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Proceedings of the 2014 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group

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Abstract

The 2014 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) meeting focused on the dual themes of the risks associated with low to moderate alcohol exposure during pregnancy and knowledge translation practices to enhance the impact of scientific research. The meeting theme was titled “Low drinking versus no drinking: Matching science with policy and public perception”. Despite decades of basic science and clinical evidence that has documented the risks associated with prenatal alcohol exposure, there still exists confusion and uncertainty on the part of health professionals and the public regarding the question of whether or not there is a “safe” level of alcohol consumption during pregnancy. The first keynote presentation reviewed the data obtained from large-scale epidemiological studies that have attempted to address the question of relative risk associated with low to moderate alcohol exposure during pregnancy. This presentation was followed by an expert panel discussion of the state of scientific evidence obtained from clinical and basic science investigations concerning this question, and strategies for moving research evidence into policy and practice. The second keynote presentation presented a framework for knowledge translation and mobilization to move research discoveries toward implementation. The conference also featured updates by government agencies, FASt data talks that highlighted new and innovative findings in FASD research, and award presentations, including a lifetime achievement award presented to Dr. Kenneth Warren to acknowledge his longstanding support for FASD research. A highlight of the meeting was the presentation of the 2014 Henry Rosett award to Dr. Philip May in recognition of his substantial contributions to epidemiological studies on FASD.

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Keywords

fetal alcohol spectrum disorders; prenatal alcohol exposure; epidemiology; knowledge mobilization; Rosett award

The Fetal Alcohol Spectrum Disorders Study Group (FASDSG) held its annual meeting on June 21, 2014 in Seattle (Bellevue), WA as a satellite of the joint meeting of the Research Society on Alcoholism and International Society for Biomedical Research on Alcoholism. Approximately 200 individuals attended the study group meeting, which included professionals and students from the United States, Canada, Australia, Denmark, and South Africa. Fifteen abstracts submitted by FASDSG members were selected for brief one-slide 5-min presentations of recent research findings, of which the majority (10) were given by trainees. Eight of these trainees also received travel awards to attend the meeting and give presentations on their research. The top-ranked trainee abstract was selected to receive the Timothy A. Cudd Award. This award was established in 2013 in memory of Dr. Timothy Cudd, a longtime FASD Study Group member who was internationally recognized for his research on FASD. New for the 2014 meeting, the Research Merit Award, given annually to the trainee judged to have made the most significant contributions to FASD research, was renamed the Kenneth R. Warren Merit Award. Dr. Warren, Deputy Director of the National Institute on Alcoholism and Alcohol Abuse (Acting Director 2008–2014), initiated NIAAA's research program on FASD more than 30 years ago, and has long been a champion for FASD research initiatives. In addition to the keynote and research presentations, the FASDSG membership received updates on FASD-related activities from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Centers for Disease Control and Prevention (CDC), and the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD). Attendees also participated in a networking lunch, which gave trainees the opportunity to interact with more senior researchers and clinicians. The capstone events of the meeting were the presentation of the Kenneth R. Warren Merit Award to recognize an outstanding young researcher, and the Rosett Award, to recognize lifetime contributions, achievement, and service toward furthering FASD research.

The theme of the 2014 meeting was “Low drinking versus no drinking: Matching science with policy and public perception”. It is generally well recognized that heavy prenatal alcohol exposure causes FASD, a broad range of developmental disorders that encompasses several diagnostic subgroups including Fetal Alcohol Syndrome (FAS), partial FAS, and Alcohol Related Neurodevelopmental Disorder (ARND). In contrast, the impact of low-to-moderate alcohol consumption on pregnancy outcomes has been more controversial. Whereas some studies have found effects of low-to-moderate maternal alcohol consumption on cognitive and behavioral outcomes in offspring (Burden, Jacobson, Sokol, & Jacobson, 2005; Day, Helsel, Sonon, & Goldschmidt, 2013; O’Leary et al., 2010; Sayal, Heron, Golding, & Emond, 2007), other studies have reported no measurable effects of low-to-moderate prenatal alcohol exposure on cognitive and socio-emotional function (Bay & Kesmodel, 2011; Bay et al., 2012; Kelley et al., 2009, 2012; Robinson et al., 2010) in children and adolescents. These discrepant reports have led to conflicting views on the part of health professionals concerning the risks associated with low-to-moderate alcohol

consumption during pregnancy. Whereas the majority of government agencies and health organizations advocate for complete abstinence during pregnancy, the general public has been exposed to numerous articles published in the lay press reporting on the results of studies suggesting that “light” drinking during pregnancy has no significant adverse effects on child development. The 2014 FASDSG meeting addressed this issue by an examination of the state of the scientific evidence surrounding the question of low-to-moderate alcohol exposure during pregnancy, and a discussion regarding strategies for knowledge translation to increase the impact of scientific discoveries.

The first keynote presentation by Dr. Katrine Strandberg-Larsen, Department of Public Health, University of Copenhagen, was titled “Evidence of risk from low-to-moderate alcohol exposure during pregnancy”. Dr. Strandberg-Larsen presented data obtained from two sources: systematic reviews of the published literature on the risks associated with low-to-moderate alcohol exposure during pregnancy, and the Danish National Birth Cohort study. The question of whether or not there is a “safe” level of alcohol consumption during pregnancy continues to be debated in the popular press, in large part stimulated by publication of the results of studies that report little or no effect of low-to-moderate alcohol exposure on child outcomes. While these studies garner headlines, the actual information contained in the published reports remains difficult to interpret because of a large number of confounding factors. For example, there is no consistent definition of what constitutes “low-to-moderate” alcohol exposure during pregnancy, and different studies focus on a wide range of outcome measures taken at different developmental stages. These factors make it very difficult to compare outcomes across different studies. Compounding this problem, the dose-response relationship for alcohol to affect fetal development is poorly defined, is likely to vary across different outcome measures and with the timing of alcohol exposure, and is significantly impacted by a variety of risk modifiers (e.g., maternal and fetal genetics) that may not be known for an individual study population. Two systematic reviews published in 2007 reported on the effects of low-to-moderate prenatal alcohol exposure on pregnancy outcomes that included studies published up until 2005 (Henderson, Gray, & Brocklehurst, 2007; Henderson, Kesmodel, & Gray, 2007). The outcome measures considered in these reviews included miscarriage, stillbirth, intrauterine growth restriction, prematurity, birth weight, small for gestational age at birth, and birth defects including Fetal Alcohol Syndrome and neurodevelopmental effects. The authors of these reviews suggested that there was an association between weekly drinking and an increased risk for spontaneous abortion, and between binge drinking and neurodevelopmental effects, but no consistent evidence for other adverse consequences of low-to-moderate prenatal alcohol exposure on pregnancy outcomes. However, the authors also acknowledged that methodological weaknesses across studies made it impossible to rule out any risk associated with low-to-moderate alcohol exposure. A subsequent review (O’Leary & Bower, 2012) similarly suggested that, whereas there is no strong evidence for adverse fetal outcomes associated with low-to-moderate prenatal alcohol exposure, the threshold of alcohol exposure before the fetus is at risk is relatively low, and therefore the authors advocated for total abstinence from alcohol during pregnancy. Of interest, these authors also suggested that a number of confounding factors relating to the personal characteristics of “drinkers” versus “non-drinkers” could have had a significant impact on the observed frequency and/or severity of

adverse outcomes associated with prenatal alcohol exposure in their sample. This phenomenon has been termed the “healthy drinker effect”, which suggests that light drinkers are more likely than abstainers to be from high-income households, better educated, older, multiparous, and non-smokers. Moreover, given the widespread consensus that alcohol is harmful during pregnancy, women who have experienced difficult pregnancies and/or who are at high risk for reproductive failure are likely over-represented among non-drinkers. Finally, Dr. Strandberg-Larsen outlined the results of a large-scale meta-analysis of studies that specifically examined the impact of prenatal alcohol exposure on child neuropsychological outcomes (Flak et al., 2014). The authors of this meta-analysis reported a significant association between any binge prenatal alcohol exposure and child cognitive deficits and, based on 3 high-quality studies of 11,900 children aged 9 months to 5 years, a statistically significant detrimental association between moderate prenatal alcohol exposure and child behavior. However, the latter effect was not evident after exclusion of one large-scale study, nor was it evident when only studies that assessed moderate prenatal alcohol exposure were considered. The authors concluded that these findings support previous studies that have identified detrimental effects of prenatal binge drinking on child cognition, and suggested that prenatal alcohol exposure at levels less than daily drinking might be detrimentally associated with child behavior.

Dr. Strandberg-Larsen then reviewed data from the Danish National Birth Cohort Study, a longitudinal study that is following the offspring of close to 90,000 pregnancies recruited between 1996 and 2002 (Strandberg-Larsen et al., 2008). In this study, pregnant women were interviewed twice during the pregnancy, and then again, when their children reached the ages of 7 and 11 years old. This cohort has been used to examine the impact of prenatal alcohol exposure on pregnancy and child outcomes using maternal self-reports of alcohol intake, including the type, frequency, and amount of alcohol consumed per drinking occasion. Dr. Strandberg-Larsen outlined the results of two published studies that were designed to investigate the effects of maternal alcohol consumption during pregnancy on two measures, namely, fetal demise and neurodevelopmental outcomes. With respect to fetal death, alcohol consumption at a level of 2–3 drinks per week was found to be associated with a significant increase in the risk for spontaneous abortion during the first and second trimesters (Andersen, Andersen, Olsen, Grønbaek, & Strandberg-Larsen, 2012). However, in subsequent studies that have examined neurodevelopmental outcomes, and after adjusting for multiple confounders (e.g., maternal IQ, smoking, education, body mass index, age, parity, and pre-pregnancy drinking), low-to-moderate prenatal alcohol exposure was not found to be associated with children's intelligence, attention, executive function, behavior, or psychomotor development up to 5 years of age (Kesmodel et al., 2012). That is, two studies published in the same year using data taken from the same birth cohort found either harm (increased spontaneous abortion) or no harm (neurodevelopmental outcomes) from the same level of prenatal alcohol exposure, which created conflicting and confusing public messages. Dr. Strandberg-Larsen ended her presentation by suggesting that future studies should adopt new experimental approaches to reduce the influence of confounding factors on the data. One approach could be to stratify participants in large-scale studies based on maternal genetics (e.g., alcohol dehydrogenase alleles), as these traits would presumably be independent of environmental factors (e.g., socio-economic status).

Immediately following Dr. Strandberg-Larsen's presentation, a panel discussion was held to address some of the key issues surrounding the question of low-to-moderate alcohol exposure during pregnancy. The panel consisted of Dr. Nancy Day (University of Pittsburgh), Dr. Sandra Jacobson (Wayne State University), Dr. Katrine Strandberg-Larsen (University of Copenhagen), Dr. C. Fernando Valenzuela (University of New Mexico), and Dr. Jocelynn Cook (Canada FASD Research Network). The moderator was Dr. James Reynolds (Queen's University). Each of the panelists was asked to address a specific question relating to the issue of low-to-moderate alcohol exposure during pregnancy.

In response to the question “What are the major factors that might account for the disparate results reported from human studies that have investigated the impact of low-to-moderate alcohol exposure?” Dr. Day opened with the comment that study design is the major factor to consider when comparing epidemiological studies. Dr. Day pointed out that spurious findings could arise in any population study, regardless of sample size, because of differences in sample selection demographics and the presence or absence of long-term follow-up. Moreover, the outcome measures used in different studies vary greatly and in some cases are poorly designed. Dr. Day described the difficulty in comparing the results of different studies due to the fact that alcohol intake is itself a variable behavior that is differentially defined across studies as to amount, frequency, and duration. Poor study design and/or definition of terms, and the presence of multiple confounding variables often make it difficult to tease out the contribution of alcohol exposure on developmental outcomes. Dr. Day concluded that the field needs to come together to agree on standard definitions of terms and outcomes that would allow for comparison of results across studies.

Dr. Jacobson was asked to address the question “What are the major barriers and limitations to the study of the impact of low-moderate alcohol exposure in humans, and what strategies should be taken to overcome these issues?” In her response, Dr. Jacobson identified the lack of sensitive endpoints, insufficient consideration of effect modifiers, and poor descriptions of alcohol intake patterns as critical factors. For example, Dr. Jacobson pointed out that repeated, prospective alcohol ascertainment interviews are necessary for the accurate determination of alcohol intake, and thus an accurate determination of effect on pregnancy outcomes. Dr. Jacobson went on to point out that, for any specific adverse effect being measured, a study sample may lack power unless a sufficient number of individuals exposed above the threshold for that specific effect are included. In addition, in many studies there are measurable differences in socio-economic status, education levels, and general health between abstainers and low-to-moderate alcohol drinkers, such that the abstainer group has an elevated risk of adverse pregnancy outcomes that may obscure any effects of alcohol exposure in the low-to-moderate drinkers. Dr. Jacobson concluded that: i) sensitive outcome measures are necessary to accurately identify the effects of low-to-moderate alcohol exposure, ii) the full range of alcohol exposures needs to be included in any analyses to provide evidence that the selected outcome measures clearly show effects of high level exposure, and iii) understanding the individual differences in vulnerability is critical for identifying the effects of alcohol exposure on pregnancy outcome.

Dr. Katrine Strandberg-Larsen was then given the opportunity to respond to the comments made by Drs. Day and Jacobson. In her response, Dr. Strandberg-Larsen agreed that it has

proven to be extremely difficult to clearly address the effects of low-to-moderate alcohol exposure on pregnancy outcome in human populations. She went on to suggest that continuing to replicate studies that have been done in the past is unlikely to clarify this issue, and that perhaps new and different study designs should be developed to address the question of low-to-moderate alcohol exposure during pregnancy.

Dr. Fernando Valenzuela was asked to address the questions “How do the results obtained in experimental animal models align with the findings from human studies? What are the major strengths and limitations of animal models?” In his response, Dr. Valenzuela stated that animal models have been extremely valuable for helping to clarify the evidence for the effects of low-to-moderate alcohol exposure on offspring behavior. Both rodent and non-human primate studies have shown that low maternal blood alcohol concentrations (0.02–0.05 g/dL) have detrimental effects on the structure and function of specific neuronal populations in the brain. Dr. Valenzuela especially referenced the work of Schneider and colleagues (Schneider et al., 2013; Schneider, Moore, & Adkins, 2011) in non-human primates, in which they have demonstrated effects of moderate alcohol exposure on offspring behavior, emotional regulation, and motor coordination. Dr. Valenzuela pointed out that animal models have established that the effects of low-to-moderate alcohol exposure may be subtle (thus requiring very sensitive outcome measures), and/or may emerge at different times during development (thus the need for longitudinal assessments). The results of animal model studies can therefore be used to inform how human studies should be designed to address the question of low-to-moderate alcohol exposure during pregnancy, in that a wide range of cognitive domains should be examined across multiple developmental stages. In summarizing the limitations of animal models, Dr. Valenzuela suggested that these models have not adequately mimicked the patterns of drinking that occur in the human population, and that few studies have included an examination of risk modifiers (e.g., poly drug use, stress, etc.) that contribute to vulnerability to prenatal alcohol exposure.

The final panel member was Dr. Jocelynn Cook, who was asked to respond to the question “What are the gaps in knowledge and barriers to the effective translation of scientific knowledge into effective public policy?” To address this question, Dr. Cook first discussed the problem that creating policy is difficult, because the motivation for changes in policy can arise from different directions and reflect different interests. For this reason, policy makers will seek out the best evidence on which to base recommendations. In the specific case of low-to-moderate alcohol exposure, the evidence from epidemiological and population studies is not clear, which makes it difficult for policy makers at various levels of government to make specific recommendations. That is, there is no identifiable amount of alcohol exposure during pregnancy that could be labeled as absolutely “safe” based on current evidence. Dr. Cook went on to state that policy messaging has to have a credible basis, and that in the case of low-to-moderate alcohol exposure the combination of differing views and lack of clarity of the evidence are barriers to policy development. Dr. Cook stressed the importance of building and maintaining strong relationships between scientists and policy makers to facilitate knowledge transfer and mobilization.

The second keynote presentation was given by Dr. David Phipps, Executive Director, Research & Innovation Services, Office of Research Services, York University, and was

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titled “Maximizing the impact of research”. Dr. Phipps outlined a process for knowledge translation/knowledge mobilization that revolves around three key concepts from the PARIHS (Promoting Action on Research Implementation in Health Services) Framework: evidence, context, and facilitation. Dr. Phipps posed three questions for consideration: 1) What is the evidence that we want to communicate/translate/mobilize? 2) What is the context into which we want to put that evidence? 3) How do we facilitate making the connections between evidence and practice and policy outcomes? Dr. Phipps then went on to explain, using a practical example, the pathway by which communities or other partner organizations can be brought together with university-based researchers to form a collaborative knowledge mobilization team that can lead to social innovation, a process he termed co-production. However, he also pointed out that knowledge-to-action cycles and other models of knowledge translation are frequently overcomplicated and can themselves act as effective barriers to the evaluation of research impacts. Dr. Phipps argued that it is possible to simplify the approach by adopting a logic model that encompasses clear start and end points, and in which activities (research) lead to outputs and subsequently to outcomes. Moreover, when this happens in a co-production space, the activities become more easily disseminated, outputs of the research are more likely to be taken up by partners, and once the outcomes of research become implemented then measureable impacts can result. Within this “actionable framework”, impact is measured at the level of the end user (e.g., a non-academic partner).

Dr. Phipps then introduced the Knowledge Translation activities being conducted within NeuroDevNet, a Canadian Network of Centres of Excellence that includes over 80 scientists and clinicians from across Canada engaged in research on neurodevelopmental disorders, including FASD, Autism Spectrum Disorder, and Cerebral Palsy. The Knowledge Translation (KT) Core of NeuroDevNet, hosted at York University's Knowledge Mobilization Unit, provides services to NeuroDevNet researchers and trainees, including knowledge brokering, helping to organize KT events, creating KT products such as videos and plain language research snapshots, evaluation of KT plans for taking research through to impact, and collaborating on KT strategies for research proposals. Dr. Phipps then described successful KT collaborations in NeuroDevNet to illustrate how these approaches can work, including: i) The production of “Jacob's Story”, a play about FASD written by a former special education teacher and father who raised a child with FASD, and produced in collaboration with NeuroDevNet, and ii) a teaching module on prenatal alcohol exposure, adapted from an *in vitro* model system designed by Dr. Kathy Sulik, designed and taught to high-school science teachers by NeuroDevNet trainees that can be incorporated into classrooms.

Dr. Phipps used these examples to lead into a discussion of the PARIHS Framework, which suggests that in order to maximize the chances that research will have a desired impact there are three key elements that need to be considered, namely, evidence, context, and facilitation. Whereas scientists have proven to be very good at creating evidence from research, the same cannot be said for efforts to either identify the context into which the evidence will be applied, or develop methods for facilitation of uptake and implementation of research outputs. Dr. Phipps pointed out that recent research in the knowledge

mobilization field has shown that the engagement of partners early in the process of determining the research question and methodology (and thus the evidence that will be generated) is a critically important element for identifying the proper context into which the evidence will be placed. Dr. Phipps ended his presentation by returning to his original theme, and posing three questions that illustrate the interconnections between evidence, context, and facilitation. First, what is the evidence (i.e., actionable messages) that will be generated by the research? Second, who is the audience, when should they receive the evidence, and where should they receive the evidence (context)? Third, who are the intermediaries who will facilitate uptake of the evidence, and what media should be used for this purpose (e.g., print media, social media, etc.).

Kenneth R. Warren Merit Award: Angelina Paolozza

A. Paolozza, R. Munn, D. P. Munoz, and J. N. Reynolds. (Queen's University). Previous studies have found that children with Fetal Alcohol Spectrum Disorder (FASD) make saccades that are quantifiably different in measures such as accuracy compared with age-matched control children, but an in-depth analysis of the metrics of saccades to a visual target has not been conducted. In the current study, children and youth with an FASD ($n = 70$) and typically developing controls ($n = 112$) aged 5–18 years performed a prosaccade task, in which they were required to make visually guided saccades, in both the right and left hemifields, to peripheral targets located 10° from a central fixation point. Metric parameters (accuracy, duration, velocity, amplitude, and the slopes of the velocity curve during the acceleration and deceleration phases of the saccade) were analyzed for sex and group differences. In the control group, the initial saccades of female participants had a greater amplitude and velocity than the males. In contrast, this difference was not present in the FASD group, and the performance of females in the FASD group was selectively reduced compared to females in the control group. The accuracy of the first saccade to a visual target was significantly poorer in the FASD group compared to controls, and this effect was driven entirely by the males with FASD. When the analysis was restricted to trials in which the saccade amplitude was $9 \pm 1^\circ$ on the horizontal axis and $\pm 1^\circ$ on the vertical axis, the FASD group had significantly lower velocity and duration, but not amplitude, compared with controls. Additionally, the slope of the velocity profile was selectively decreased during the deceleration phase but not the acceleration phase in the FASD group, which led to a significantly different skew index compared to controls. These data suggest that children with FASD exhibit deficits in eye movement control and sensory-motor integration that implicate impairment in cerebellar and/or brainstem circuits. Moreover, the authors showed for the first time that prenatal alcohol exposure might have a sexually dimorphic impact on eye movement control, with females exhibiting differential vulnerability in saccade metrics, and males exhibiting less accurate saccades.

Timothy A. Cudd Award Presentation: Maria A. Infante

M. A. Infante, A. Bischoff-Grethe, E. M. Moore, R. Migliorini, S. N. Mattson, and E. P. Riley, (San Diego State University). The process of gyrification (i.e., brain surface generates sulci and gyri) allows a complex structure such as the cerebral cortex to fit within the limits of the cranium. A recent study showed that heavy prenatal ethanol exposure reduces cortical

folding complexity in 9-year-old children, even in those with normal brain size (De Guio et al., 2014). The purpose of this study was to investigate whether heavy prenatal ethanol exposure could affect cortical gyrification during adolescence. High-resolution T1-weighted anatomical magnetic resonance imaging scans were obtained from control and heavily prenatally ethanol-exposed adolescents ranging between 12 and 16 years of age. After controlling for age and sex, it was found that gyrification was reduced in prenatally ethanol-exposed adolescents in five clusters, with peak vertices in the bilateral superior parietal region, right postcentral region, and left precentral and lateral occipital regions (p 's < .001). After controlling for sex, significant age-by-group interactions were observed in four clusters. Peak vertices for these clusters were located in the right precentral and lateral occipital regions (p 's < .001) and in the left pars opercularis (p = .002) and inferior parietal regions (p = .006). The alcohol-exposed group showed age-related reductions in gyrification in all clusters whereas the control group showed increased gyrification with age in the lateral occipital cluster only. These findings suggest that heavy prenatal ethanol exposure alters cortical developmental processes during adolescence. Moreover, altered gyrification may be associated with impaired brain connectivity that may be responsible for some of the cognitive dysfunctions associated with FASD.

FAST data presentations

The presentations were divided into three sessions, each of which included a mixture of pre-clinical and clinical talks. Session I was named in honor of Dr. Kenneth R. Warren, Deputy Director of the National Institute of Alcohol Abuse and Alcoholism. The name of the presenter is highlighted in bold.

Kenneth R. Warren FAST Data Presentation Session I

J. L. Cook, C. R. Green, C. Loock, A. Chudley, N. LeBlanc, C. Lilley, J. Conry, M. Baldwin, V. Temple, M. Gillis, T. Rosales, J. Lutke, S. Clarren, B. Mallon, S. Anderson, and A. McFarlane (Canada FASD Research Network) gave a presentation on the revised and updated Canadian diagnostic guidelines for fetal alcohol spectrum disorder, which were originally released in 2005. An oversight committee of international experts has been involved in this process, and input from the FASD community has been obtained via surveys, workshops, and consultations. Particular emphasis was given to issues related to nomenclature, impaired brain domains, and morphological alterations. The current draft of the FASD diagnostic guidelines includes three categories: 1) FASD: Neurodevelopmental disorder associated with prenatal ethanol exposure with sentinel facial features (this category includes the presence of three sentinel facial features and alterations in three brain domains but does not require confirmation of prenatal ethanol exposure); 2) FASD: Neurodevelopmental disorder associated with prenatal ethanol exposure without sentinel facial features (this category includes confirmed prenatal ethanol exposure and the presence of alterations in three brain domains); and 3) Prenatal ethanol exposure: At risk for neurodevelopmental disorders (this category also includes confirmed prenatal ethanol exposure and the presence of some impairment in brain domains). The guidelines are expected to be finalized in the fall of 2014.

R. C. Carter¹, C. D. Molteno², C. Duggan³, L. Bechard³, E. M. Meintjes², M. K. Georgieff⁴, J. L. Jacobson^{2,5}, and S. W. Jacobson^{2,5} (¹Columbia University, ²University of Cape Town, ³Boston Children's Hospital, ⁴University of Minnesota Medical School and ⁵Wayne State University School of Medicine) reported on the impact of heavy drinking during pregnancy on iron status in Cape Town, South Africa. Animal and human studies have demonstrated that prenatal ethanol exposure is associated with iron deficiency in offspring. The purpose of this study was to investigate whether this is related to alcohol-induced maternal iron deficiency. Maternal ferritin and iron status levels were measured in the placentas of control and heavy binge-drinking pregnant women with similar levels of iron intake. It was found that maternal ferritin levels are increased in heavily drinking women and that there was a lower percent of women with iron deficiency in this group. The mechanism of this effect is unknown but could involve increased iron absorption in heavily drinking women. Importantly, the infants (6.5 months old) of heavily drinking women had lower ferritin levels and were more likely to have iron deficiency than those of control women. At this age, infant iron stores are determined by iron accumulation during fetal development, which depends on both maternal iron status and placental iron transport. Given that maternal iron status was better in the heavily drinking group, it was concluded that alterations in placental iron transport might be responsible for the iron deficiency observed in the 6.5-month-old infants.

K. Moritz, E. Dorey, J. Kalisch-Smith, M. Wlodek, M. Pantaleon and E. Gardebjer (University of Queensland, Australia) explored the effect of periconception alcohol exposure on insulin resistance and renal-cardiovascular function in rats. Rats were exposed to ethanol for 4 days before mating and the first 4 days of gestation (i.e., prior to implantation) using a liquid diet paradigm that produces blood alcohol levels near 0.15 g/dL. It was found that alcohol exposure resulted in a similar degree of insulin resistance to that caused by a high fat diet in adult offspring. This was associated with hyperinsulinemia, increased adiposity, elevated diuresis, and left ventricular hypertrophy in ethanol-exposed animals. These findings indicate that ethanol exposure during early stages of pregnancy can result in long-lasting metabolic, renal, and cardiovascular alterations in adult offspring.

T. T. Nguyen, R. Risbud, C. Chambers, and J. D. Thomas (San Diego State University) investigated the possible association between dietary nutrient intake and neuropsychological performance in children with prenatal alcohol exposure. It is well known that nutritional deficiencies can exacerbate the effects of prenatal ethanol exposure and that nutritional supplementation can mitigate its effects. In this study, dietary intake was measured in children (5–10 years old) with confirmed history of heavy prenatal ethanol exposure using parent interviews. The Quotient Attention Deficit Hyperactivity Disorder System was administered to these children to assess attention, hyperactivity, and impulsivity. Compared to recommended intake levels, children with confirmed heavy prenatal ethanol were found to consume inadequate levels of several key nutrients, including vitamins E and K, choline, omega-3 fatty acids, calcium, and potassium. Importantly, levels for several nutrients (vitamins A, B2, B12, and D; choline, omega-3 fatty acids, calcium, magnesium, phosphorous, and potassium) were found to be negatively correlated with measures of hyperactivity. For example, higher dietary choline levels were associated with increased

time sitting still. These findings suggest that lower intake of key nutrients in prenatally ethanol-exposed children is associated with increased hyperactivity, providing further support for the potential utility of nutritional supplementation in the treatment of FASD.

R. Wang, K. A. Hausknecht, Y. L. Shen, P. Slepian, A. Wen, and R. Y. Shen (University at Buffalo) studied the effect of postnatal environmental enrichment on the prenatal ethanol exposure-induced increase of drug addiction risk. Pregnant rats were administered alcohol in a binge-like manner via intragastric gavage between gestational days 8 and 20. Offspring were reared either under enriched (handled daily before weaning and group housed in large cages with toys that were moved daily to create novelty) or impoverished (not handled before weaning and singly housed in small cages after weaning) conditions. At 11 weeks of age, rats were then trained to self-administer amphetamine using a progressive ratio schedule. In rats that were raised under impoverished conditions, prenatal ethanol exposure enhanced amphetamine self-administration. However, this long-lasting effect of prenatal ethanol exposure was abolished in rats raised under enriched conditions. These results suggest that environmental enrichment could be an effective therapeutic intervention against the increased risk of developing substance abuse disorders associated with FASD.

FASt Data Presentations II

S. K. Clarren, C. Halliwell, R. Seboldt, and J. Cook (Canada FASD Research Network) explored the development of a database that would enable the collection of FASD diagnostic and treatment data from clinics across Canada, which could then be used for research, surveillance, and informing best practices and policies. Twenty-five clinics in four provinces provided data. Abnormal adaptive scores were consistently found. Highly variable patterns of neuropsychological dysfunctions were found, with alterations in executive function and memory among the most common. No specific patterns of domain abnormalities or functional diagnoses were identified and treatment recommendations were complex, involving 10 or more interventions per client (for example, special education, social services, and mental health). These findings reflect the severe and diverse clinical characteristics of dysfunctions associated with FASD, and emphasize the need for multidisciplinary interventions to effectively help both the patients and their families.

S. W. Jacobson^{1,2}, J. L. Jacobson^{1,2}, C. D. Molteno², F. Warton², N. Lindinger², P. Wintermark⁵, P. Taylor², N. Dodge¹, E. Grant³, L. Zollei³, S. Warfield⁴, H. E. Hoyme⁶, C. Warton², A. van der Kouwe⁴, and E. M. Meintjes² (¹Wayne State University School of Medicine, ²University of Cape Town, ³Boston Children's Hospital/Harvard University, ⁴Martinos Center for Biomedical Imaging/Massachusetts General Hospital, ⁵Montréal Children's Hospital, ⁶Sanford School of Medicine, University of South Dakota, Vermillion, South Dakota) investigated the use of magnetic resonance imaging (MRI) studies to assess structural brain alterations in newborns exposed to ethanol prenatally. Non-sedated newborns were assessed using a custom-designed birdcage coil that increases the signal-to-noise ratio of the MRI scan by about 2-fold. It was found that the corpus callosum was disproportionately smaller in ethanol-exposed newborns compared to controls. Importantly, reduced corpus callosum size was observed, not only in newborns with fetal alcohol syndrome (FAS), but also in newborns that did not display the full

spectrum of the characteristics of FAS. These findings indicate that structural MRI could be useful for the early detection of FASD.

K. Uban¹, K. Lynch¹, M. Herting¹, P. Gautam¹, E. Kan¹, J. Colby², and E. Sowell^{1,3}
(¹Children's Hospital Los Angeles, Department of Pediatrics, Los Angeles, CA 90027, ²UCLA, David Geffen School of Medicine, Los Angeles, CA 90095, ³USC, Neuroscience, Los Angeles, CA 90089) used diffusion tensor imaging (DTI) to assess the impact of prenatal ethanol exposure on white matter tract integrity in children and adolescents (age 8–18 years). This technique measures the directional restriction of water diffusion, known as fractional anisotropy, which is associated with white matter integrity, including myelination status. These studies revealed an overall reduction in fractional anisotropy in the brains of individuals with FASD. The symmetry of white matter microstructure was reduced in the anterior thalamic radiation (which connects the thalamus with the prefrontal cortex) of females, and in the corticospinal tracts of both males and females. These findings indicate that prenatal ethanol exposure produces sex-dependent alterations in the symmetry of thalamocortical and corticospinal connections.

C. W. Bird¹, F. Candelaria-Cook¹, C. Magcalas¹, S. Davies², D. D. Savage², C. F. Valenzuela², and D. A. Hamilton^{1,2} (¹University of New Mexico, Department of Psychology, ²University of New Mexico Health Sciences Center, Department of Neurosciences) studied the impact of moderate prenatal ethanol exposure on the function of N-methyl-D-aspartate (NMDA) receptors in the rat ventrolateral frontal cortex. Rats were exposed to ethanol during pregnancy using a limited-access drinking paradigm that produces blood alcohol levels near the legal intoxication limit. In the adult offspring of these rats, it was found that ethanol exposure increases binding of [³H]-ifenprodil to GluN2B subunit-containing NMDA receptors in cortical layers II/III of the agranular insular cortex. Consistent with this finding, whole-cell patch-clamp electrophysiological studies revealed an enhanced inhibitory effect of ifenprodil on NMDA receptor-mediated excitatory postsynaptic currents. These results suggest that moderate prenatal ethanol exposure alters glutamatergic transmission in the agranular insular cortex, which may explain some of the behavioral deficits associated with FASD, including social behavior and executive function alterations.

FASt Data Presentations III

R. Migliorini, **E. M. Moore**, M. A. Infante, L. Glass, S. N. Mattson, and E. P. Riley (San Diego State University) investigated whether prenatal ethanol exposure alters the structural correlates of inhibitory control by modeling the relationship between cortical thickness and behavioral inhibition. In addition, the degree to which multi-method inhibition assessments reflect the same underlying brain structure was investigated by analyzing both a neurocognitive and caregiver-report measure. In adolescents (11–17 years of age), it was found that a thinner cortex in both the right anterior cingulate and ventromedial prefrontal regions was associated with better performance in a neurocognitive test that assesses inhibitory control in prenatally alcohol-exposed subjects. In contrast, these findings were associated with worse performance for control subjects. In the left middle and inferior temporal gyri, thinner cortex was associated with poorer inhibition scores in the

neurocognitive test for alcohol-exposed subjects, but better inhibition scores in the caregiver-report questionnaire for controls. These results indicate that performance on the neuropsychological test is associated with cortical thickness in frontal regions important for inhibition and executive control, whereas the caregiver report is related to temporal regions involved in socio-emotional processes. These findings suggest that the two measures capture different components of inhibition, potentially providing an anatomical basis for discrepancies between caregiver reports and neuropsychological tests of inhibition.

N. M. Lindinger¹, J. L. Jacobson^{1,2}, V. Diwadkar², S. Malcolm-Smith¹, C. D. Molteno¹, E. M. Meintjes¹, K. Thomas¹, and S. W. Jacobson^{1,2} (¹University of Cape Town, Cape Town, South Africa, and ²Wayne State University, Detroit, MI 48201) investigated affective appraisal and working memory in children with fetal alcohol spectrum disorders. Previous studies suggest that children with FAS have difficulty reading people's emotions and social cues. In this study, an affective appraisal task was administered to control and prenatally ethanol-exposed children (9–12 years old). This task includes sequentially presented neutral, happy, sad, angry, and fearful faces. The subject presses buttons to indicate whether the current face shows the same or different affect as the previous face. It was found that children with partial FAS were less likely to correctly identify an angry face and more likely to misidentify a non-angry face as angry. Qualitative analysis of responses suggests that children in the FAS group engaged in affective appraisal by performing more slowly, while those with partial FAS responded more impulsively and less accurately, particularly when assessing angry and non-angry faces.

J. L. Wagner, and C. R. Goodlett (Indiana University Purdue University, Indianapolis) explored the effect of three different models of single-episode binge-like developmental ethanol exposure on spatial learning and memory in adult mice: 1) a single very high dose of ethanol (5.8 g/kg 25% v/v alcohol, intraperitoneal [i.p.]; peak blood alcohol level near 700 mg/dL) administered once daily on gestational day 8; 2) the same very high dose, but separated into two i.p. injections administered 4 h apart on gestational day 8 (peak blood alcohol level after first injection near 300 mg/dL and after second injection near 500 mg/dL); and 3) injection of 5.0 g/kg alcohol divided into two subcutaneous injections administered 2 h apart on postnatal day 7. Mice were then gavaged with two neuroprotective peptides (D-NAP + D-SAL) between postnatal days 67 and 76 and their performance in the Morris water maze task was assessed. In contrast to recent results (Incerti et al., 2010), injection of ethanol during gestational day 8 did not produce significant alterations in spatial learning and memory. In contrast, injection during postnatal day 7 did produce significant alterations in the Morris water maze test. However, treatment with the neuroprotective peptides did not improve learning and memory in any of these developmental ethanol-exposure models.

V. Lam, C. Rainekei, W. Comeau, L. Ellis, W. Yu, and J. Weinberg (University of British Columbia) characterized the effects of hypothalamic-pituitary-adrenal (HPA) axis dysregulation by prenatal alcohol exposure on behavior in novel and stressful contexts following chronic mild stress. Pregnant rats were exposed to ethanol using a liquid diet paradigm. Pair-fed and *ad libitum*-fed controls were included in the experimental design. Sham surgery or adrenalectomy with corticosterone replacement at low basal levels in

drinking water was performed in adult offspring. After recovery, rats were exposed to chronic mild stress or left untreated. No significant differences among treatment groups were found in male rats. However, it was found that in the elevated plus-maze test, prenatal alcohol exposure increases time spent in the open arm in female sham animals not exposed to chronic mild stress, and chronic mild stress reduced open arm time in these animals to control levels. Risk assessment (i.e., the time spent stretching into the open arm to determine if it is safe to go into it) was not significantly different among treatment groups in female rats not exposed to chronic mild stress but was decreased in prenatally ethanol-exposed females that underwent chronic mild stress. Adrenalectomy plus corticosterone supplementation eliminated differences in open-arm time and risk assessment in female rats from the three diet groups. These findings suggest that prenatal alcohol exposure alters anxiety-like behavior in a manner that depends on whether rats undergo chronic mild stress, and that this effect may depend on HPA axis dysregulation.

X. Dou¹, X. Chen², Y.-S. Chen², and M.-E. Charness¹ (¹VA Boston Healthcare System and Department of Neurology, Harvard Medical School, West Roxbury, MA, 02132; ²University of Illinois College of Medicine at Peoria; Peoria, IL 61605) studied the role of tyrosine phosphorylation on ethanol-induced inhibition of cell adhesion mediated by the L1 adhesion protein. L1 is phosphorylated on tyrosine 1176 by Src kinase, and mutation of this residue into leucine abolished ethanol-induced inhibition of L1 adhesion. Inhibitors of Src block ethanol-induced inhibition of L1 adhesion. Western blot studies with an antibody that selectively recognizes the dephosphorylated form of L1 showed that tyrosine 1176 phosphorylation is higher in ethanol sensitive NIH/3T3 cells and day-10 embryos from ethanol-sensitive C57BL/6J mice (which display a higher incidence of ethanol-induced ocular defects) but not ethanol-insensitive C57BL/6N mice. These results indicate that tyrosine phosphorylation of these key adhesion molecules modulate sensitivity to the actions of ethanol during development. The investigators postulate that genes for proteins that regulate tyrosine phosphorylation may be susceptibility genes for FASDs.

Henry Rosett Award

The 2014 Henry Rosett Award recipient was Dr. Philip May (University of North Carolina). Dr. May was introduced by Dr. Sandra Jacobson (Wayne State University). Dr. Jacobson outlined Dr. May's career spanning more than 30 years as a leader in FASD epidemiological research in the US and worldwide. Dr. Jacobson described how Dr. May's methodology of active case ascertainment of FASD in school-age children has had enormous impact for accurately estimating the prevalence of FASD in various populations and for alerting governments to the scope of this major public health issue.

Dr. May recounted his career directing epidemiological studies in FASD, which he described as "Shoe-Leather Epidemiology" because it entailed getting out into the field and immersing clinical, epidemiological, and basic science researchers in active case ascertainment studies. The first epidemiological study that Dr. May was involved in began in 1979 with a prevalence study of FAS/FAE among American Indians of the Southwestern US. It was funded by the Indian Health Service. Dr. May's group found highly variable rates of FAS/FAE among different Indian tribes (May, Hymbaugh, Aase, & Samet, 1983), with

very high rates found in Southwest Plains tribes, which also had the highest rates of binge drinking. These studies convinced Dr. May that FAS/FAE were indeed real conditions with higher prevalence than previously recognized. The FAS Epidemiology Research (FASER) group was established in 1992 with funding from the Centers for Disease Control to conduct FASD prevalence studies in New Mexico. Since 1994, FASER has been continuously funded by NIAAA. Dr. May acknowledged the large number of individuals who have been part of the multi-disciplinary FASER teams, including pediatric dysmorphologists, educational diagnosticians and psychologists, maternal interviewers, field administrators and field workers, data and statistical specialists, epidemiologists, and other public health researchers who have worked together in various parts of the United States, Italy, and South Africa since 1997.

Dr. May outlined how the active case ascertainment process has evolved over many years, including the critical role that dysmorphology examinations have played as the most direct and valid indicator of prenatal alcohol exposure. Dr. May also acknowledged that while active case ascertainment is the best method to identify the prevalence of FASD, this approach will generally yield minimal prevalence estimates, in that many cases on the milder end of the spectrum are likely to be missed. However, in-school prevalence studies using active case ascertainment methods in the US have consistently found that: i) FASD is equally represented across different ethnic groups, and ii) the prevalence rates of FASD in the population are much higher than the generally accepted rate of 1%. Dr. May ended his presentation with the conclusion that prenatal alcohol exposure may well be the leading cause of intellectual deficiency in many societies around the world.

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References

- Andersen AM, Andersen PK, Olsen J, Grønbaek M, Strandberg-Larsen K. Moderate alcohol intake during pregnancy and risk of fetal death. *International Journal of Epidemiology*. 2012; 41:405–413. [PubMed: 22253313]
- Bay B, Kesmodel US. Prenatal alcohol exposure – a systematic review of the effects on child motor function. *Acta Obstetrica et Gynecologica Scandinavica*. 2011; 90:210–226.
- Bay B, Støvring H, Wimberley T, Denny CH, Mortensen EL, Eriksen HL, et al. Low to moderate alcohol intake during pregnancy and risk of psychomotor deficits. *Alcoholism: Clinical and Experimental Research*. 2012; 36:807–814.
- Burden MJ, Jacobson SW, Sokol RJ, Jacobson JL. Effects of prenatal alcohol exposure on attention and working memory at 7.5 years of age. *Alcoholism: Clinical and Experimental Research*. 2005; 29:443–452.
- Day NL, Helsel A, Sonon K, Goldschmidt L. The association between prenatal alcohol exposure and behavior at 22 years of age. *Alcoholism: Clinical and Experimental Research*. 2013; 37:1171–1178.
- De Guio F, Mangin JF, Rivière D, Perrot M, Molteni CD, Jacobson SW, et al. A study of cortical morphology in children with fetal alcohol spectrum disorders. *Human Brain Mapping*. 2014; 35:2285–2296. [PubMed: 23946151]

- Flak AL, Su S, Bertrand J, Denny CH, Kesmodel US, Cogswell ME. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. *Alcoholism: Clinical and Experimental Research*. 2014; 38:214–226.
- Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2007; 114:243–252. [PubMed: 17233797]
- Henderson J, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. *Journal of Epidemiology and Community Health*. 2007; 61:1069–1073. [PubMed: 18000129]
- Incerti M, Vink J, Roberson R, Wood L, Abebe D, Spong CY. Reversal of alcohol-induced learning deficits in the young adult in a model of fetal alcohol syndrome. *Obstetrics and Gynecology*. 2010; 115:350–356. [PubMed: 20093910]
- Kelly Y, Sacker A, Gray R, Kelly J, Wolke D, Quigley MA. Light drinking in pregnancy, a risk for behavioural problems and cognitive deficits at 3 years of age? *International Journal of Epidemiology*. 2009; 38:129–140. [PubMed: 18974425]
- Kelly YJ, Sacker A, Gray R, Kelly J, Wolke D, Head J, et al. Light drinking during pregnancy: still no increased risk for socioemotional difficulties or cognitive deficits at 5 years of age? *Journal of Epidemiology and Community Health*. 2012; 66:41–48. [PubMed: 20924051]
- Kesmodel US, Eriksen HL, Underbjerg M, Kilburn TR, Støvring H, Wimberley T, et al. The effect of alcohol binge drinking in early pregnancy on general intelligence in children. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2012; 119:1222–1231. [PubMed: 22712770]
- May PA, Hymbaugh KJ, Aase JM, Samet JM. Epidemiology of fetal alcohol syndrome among American Indians of the Southwest. *Social Biology*. 1983; 30:374–387. [PubMed: 6336013]
- O'Leary CM, Bower C. Guidelines for pregnancy: what's an acceptable risk, and how is the evidence (finally) shaping up? *Drug and Alcohol Review*. 2012; 31:170–183. [PubMed: 21955332]
- O'Leary CM, Bower C, Zubrick SR, Geelhoed E, Kurinczuk JJ, Nassar N. A new method of prenatal alcohol classification accounting for dose, pattern and timing of exposure: improving our ability to examine fetal effects from low to moderate alcohol. *Journal of Epidemiology and Community Health*. 2010; 64:956–962. [PubMed: 19843498]
- Robinson M, Oddy WH, McLean NJ, Jacoby P, Pennell CE, de Klerk NH, et al. Low-moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2010; 117:1139–1150. [PubMed: 20528867]
- Sayal K, Heron J, Golding J, Emond A. Prenatal alcohol exposure and gender differences in childhood mental health problems: a longitudinal population-based study. *Pediatrics*. 2007; 119:e426–e434. [PubMed: 17272604]
- Schneider ML, Larson JA, Rypstat CW, Resch LM, Roberts A, Moore CF. Moderate-level prenatal alcohol exposure enhances acoustic startle magnitude and disrupts prepulse inhibition in adult rhesus monkeys. *Alcoholism: Clinical and Experimental Research*. 2013; 37:1729–1736.
- Schneider ML, Moore CF, Adkins MM. The effects of prenatal alcohol exposure on behavior: rodent and primate studies. *Neuropsychology Review*. 2011; 21:186–203. [PubMed: 21499982]
- Strandberg-Larsen K, Nielsen NR, Grønbaek M, Andersen PK, Olsen J, Andersen AM. Binge drinking in pregnancy and risk of fetal death. *Obstetrics and Gynecology*. 2008; 111:602–609. [PubMed: 18310362]

- Review of evidence for effects of low-to-moderate prenatal alcohol exposure on offspring
- Expert panel discussion concerning the state of scientific evidence obtained from clinical and basic science investigations of low-to-moderate prenatal alcohol exposure
- Framework for knowledge translation and mobilization to move research discoveries towards implementation

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