Preventing the Preventable: Where Do We Stand on Fetal Alcohol Spectrum Disorders in 2016?

Christina Chambers, PhD, MPH
University of California San Diego
Robert L. Brent Lecture
Teratogen Update
Prevalence of Alcohol Consumption

Last 30 days women 18-44; 1991-2005; MMWR 2009;58:529
Binge Episodes $\geq 4$ Drinks

Last 30 days women 18-44 who binged; 2006-2010; MMWR 2012;61:534
Fast Forward: 2013

Map 1: State-Specific Weighted Prevalence Estimates of Alcohol Use
(Percentage of Any Use* & Binge Drinking†)
Among Women Aged 18 – 44 Years — BRFSS, 2013

* One or more drinks during the last 30 days
† Four or more drinks on any one occasion during the last 30 days
Fast Forward: 2013

Map 4: Percentage of Binge Drinkers† Among Women Who Reported Any Alcohol Use*, Women Aged 18-44 Years — BRFSS, 2013

†Four or more drinks on any one occasion during the last 30 days
*One or more drinks during the last 30 days
Prevalence of Fetal Alcohol Spectrum Disorders

Critical Review

Worldwide Prevalence of Fetal Alcohol Spectrum Disorders: A Systematic Literature Review Including Meta-Analysis

Sylvia Roozen, Gjaalt-Jorn Y. Peters, Garjo Kok, David Townend, Jan Nijhuis, and Leopold Curfs

Background: Although fetal alcohol spectrum disorders (FASD) affect communities worldwide, little is known about its prevalence. The objective of this study was to provide an overview of the global FASD prevalence.

Methods: We performed a search in multiple electronic bibliographic databases up to August 2015, supplemented with the ascendency and descendancy approach. Studies were considered when published in English, included human participants, and reported empirical data on prevalence or incidence estimates of FASD. Raw prevalence estimates were transformed using the Freeman-Tukey double arc sine transformation so that the data followed an approximately normal distribution. Once the pooled prevalence estimates, 95% confidence intervals and prediction intervals were calculated based on multiple meta-analyses with transformed proportions using random effects models, these estimates were transformed back to regular prevalence rates. Heterogeneity was tested using Cochran’s Q and described using the I² statistic.

Results: Amongst studies that estimated prevalence in general population samples, considerable differences in prevalence rates between countries were found and therefore separate meta-analyses for country were conducted. Particularly high-prevalence rates were observed in South Africa for fetal alcohol syndrome (55.42 per 1,000), for alcohol-related neurodevelopmental disorder (20.25 per 1,000), and FASD (113.22 per 1,000). For partial fetal alcohol syndrome high rates were found in Croatia (43.01 per 1,000), Italy (66.89 per 1,000), and South Africa (28.29 per 1,000). In the case of alcohol-related birth defects, a prevalence of 10.82 per 1,000 was found in Australia. However, studies into FASD exhibited substantial heterogeneity, which could only partly be explained by moderators, most notably geography and descent, in meta-regressions. In addition, the moderators were confounded, making conclusions as to each moderator’s relevance tentative at best.

• Common ascertainment methods among population-based samples of first grade children in 4 U.S. communities

• Common tools/protocols for assessing
  – Alcohol consumption in pregnancy
  – Physical features
  – Neurobehavioral performance

• Common diagnostic classification criteria

Hoyme et al, Pediatrics, in press
FAS + pFAS 1.1-2.5%; FASD 2.4-4.8%

*Pediatrics*, 2014;134:855
What Can Be Done?
Prevention & Intervention

- Screening, referral and brief intervention in primary care for women of reproductive age
- Better biomarkers of exposure in pregnancy
- Earlier and more accurate diagnosis of affected children
- Understanding of potential protective/susceptibility factors that can lead to treatments or interventions
- Engagement of the medical community to recognize that FASD is not a rare phenomenon
Prevention & Intervention

• Screening, referral and brief intervention in primary care for women of reproductive age
• Better biomarkers of exposure in pregnancy
• Earlier and more accurate diagnosis of affected children
• Understanding of potential protective/susceptibility factors that can lead to treatments or interventions
• Engagement of the medical community to recognize that FASD is not a rare phenomenon
Planning and Implementing Screening and Brief Intervention for Risky Alcohol Use

A Step-by-Step Guide for Primary Care Practices
Prevention & Intervention

• Screening, referral and brief intervention in primary care for women of reproductive age
• Better biomarkers of exposure in pregnancy
• Earlier and more accurate diagnosis of affected children
• Understanding of potential protective/susceptibility factors that can lead to treatments or interventions
• Engagement of the medical community to recognize that FASD is not a rare phenomenon
CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

Our Mission

The purpose of this consortium is to inform and develop effective interventions and treatment approaches for FASD, through multidisciplinary research involving basic, behavioral and clinical investigators and projects. We hope to develop an infrastructure to foster collaboration and coordinate basic, clinical and translational research on FASD. We welcome your input and your feedback.

National Institute on Alcohol Abuse and Alcoholism
Ukraine Cohort Study

- Prospective pregnancy cohort, 2004-2017
- Collaboration with Omni-Net Centers in Ukraine
- Participants were recruited at Rivne Regional Medical Diagnostic Center and the Khmelnytsky Perinatal Center
- Moderate to heavily exposed women in early pregnancy and low/unexposed women enrolled
- Blood samples collected 2nd and 3rd trimesters
- Physical evaluations for features of FASD and growth
- Neurobehavioral evaluations at 6 and 12 months and again at preschool age
Ukraine Cohort Study
Ukraine Cohort Study
Ukraine Cohort Study – Protective Factors

Additional 750 mg choline supplement for 25%

Multivitamin/mineral supplement provided for 50%
Bayley Scales of Infant Development MDI at 6 Months by Alcohol Group and by Micronutrient Supplement

Coles et al., 2015 Matern Child Health J

Alcohol dose p < 0.001

1 Mean difference: Supplement use = -5.64, df=1, p<.004, MMV+>MMV-
2 Mean difference, Child Sex = -4.46, df=1, p<.024, girls> boys
Additional Questions

How do mothers who drink differ from mothers who do not?

Biomarker of exposure

Could help with identifying who needs intervention
Additional Questions

How do mothers of FASD children differ from mothers who drink and have unaffected children?

Biomarker of effect

Could help with developing treatments
In What Ways Can We Address These Questions?

• Epigenetics: In mouse models of prenatal alcohol, evidence that epigenetic processes such as DNA methylation may underlie long-term changes in gene expression patterns

• MicroRNAs: In mouse models of prenatal alcohol, transcription may be further fine-tuned by altered microRNA expression

In What Ways Can We Address These Questions?

- MicroRNAs: One human study of 14 drinking mothers found specific serum microRNA expression significantly altered.
- Inflammation: Inflammatory and stress markers are altered in mouse models of prenatal alcohol exposure.

Ukraine Cohort Study Design

• Nested case-control analysis
  – Group 1: HEa – Alcohol-Exposed with FASD affected child
  – Group 2: HEua – Alcohol-Exposed with unaffected child
  – Group 3: UE – Low or no alcohol exposure

• Three independent analyses of same datasets
  – Maternal methylation status (Kelly Frazer, UCSD) N’s = 19, 21, 55
  – Maternal miRNA status (Rajesh Miranda, Texas A&M) N’s = 22, 22, 23
  – Maternal inflammatory marker status (Joanne Weinberg, UBC) N’s = 35, 22, 95
Maternal Methylation Status
2\textsuperscript{nd} and 3\textsuperscript{rd} Trimester
Differential Methylation

- **Group 1 vs 2**
  - 9 significant CpGs
  - (padj < 0.05)
    - all Hypomethylated in Group 1
    - Genes: OR2A2, PCDHB17, LOC115110, TBC1D16, ITPK1

- **Group 1 vs 3**
  - 4 significant CpGs
    - (padj < 0.05)
    - Genes: ADARB2, PANX2
Differentially Methylated Genes – 1 vs 2

- OR2A1, PCDHB17, LOC115110, TBC1D16, ITPK1

OR2A1

From Wikipedia, the free encyclopedia

Olfactory receptor 2A1 (OR2A1) is a protein that in humans is encoded by the OR2A1 gene.

Olfactory receptors interact with odorant molecules in the nose, to initiate a neuronal response that triggers the perception of a smell. The olfactory receptor proteins are members of a large family of G-protein-coupled receptors (GPCRs) arising from single coding-exon genes. Olfactory receptors share a 7 transmembrane domain structure with many neurotransmitter and hormone receptors and are responsible for the recognition and G-protein-mediated transduction of odorant signals. The olfactory receptor gene family is the largest in the genome. The nomenclature assigned to the olfactory receptor genes and proteins for the organism is independent of other organisms.

ITPK1

From Wikipedia, the free encyclopedia

Inositol-tetrakisphosphate 1-kinase is an enzyme that in humans is encoded by the ITPK1 gene.

It is involved in inositol signaling pathways which regulate the conductance of calcium-activated chloride channels, and therefore could be relevant in the study of cystic fibrosis.
Maternal miRNA Expression
2nd and 3rd Trimester
<table>
<thead>
<tr>
<th>miRNA</th>
<th>MIMAT#</th>
<th>Exposure Group p&lt; BH</th>
<th>UE</th>
<th>HEua</th>
<th>HEa</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsa-miR-222-5p</td>
<td>MIMAT0004569</td>
<td>0.006</td>
<td>Mid Preg 16.8686</td>
<td>Late Preg 16.7660</td>
<td>Mid Preg 16.3727</td>
</tr>
<tr>
<td>hsa-miR-187-5p</td>
<td>MIMAT0004561</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-299-3p</td>
<td>MIMAT0000687</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-491-3p</td>
<td>MIMAT0004765</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-885-3p</td>
<td>MIMAT0004948</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-518f-3p</td>
<td>MIMAT0002842</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-760</td>
<td>MIMAT0004957</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-671-5p</td>
<td>MIMAT0003880</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-449a</td>
<td>MIMAT0001541</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-204-5p</td>
<td>MIMAT0000265</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-519a-3p</td>
<td>MIMAT0002869</td>
<td>0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-363-3p</td>
<td>MIMAT0000707</td>
<td>0.065</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-378a-5p</td>
<td>MIMAT0000731</td>
<td>0.065</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-539-5p</td>
<td>MIMAT0003163</td>
<td>0.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-518b</td>
<td>MIMAT0002844</td>
<td>0.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-133b</td>
<td>MIMAT0000770</td>
<td>0.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-10b-5p</td>
<td>MIMAT0000254</td>
<td>0.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-517c-3p</td>
<td>MIMAT0002866</td>
<td>0.076</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-518e-5p</td>
<td>MIMAT0005450</td>
<td>0.076</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-524-3p</td>
<td>MIMAT0002850</td>
<td>0.088</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsa-miR-147b</td>
<td>MIMAT0004928</td>
<td>0.097</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Top 5% high-variance miRNAs*,#

Confusion Matrix for Group HEa vs. UE

<table>
<thead>
<tr>
<th>Classification</th>
<th>True HEa</th>
<th>True UE</th>
<th>Classification error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classified as HEa</td>
<td>18</td>
<td>2</td>
<td>0.182</td>
</tr>
<tr>
<td>Classified as UE</td>
<td>4</td>
<td>21</td>
<td>0.087</td>
</tr>
</tbody>
</table>

*With demographic and clinical variables. Overall misclassification rate = 13.33
#Mid- and late-pregnancy miRNAs included in model as separate variables

Overall misclassification rate = 13.33

*Mid- and late-pregnancy miRNAs included in model as separate variables
Maternal Markers of Inflammation
2\textsuperscript{nd} and 3\textsuperscript{rd} Trimester

Cytokines, Chemokines, Angiogenesis and Vascular Injury Markers
Heat Map 40 Analytes 2\textsuperscript{nd} Trimester
Heat Map 40 Analytes 3rd Trimester
2\textsuperscript{nd} to 3\textsuperscript{rd} Trimester
Prevention & Intervention

- Screening, referral and brief intervention in primary care for women of reproductive age
- Better biomarkers of exposure in pregnancy
- Earlier and more accurate diagnosis of affected children
- Understanding of potential susceptibility factors that can lead to treatments/interventions
- Engagement of the medical community to recognize that FASD is not a rare phenomenon
CDC Practice and Implementation Centers (PIC)

- Regional initiative to increase awareness and skill level for various specialists
- In 2014, focus shifted from individual training for medical and allied health care professionals to impacting healthcare practice at the systems level and focusing on prevention opportunities
- National partnerships with AAP, ACOG, University of Pittsburgh School of Nursing, University of Texas Austin School of Social Work, and NOFAS
Our Challenge
Questions or Comments?