory-guided saccade task. Manual deterministic tractography was used to delineate six regions of the corpus callosum and calculate fractional anisotropy (FA), mean diffusivity (MD), parallel diffusivity, and perpendicular diffusivity. Group differences in saccade measures were assessed using t-tests, followed by partial correlations between eye movement inhibition scores and corpus callosum FA and MD, controlling for age. Children with FASD made more saccade direction errors and more timing errors, which indicates a deficit in response inhibition. The only group difference in DTI metrics was significantly higher MD of the splenium in FASD compared to controls. Notably, direction errors in the antisaccade task were correlated negatively to FA and positively to MD of the splenium in the control, but not the FASD group, which suggests that alterations in connectivity between the two hemispheres of the brain may contribute to inhibition deficits in children with FASD.

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97. Gene-specific disruption of endocannabinoid receptor 1 (cnr1α) by ethanol probably leads to the development of fetal alcohol spectrum disorder (FASD) phenotypes in Japanese rice fish (Oryzias latipes) embryogenesis
Asok K. Dasmahapatra, Ikhlas A. Khana, USA

Abstract
The present study was designed to investigate the probable roles played by cannabinoid (CB) receptors in fetal alcohol spectrum disorder (FASD) induction in Japanese rice fish (Oryzias latipes). Searching of public databases (GenBank, Ensembl) indicated that the Japanese rice fish genome includes three human ortholog CB receptor genes (cnr1α, cnr1β and cnr2). Quantitative real-time PCR (qPCR) and whole mount in situ hybridization (WMISH) techniques were used to analyze the expression of these cnr genes during Japanese rice fish embryogenesis and also in response to developmental ethanol exposure. qPCR analyses showed that the expression of all three CB receptor genes were developmentally regulated and only cnr2 showed maternal expression. The mRNA concentrations of these genes were found to be enhanced after 3 dpf and attained maximal levels either prior to or after hatching. WMISH technique indicated that all three cnr genes were expressed in the head region of hatchlings. During development, ethanol selectively attenuated the expression of cnr1α mRNA only. Blocking of cnr1α mRNA by CB1 receptor antagonists rimonabant (10–20 μM) or AM251 (0.2–1 μM) 0–2 dpf were unable to induce any FASD-related phenotypic features in embryos or in hatchlings. However, continuous exposure of the embryos (0–6 dpf) to AM251 (1 μM) was able to reduce the hatching efficiency of the embryos. Our data indicated that in Japanese rice fish, ethanol disrupted the expression of only cnr1α in a concentration-dependent manner that induced delay in hatching and might be responsible for the development of FASD phenotypes.


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98. Molecular and morphological changes in zebrafish following transient ethanol exposure during defined developmental stages

Zhang C¹, Frazier JM², Chen H¹, Liu Y¹, Lee JA³, Cole GJ³.
1Julius L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, NC 27707, United States.
2Julius L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, NC 27707, United States; Department of Biology, North Carolina Central University, Durham, NC 27707, United States.
3Julius L. Chambers Biomedical/Biotechnology Research Institute, North Carolina Central University, Durham, NC 27707, United States; Department of Biology, North Carolina Central University, Durham, NC 27707, United States. Electronic address: gcole@nccu.edu

Abstract

Alcohol is a teratogen that has diverse effects on brain and craniofacial development, leading to a constellation of developmental disorders referred to as fetal alcohol spectrum disorder (FASD). The molecular basis of ethanol insult remains poorly understood, as does the relationship between molecular and behavioral changes as a consequence of prenatal ethanol exposure. Zebrafish embryos were exposed to a range of ethanol concentrations (0.5–5.0%) during defined developmental stages, and examined for morphological phenotypes characteristic of FASD. Embryos were also analyzed by in situ hybridization for changes in expression of defined cell markers for neural cell types that are sonic hedgehog-dependent. We show that transient binge-like ethanol exposures during defined developmental stages, such as early gastrulation and early neurulation, result in a range of phenotypes and changes in expression of Shh-dependent genes. The severity of fetal alcohol syndrome (FAS) morphological phenotypes, such as microphthalmia, depends on the embryonic stage and concentration of alcohol exposure, as does diminution of retinal Pax6a or forebrain and hindbrain GAD1 gene expression. We also show that changes in eye and brain morphology correlate with changes in Pax6a and GAD1 gene expression. Our results therefore show that transient binge-like ethanol exposures in zebrafish embryos produce the stereotypical morphological phenotypes of FAS, with the severity of phenotypes depending on the developmental stage and alcohol concentration of exposure.

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99. An fMRI study of behavioral response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure

Ashley L. Ware¹, M. Alejandra Infante¹, Jessica W. O'Brien¹, Susan F. Tapert², Kenneth Lyons Jones³, Edward P. Riley, Sarah N. Mattson⁴
1Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120, USA.
2Department of Psychiatry, University of California, San Diego, San Diego, CA 92037, USA; VA San Diego Healthcare System, San Diego, CA 92161, USA.
3University of California, San Diego, School of Medicine, Department of Pediatrics, San Diego, CA 92093, USA.
4Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120, USA. Electronic address: sarah.mattson@sdsu.edu.
Abstract

Heavy prenatal alcohol exposure results in a range of deficits, including both volumetric and functional changes in brain regions involved in response inhibition such as the prefrontal cortex and striatum. The current study examined blood oxygen level-dependent (BOLD) response during a stop signal task in adolescents (ages 13–16 y) with histories of heavy prenatal alcohol exposure (AE, n = 21) and controls (CON, n = 21). Task performance was measured using percent correct inhibits during three difficulty conditions: easy, medium, and hard. Group differences in BOLD response relative to baseline motor responding were examined across all inhibition trials and for each difficulty condition separately. The contrast between hard and easy trials was analyzed to determine whether increasing task difficulty affected BOLD response. Groups had similar task performance and demographic characteristics, except for full scale IQ scores (AE < CON). The AE group demonstrated greater BOLD response in frontal, sensorimotor, striatal, and cingulate regions relative to controls, especially as task difficulty increased. When contrasting hard vs. easy inhibition trials, the AE group showed greater medial/superior frontal and cuneus BOLD response than controls. Results were unchanged after demographics and FAS diagnosis were statistically controlled. This was the first fMRI study to utilize a stop signal task, isolating fronto-striatal functioning, to assess response inhibition and the effects task difficulty in adolescents with prenatal alcohol exposure. Results suggest that heavy prenatal alcohol exposure disrupts neural function of this circuitry, resulting in immature cognitive processing and motor-association learning and neural compensation during response inhibition.

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100. Prenatal alcohol exposure reduces magnetic susceptibility contrast and anisotropy in the white matter of mouse brains

Wei Cao1, Wei Li2, Hui Han2, Shonagh K. O'Leary-Moore3, Kathleen K. Sulik3, G. Allan Johnson4, Chunlei Liu5
1Brain Imaging and Analysis Center, Duke University, Durham, NC, United States; Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.
2Brain Imaging and Analysis Center, Duke University, Durham, NC, United States.
3Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC, United States.
4Center for In Vivo Microscopy, Duke University, Durham, NC, United States.
5Brain Imaging and Analysis Center, Duke University, Durham, NC, United States; Department of Radiology, Duke University, Durham, NC, United States. Electronic address: chunlei.liu@duke.edu

Abstract

Prenatal alcohol exposure can result in long-term cognitive and behavioral deficits. Fetal alcohol spectrum disorder (FASD) refers to a range of permanent birth defects caused by prenatal alcohol exposure, and is the most common neurodevelopmental disorder in the US. Studies by autopsy and conventional structural MRI indicate that the midline structures of the brain are particularly vulnerable to prenatal alcohol exposure. Diffusion tensor imaging (DTI) has shown that abnormalities in brain white matter especially the corpus callosum are very common in FASD. Quantitative susceptibility mapping (QSM) is a novel technique that measures tissue's magnetic property. Such magnetic property is affected by tissue microstructure and molecular composition including that of myelin in the white matter. In this work, we studied three major white matter fiber bundles of a mouse model of FASD and compared it to control mice using both QSM and DTI. QSM revealed clear and significant abnormalities in anterior commissure, corpus callosum, and hippocampal commissure, which were likely due to reduced myelination. Our data also suggested that QSM may be even
more sensitive than DTI for examining changes due to prenatal alcohol exposure. Although this is a preclinical study, the technique of QSM is readily translatable to human brain.

101. **Chronic prenatal ethanol exposure alters expression of central and peripheral insulin signaling molecules in adult guinea pig offspring**

Christine C. Dobson¹, Kersh Thevasundaram¹, Daniel L. Mongillo¹, Andrew Winterborn², Alison C. Holloway³, James F. Brien⁴, James N. Reynolds⁵

¹Department of Biomedical and Molecular Sciences, Pharmacology and Toxicology Graduate Program, Queen's University, Kingston, ON, Canada K7L 3N6.
²Office of the University Veterinarian, Queen’s University, Kingston, ON, Canada K7L 3N6.
³Department of Obstetrics and Gynecology, McMaster University, Hamilton, ON, Canada L8S 4K1.
⁴Department of Biomedical and Molecular Sciences, Pharmacology and Toxicology Graduate Program, Queen’s University, Kingston, ON, Canada K7L 3N6; Centre for Neuroscience Studies, Queen’s University, Kingston, ON, Canada K7L 3N6.
⁵Department of Biomedical and Molecular Sciences, Pharmacology and Toxicology Graduate Program, Queen’s University, Kingston, ON, Canada K7L 3N6; Centre for Neuroscience Studies, Queen’s University, Kingston, ON, Canada K7L 3N6. Electronic address: jnr@queensu.ca.

**Abstract**

Maternal ethanol consumption during pregnancy can produce a range of teratogenic outcomes in offspring. The mechanism of ethanol teratogenicity is multi-faceted, but may involve alterations in insulin and insulin-like growth factor (IGF) signaling pathways. These pathways are not only important for metabolism, but are also critically involved in neuronal survival and plasticity, and they can be altered by chronic prenatal ethanol exposure (CPEE). The objective of...
this study was to test the hypothesis that CPEE alters expression of insulin and IGF signaling molecules in the prefrontal cortex and liver of adult guinea pig offspring. Pregnant Dunkin-Hartley-strain guinea pigs received ethanol (4 g/kg maternal body weight/day) or isocaloric-sucrose/pair-feeding (nutritional control) throughout gestation. Fasting blood glucose concentration was measured in male and female offspring at postnatal day 150–200, followed by euthanasia, collection of prefrontal cortex and liver, and RNA extraction. IGF-1, IGF-1 receptor (IGF-1R), IGF-2, IGF-2 receptor (IGF-2R), insulin receptor substrate (IRS)-1, IRS-2, and insulin receptor (INSR) mRNA expression levels were measured in tissues using quantitative real-time PCR. The mean maternal blood ethanol concentration was 281 ± 15 mg/dL at 1 h after the second divided dose of ethanol on GD 57. CPEE resulted in increased liver weight in adult offspring, but produced no difference in fasting blood glucose concentration compared with nutritional control. In the liver, CPEE decreased mRNA expression of IGF-1, IGF-1R, and IGF-2, and increased IRS-2 mRNA expression in male offspring only compared with nutritional control. Female CPEE offspring had decreased INSR hepatic mRNA expression compared with male CPEE offspring. In the prefrontal cortex, IRS-2 mRNA expression was increased in CPEE offspring compared with nutritional control. The data demonstrate that CPEE alters both central and peripheral expression of insulin and IGF signaling molecules at the mRNA level, which may be related to metabolic dysregulation in adult offspring. Furthermore, altered insulin and IGF signaling may be a mechanism of ethanol neurobehavioral teratogenicity.

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102. Pre-administration of G9a/GLP inhibitor during synaptogenesis prevents postnatal ethanol-induced LTP deficits and neurobehavioral abnormalities in adult mice

Shivakumar Subbanna¹, Balapal S. Basavarajappa²
1Division of Analytical Psychopharmacology, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962, USA.
2Division of Analytical Psychopharmacology, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY 10962, USA; New York State Psychiatric Institute, New York, NY 10032, USA; Department of Psychiatry, College of Physicians & Surgeons, Columbia University, New York, NY 10032, USA. Electronic address: Basavaraj@nki.rfmh.org.

Abstract

It has been widely accepted that deficits in neuronal plasticity underlie the cognitive abnormalities observed in fetal alcohol spectrum disorder (FASD). Exposure of rodents to acute ethanol on postnatal day 7 (P7), which is equivalent to the third trimester of fetal development in human, induces long-term potentiation (LTP) and memory deficits in adult animals. However, the molecular mechanisms underlying these deficits are not well understood. Recently, we found that histone H3 dimethylation (H3K9me2), which is mediated by G9a (lysine dimethyltransferase), is responsible for the neurodegeneration caused by ethanol exposure in P7 mice. In addition, pharmacological inhibition of G9a prior to ethanol treatment at P7 normalized H3K9me2 proteins to basal levels and prevented neurodegeneration in neonatal mice. Here, we tested the hypothesis that pre-administration of G9a/GLP inhibitor (Bix-01294, Bix) in conditions in which ethanol induces neurodegeneration would be neuroprotective against P7 ethanol-induced deficits in LTP, memory and social recognition behavior in adult mice. Ethanol treatment at P7 induces deficits in LTP, memory and social recognition in adult mice and these deficits were prevented by Bix pretreatment at P7. Together, these findings provide physiological and behavioral evidence that the long-term harmful consequences on brain function after ethanol exposure with a third trimester equivalent have an epigenetic origin.
Involvement of seven in absentia homolog-1 in ethanol-induced apoptosis in neural crest cells

Haijing Sun¹, Xiaopan Chen¹, Fuqiang Yuan¹, Jie Liu¹, Yingming Zhao², Shao-yu Chen³

¹Department of Cancer Biology and Pharmacology, University of Illinois College of Medicine, Peoria, IL 61605, United States.
²Ben May Department for Cancer Research, The University of Chicago, Chicago, IL 60637, United States.
³Department of Cancer Biology and Pharmacology, University of Illinois College of Medicine, Peoria, IL 61605, United States.
Electronic address: sychen@uic.edu.

Abstract

Ethanol-induced apoptosis in selected cell populations is a major component of pathogenesis underlying ethanol-induced teratogenesis. However, there is a fundamental gap in understanding how ethanol leads to apoptosis in embryos. In this study, we investigate the role of seven in absentia homolog-1 (Siah1) protein, an E3 ubiquitin ligase, in ethanol-induced apoptosis. Using an in vitro model of neural crest cell (NCC), JoMa1.3 cells, we found that exposure to 100 mM ethanol resulted in a significant increase in Siah1 mRNA expression in NCCs, an ethanol-sensitive cell population implicated in Fetal Alcohol Spectrum Disorders (FASD). Treatment with 100 mM ethanol for 24 h also significantly increased the protein expression of Siah1 in JoMa1.3 cells. The nuclear translocation and accumulation of Siah1 was evidenced in the cells exposed to ethanol. In addition, we have found that the inhibition of Siah1 function with siRNA prevents ethanol-induced increase in Siah1 protein expression and nuclear translocation in NCCs. Down-regulation of Siah1 by siRNA also greatly diminished ethanol-induced cell death and caspase-3 activation, indicating that inhibition of Siah1 can attenuate ethanol-induced apoptosis. These results strongly suggest that Siah1 plays an important role in ethanol-induced apoptosis in NCCs.
104. **Objective assessment of ADHD core symptoms in children with heavy prenatal alcohol exposure**

M. Alejandra Infante1, Eileen M. Moore2, Tanya T. Nguyen3, Nikolaos Fourligas4, Sarah N. Mattson2, Edward P. Riley2

1Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120, United States; San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA 92120, United States. Electronic address: minfante@mail.sdsu.edu.

2Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120, United States.

3Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120, United States; San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA 92120, United States.

4Systems Engineering, Quotient ADHD System, Clinical Assessment, Pearson, Westford, MA 01886, United States.

**Abstract**

Attention deficits are often observed in children with prenatal alcohol exposure and attention-deficit/hyperactivity disorder (ADHD) is commonly diagnosed in this population. This study used an objective assessment tool to examine differences between alcohol-exposed and non-exposed children on core symptoms of ADHD: inattention, impulsivity, and hyperactivity. Two groups of individuals, aged 7–14 years, participated in the study: alcohol-exposed children (AE, n = 43), and non-exposed children (CON, n = 54). Subjects were evaluated with the Quotient ADHD System, which provides objective data on ADHD core symptoms by combining an infrared motion tracking system and a computerized continuous performance task. Twelve separate ANCOVAs controlling for the effects of age and sex, were conducted on attention and motion variables. Results revealed that in comparison to the CON group, the AE group was significantly (p's < .05) less accurate, made an increased number of omission errors, had longer response latencies, and increased variability in response time. Moreover, the AE group spent less time staying still, and made an increased number of head movements, which traveled a larger distance, covered a greater area, and demonstrated a less complex movement pattern. No significant group differences were observed on the number of commission errors and temporal scaling. Our findings provide further support for the notion that inattention is a core deficit in children prenatally exposed to alcohol. Results from this study are also consistent with parent reports of increased hyperactivity. The Quotient ADHD System may be a useful objective measure of ADHD symptomatology in children with FASD.


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Abstract

Astaxanthin is a strong antioxidant with the ability of reducing the markers of inflammation. To explore the protective effect of astaxanthin on maternal ethanol induced embryonic deficiency, and to investigate the underlying mechanisms, we detected the morphology, expression of neural marker genes, oxidative stress indexes, and inflammatory factors in mice model of fetal alcohol spectrum disorder with or without astaxanthin pretreatment. Our results showed that astaxanthin blocked maternal ethanol induced retardation of embryonic growth, and the down-regulation of neural marker genes, Otx1 and Sox2. Moreover, astaxanthin also reversed the increases of malondialdehyde (MDA), hydrogen peroxide (H2O2), and the decrease of glutathione peroxidase (GPx) in fetal alcohol spectrum disorder. In addition, maternal ethanol induced up-regulation of toll-like receptor 4 (TLR4), and the down-streaming myeloid differentiation factor 88 (MyD88), NF-κB, TNF-α, and IL-1β in embryos, and this was inhibited by astaxanthin pretreatment. These results demonstrated a protective effect of astaxanthin on fetal alcohol spectrum disorder, and suggested that oxidative stress and TLR4 signaling associated inflammatory reaction are involved in this process.


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106. Effects of moderate prenatal ethanol exposure and age on social behavior, spatial response perseveration errors and motor behavior

Derek A. Hamilton1, Daniel Barto2, Carlos I. Rodriguez2, Christy M. Magcalas2, Brandi C. Fink3, James P. Rice2, Clark W. Bird2, Suzy Davies4, Daniel D. Savage5
1Department of Psychology, University of New Mexico, Albuquerque, NM 87131, United States; Department of Neurosciences, University of New Mexico, Albuquerque, NM, United States. Electronic address: dahamilt@unm.edu.
2Department of Psychology, University of New Mexico, Albuquerque, NM 87131, United States.
3Department of Psychology, University of New Mexico, Albuquerque, NM 87131, United States; Department of Psychiatry and Behavioral Sciences, University of New Mexico, Albuquerque, NM, United States.
4Department of Neurosciences, University of New Mexico, Albuquerque, NM, United States.
5Department of Psychology, University of New Mexico, Albuquerque, NM 87131, United States; Department of Neurosciences, University of New Mexico, Albuquerque, NM, United States.

Abstract

Persistent deficits in social behavior are among the major negative consequences associated with exposure to ethanol during prenatal development. Prior work from our laboratory has linked deficits in social behavior following moderate prenatal alcohol exposure (PAE) in the rat to functional alterations in the ventrolateral frontal cortex [21]. In addition to social behaviors, the regions comprising the ventrolateral frontal cortex are critical for diverse processes ranging from orofacial motor movements to flexible alteration of behavior in the face of changing consequences. The broader behavioral implications of altered ventrolateral frontal cortex function following moderate PAE have, however, not been examined. In the present study we evaluated the consequences of moderate PAE on social behavior, tongue protrusion, and flexibility in a variant of the Morris water task that required modification of a well-established spatial response. PAE rats displayed deficits in tongue protrusion, reduced flexibility in the spatial domain, increased wrestling, and decreased investigation, indicating that several behaviors associated with ventrolateral frontal cortex function are impaired following
moderate PAE. A linear discriminant analysis revealed that measures of wrestling and tongue protrusion provided the best discrimination of PAE rats from saccharin-exposed control rats. We also evaluated all behaviors in young adult (4–5 months) or older (10–11 months) rats to address the persistence of behavioral deficits in adulthood and possible interactions between early ethanol exposure and advancing age. Behavioral deficits in each domain persisted well into adulthood (10–11 months), however, there was no evidence that aging enhances the effects of moderate PAE within the age ranges that were studied.

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107. **Melanin-concentrating hormone expression in the rat hypothalamus is not affected in an experiment of prenatal alcohol exposure**

Sandrine Chometton¹, Gabrielle Franchi-Bernard¹, Christophe Houdayer¹, Amandine Mariot¹, Fabrice Poncet¹, Dominique Fellmann¹, Pierre-Yves Risold²

1EA3922, SFR-FED 4234, UFR Sciences Méridicales et Pharmaceutiques, Université de Franche-Comté, Besançon, France.
2EA3922, SFR-FED 4234, UFR Sciences Médicales et Pharmaceutiques, Université de Franche-Comté, Besançon, France.

Electronic address: pierre-yves.risold@univ-fcomte.fr

**Abstract**

Alcohol consumption during pregnancy can cause a “fetal alcoholic syndrome” (FAS) in the progeny. This syndrome is characterized by important brain defects often associated to a decreased expression of the morphogenic protein sonic hedgehog (Shh). The goal of this study was to verify if a FAS could modify the differentiation of hypothalamic neurons producing MCH. Indeed, the expression of this peptide and neurons producing it are dependent of a Shh controlled genetic cascade in the embryo. To address this question, female rats received a 15% ethanol solution to drink during pregnancy and lactation. Higher abortion rate and smaller pups at birth confirmed that descendants were affected by this experimental condition. MCH expression was analyzed by RT-qPCR and immunohistochemistry in embryos taken at E11 and E13, or in pups and young adults born from control and alcoholic mothers. MCH expression level, number of MCH neurons or ratio of MCH sub-populations were not modified by our experimental conditions. However, Shh expression was significantly lower at E11 and we also observed that hindbrain serotonergic neurons were affected as reported in the literature. These findings as well as other data from the literature suggest that protective mechanisms are involved to maintain peptide expressions and differentiation of some specific neuron populations in the ventral diencephalon in surviving embryos exposed to ethanol during pregnancy.

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108. **Training nurses and nursing students about prevention, diagnoses, and treatment of fetal alcohol spectrum disorders**

Roger J. Zoorob¹, Kristy M. Durkin², Sandra J. Gonzalez³, Susie Adams⁴

1Department of Family and Community Medicine, Meharry Medical College, Nashville, TN, USA.
2Department of Social Work, University of West Florida, Pensacola, FL, USA; University of Alabama, Tuscaloosa, USA.
3Department of Family and Community Medicine, Meharry Medical College, Nashville, 37208-3599 TN, USA. Electronic address: sgonzalez@mmc.edu.
Alcohol consumption during pregnancy can result in birth defects known as fetal alcohol spectrum disorders. This study examined whether 1-h training sessions on alcohol screening, brief intervention, diagnoses, and treatment of fetal alcohol spectrum disorders could increase practical knowledge and confidence in nurses and student nurses. Data were collected from 420 nurses (n = 95) and student nurses (n = 325) in the southeastern United States, from 2009 to 2011. Pre- and post-test data were analyzed using chi-square tests and t-tests. The post-training response rate was 84%. Nurses were more likely to know what constitutes binge drinking, facial abnormalities associated with fetal alcohol syndrome, and criteria for diagnosis. Nurses were also more confident in educating about effects of prenatal alcohol use, identifying fetal alcohol spectrum disorders and utilizing resources. Training materials may need to be improved and/or longer training programs developed for student nurses, and nursing school programs should place more emphasis on educating and preparing student nurses regarding this topic area.


109. Prenatal ethanol exposure differentially affects hippocampal neurogenesis in the adolescent and aged brain


1Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada. Electronic address: jgil@uvic.ca; 2Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada. Electronic address: okayandrea@gmail.com; 3Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada. Electronic address: anna.r.patten@gmail.com; 4Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada. Electronic address: slf@uvic.ca; 5Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada. Electronic address: aef@uvic.ca; 6Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada. Electronic address: timothy.ratzlaff@hotmail.com; 7Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada. Electronic address: helferj@gmail.com; 8Division of Medical Sciences, Island Medical Program, University of Victoria, Victoria, British Columbia, Canada; The Brain Research Centre and Program in Neuroscience, University of British Columbia, Vancouver, British Columbia, Canada; The Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, British Columbia, Canada. Electronic address: brain64@uvic.ca.

Abstract

Exposure to ethanol in utero is associated with a myriad of sequelae for the offspring. Some of these effects are morphological in nature and noticeable from birth, while others involve more subtle changes to the brain that only become apparent later in life when the individuals are challenged cognitively. One brain structure that shows both functional and structural deficits following prenatal ethanol exposure is the hippocampus. The hippocampus is composed of two interlocking gyri, the cornu ammonis (CA) and the dentate gyrus (DG), and they are differentially affected by prenatal...
ethanol exposure. The CA shows a more consistent loss in neuronal numbers, with different ethanol exposure paradigms, than the DG, which in contrast shows more pronounced and consistent deficits in synaptic plasticity.

In this study we show that significant deficits in adult hippocampal neurogenesis are apparent in aged animals following prenatal ethanol exposure. Deficits in hippocampal neurogenesis were not apparent in younger animals. Surprisingly, even when ethanol exposure occurred in conjunction with maternal stress, deficits in neurogenesis did not occur at this young age, suggesting that the capacity for neurogenesis is highly conserved early in life. These findings are unique in that they demonstrate for the first time that deficits in neurogenesis associated with prenatal ethanol consumption appear later in life.

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110. Early life ethanol exposure causes long-lasting disturbances in rat mesenchymal stem cells via epigenetic modifications

Leu YW1, Chu PY2, Chen CM3, Yeh KT4, Liu YM1, Lee YH1, Kuo ST1, Hsiao SH5
1Department of Life Science and Institute of Molecular Biology, National Chung Cheng University, Chia-Yi 621, Taiwan.
2Department of Pathology, Show Chwan Memorial Hospital, Changhua 500, Taiwan.
3Division of Neurosurgery, Changhua Christian Hospital, Changhua 500, Taiwan.
4Department of Pathology, Changhua Christian Hospital, Changhua 500, Taiwan.
5Department of Life Science and Institute of Molecular Biology, National Chung Cheng University, Chia-Yi 621, Taiwan. Electronic address: bioshh@ccu.edu.tw.

Abstract

Fetal alcohol syndrome (FAS) is a birth defect due to maternal alcohol consumption during pregnancy. Because mesenchymal stem cells (MSCs) are the main somatic stem cells in adults and may contribute to tissue homeostasis and repair in adulthood, we investigated whether early life ethanol exposure affects MSCs and contributes to the propensity for disease onset in later life. Using a rodent model of FAS, we found that ethanol exposure (5.25g/kg/day) from postnatal days 4 to 9 in rat pups (mimic of human third trimester) caused long-term anomalies in bone marrow-derived MSCs. MSCs isolated from ethanol-exposed animals were prone to neural induction but resistant to osteogenic and adipogenic inductions compared to their age-matched controls. The altered differentiation may contribute to the severe trabecular bone loss seen in ethanol-exposed animals at 3months of age as well as overt growth retardation. Expression of alkaline phosphatase, osteocalcin, aP2, and PPARγ were substantially inhibited, but BDNF was up-regulated in MSCs isolated from ethanol-exposed 3month-old animals. Several signaling pathways were distorted in ethanol-exposed MSCs via altered trimethylation at histone 3 lysine 27. These results demonstrate that early life ethanol exposure can have long-term impacts in rat MSCs by both genetic and epigenetic mechanisms.

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111. Preconception care: caffeine, smoking, alcohol, drugs and other environmental chemical/radiation exposure

Lassi ZS¹, Imam AM¹, Dean SV¹, Bhutta ZA¹
1Division of Women and Child Health, Aga Khan University Karachi, Pakistan
Corresponding author.
Zohra SLassi:ude.uka@issal.arhoz; Ayesha M Imam:moc.liamg@90mamiahseya;Solni V
Dean:moc.liamg@naed.inhos;Zulfiqar A Bhutta:ifluzude.uka@attuhb.raq

Abstract

INTRODUCTION
As providing health education, optimizing nutrition, and managing risk factors can be effective for ensuring a healthy outcome for women and her yet un-conceived baby, external influences play a significant role as well. Alcohol, smoking, caffeine use and other similar lifestyle factors, have now become an integral part of the daily life of most men and women, who use/misuse one or more of these harmful substances regularly despite knowledge of their detrimental effects. The adverse health outcomes of these voluntary and involuntary exposures are of even greater concern in women of child bearing age where the exposure has the potential of inflicting harm to two generations. This paper is examining the available literature for the possible effects of caffeine consumption, smoking, alcohol or exposure to chemicals may have on the maternal, newborn and child health (MNCH).

METHODS
A systematic review and meta-analysis of the evidence was conducted to ascertain the possible impact of preconception usage of caffeine, tobacco, alcohol and other illicit drugs; and exposure to environmental chemicals and radiant on MNCH outcomes. A comprehensive strategy was used to search electronic reference libraries, and both observational and clinical controlled trials were included. Cross-referencing and a separate search strategy for each preconception risk and intervention ensured wider study capture.

RESULTS
Heavy maternal preconception caffeine intake of >300mg/d significantly increase the risk of a subsequent fetal loss by 31% (95% CI: 8-58%). On the other hand, preconception alcohol consumption leads to non-significant 30% increase in spontaneous abortion (RR 1.30; 95% CI: 0.85-1.97). Preconception counselling can lead to a significant decrease in the consumption of alcohol during the first trimester (OR 1.79; 95% CI: 1.08-2.97). Periconception smoking, on the other hand, was found to be associated with an almost 3 times increased risk of congenital heart defects (OR 2.80; 95% CI 1.76-4.47). While the review found limited evidence of preconception environmental exposure on maternal, newborn and child health outcomes, occupational exposure in female radiation workers before conception showed an increased impact in risk of early miscarriages.

CONCLUSION
Identification of substance abuse and environmental history during preconception period provides an opportunity to assist women in reducing major health risks and identify key determinants of healthy pregnancy. Studies have shown that the aversion and prevention of exposure feasibility can play an important role in improving the health of women and their families, however, the results should be interpreted with great caution as there were few studies in each section. Therefore, there is a need for more rigorous studies to test the hypotheses.

Read Full Article,

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4196566/

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112. Fetal alcohol spectrum disorders: Notifications to the Western Australian Register of Developmental Anomalies

Mutch RC¹, Watkins R², Bower C³
Abstract

AIM
There is increasing attention on fetal alcohol spectrum disorders (FASD) in Australia, but there are limited data on their birth prevalence. Our aim was to report on the birth prevalence of FASD in Western Australia.

METHODS
Data on notified cases of FASD born in Western Australia 1980-2010 were identified from the Western Australian Register of Developmental Anomalies. Tabulated denominator data were obtained from the Midwives Notification System. Prevalence rates per 1000 births were calculated by demographic variables. Prevalence ratios (PRs) and 95% confidence intervals (CIs) of Aboriginal compared with non-Aboriginal prevalence rates were calculated. PRs were also calculated to compare rates for births 2000-2010 with 1980-1989.

RESULTS
Two hundred ten cases of FASDs were identified: a birth prevalence of 0.26/1000 births (95% CI 0.23-0.30). The majority of cases reported were Aboriginal (89.5%), a rate of 4.08/1000, compared with 0.03/1000 in notified non-Aboriginal cases, giving a PR of 139 (95% CI 89-215). The prevalence of FASD in 2000-2010 was over twice that in 1980-1989 for both Aboriginal (PR 2.37; CI 1.60-3.51) and non-Aboriginal (PR 2.13; CI 0.68-6.69) children.

CONCLUSIONS
There has been a twofold increase in FASD notifications in Western Australia over the last 30 years. Population surveillance data such as these are valuable in advocating for and monitoring the effectiveness of preventive activities and diagnostic and management services.

Read Full Article,
http://www.unboundmedicine.com/medline/citation/25412883/Fetal_alcohol_spectrum_disorders:_Notifications_to_the_Western_Australian_Register_of_Developmental_Anomalies.

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113. Species Extrapolation of Life-Stage Physiologically-Based Pharmacokinetic (PBPK) Models to Investigate the Developmental Toxicology of Ethanol using In vitro to In vivo (IVIVE) Methods

Martin SA1, McLanahan ED2, Bushnell PJ2, Hunter ES2, El-Masri H2
1National Health and Environmental Effects Research Laboratory, National Center for Environmental Assessment, United States Environmental Protection Agency sam506@gmail.com.
2National Health and Environmental Effects Research Laboratory, National Center for Environmental Assessment, United States Environmental Protection Agency.

Abstract
To provide useful alternatives to in vivo animal studies, in vitro assays for dose-response assessments of xenobiotic chemicals must use concentrations in media and target tissues that are within biologically-plausible limits. Determining these concentrations is a complex matter, which can be facilitated by applying physiologically-based pharmacokinetic (PBPK) models in an in vitro to in vivo extrapolation (IVIVE) paradigm. We used ethanol (EtOH), a ubiquitous chemical with defined metrics for in vivo and in vitro embryotoxicity, as a model chemical to evaluate this paradigm. A published series of life-stage PBPK models for rats was extended to mice, yielding simulations that adequately predicted in vivo blood EtOH concentrations (BECs) from oral, intraperitoneal, and intravenous routes in non-pregnant and pregnant adult mice. The models were then extrapolated to non-pregnant and pregnant humans, replicating BEC data within a factor of two. The rodent models were then used to conduct IVIVEs for rodent and whole-embryo culture embryotoxicity data.
(neural tube closure defects, morphological changes). A second IVIVE was conducted for exposure scenarios in pregnant women during critical windows of susceptibility for developmental toxicity, such as the first six-to-eight weeks (pre-recognition period) or mid-to-late pregnancy period, when EtOH consumption is associated with fetal alcohol spectrum disorders. Incorporation of data from human embryonic stem cell studies led to a model-supported linkage of in vitro concentrations with plausible exposure ranges for pregnant women. This effort demonstrates benefits and challenges associated with use of multi-species PBPK models to estimate in vivo tissue concentrations associated with in vitro embryotoxicity studies.

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**114. Fetal Alcohol Exposure Alters Proopiomelanocortin Gene Expression and Hypothalamic-Pituitary-Adrenal Axis Function via Increasing MeCP2 Expression in the Hypothalamus**

Gangisetty O, Bekdash R, Maglakelidze G, Sarkar DK
Endocrine Program, Department of Animal Sciences, Rutgers University, New Brunswick, New Jersey, United States of America

**Abstract**

Proopiomelanocortin (POMC) is a precursor gene of the neuropeptide β-endorphin in the hypothalamus and is known to regulate various physiological functions including stress response. Several recent reports showed that fetal alcohol exposure programs the hypothalamus to produce lower levels of POMC gene transcripts and to elevate the hypothalamic-pituitary-adrenal (HPA) axis response to stressful stimuli. We investigated the role of methyl CpG binding protein (MeCP2) in the effects of prenatal ethanol on POMC gene expression and hypothalamic-pituitary-adrenal (HPA) axis function. Pregnant Sprague Dawley rats were fed between GD 7 and 21 with a liquid diet containing 6.7% alcohol, pair-fed with isocaloric liquid diet, or fed ad libitum with rat chow, and their male offsprings were used at 60 days after birth in this study. Fetal alcohol exposure reduced the level of POMC mRNA, but increased the level of DNA methylation of this gene in the arcuate nucleus (ARC) of the hypothalamus where the POMC neuronal cell bodies are located. Fetal alcohol exposed rats showed a significant increase in MeCP2 protein levels in POMC cells, MeCP2 gene transcript levels as well as increased MeCP2 protein binding on the POMC promoter in the arcuate nucleus. Lentiviral delivery of MeCP2 shRNA into the third ventricle efficiently reduced MeCP2 expression and prevented the effect of prenatal ethanol on POMC gene expression in the arcuate nucleus. MeCP2-shRNA treatment also normalized the prenatal ethanol-induced increase in corticotropin releasing hormone (CRH) gene expression in the hypothalamus and elevated plasma adrenocorticotrophic hormone (ACTH) and corticosterone hormone responses to lipopolysaccharide (LPS) challenge. These results suggest that fetal alcohol programming of POMC gene may involve recruitment of MeCP2 on to the methylated promoter of the POMC gene to suppress POMC transcript levels and contribute to HPA axis dysregulation.

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**115. Nutrition Implications for Fetal Alcohol Spectrum Disorder**

Young JK1, Giesbrecht HE1, Eskin MN1, Aliani M1, Suh M2
1Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, Manitoba, Canada.  
2Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, Manitoba, Canada 
miyoung.suh@umanitoba.ca.
Abstract
Prenatal alcohol exposure produces a multitude of detrimental alcohol-induced defects in children collectively known as fetal alcohol spectrum disorder (FASD). Children with FASD often exhibit delayed or abnormal mental, neural, and physical growth. Socioeconomic status, race, genetics, parity, gravidity, age, smoking, and alcohol consumption patterns are all factors that may influence FASD. Optimal maternal nutritional status is of utmost importance for proper fetal development, yet is often altered with alcohol consumption. It is critical to determine a means to resolve and reduce the physical and neurological malformations that develop in the fetus as a result of prenatal alcohol exposure. Because there is a lack of information on the role of nutrients and prenatal nutrition interventions for FASD, the focus of this review is to provide an overview of nutrients (vitamin A, docosahexaenoic acid, folic acid, zinc, choline, vitamin E, and selenium) that may prevent or alleviate the development of FASD. Results from various nutrient supplementation studies in animal models and FASD-related research conducted in humans provide insight into the plausibility of prenatal nutrition interventions for FASD. Further research is necessary to confirm positive results, to determine optimal amounts of nutrients needed in supplementation, and to investigate the collective effects of multiple-nutrient supplementation.


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116. Developmental Ethanol Exposure Leads to Dysregulation of Lipid Metabolism and Oxidative Stress in Drosophila
Logan-Garbisch T1, Bortolazzo A2, Luu P3, Ford A3, Do D3, Khodabakhshi P3, French RL4
1San José State University; Stanford University;
2San José State University; University of Wisconsin-Madison;
3San José State University.
4San José State University rachael.french@sjsu.edu.

Abstract
Ethanol exposure during development causes an array of developmental abnormalities, both physiological and behavioral. In mammals, these abnormalities are collectively known as Fetal Alcohol Effects (FAE) or Fetal Alcohol Spectrum Disorder (FASD). We have established a Drosophila melanogaster model of FASD, and have previously shown that developmental ethanol exposure in flies leads to reduced expression of insulin like peptides (dILPs) and their receptor. In this work, we link that observation to dysregulation of fatty acid metabolism and lipid accumulation. Further, we show that developmental ethanol exposure in Drosophila causes oxidative stress, that this stress is a primary cause of the developmental lethality and delay associated with ethanol exposure, and, finally, that one of the mechanisms by which ethanol increases oxidative stress is through abnormal fatty acid metabolism. These data suggest a previously uncharacterized mechanism by which ethanol causes the symptoms associated with FASD.


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117. The Making of a Medical Disorder: Tracing the Emergence of Fetal Alcohol Spectrum Disorder in Alberta
Shankar I
Sociology, Mount Royal University , Calgary, Alberta , Canada
Abstract
This article examines the processes through which health disorders become accepted as a public health concern, and the defining role played by social actors responsible for bringing such disorders to public attention. Such analysis provides us with a particular history of health disorders and the implications of this early history in the current conceptualization of such disorders within contemporary health programs and policies. This article traces the emergence and acceptance of fetal alcohol spectrum disorder (FASD) as a public health concern in Alberta and the ongoing tensions resulting from this early history. Specifically, the author examines the integral role of social workers and various government officials in getting FASD recognized as a health concern. This Alberta case study demonstrates the importance of investigating the sociopolitical context in which health disorders emerge and become accepted.

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http://www.ncbi.nlm.nih.gov/pubmed/?term=117.%09The+Making+of+a+Medical+Disorder%3A+Tracing+the+Emergence+of+Fetal+Alcohol+Spectrum+Disorder+in+Alberta

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118. Oxidative DNA damage in the in utero initiation of postnatal neurodevelopmental deficits by normal fetal and ethanol-enhanced oxidative stress in oxoguanine glycosylase 1 (ogg1) knockout mice
Miller-Pinsler L1, Pinto DJ1, Wells PG2
1Department of Pharmacology and Toxicology, Faculty of Medicine.
2Department of Pharmacology and Toxicology, Faculty of Medicine; Division of Biomolecular Sciences, Faculty of Pharmacy, University of Toronto, Toronto, ON M5S 3M2, Canada. Electronic address: pg.wells@utoronto.ca.

Abstract
Studies in mice with deficient antioxidative enzymes have shown that physiological levels of reactive oxygen species (ROS) can adversely affect the developing embryo and fetus. Herein, DNA repair-deficient progeny of oxoguanine glycosylase 1 (ogg1) knockout mice lacking repair of the oxidative DNA lesion 8-oxo-2'-deoxyguanosine (8-oxodGuo) exhibited enhanced postnatal neurodevelopmental deficits, revealing the pathogenic potential of 8-oxodGuo initiated by physiological ROS production in fetal brain, and providing the first evidence of a pathological phenotype for ogg1 knockout mice. Moreover, when exposed in utero to ethanol (EtOH), ogg1 knockout progeny exhibited higher levels of 8-oxodGuo in fetal brain and more severe postnatal neurodevelopmental deficits than wild-type littermates, both of which were blocked by pretreatment with the free radical trapping agent phenylbutynitrone. These results suggest ROS-initiated DNA oxidation, as distinct from altered signal transduction, contributes to neurodevelopmental deficits caused by in utero EtOH exposure, and fetal DNA repair is a determinant of risk.

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http://www.ncbi.nlm.nih.gov/pubmed/?term=Oxidative+DNA+damage+in+the+in+utero+initiation+of+postnatal+neurodevelopmental+deficits+by+normal+fetal+and+ethanol-enhanced+oxidative+stress+in+oxoguanine+glycosylase+1+(ogg1)+knockout+mice

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119. Effects of Acute Prenatal Exposure to Ethanol on microRNA Expression are Ameliorated by Social Enrichment
Ignacio C1, Mooney SM2, Middleton FA1
1Department of Neuroscience and Physiology, State University of New York Upstate Medical University, Syracuse, NY, USA; Department of Biochemistry and Molecular Biology, State University of New York Upstate Medical University, Syracuse, NY, USA; Developmental Exposure Alcohol Research Center (DEARC), Binghamton University, Binghamton, NY, USA.

www.nofas-uk.org
Abstract

Fetal alcohol spectrum disorders (FASDs) are associated with abnormal social behavior. These behavioral changes may resemble those seen in autism. Rats acutely exposed to ethanol on gestational day 12 show decreased social motivation at postnatal day 42. We previously showed that housing these ethanol-exposed rats with non-exposed controls normalized this deficit. The amygdala is critical for social behavior and regulates it, in part, through connections with the basal ganglia, particularly the ventral striatum. MicroRNAs (miRNAs) are short, hairpin-derived RNAs that repress mRNA expression. Many brain disorders, including FASD, show dysregulation of miRNAs. In this study, we tested if miRNA and mRNA networks are altered in the amygdala and ventral striatum as a consequence of prenatal ethanol exposure and show any evidence of reversal as a result of social enrichment. RNA samples from two different brain regions in 72 male and female adolescent rats were analyzed by RNA-Seq and microarray analysis. Several miRNAs showed significant changes due to prenatal ethanol exposure and/or social enrichment in one or both brain regions. The top predicted gene targets of these miRNAs were mapped and subjected to pathway enrichment analysis. Several miRNA changes caused by ethanol were reversed by social enrichment, including mir-204, mir-299a, miR-384-5p, miR-222-3p, miR-301b-3p, and mir-6239. Moreover, enriched gene networks incorporating the targets of these miRNAs also showed reversal. We also extended our previously published mRNA expression analysis by directly examining all annotated brain-related canonical pathways. The additional pathways that were most strongly affected at the mRNA level included p53, CREB, glutamate, and GABA signaling. Together, our data suggest a number of novel epigenetic mechanisms for social enrichment to reverse the effects of ethanol exposure through widespread influences on gene expression.

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http://www.ncbi.nlm.nih.gov/pubmed/?term=119.%09Effects+of+Acute+Prenatal+Exposure+to+Ethanol+on+microRNA+Expression+are+Ameliorated+by+Social+Enrichment

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120. Epidemiology of drinking, alcohol use disorders, and related problems in US ethnic minority groups

Caetano R1, Vaeth PA2, Chartier KG2, Mills BA2
1School of Public Health, Dallas Regional Campus, University of Texas Health Science Center at Houston, Dallas, TX, USA.
Electronic address: Raul.Caetano@utsouthwestern.edu.
2School of Public Health, Dallas Regional Campus, University of Texas Health Science Center at Houston, Dallas, TX, USA.

Abstract

This chapter reviews selected epidemiologic studies on drinking and associated problems among US ethnic minorities. Ethnic minorities and the White majority group exhibit important differences in alcohol use and related problems, including alcohol use disorders. Studies show a higher rate of binge drinking, drinking above guidelines, alcohol abuse, and dependence for major ethnic and racial groups, notably, Blacks, Hispanics, and American Indians/Alaskan Natives. Other problems with a higher prevalence in certain minority groups are, for example, cancer (Blacks), cirrhosis (Hispanics), fetal alcohol syndrome (Blacks and American Indians/Alaskan Natives), drinking and driving (Hispanics, American Indians/Alaskan Natives). There are also considerable differences in rates of drinking and problems within certain ethnic groups such as Hispanics, Asian Americans, and American Indians/Alaskan Natives. For instance, among Hispanics, Puerto Ricans and Mexican Americans drink more and have higher rates of disorders such as alcohol abuse and dependence than Cuban Americans. Disparities also affect the trajectory of heavy drinking and the course of alcohol dependence among minorities. Theoretical accounts of these disparities generally attribute them to the historic experience of discrimination and to minority socioeconomic disadvantages at individual and environmental levels.

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http://www.ncbi.nlm.nih.gov/pubmed/?term=120.%09Epidemiology+of+drinking%2C+alcohol+use+disorders%2C+and+related+problems+in+US+ethnic+minority+groups

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**Abstract**

**Background:**
Effective interventions are needed to reduce neurobehavioral impairments in children due to maternal alcohol use during pregnancy. Currently, health-counseling interventions have shown inconsistent results to reduce prenatal alcohol use. Thus, more research using health counseling is needed to gain more knowledge about the effectiveness of this type of intervention on reducing alcohol use during pregnancy. An alternative and promising strategy is computer tailoring. However, to date, no study has shown the effectiveness of this intervention mode.

**Objective:**
The aim was to test the effectiveness of health counseling and computer tailoring on stopping and reducing maternal alcohol use during pregnancy in a Dutch sample of pregnant women using alcohol.

**Methods:**
A total of 60 Dutch midwifery practices, randomly assigned to 1 of 3 conditions, recruited 135 health counseling, 116 computer tailoring, and 142 usual care respondents from February to September 2011. Health-counseling respondents received counseling from their midwife according to a health-counseling protocol, which consisted of 7 steps addressed in 3 feedback sessions. Computer-tailoring respondents received usual care from their midwife and 3 computer-tailored feedback letters via the Internet. Usual care respondents received routine alcohol care from their midwife. After 3 and 6 months, we assessed the effect of the interventions on alcohol use.

**Results:**
Multilevel multiple logistic regression analyses showed that computer-tailoring respondents stopped using alcohol more often compared to usual care respondents 6 months after baseline (53/68, 78% vs 51/93, 55%; P=.04). Multilevel multiple linear regression analyses showed that computer-tailoring respondents (mean 0.35, SD 0.31 units per week) with average (P=.007) or lower (P<.001) alcohol use before pregnancy or with average (P=.03) or lower (P=.002) social support more strongly reduced their alcohol use 6 months after baseline compared to usual care respondents (mean 0.48, SD 0.54 units per week). Six months after baseline, 72% (62/86) of the health-counseling respondents had stopped using alcohol. This 17% difference with the usual care group was not significant.

**Conclusions:**
This is the first study showing that computer tailoring can be effective to reduce alcohol use during pregnancy; health counseling did not effectively reduce alcohol use. Future researchers developing a health-counseling intervention to reduce alcohol use during pregnancy are recommended to invest more in recruitment of pregnant women and implementation by health care providers. Because pregnant women are reluctant to disclose their alcohol use to health professionals and computer tailoring preserves a person’s anonymity, this effective computer-tailoring intervention is recommended as an attractive intervention for pregnant women using alcohol.

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http://www.jmir.org/2014/12/e274

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122. Transgenerational effects of binge drinking in a primate model: implications for human health

VandeVoort CA¹, Grimsrud KN², Midic U³, Mtango N⁴, Latham KE⁵
¹California National Primate Research Center, University of California, Davis, California; Department of Obstetrics and Gynecology, University of California, Davis, California. Electronic address: cavandevoort@ucdavis.edu.
²California National Primate Research Center, University of California, Davis, California.
³The Fels Institute for Cancer Research & Molecular Biology, Temple University School of Medicine, Philadelphia, Pennsylvania; Department of Animal Science, Michigan State University, East Lansing, Michigan.
⁴The Fels Institute for Cancer Research & Molecular Biology, Temple University School of Medicine, Philadelphia, Pennsylvania.
⁵The Fels Institute for Cancer Research & Molecular Biology, Temple University School of Medicine, Philadelphia, Pennsylvania; Department of Animal Science, Michigan State University, East Lansing, Michigan; Department of Biochemistry, Temple University School of Medicine, Philadelphia, Pennsylvania.

Abstract

OBJECTIVE:
To determine if binge ethanol consumption before ovulation affects oocyte quality, gene expression, and subsequent embryo development.

DESIGN:
Binge levels of ethanol were given twice weekly for 6 months, followed by a standard in vitro fertilization cycle and subsequent natural mating.

INTERVENTION(S):
Binge levels of ethanol, given twice weekly for 6 months before a standard in vitro fertilization cycle with or without embryo culture. With in vivo development, ethanol treatment continued until pregnancy was identified.

MAIN OUTCOME MEASURE(S):
Oocyte and cumulus/granulosa cell gene expression, embryo development to blastocyst, and pregnancy rate.

RESULT(S):
Embryo development in vitro was reduced; changes were found in oocyte and cumulus cell gene expression; and spontaneous abortion during very early gestation increased.

CONCLUSION(S):
This study provides evidence that binge drinking can affect the developmental potential of oocytes even after alcohol consumption has ceased.

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123. CB1-Receptor Knockout Neonatal Mice are Protected Against Ethanol-induced Impairments of DNMT1, DNMT3A and DNA Methylation

Nagre NN¹, Subbanna S, Shivakumar M, Psychoyos D, Basavarajappa BS

www.nofas-uk.org
Abstract

The significant consequences of ethanol use during pregnancy are neurobehavioral abnormalities involving hippocampal and neocortex malfunctions that cause learning and memory deficits collectively named fetal alcohol spectrum disorder (FASD). However, the molecular mechanisms underlying these abnormalities are still poorly understood and therefore warrant systematic research. Here, we document novel epigenetic abnormalities in the mouse model of FASD. Ethanol treatment of P7 mice, which induces activation of caspase-3, impaired DNA methylation through reduced DNA methyltransferases (DNMT1 and DNMT3A) levels. Inhibition of caspase-3 activity, before ethanol treatment, rescued DNMT1, DNMT3A proteins as well as DNA methylation levels. Blockade of histone methyltransferase (G9a) activity or cannabinoid receptor type-1 (CB1R), prior to ethanol treatment, which respectively inhibits or prevents activation of caspase-3, rescued the DNMT1 and DNMT3A proteins and DNA methylation. No reduction of DNMT1 and DNMT3A proteins and DNA methylation was found in P7 CB1R null mice, which exhibit no ethanol-induced activation of caspase-3. Together, these data demonstrate that ethanol-induced activation of caspase-3 impairs DNA methylation through DNMT1 and DNMT3A in the neonatal mouse brain, and such impairments are absent in CB1R null mice. Epigenetic events mediated by DNA methylation may be one of the essential mechanisms of ethanol teratogenesis. This article is protected by copyright. All rights reserved.

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125. **Autophagy and ethanol neurotoxicity**
Luo J^1^  
^1^a Department of Pharmacology and Nutritional Sciences; University of Kentucky College of Medicine; Lexington, KY USA.

**Abstract**
Excessive ethanol exposure is detrimental to the brain. The developing brain is particularly vulnerable to ethanol such that prenatal ethanol exposure causes fetal alcohol spectrum disorders (FASD). Neuronal loss in the brain is the most devastating consequence and is associated with mental retardation and other behavioral deficits observed in FASD. Since alcohol consumption during pregnancy has not declined, it is imperative to elucidate the underlying mechanisms and develop effective therapeutic strategies. One cellular mechanism that acts as a protective response for the central nervous system (CNS) is autophagy. Autophagy regulates lysosomal turnover of organelles and proteins within cells, and is involved in cell differentiation, survival, metabolism, and immunity. We have recently shown that ethanol activates autophagy in the developing brain. The autophagic preconditioning alleviates ethanol-induced neuron apoptosis, whereas inhibition of autophagy potentiates ethanol-stimulated reactive oxygen species (ROS) and exacerbates ethanol-induced neuroapoptosis. The expression of genes encoding proteins required for autophagy in the CNS is developmentally regulated; their levels are much lower during an ethanol-sensitive period than during an ethanol-resistant period. Ethanol may stimulate autophagy through multiple mechanisms; these include induction of oxidative stress and endoplasmic reticulum stress, modulation of MTOR and AMPK signaling, alterations in BCL2 family proteins, and disruption of intracellular calcium (Ca2+) homeostasis. This review discusses the most recent evidence regarding the involvement of autophagy in ethanol-mediated neurotoxicity as well as the potential therapeutic approach of targeting autophagic pathways.

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Abstract

BACKGROUND:
Although a number of studies have found significant associations between maternal psychological distress, anxiety and changes in fetoplacental blood flow, findings remain inconsistent. A recent pilot study by our group highlighted some of these inconsistencies. In the current study, we expanded this pilot analysis to include psychological distress, anxiety and a range of antenatal variables, with the aim of identifying predictors of fetoplacental blood flow.

METHODS:
Healthy pregnant women (n=148) underwent Doppler flow studies on uterine, umbilical and fetal arteries; as well as assessments of distress, anxiety and other antenatal variables (e.g. perceived social support, resilience, nicotine and alcohol use) in each trimester.

RESULTS:
Stepwise regression analyses found that state anxiety was associated with lower mid-cerebral artery pulsatility index at trimester 3.

LIMITATIONS:
Subjects were recruited from selected midwife obstetric units in the same health district, so the generalizability of our results may be limited. While most subjects received Doppler assessment at trimesters 2 and 3, only approximately half of our sample was assessed at trimester 1.

CONCLUSION:
The finding that anxiety is associated with increased blood flow to the fetal brain during trimester 3 of pregnancy, coincide with previous work. The findings emphasize a growing appreciation of the potential importance of psychological well-being during pregnancy for infant development. However, as associations were small and variable, further research using multivariate models to determine the precise mechanisms underlying these associations would be warranted.

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127. An animal model of fetal alcohol spectrum disorder: Trace conditioning as a window to inform memory deficits and intervention tactics

Hunt PS1, Barnet RC2
1Department of Psychology, College of William & Mary, USA. Electronic address: pshunt@wm.edu.
2Department of Psychology, College of William & Mary, USA.

Abstract
Animal models of Fetal Alcohol Spectrum Disorders (FASD) afford the unique capacity to precisely control timing of alcohol exposure and alcohol exposure amounts in the developing animal. These models have powerfully informed neurophysiological alterations associated with fetal and perinatal alcohol. In two experiments presented here we expand use of the Pavlovian Trace Conditioning procedure to examine cognitive deficits and intervention strategies in a rat model.
of FASD. Rat pups were exposed to 5g/kg/day ethanol on postnatal days (PD) 4-9, simulating alcohol exposure in the third trimester in humans. During early adolescence, approximately PD 30, the rats were trained in the trace conditioning task in which a light conditioned stimulus (CS) and shock unconditioned stimulus (US) were paired but separated by a 10-s stimulus free trace interval. Learning was assessed in freezing behavior during shock-free tests. Experiment 1 revealed that neonatal ethanol exposure significantly impaired hippocampus-dependent trace conditioning relative to controls. In Experiment 2 a serial compound conditioning procedure known as ‘gap filling’ completely reversed the ethanol-induced deficit in trace conditioning. We also discuss prior data regarding the beneficial effects of supplemental choline and novel preliminary data regarding the pharmacological cognitive enhancer physostigmine, both of which mitigate the alcohol-induced cognitive deficit otherwise seen in trace conditioning controls. We suggest trace conditioning as a useful tool for characterizing some of the core cognitive deficits seen in FASD, and as a model for developing effective environmental as well as nutritional and pharmacological interventions.

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**128. Increasing accurate self-report in surveys of pregnancy alcohol use**

Muggli Mph Senior Research Officer E1, Cook B2, O’Leary C3, Forster D4, Halliday J5
1Murdoch Childrens Research Institute, Parkville 3052, Vic., Australia; Department of Paediatrics, The University of Melbourne, 3010 Vic., Australia. Electronic address: evi.muggli@mcri.edu.au.
2Murdoch Childrens Research Institute, Parkville 3052, Vic., Australia; Central Australian Aboriginal Congress, Alice Springs, 0870 NT, Australia.
3Telethon Kids Institute, Perth 6845, WA, Australia.
4La Trobe University, Melbourne 3000, Vic., Australia; Midwifery and Maternity Services Research, The Royal Women’s Hospital, Parkville, 3052 Vic., Australia.
5Murdoch Childrens Research Institute, Parkville 3052, Vic., Australia; Department of Paediatrics, The University of Melbourne, 3010 Vic., Australia.

**Abstract**

**BACKGROUND:**
Pregnancy alcohol research relies on self-reports of alcohol consumption. Reporting bias may contribute to ambiguous and conflicting findings on fetal effects of low to moderate pregnancy alcohol exposure.

**OBJECTIVE:**
This study aimed to identify the determinants, which would enable women to provide accurate data in surveys of alcohol use in pregnancy.

**DESIGN AND PARTICIPANTS:**
six focus groups were held with a total of 26 pregnant women and new mothers. Participants reviewed a set of alcohol survey questions followed by a guided discussion. Transcripts were analysed using inductive content analysis.

**SETTING:**
Public hospital antenatal clinics and Mother & Child Health Centres, Melbourne, Victoria, Australia.

**FINDINGS:**
Women’s emotional responses were generally favourable, although the potential for anxiety and fear of judgement was acknowledged. Barriers to accurate self-report were recall, complexity and use of subjective language. Facilitators were
appropriate drink choices, occasional drinking options and contextualising of questions. Confidentiality and survey method, including a preference for methods other than face-to-face, were also important factors.

KEY CONCLUSIONS AND IMPLICATIONS FOR PRACTICE:
Questions embedded in clear context may reduce anxiety around questions about alcohol use in pregnancy. Methods using shorter recall periods, a list of drinks choices, measures of special occasion drinking and minimising complex and subjective language will increase accurate self-report. A setting perceived as confidential and anonymous may reduce a desire to provide socially acceptable answers.

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129. Fetal alcohol exposure and mammary tumorigenesis in offspring: role of the estrogen and insulin-like growth factor systems

Cohick WS¹, Crismale-Gann C, Stires H, Katz TA
1Department of Animal Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ, 08901-8520, USA, cohick@aesop.rutgers.edu.

Abstract
Fetal alcohol spectrum disorders affect a significant number of live births each year, indicating that alcohol consumption during pregnancy is an important public health issue. Environmental exposures and lifestyle choices during pregnancy may affect the offspring's risk of disease in adulthood, leading to the idea that a woman's risk of breast cancer may be pre-programmed prior to birth. Exposure of pregnant rats to alcohol increases tumorigenesis in the adult offspring in response to mammary carcinogens. The estrogen and insulin-like growth factor (IGF-I) axes occupy central roles in normal mammary gland development and breast cancer. 17-β estradiol (E2) and IGF-I synergize to regulate formation of terminal end buds and ductal elongation during pubertal development. The intracellular signaling pathways mediated by the estrogen and IGF-I receptors cross-talk at multiple levels through both genomic and non-genomic mechanisms. Several components of the E2 and IGF-I systems are altered in early development in rat offspring exposed to alcohol in utero, therefore, these changes may play a role in the enhanced susceptibility to mammary carcinogens observed in adulthood. Alcohol exposure in utero induces a number of epigenetic alterations in non-mammary tissues in the offspring and other adverse in utero exposures induce epigenetic modifications in the mammary gland. Future studies will determine if fetal alcohol exposure can induce epigenetic modifications in genes that regulate E2/IGF action at key phases of mammary development, ultimately leading to changes in susceptibility to carcinogens.

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130. Glia and neurodevelopment: focus on fetal alcohol spectrum disorders

Guizzetti M¹, Zhang X², Goeke C², Gavin DP²

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Abstract

During the last 20 years, new and exciting roles for glial cells in brain development have been described. Moreover, several recent studies implicated glial cells in the pathogenesis of neurodevelopmental disorders including Down syndrome, Fragile X syndrome, Rett Syndrome, Autism Spectrum Disorders, and Fetal Alcohol Spectrum Disorders (FASD). Abnormalities in glial cell development and proliferation and increased glial cell apoptosis contribute to the adverse effects of ethanol on the developing brain and it is becoming apparent that the effects of fetal alcohol are due, at least in part, to effects on glial cells affecting their ability to modulate neuronal development and function. The three major classes of glial cells, astrocytes, oligodendrocytes, and microglia as well as their precursors are affected by ethanol during brain development. Alterations in glial cell functions by ethanol dramatically affect neuronal development, survival, and function and ultimately impair the development of the proper brain architecture and connectivity. For instance, ethanol inhibits astrocyte-mediated neuritogenesis and oligodendrocyte development, survival and myelination; furthermore, ethanol induces microglia activation and oxidative stress leading to the exacerbation of ethanol-induced neuronal cell death. This review article describes the most significant recent findings pertaining the effects of ethanol on glial cells and their significance in the pathophysiology of FASD and other neurodevelopmental disorders.

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131. The clinical utility and specificity of parent report of executive function among children with prenatal alcohol exposure.

Nguyen TT1, Glass L1, Coles CD2, Kable JA2, May PA3, Kalberg WO4, Sowell ER5, Jones KL6, Riley EP1, Mattson SN1
1Department of Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, California.
2Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia.
3Department of Nutrition, Gillings School of Global Public Health, University of North Carolina Nutrition Research Institute, Kannapolis, North Carolina.
4Center on Alcoholism, Substance Abuse and Addictions, The University of New Mexico, Albuquerque, New Mexico.
5Developmental Cognitive Neuroimaging Laboratory, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, California.
6Department of Pediatrics, School of Medicine, University of California, San Diego, California.

Abstract

Prenatal alcohol exposure and attention-deficit/hyperactivity disorder (ADHD) result in behavioral issues related to poor executive function (EF). This overlap may hinder clinical identification of alcohol-exposed children. This study examined the relation between parent and neuropsychological measures of EF and whether parent ratings aid in differential diagnosis. Neuropsychological measures of EF, including the Delis-Kaplan Executive Function System (D-KEFS), were administered to four groups of children (8-16 years): alcohol-exposed with ADHD (AE+, n=80), alcohol-exposed without ADHD (AE-, n=36), non-exposed with ADHD (ADHD, n=93), and controls (CON, n=167). Primary caregivers completed the Behavior Rating Inventory of Executive Function (BRIEF). For parent ratings, multivariate analyses of variance revealed main effects of Exposure and ADHD and an interaction between these factors, with significant differences between all groups on nearly all BRIEF scales. For neuropsychological measures, results indicated main effects of Exposure and ADHD, but no interaction. Discriminant function analysis indicated the BRIEF accurately classifies groups. These findings confirm compounded behavioral, but not neuropsychological, effects in the AE+ group over the other.
clinical groups. Parent-report was not correlated with neuropsychological performance in the clinical groups and may provide unique information about neurobehavior. Parent-report measures are clinically useful in predicting alcohol exposure regardless of ADHD. Results contribute to a neurobehavioral profile of prenatal alcohol exposure.

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ARTICLE ABSTRACTS

1. Fetal alcohol and the right to be born healthy...
Shiva M. Singh, Benjamin I. Laufer, Joachim Kapalanga

Finding the cause and applying the insights toward prevention and treatment forms the ultimate goal of most disease research. This strategy has been successfully used to make diseases like Scurvy and Smallpox, a history. The impact of this research during the last few years has been nothing less than miraculous. More and more people are living longer with healthy and productive lives, well into the 80’s and 90’s. Discovery of the cause(s) of disease(s) however is a demanding, time consuming, and expensive exercise. Also, there is no guarantee for success. Yet, even the modest success in search for causes have the potential to change the outcome and perception. Early diagnosis of a number of cancers for example is now viewed as treatable with reasonable chance of recovery. Also, some heart diseases are being managed and treated with high rate of success. Given this record of success, the research on disease causations continues to increase and the results have begun to pay increasing dividend. Unfortunately, there are cases of diseases where even full understanding of the cause has not resulted in the prevention or treatment of some common and devastating diseases. One such disease is the fetal alcohol spectrum disorder (FASD).

FASD is caused by the exposure of developing fetus to alcohol via maternal drinking during pregnancy (Jones and Smith, 1973). It represents the biggest single cause of mental retardation and developmental disabilities among babies born in the Western World (Barry et al., 2009). In the U.S. more than 50,000 babies are born with FASD every year (May and Gossage, 2001) and the annual cost of treating FASD in Canada and U.S. exceeds $6 and $8 billions, respectively (Lupton et al., 2004; Popova et al., 2013). Although, the prevention of FASD is a high priority, the failure to prevent it is attributed to our alcohol culture. Most people drink for social and recreational purposes. Others are addicted to alcohol.

As it stands, there is no consensus on whether there is a “safe” limit for alcohol consumptions during pregnancy. Recent research involving animal (mice) models has shown that continuous exposure of low-to-moderate dose of alcohol during pregnancy impacts behavioral and cognitive outcomes of resulting pups (Kleiber et al., 2011) and even a single binge dose of alcohol at any time during pregnancy results in alterations in gene expression (Kleiber et al., 2012, 2013) and associated FASD related phenotypes. Furthermore, the molecular alterations may be initiated and maintained for life by alcohol's effect on epigenetic features that includes DNA methylation (Laufer et al., 2013). The results on animal models argue that clinical features of FASD represent “tip of the iceberg.” They are also backed by results on humans. For example, exposure of human embryonic stem cells to low alcohol can alter gene expression leading to the abnormal development of prefrontal cortex (Krishnamoorthy et al., 2010). Also, fetal alcohol exposed school children show “a small but potentially important detrimental effect” on educational outcomes (Zuccolo et al., 2013) as well as generalized deficit of conceptualization (Quattlebaum and O’Connor, 2013).
We feel that such results deserve due consideration given that Royal College of Obstetrics and Gynecologists (Royal College of Obstetrician and Gynaecology, 2006) states that, “there is no evidence of harm from low levels of alcohol consumption, defined as no more than one or two units of alcohol once or twice a week.” Also, “there is considerable doubt as to whether infrequent and low level of alcohol consumption during pregnancy convey any long-term harm”—in other words they suggest a safe amount of alcohol consumption in pregnancy. Unfortunately, this limit has not been defined and may vary from individual to individual. Individual women process alcohol differently. Also, the age of the mother, the timing and regularity of the alcohol ingestion, and whether the mother has eaten any food while drinking may be important. We argue that there is no logistic evidence to define this limit. What is needed is to undertake thorough studies on neurodevelopment and assess the significance of such factors as maternal and fetal genotype, stress during pregnancy and childbirth, prenatal drinking patterns (mild, medium, heavy), post-natal environment, and socioeconomic status, as most of these may contribute to the manifestation of the effect of prenatal alcohol on the newborn. We note that some of these studies will be problematic if not impossible on humans. The rational question is “does no evidence of harm from low levels of alcohol consumption means 100% exclusion of the possibility of any harm to the fetus?” To the best of our understanding the answer is “no.”

The issue is particularly problematic as there is a rise in heavy drinking by young people, particularly women. Often, it is framed, as freedom of choice or “a single drink will not harm.” Not surprisingly, 1 in 8 adult women and 1 in 5 high school girls binge drink (CDC, 2013) and there is ample evidence from animal experiments, which argue for a life-long effect of even a single exposure of alcohol during pregnancy. The developing brain is a sequential, multistage, closely orchestrated, and highly sensitive to stresses. Also, any aberration could lead to life-long abnormality. For now, it is prudent to prevent a brain disorder than to attempt to ameliorate or cure it. Preventing a single case of FASD will save the society $1 million. More importantly it will save a productive life. The business as usual model is not helpful. It continues to result in births with alcohol effects. Any harm caused by prenatal alcohol is currently not reversible. It will affect the child for life.

With the current knowledge of what causes FASD it is prudent to stay on the safe side and avoid any drinking during and around the pregnancy. FASD is an alcohol problem. It is possible to prevent this calamity by avoiding alcohol during pregnancy and the time is now! FASD is a preventable disease—by not drinking during pregnancy. On the other hand, finding “cure” will be much more challenging, costly and time taking. It is critical to undertake active measures to reduce the occurrence of this disorder by a message of “no alcohol dose is guaranteed to be 100% safe for the embryo/fetus.” Also, “no time during pregnancy is 100% safe to drink.” Any adult has the right to drink if they so wish. Also, every child has the right to be born healthy!

**Conflict of interest statement**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**References**


[www.nofas-uk.org](http://www.nofas-uk.org)
2. Sanford study reveals fetal alcohol spectrum disorders prevalence in U.S.

Dr. Gene Hoyme, Dr. Amy Elliott

SIOUX FALLS, S.D. – Nearly 5 percent of U.S. children may be affected by fetal alcohol spectrum disorders, according to a new study co-authored by Sanford Research’s Gene Hoyme, M.D., and Amy Elliott, Ph.D., and published by Pediatrics.
The study, "Prevalence and characteristics of fetal alcohol spectrum disorders (FASD)," explored the incidence of fetal alcohol spectrum disorders (FASD) among first-grade students, or 6 to 7 year olds, in a representative Midwestern U.S. community, which was Sioux Falls. According to Hoyme, students were enrolled from all the elementary schools in Sioux Falls, both public and parochial. The study is the first school-based ascertainment study to be completed as a measure of FASD prevalence in American children.

FASD are a group of conditions that can occur in the children of mothers who drank alcohol during pregnancy. Characteristics are both physical and cognitive and can include abnormal facial features, smaller-than-average physical growth, poor coordination, learning disabilities and vision and hearing problems.

The research team gathered data on two groups of children related to physical growth, development, dysmorphology, cognition and behavior. The first group was made up of small children who were in the 25th percentile or less in height, weight and head circumference; the second group, or the control group, was randomly selected. The mothers of children from both groups were interviewed for maternal risk related to alcohol consumption while pregnant.

Around 2.4 percent to 4.8 percent of all the children studied were found to have some form of FASD based on cognitive and physical attributes. Furthermore, women who had affected children displayed higher levels of weekend binge drinking before discovering they were pregnant, sought prenatal care later and less frequently and noted the fathers of their children were frequent drinkers.

"Previous estimates of fetal alcohol spectrum disorders put the occurrence at around 1 percent in the United States," said Hoyme. "By actively assessing the children who were part of this study, our team was able to develop a more accurate figure for the prevalence of this disorder among the predominately middle class population of Sioux Falls and identify key risk factors that can predict it."

Hoyem is internationally known for his work with FASD and also serves as president of Sanford Research and chief academic officer for Sanford Health. He has led FASD research studies in South Africa for the past 15 years and helped establish the prevalence rate in South Africa, which remains the highest documented rate in the world. In 2012, Hoyme was the recipient of the National Organization on Fetal Alcohol Syndrome Excellence Award, joining the ranks of almost 40 past recipients that include Senator John McCain and the late Ted Kennedy.

Elliott leads the Center for Health Outcomes and Prevention at Sanford Research and is involved with national and international investigations about FASD and its consequences. Amy Baete and Jaymi Russo, research staff of the Center for Health Outcomes and Prevention, also contributed to the study.

**About Sanford Research**

Sanford Research is a non-profit research organization and is part of Sanford Health, an integrated health system headquartered in the Dakotas. Sanford represents the largest, rural, not-for-profit health care system in the nation with a presence in 111 communities, nine states and two countries. In 2007, a transformational gift of $400 million by Denny Sanford provided for an expansion of children’s and research initiatives, one of which was to find a cure for type 1 diabetes, and has given Sanford Research significant momentum in its goal of becoming one of the premiere research institutions in the United States and the world. Most recently, subsequent gifts of more than $200 million by Mr. Sanford have paved the way to establish Edith Sanford Breast Cancer Research and Sanford Imagenetics.

With a team of more than 200 researchers, Sanford Research comprises several research centers, including Children's Health Research, Edith Sanford Breast Cancer, Cancer Biology, Center for Health Outcomes and Prevention and Sanford Sports Science Institute.
3. **Prenatal alcohol exposure alters development of brain function: Neural basis for symptoms of fetal alcohol spectrum disorders**

**Summary:**

Medical researchers have found that children with fetal alcohol spectrum disorders (FASD) showed weaker brain activation during specific cognitive tasks than their unaffected counterparts.

In the first study of its kind, Prapti Gautam, PhD, and colleagues from The Saban Research Institute of Children's Hospital Los Angeles found that children with fetal alcohol spectrum disorders (FASD) showed weaker brain activation during specific cognitive tasks than their unaffected counterparts. These novel findings suggest a possible neural mechanism for the persistent attention problems seen in individuals with FASD. The results of this study will be published in *Cerebral Cortex* on August 4.

"Functional magnetic resonance imaging (fMRI) has been used to observe brain activity during mental tasks in children with FASD, but we are the first to utilize these techniques to look at brain activation over time," says Gautam. "We wanted to see if the differences in brain activation between children with FASD and their healthy peers were static, or if they changed as children got older."

FASD encompasses the broad spectrum of symptoms that are linked to in utero alcohol exposure, including cognitive impairment, deficits in intelligence and attention and central nervous system abnormalities. These symptoms can lead to attention problems and higher societal and economic burdens common in individuals with FASD.

During the period of childhood and adolescence, brain function, working memory and attention performance all rapidly improve, suggesting that this is a crucial time for developing brain networks. To study how prenatal alcohol exposure may alter this development, researchers observed a group of unaffected children and a group of children with FASD over two years. They used fMRI to observe brain activation through mental tasks such as visuo-spatial attention -- how we visually perceive the spatial relationships among objects in our environment -- and working memory.

"We found that there were significant differences in development brain activation over time between the two groups, even though they did not differ in task performance," notes Elizabeth Sowell, PhD, director of the Developmental Cognitive Neuroimaging Laboratory at The Saban Research Institute and senior author on the manuscript. "While the healthy control group showed an increase in signal intensity over time, the children with FASD showed a decrease in brain activation during visuo-spatial attention, especially in the frontal, temporal and parietal brain regions."

These results demonstrate that prenatal alcohol exposure can change how brain signaling develops during childhood and adolescence, long after the damaging effects of alcohol exposure in utero. The atypical development of brain activation observed in children with FASD could explain the persistent problems in cognitive and behavioral function seen in this population as they mature.

**Journal Reference:**


**Read Full Article,**

4. Fetal Alcohol Spectrum Disorders ‘Health Crisis’ Hot Topic At World-Renowned Conference

Experts Will Examine Canadian Strategies For Ideas To Improve FASD Awareness Around The World

TORONTO, CANADA – The world’s leading teratology experts at MotherToBaby USA and Motherisk Canada, members of the international non-profit Organization of Teratology Information Specialists (OTIS), will converge with the European Network of Teratology Information Services (ENTIS) in Toronto on September 19th – 21st to share breakthrough research and discuss how to prevent alcohol consumption during pregnancy.

Since the sensitivity to alcohol varies from one pregnancy to the next, no safe level of alcohol during pregnancy has been established. The exposure to the fetus can result in a range of neurobehavioral disabilities, now known as Fetal Alcohol Spectrum Disorders (FASD). Globally, September is commemorated as FASD Awareness Month.

"FASD is the leading cause of developmental disability in Canada and this area of research is critical," said Gideon Koren, MD, FRCPC, director of the Motherisk program at The Hospital For Sick Children (SickKids) in Toronto and program host of this year’s conference. “When prenatal alcohol exposure affects as many as one in 100 babies to some degree, FASD really should be considered more than a problem… it’s a health crisis," he added.

It’s been more than 40 years since Kenneth Lyons Jones, MD, OTIS and MotherToBaby’s president, along with David Smith, MD, first identified Fetal Alcohol Syndrome (FAS) after examining several children with similar traits who had all been born to chronic alcoholic mothers, yet there is still misinformation circling the globe about prenatal alcohol exposure.

“Studies, primarily out of Europe, suggesting that low to moderate levels of alcohol during pregnancy are safe add to one of the biggest health challenges today,” said Jones. “Learning from each other is an obvious and important focus of the conference.”

Jones acknowledges that Canada is farther ahead of most of the world in its awareness of FASD and is, as a result, a fitting host for the international joint meeting with ENTIS, which only takes place every four years. “There are important things about intervention strategies, providing services to underserved populations and getting certain professional groups such as the Canadian Bar Association involved that can be learned from the Canadians.”

Despite this progress and the well-documented spectrum of negative physical and mental effects alcohol can have on the developing fetus, as many as 15% of Canadian women report drinking during pregnancy, according to The Society Of Obstetricians And Gynaecologists of Canada.

Motherisk Canada is home to the Fetal Alcohol Canadian Expertise (FACE) Research Network, which will celebrate its 15th anniversary on September 17th at SickKids and will feature Jones as the keynote speaker. All North Americans can be connected with experts through the MotherToBaby and Motherisk programs. Women can receive personalized risk assessments regarding alcohol, medications and other exposures during pregnancy and breastfeeding toll-free at MotherToBaby 1-866-626-6847 and Motherisk 1-877-439-2744.

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5. FASD Awareness: Alcohol During Pregnancy Still Affecting 40,000 Babies Each Year

MotherToBaby is joining the cause to increase awareness of the risks of drinking alcohol while pregnant as September’s Fetal Alcohol Spectrum Disorders (FASD) Awareness Month kicks off. It is estimated that 40,000 babies are born each year with FASDs, which describe a range of effects that can happen to a fetus when a woman drinks alcohol during her pregnancy.1 The U.S. Surgeon General advises pregnant women and women who are considering becoming pregnant to abstain from alcohol consumption to eliminate FASD.2

When alcohol is consumed during pregnancy, the mother’s blood passes the alcohol to the baby through the placenta and the umbilical cord. There is no known safe amount or type of alcohol to drink during pregnancy. There is also no safe time to drink during pregnancy, including before a woman knows she is pregnant. FASDs can impact children’s physical, mental, behavioral, or cognitive development. It considered the most preventable form of mental retardation.

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To prevent FASDs, a woman should not drink alcohol while she is pregnant or if she might be pregnant. “There is a huge number of women that don’t know that they’re pregnant so they are behaving in that period of time the same way they would behave if they weren’t pregnant,” said Kenneth Lyons Jones, MD, MotherToBaby president and one of two doctors who first identified the most severe form of FASD, Fetal Alcohol Syndrome (FAS), in 1973. “It’s a major problem when it comes to FASD, but it’s important to note that it’s never too late to stop drinking.” Because brain growth takes place throughout pregnancy, the sooner a woman stops drinking, her baby’s chances for a healthier outcome increases.

For a personalized risk assessment, as well as resources about the effects of alcohol during pregnancy, contact MotherToBaby toll-FREE from anywhere in North America at 866-626-6847. We also have a Fact Sheet on alcohol in pregnancy available in English, and in Spanish. You’re also encouraged to read information from our partners at the Centers for Disease Control and Prevention.

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6. Breaking the cycle (BTC) – 20 years of breaking records in managing addicted mothers & their young children

Gideon Koren
The Hospital for Sick Children, Toronto, Canada

Addressing the needs of addicted mothers and their young children is a major challenge worldwide, marred by high failure rates and breakage of the mother-child dyad. The multidimensional impacts of addiction, compounded by psychiatric comorbidities, neglect, abuse and poverty, make the task of “breaking the cycle” an uphill battle and very often against all odds. In 1994, a coalition of Toronto-based organizations dealing with the social and medical aspects of child care, inaugurated BTC with the hope of creating an effective and sustainable model to support these mothers and their children. With no map to guide such a journey, it was clear that the team will have to create its own map, as well as the textbook that will inform the path. The inaugural team visited different institutions in North America, identifying what seemed as best practices, although often these practices were not anchored in strong evidence of effectiveness. The approach selected was eclectic in its nature, covering addiction counseling, child care and parenting skills, medical aspects, child protection, to mention a few. Critically, it was agreed among the founding partners that a climate and framework of continuous learning and research should be developed to guide BTC practices, so that the effectiveness of the processes involving in improving the abilities of the mothers to care for themselves and their young children can be documented through qualitative and quantitative research.

As presented in the 20 year research event on November 27 2014, it is very clear that these targets have been achieved. BTC team members and students have been involved in a wide range of research including the diagnoses of the mother and child, identification of risks and protective factors, and effective methods of management and therapy. For the sake of the 20 year celebration, the focus was on a large research project funded by the Canadian Institutes of Health Research, comparing BTC treatments of the mother-child dyad with a control group of mothers in Kingston Ontario, where the treatment focuses on the mother without involving the child.

In this short report I will share my remarks after listening to the presentations and reading the scientific reports produced by the group, all in the context of the powerful effects BTC has on this emerging field.

Mother-child relationship, cumulative child risks and developmental outcomes It is intuitively sensible that a dynamic balance between the quality of mother-child relationship vs. cumulative child risk, will define outcomes of IQ and neurobehavioral functioning. However, validation and quantification of such trends are difficult to prove due to the complexities of defining each of the elements of this equation.

Motz and colleagues studied 40 infants- children/mother dyads, where the mothers were substance users.1 They aimed to clarify the role of the quality of mother-child relationship in modifying cumulative risk for children to be adversely affected in their neurobehavioral functioning and IQ. Mother-child relationship quality was measured retrospectively using the validated Parent-Infant Relationship Global Assessment Scale from the Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood: Revised Edition (PIR-GAS). The Cumulative Risk Index was created by the authors using potential prenatal and postnatal risk factors previously identified in the literature, acknowledging that “a cumulative risk scale….was unavailable in the literature”. The Scale includes 12 pre-natal and 23 postnatal factors, each of which scores one point.

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Neurobehavioral and IQ measurements were done on these children as part of their participation in BTC. Analysis of this cohort revealed that the quality of the mother-child relationship significantly mediated the direct relationship between cumulative risk and neurobehavioral functioning, and cumulative risk correlated with IQ indirectly through mother-child relationship. The authors concluded that the quality of mother-child relationship plays an important role in determining young children’s outcome in this high risk group. Several methodological challenges make the interpretation of these results less straightforward:

The Cumulative Risk Index, although anchored in known risk factors has not been validated. A brief review of the list of pre-natal risks reveals that many items dealing with maternal drinking are overlapping and not mutually exclusive. Because this tool is critical for the core activities of BTC, it would make a lot of sense to further validate, including factor analysis that may eliminate some items.

It is quite reasonable to assume that mothers endorsing high cumulative risks also have, for the same reasons, a tendency toward low quality of relationship. Mental disease, addiction, neglect and many other causes may affect both the cumulative risk index as well as the quality of interaction. Under these circumstances it is difficult to prove cause and effect, as co-linearity must be considered and resolved.

Comparing a novel relationship-focus intervention (RFI) and standard integrated treatment (SIT) Over the years BTC has developed a novel relationship-focus intervention, where the central focus is on promoting healthy maternal relationships with particular emphasis on fostering mother-child interactions and hence the mother-child dyad is the central piece of the intervention. In contrast, SIT involves primarily the mother, while the child is involved only tangentially by providing basic parenting information. In this study 65 BTC women receiving RFI were compared to 25 mothers receiving SIT in Kingston, Ontario.2

Compared to their baseline, both groups decreased their use of substances. The BTC-practiced RFI approach was associated with better improvement in substance use. Moreover, more women from BTC improved their mental health than in the comparison site, and the BTC women improved significantly their relationship capacity. The BTC children, even those exposed in utero to substances, did better when their mothers had relationship-focused intervention as compared to the control group.

Within the BTC group, improvement in relationship capacity correlated with greater decrease in their substance abuse. This, however, cannot be used as a proof of causation, as it is possible that those who improved in both aspects are a more resilient and of characteristics that improve both aspects in parallel. Moreover, not being a randomized trial, it is possible that the overall environment at BTC is more favorable and affects positively maternal and child outcomes in ways which are not intervention-specific. Ethically though, BTC could not randomize mother-child dyads not to receive their special, eclectic relationship-focused intervention. This of course can be done by other centers, but they will have to decide whether the study described here allow them to give the SIT protocol. The principle of clinical equipoise dictates that one cannot randomize patients to receive therapy shown to be inferior to another intervention.3

The science developed in BTC over the last 20 years was effective in drawing a new map for identification of at risk cases, understanding their determinants of risk and managing them. The multidisciplinary team, the open mindedness, the critical appraisal of existing and new methods, all helped in creating new climate, where mothers can break the cycle and start new and positive one.

*Gideon Koren is the Chair of BTC Steering Committee.

Corresponding Author: gkoren@sickkids.ca

REFERENCES


7. **Preventing Fetal Alcohol Syndrome is a collective responsibility**

Dr. Alain Fourmaintraux

Congratulations to Le Quotidien to its issue on the economy (14 October 2014). Illiteracy, I read, is one of the major barriers to employment. According to the consulted economists, the population of Reunion Island involve about 100,000 illiterates.

Now, one of the causes of illiteracy is known: it is the achievement brain Fetal Alcohol. According to competent professionals in the field, a **Reunionese in utero exposed to alcohol is born every two days**; after 20 years it is 3200, after 50 years 9000. Just under 10% of the illiterate, it is a lot, right? Yet it is preventable!

The care given to 7600 dependent women (according to the SAOME network), if it exists (CSAPA and associated networks), provided by qualified health care providers, it does not seem to respond by far the potential demand (- 10 % of dependent women are monitored by these competent services). According to midwives and maternity doctors, most alcoholic women during pregnancy are not accessing care. This statement is shared by mothers who have escaped their addiction. It means that this low care that is provided depends of the voluntary patients. However, alcoholic women live in shame, guilt, exclusion and confinement. In addition, many of them are themselves victims of fetal alcohol syndrome. They are in practice unable to make the necessary arrangements and even less to honor the successive appointments. It should be added that the fetus despite himself in the womb cannot ask an appointment! In terms of alcoholic disease of women and especially pregnant women, medical action cannot function without a professional link with social action. The International Convention for the prevention of disorder Caused by fetal Alcoholization signed by 35 countries in Canada in 2013 stipulates that the responsibility for the prevention of Fetal Alcoholization should not be born solely by women, that prevention is a collective responsibility and must be based on compassion. In other words, competent people in social action and federating are needed at home and regularly to create bonds of trust and rehabilitation, which only allow alcoholic women get out of their confinement and lead them and their children by hand up care. This is what was, with some success, the network Réunisaf. Its success came from a collective will patiently built over many years (1996-2001) by all local actors (health, national, social, education, justice), expert families in experience and supported by a dedicated regional program. The ARS, removing with no real relay in 2012 this organizational model and decreeing that it could replaced overnight by CSAPA already overbooked, are doing a stepback of 15 years, and especially are not preventing the birth of many brain-damaged babies whose road to illiteracy is clear.

So we call all decision-makers to take responsibility. If they have a true collective ambition for Reunion Island, they need to invest on what is the true wealth of our society that is children's future and rally to protect promptly brains of Reunion children of this preventable scourge.

**For the collective of Reunion**: **Invest in the future of our children, protect their brains**

**Dr. Alain Fourmaintraux** Pediatrician, Expert in social issues Disorders Caused by Fetal Alcoholization  
**Dr. Thierry Maillard**, General Practitioner, Addictologist  
**Dr. Denis Lamblin**, Pediatrician, National Prevention Expert of Disorders Caused by Fetal Alcoholization
8. **NIH statement on International FASD Awareness Day**

George Koob, Ph.D., director, & Kenneth R. Warren, Ph.D., deputy director National Institute on Alcohol Abuse and Alcoholism

International Fetal Alcohol Spectrum Disorders (FASD) Awareness Day, recognized every year on Sept. 9th, is an important reminder that prenatal alcohol exposure is the leading preventable cause of birth defects and developmental disorders in the United States. Almost 40 years have passed since we recognized that drinking during pregnancy can result in a wide range of disabilities for children, of which fetal alcohol syndrome (FAS) is the most severe. Yet, 1 in 13 pregnant women reports drinking in the past 30 days. Of those, about 1 in 6 reports binge drinking during that time.

September 9th is International Fetal Alcohol Spectrum Disorders Awareness Day, a reminder that all nine months of pregnancy should be alcohol-free for the health of your child.

The disabilities associated with FASD can persist throughout life and place heavy emotional and financial burdens on individuals, their families, and society. FASD often brings to mind the distinct pattern of facial features associated with FAS, such as wide-set and narrow eyes, a smooth ridge on the upper lip, and a thin upper lip border. We now understand, however, that the neurobehavioral effects associated with FASD, such as intellectual disabilities, speech and language delays, and poor social skills, can exist without the classic defining facial characteristics.

For many years, the National Institute on Alcohol Abuse and Alcoholism has supported research to understand how alcohol exposure during pregnancy interferes with fetal development and how FASD can be identified and prevented. Scientists continue to make tremendous strides, providing important new insights into the nature of FASD and potential intervention and treatment strategies.

The message is simple, not just on Sept. 9, but every day. There is no known safe level of drinking while pregnant. Women who are, who may be, or who are trying to become pregnant, should not drink alcohol.

**Learn more about alcohol and pregnancy**

The National Institute on Alcohol Abuse and Alcoholism, part of the National Institutes of Health, is the primary U.S. agency for conducting and supporting research on the causes, consequences, prevention, and treatment of alcohol abuse, alcoholism, and alcohol problems. NIAAA also disseminates research findings to general, professional, and academic audiences. Additional alcohol research information and publications are available at http://www.niaaa.nih.gov.

About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

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1. **Prenatal alcohol consumption linked to mental health problems**

   By Denis Campbell  
   11th September 2014

Children whose mothers drink four units of alcohol even once are more likely to suffer from hyperactivity, study shows

Children of mothers who drink as little as four units of alcohol in a day even once while pregnant are at greater risk of developing mental health problems and doing less well at school, new research claims.

The study found that the 11-year-old offspring of women who consumed the equivalent of two medium-sized glasses of wine in one session during pregnancy are more likely to suffer from hyperactivity and inattention.

The findings, from a British study of more than 4,000 children in the Bristol area, have reopened the debate about how much, if any, alcohol women should consume while carrying a child.

The Department of Health advised pregnant women and those trying to conceive to remain abstinent. "If they do choose to drink, to minimise the risk to the baby, they should not drink more than one to two units of alcohol once or twice a week and should not get drunk," said a DoH spokesman.

Academics found that 11-year-olds born in 1991-92 to mothers who had drunk that amount one or more times in pregnancy had "slightly higher" levels of hyperactivity and inattention, in the opinion of both their parents and their teachers, who each filled out questionnaires.

Girls seemed to display such behaviour more often than boys, the study found.

Among 7,000 children in the study, those affected by their mother's prenatal drinking scored on average one point lower in key stage 2 exams taken in their last year at primary school, according to an analysis of results.
The lead author of the research, Professor Kapil Sayal of Nottingham University, said: "Women who are pregnant or who are planning to become pregnant should be aware of the possible risks associated with episodes of heavier drinking during pregnancy, even if this only occurs on an occasional basis.

"The consumption of four or more drinks in a day may increase the risk for hyperactivity and inattention problems and lower academic attainment even if daily average levels of alcohol consumption during pregnancy are low."

However, children of women who had one drink a day while pregnant did not have any higher risk of either problem, Sayal and colleagues found.

The findings are from ongoing, long-term research called the Avon Longitudinal Study of Parents and Children, which looked at and followed the health of children born to mothers in Avon in 1991-92. They are published on Thursday in the journal European Child and Adolescent Psychiatry.

Belinda Phipps, chief executive of the parenting charity NCT, said better awareness of the risks meant far fewer mothers-to-be now drink more than they should compared to when the children in this study were born.

Phipps said: "According to the latest Infant Feeding Survey in 2010, only 3% of pregnant women reported drinking more than two units of alcohol per week on average, compared to 24% drinking four or more units a day at least once while they were pregnant in 1990-1992."

The director of the Institute of Alcohol Studies thinktank, Katherine Brown, said: "Exposure to alcohol can lead to foetal alcohol spectrum disorder, which manifests itself in a range of symptoms including hyperactivity, poor attention span and memory deficits, all of which can adversely impact on a child's ability to learn and socialise. So it's no surprise that this study found poor performance at school was linked to pre-natal drinking."

However, FASD gets little attention in the UK and there is "huge under recording" of how common it is, with symptoms often not picked up until children are at school and sometimes misdiagnosed, Brown added.

"Greater awareness is needed about the risks of drinking during pregnancy, with a clear message that no amount alcohol is safe. There also needs to be increased levels of support for those women who struggle to stop drinking due to dependency, and better diagnosis and treatment for babies with FASD," she said.

Professor Dame Sally Davies, the chief medical officer for England and government's chief scientific adviser, is currently reviewing guidelines on safe levels of drinking, including in pregnancy.


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2. Prenatal alcohol exposure tied to balance, coordination problems

BY ANDREW M. SEAMAN
9th June 2014

(Reuters Health) - Children who are diagnosed with fetal alcohol spectrum disorder are at higher risk of having impaired gross motor skills, according to a review of past studies.

Balance, coordination and ball skills were the areas where children exposed to alcohol in the womb had the most problems, researchers found.

"This is biologically plausible as alcohol is a teratogen which causes damage to the developing brain," Barbara Lucas told Reuters Health in an email. "Areas of the brain that may be damaged include those which are important for motor control."

Lucas is the study's lead author from The George Institute for Global Health in Sydney, Australia.

Researchers aren't sure how many Americans have fetal alcohol spectrum disorder (FASD), which is a collection of conditions that occur among children whose mothers drank during pregnancy.
Fetal alcohol syndrome, one of the more severe forms of FASD featuring abnormal facial features and growth problems, is estimated to occur in between 0.2 and 1.5 of every 1,000 live births, according to the U.S. Centers for Disease Control and Prevention.

Lucas and her colleagues reviewed past studies to determine how gross motor skills, which include sitting up and rolling over, may be affected by prenatal alcohol exposure.

They looked at studies that included children up to 18 years old with FASD, moderate to heavy alcohol exposure while in the womb or a mother with alcohol dependency and compared them to children without prenatal alcohol exposure or related problems.

The researchers found 14 studies to include in the analysis and were able to combine data from 10 of those studies.

Overall, the odds of a child having gross motor skill impairment tripled when the child had a FASD diagnosis or was exposed to a moderate to heavy amount of alcohol while in the womb.

The researchers were not able to determine exactly what proportion of alcohol-exposed children has motor problems.

About 10 drinks per week constitutes moderate to high levels of alcohol exposure, Lucas said, but no safe level of drinking during pregnancy has been established.

“The safest option is to avoid alcohol,” she said.

Specifically, the researchers found problems with balance, coordination and how children were able to play with a ball were more common among those with alcohol exposure in the womb.

“Children who are exposed to alcohol prenatally would benefit from assessment of their gross motor skills,” Lucas said.

If problems are found, she said physiotherapists, who are specialists in movement, can help children improve their skills.

Read Full Article,

http://in.reuters.com/article/2014/06/09/us-prenatal-alcohol-motor-skills-idINKBN0EK1MD20140609

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3. Prenatal alcohol exposure can lead to abnormalities

Times of India
5th August 2014

Washington: Drinking alcohol during pregnancy can cause a spectrum of abnormalities referred to as Fetal Alcohol Spectrum Disorders in the offspring, experts say. Physical features of the more serious Fetal Alcohol Syndrome (FAS) include smooth philtrum, thin vermilion border, short palpebral fissures, microcephaly, and growth deficiencies in weight and height. A new study has specified how specific quantities of alcohol exposure, patterns of drinking, and timing of exposure can have an impact on each of these features. Numerous specific associations were found, the most significant ones during the second half of the first trimester of pregnancy.

Haruna Sawada Feldman, a post-doctoral student in the department of pediatrics under the mentorship of professor Christina Chambers at the University of California, San Diego, and her colleagues used data gathered on 992 women and their singleton infants in California between 1978 and 2005, examining patterns of drinking and timing of alcohol exposure in relation to selected FAS features. Structural features were assessed by a dysmorphologist who performed a blinded physical examination of all infants. Patterns of drinking were evaluated by drinks per day, number of binge episodes, and maximum number of drinks.

Timing of exposure was evaluated zero to six weeks post-conception, six to 12 weeks post-conception, and during the
first, second, and third trimesters. “Higher prenatal alcohol exposure (PAE) in every pattern we examined was significantly associated with an increased risk for having an infant born with reduced birth length or weight or having a smooth philtrum or thin vermillion border or microcephaly,” said Feldman. “The most significant associations were seen during the second half of the first trimester; for every one drink increase in the average number of drinks consumed daily, there was a 25 percent increased risk for smooth philtrum, a 22 percent increased risk for thin vermillion border, a 12 percent increased risk for microcephaly, a 16 percent increased risk for reduced birth weight, and an 18 percent increased risk for reduced birth length,” the researcher stated.

Feldman added that the lack of associations found during first-half of the first trimester between alcohol and outcomes should not be interpreted to mean that alcohol consumption during this time period is somehow safe. “Due to the study design, we were only able to include women who gave birth to live infants,” she said. “Therefore, we did not include women who may have had miscarriages or stillbirths. It is important to know that alcohol-exposed infants who would have exhibited alcohol-related minor malformations might also be more likely to be lost to miscarriage following exposure during the first six-week window,” she added.

Both Feldman and Philip A. May, a research professor in the Gillings School of Global Public Health at The University of North Carolina, believe these findings reinforce the warning that there is no “safe” level of alcohol consumption during pregnancy.

Read Full Article,

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4. Drinking alcohol during pregnancy could be ruled a crime

By Sam Marsden
2nd February 2014

Lawyers plan to take a test case to the Court of Appeal over claims that children harmed in the womb by their mother’s drinking should receive compensation as victims of crime

Harming an unborn child by consuming alcohol during pregnancy could be classified as a crime if an unusual legal challenge succeeds.

A council is planning to go to the Court of Appeal in an attempt to secure criminal injuries compensation for a six-year-old girl who was born with foetal alcohol spectrum disorder as a result of her mother’s drinking while she was in the womb. A tribunal ruled in 2011 that the unnamed child had sustained personal injury “directly attributable to a crime of violence” and so was eligible for a payout.
Her mother, who drank “grossly excessive quantities of alcohol” during her pregnancy, was never convicted of any offence.

But she was alleged to have maliciously administered poison so as to endanger life or inflict grievous bodily harm, a crime under section 23 of the Offences Against the Person Act 1861.

However, the Criminal Injuries Compensation Authority challenged the judgment, and it was overturned in December by the upper tribunal of the Administrative Appeals Chamber.

Judge Howard Levenson found that there had been “administration of a poison or other destructive or noxious thing, so as thereby to inflict grievous bodily harm”. However, he concluded that the girl was “not a person” in legal terms at the time because she was still a foetus.

The judge added: “I conclude that the section 23 offence cannot be committed by a pregnant woman drinking alcohol during her pregnancy and thereby causing damage to her unborn child and that, in the present case, no evidence or argument has been offered in respect of the commission of any other offence.”

Now the council in northwest England which brought the original application for compensation on behalf of the girl, who is now in foster care, is preparing to take the case to the Court of Appeal, The Sunday Times reported.

Neil Sugarman, a managing partner at GLP Solicitors in Greater Manchester, who is handling the case, told the paper: “Sadly, we act for many, many children who have been damaged by excessive alcohol intake during pregnancy. We were approached by a local authority with responsibility for a child very badly damaged as a consequence of foetal alcohol spectrum disorder.

“They considered making an application under the criminal injuries compensation scheme because they thought there was an argument that the child had been damaged by being victim of a crime. The crime being the birth mother carrying on drinking knowing that it could damage the child.”

He added: "In all the cases we have, there is good evidence that warnings have been given either by social workers or treating consultants and nurses to say, 'you cannot go on doing this, you are going to damage your child'."

Read Full Article,


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5. **Too Young To Drink: International Campaign to Raise Awareness of the Risks of Drinking in Pregnancy**

BY EUFASD

The Too Young To Drink campaign was launched on September 9, 2014 (International FASD Awareness Day).

The launch of the campaign involved individuals and organizations displaying a banner of the campaign in a busy area of their hometowns at 9:09am on September 9, 2014. Groups all over the world took pictures and made videos of themselves with the banners and shared them via social media, including Facebook, Twitter, and Instagram.

![Image of Too Young To Drink campaign banner]

**Read more about the campaign**

[http://tooyoungtodrink.org/](http://tooyoungtodrink.org/)

**Read Awareness Strategy**


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6. **Girl harmed by alcohol in womb wins payout**

Molly, 16, from the northwest of England, was considered a victim of a crime because her mother persisted in heavy drinking despite health workers and police warning her about the risks to her unborn child. Molly was diagnosed with foetal alcohol syndrome when she was 4.

News of the payout, made by the Criminal Injuries Compensation Authority last September, comes ahead of a test case at the Court of Appeal to overturn a ban on such payments. Under changes introduced in November 2012, after Molly
lodged her claim, the authority no longer considers that foetuses damaged in the womb as a result of the mother’s excessive alcohol intake are victims of violent crime and are therefore no longer eligible for compensation. However, a council is challenging the policy arguing that a 6-year-old girl with FAS is entitled to compensation for the brain damage caused by her pregnant mother’s drinking. It believes the mother criminally “poisoned” her unborn child because she too was warned of the potential dangers of her actions.

If successful, the case could have far-reaching implications. Lawyers acting for the council are representing 80 children in Britain who suffered physical and mental damage as a result of their mothers’ heavy drinking. They will argue that payouts to Molly and previously a small number of other children have in effect set a legal precedent.

Neil Sugarman, a managing partner at GLP solicitors in Greater Manchester who is acting in the case, said: “It is very unfair that some children should have an award, which they very much merit and need, and others won’t get it. I think from a lay person’s perspective or to a victim of this syndrome, it just seems that they [CICA] accepted that drinking alcohol to excess, knowing it will damage your baby, is a crime for the purposes of the scheme and all of a sudden it isn’t.”

Read Full Article,
http://www.thetimes.co.uk/sto/news/article1412028.ece

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7. **Drinking when pregnant: Is it harmless or an act of denial?**
By Aoife Stuart Madge

With 80 per cent of women in Ireland admitting to drinking alcohol when pregnant, Aoife Stuart Madge asks if we are ignoring the risks.

As a doctor and first-time mother, Maria 35, from County Down, wants to do everything in her power to give her 18-month-old son the best start in life.

While pregnant, she read up on all the childcare and pregnancy manuals, baby-proofed her home and made sure the nursery was decked out in the very best baby gear. Controversially, she also drank - not excessively - but just a couple of glasses a week over dinner. "I enjoy unwinding with a glass of wine and didn't see why I had to sacrifice that just because I was pregnant," she says.

And Maria is not alone. Increasingly Irish women are breaking the biggest pregnancy taboo and partaking in a drink or two - and it's educated women like Maria who are leading the charge.

Last year, a study funded by the Health Research Board found that 80pc of Irish women drank at some point during their pregnancy; while a separate study in 2010, titled Growing Up in Ireland, found that women with the highest levels of education are most likely to consume alcohol during pregnancy.

Maria is quick to point out that it is not a case of choosing to ignore official health warnings (earlier this year, the country’s three largest maternity hospitals, The National Maternity Hospital, The Rotunda Hospital and the Coombe Women & Infants University Hospital, joined forces with Alcohol Action Ireland to launch a campaign in an attempt to tackle the problem), which advocate avoiding alcohol during pregnancy. Rather, it's an informed choice, she insists, and one she is capable of making. "I'm a GP, so I am well-placed to know what is responsible drinking. I've done my research, and I know that a unit a day or the odd glass of wine does no harm to an unborn baby."

As a health care professional, Maria may be well-placed to know what constitutes a safe level of alcohol for her to consume during pregnancy, but Dr Aoife Mullally, a consultant obstetrician/gynaecologist at the Coombe Women & Infants University Hospital says that for most expectant women, the facts are blurred. "There is a lot of confusion out
there because women are getting conflicting advice from their health care professionals and even from their peers and their family," she says.

Part of the problem is that at the same time as Irish health officials are issuing warnings to pregnant women to abstain from drinking altogether, conflicting reports emerge which claim that low levels of alcohol during pregnancy are safe. Take the 2012 Danish study of 1,628 pregnant women, published in the British Journal of Obstetrics and Gynaecology, which found that a small alcoholic drink a day had no affect on a growing baby. A previous study by the Royal College of Obstetricians and Gynaecologists concluded that low to moderate drinking (10.5 units or seven glasses of wine a week) showed no adverse affects on a baby's development.

There have even been studies to suggest that the children of mothers who drank moderately throughout pregnancy had a higher IQ than those that abstained. It's hardly surprising then that women - especially those going through such an emotionally exhausting and anxious time as pregnancy - are reaching for a glass of wine to relax.

However, Dr Mullally warns that what is regarded as moderate levels of alcohol consumption during pregnancy is a grey area, especially in the age of three-unit wine measures (not to mention generous home measures). With so much conflicting information out there, it's easy to get misled (am I allowed two or three units? And was it once or twice a week?)

"There is no good evidence to suggest that having the occasional drink or even drinking continually at low levels during pregnancy is harmful," explains Dr Mullally. "But the problem is there is no known 'safe' level. Women also under-report how much they drink, and one person's idea of a unit, glass or measure of alcohol may vary. There are some babies that are more sensitive to the effects of alcohol than others, and there is no way of telling if your baby will be affected."

And when you consider the potentially devastating effects of alcohol misuse during pregnancy, there is little room for error. Most women who have considered drinking in pregnancy are aware of Foetal Alcohol Syndrome (FAS), which is characterised by distinctive features: small and narrow eyes, a small head, a smooth area between the nose and the lips and a thin upper lip.

According to Dublin-based alcohol abuse charity the Hanly Centre, between 177 and 354 babies are born each year in Ireland with FAS, while the number of babies being born with FAS in the UK has risen 40pc in the last three years. But while the recorded incidences of FAS are relatively rare, the figures may be deceptive. It's estimated by the Hanly Centre that the number of cases in Ireland increases to 1,770 annually, if you factor in all alcohol-related neurological disorders.

Alcohol has a spectrum of effects on pregnancy, explains Mary Brosnan, Director of Midwifery and Nursing at The National Maternity Hospital. "The term Foetal Alcohol Spectrum Disorder (FASD) describes the range of alcohol effects on a child. The problems range from mild to severe. Alcohol can cause a child to have physical or mental problems that may last all of his or her life," she says.

"Aside from distinctive facial features, a child may have growth problems and there are linkages with impairment of brain development and behavioural and learning problems with children as they grow older." These can include more subtle behavioural and neurological problems, such as attention deficit disorder, problems with decision-making and problems with socialising.

The spotlight was firmly on FAS last month with the news that a local authority in the north west of England is seeking criminal injuries compensation for a six-year-old girl in care who has 'growth retardation' caused by her mother's alcohol
consumption during pregnancy. If the Court of Appeal agrees that the mother committed a crime, the ruling could lead to the criminalisation of alcohol consumption during pregnancy.

It's worth noting that it's not just pregnant women who are drinking more - we are drinking more as a country. According to Alcohol Ireland, 14,000 people are admitted to hospital for treatment for alcohol dependency every year while St Vincent's Hospital in Dublin has reported a 335pc increase in admissions with alcoholic liver disease between 1995 and 2010. Let's face it, most Irish women drink habitually, but do pregnant women need to pay more attention to that large glass of pinot with lunch or that warming glass of red at Christmas time?

In the US, only 22pc of women drink during pregnancy, almost a quarter of the percentage of Irish women, perhaps because drinking is not so culturally widespread in America, but also because our US cousins hammer home the affects of Foetal Alcohol Syndrome in hard-hitting public service announcements, with a similar shock value to our drink-driving adverts.

A recent USA anti-prenatal drink campaign shows a small girl taking a bar stool beside a 30-something woman, telling the barman, "I'll have what she's having." This is followed by a solemn reminder from the voiceover that, "Pregnant women never drink alone."

Dr Mullally sees these campaigns as a more effective way of educating women, rather than criminalisation. "In the UK and Ireland we haven't been very good at getting the message out there about the kind of problems drinking in pregnancy can cause, whereas in the US, they have been much better at naming the specific problems. If we did have more targeted messages like that, I think that would be more helpful than criminalising drinking in pregnancy," says Dr Mullally.

Let's face it, no mother wants to deliberately harm her child, and the majority of Irish mothers who are drinking during pregnancy are not reckless or uninformed. In fact, according to Growing Up In Ireland, the demographic most likely to drink during pregnancy are university-educated mothers in their 30s - the same group most likely to breastfeed and to give up smoking when pregnant. They know the effects binge-drinking can have on an unborn baby. But do they need a wake-up call when it comes to moderate drinking during pregnancy too? Mary seems to think so.

She warns: "Due to the emerging evidence of even small amounts of alcohol having a negative effect, we always advise abstinence as the best option. What is very clear is that there are no benefits for the unborn child from exposure to alcohol, just risks."

As far as Anna is concerned, she would like more trust given to women to judge what is right for them, and that they know how to drink responsibly. "Making pregnant women feel guilty, scaremongering them or patronising them is not the answer. We need to educate mums and give them access to all the information so they can do their own research and make their own informed choice."

'I enjoyed a glass (or three) when I was pregnant'

Clare Reilly, 35, a freelance writer, is mum to Eddie, 10, Sammy, 6 and Annie, 3. She drank moderately throughout all her pregnancies.

"I'm not some selfish woman who doesn't care about the health of her children. In fact, you'll struggle to find anyone who isn't a doctor who knows more about drinking during pregnancy than me. I'm a proud mother of three wonderfully
healthy, happy and smart children. I drank through each of their pregnancies, mostly one glass of wine in the evening after dinner but, sometimes - if it was a special occasion - I would have two or three over the course of a meal. I'm not advocating that pregnant women get drunk, just that they be allowed to drink responsibly.

"I've read practically every piece of literature and study on the effects of drinking during pregnancy and have come to the educated conclusion that my alcohol intake during each of my three pregnancies has not adversely affected any of my three children. Like most mothers, I'm aware of Foetal Alcohol Syndrome, but the studies used to scare us away from alcohol are all based on results from heavy drinkers and alcoholic mothers-to-be.

"Pregnant women aren't trusted to know when light-to-moderate drinking stops and heavy drinking begins. I've been fortunate enough to have all three doctors I've seen through each of my pregnancies tell me the truth; the current medical advice to abstain entirely comes from the medical profession's distrust for the public."

**Allison Keating is a psychologist at the Bwell Clinic in Dublin**

She says: "We have a dysfunctional relationship with alcohol in general Ireland. Women as a whole are drinking more, and it's an issue for 30-something women in particular. Stressed working mothers are struggling, and feeling anxious and overwhelmed trying to balance careers with family life. Pregnancy is an anxious time anyway. You can feel very tired and you are having massive hormonal surges up and down, so you can understand why someone wants to sit down at the end of the day, have a glass of wine and watch some TV. That becomes their only out.

"There is also a lot of pressure that comes from other people. Drinking alcohol is considered so normal that it is nearly unacceptable to not have a drink. It makes other people uncomfortable. There is a lot of projection going on, so if one pregnant woman sees another pregnant woman not drinking, it makes them feel uncomfortable.

"Middle class, educated pregnant women tend to get a lot of their information from their peers. It's common to hear people say, 'Well, my consultant said it was fine to have one.' Then that anecdotal evidence becomes fact. People then think, 'Sure I'll only have one.' Most women know the effects of serious drinking and about FAS, and that is very much frowned upon, but perhaps we need to sit back and think, 'Do I really need that glass?' It's important to open your mind and make sure you are not just taking information from your peer group when it comes to the good health of your baby.

"Being pregnant is a big sacrifice and it takes a lot of effort. We are living in a society where people are harried and stressed.

"Pregnant women need something else to relax. The best thing is to go out for a 20-minute walk to clear your brain completely. Learn techniques to use your five senses to soothe yourself: the taste of a cup of tea, the texture of a body lotion, the scent of a candle...

"These are simple things you can do at home. Women will always put family first, and that's where alcohol creeps in and has a negative effect. Instead, consciously take 10 minutes to half an hour at the end of the day for yourself, to wind down and reconnect with yourself."
‘Drinking while pregnant is not worth the risk’

Eleanor McAlister, 33, a teacher, is mum to Cara, 2, and Ben, 10 months. She didn’t drink at all throughout any of her pregnancies.

“When my first pregnancy ended in miscarriage, it impressed on me the fragility of pregnancy — sometimes it goes away for no known reason and leaves you feeling shattered and empty. So when I found out I was pregnant again with Cara I was willing to make sacrifices to ensure the health of my baby.

“Any risk, no matter how small, is too big a risk for me. In the same way I cut out blue unpasteurised cheeses, shell fish, eggs with runny yolks to name a few, I also cut out alcohol. To be honest it didn’t seem like that big a deal for me. I think I’ll have plenty of time to enjoy a glass of wine in my life and only a short time to be pregnant.

“I am aware that a lot of women have a glass or two of wine during pregnancy and that is their choice. In fact, everyone insisted on reminding me when I refused a drink at social occasions that ‘you’re allowed one!’ Some people seemed to think that by my refusing to drink I was judging their choice to have a glass of wine.

“To be clear, I’m not. I made my own choice. When I fell pregnant with my second child, Ben, I made the same choice again. While there is a lot of conflicting information and arguments around this subject, I felt that an unknown risk wasn’t one I was willing to take.”


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1. **The House of Commons Debate on FASD**
   14th October 2014

   [http://www.parliamentlive.tv/Main/Player.aspx?meetingId=16019&player=silverlight](http://www.parliamentlive.tv/Main/Player.aspx?meetingId=16019&player=silverlight)

   You can download the debate Hansard as an MSWord file, or a PDF from [www.nofas-uk.org](http://www.nofas-uk.org)

2. **Together we can make the difference!**
   By EUFASD Alliance

   [https://www.youtube.com/watch?v=FV5nyGlnuQI](https://www.youtube.com/watch?v=FV5nyGlnuQI)

3. **Call To Make Drinking While Pregnant A Crime**
   By Sky News

   [https://www.youtube.com/watch?v=SRYdcqpgfA0](https://www.youtube.com/watch?v=SRYdcqpgfA0)

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