Mental Health and Brain Abnormalities in Children with PAE and Co-Occurring Risks

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Disclosure of Conflict of Interest

• CL’s spouse is an employee of General Electric Healthcare

• The speakers declare no other affiliations (financial or otherwise) with pharmaceutical, medical device or communications organizations

• None of the speakers will make therapeutic recommendations for medications that have not received regulatory approval.
Objectives

1. Identify underlying neurological correlates of mental health in children and youth with prenatal alcohol exposure (PAE).

2. Identify how neuropsychological processes of children and youth with PAE are associated with mental health issues.

3. Describe how mental health issues in FASD impacts diagnosis and service delivery.

4. Explore how co-occurring exposures interact with PAE.
Child Development Centre
Development of a Cumulative Risk Diagnostic Clinic (CRDC)

• A Collaboration between Health and Children’s Services
  – Literature Review and Expert Consultation
  – Two-year pilot with Paediatrics for Kids in Care (P-KIC) (2011-2013)

• CRDC Established (2015-Present)
CRDC Background: Individuals Have Other Adverse Exposures

• Community pediatricians’ feedback that PAE is not the only important exposure.

• Child Welfare feedback that the comprehensive journey of a child and understanding the resulting functional needs is a priority.

• Literature regarding the importance of postnatal exposures on child outcomes.

• Our local clinical and research collaboration with Developmental Psychiatry, the Child Abuse Service, and Medical Genetics.
## Cumulative Risk in FASD Populations

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<tbody>
<tr>
<td>Tobacco</td>
<td>89%</td>
<td>62.4%</td>
<td>44%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>50%</td>
<td>36.5%</td>
<td>19%</td>
</tr>
<tr>
<td>Any Street Drugs</td>
<td>27%</td>
<td>No Data</td>
<td>50%</td>
</tr>
<tr>
<td>Any Maltreatment</td>
<td>67%</td>
<td>No Data</td>
<td>100%</td>
</tr>
<tr>
<td>Neglect</td>
<td>56%</td>
<td>64.4%</td>
<td>94%</td>
</tr>
<tr>
<td>Physical Abuse</td>
<td>37%</td>
<td>34.3%</td>
<td>50%</td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>33%</td>
<td>23.5%</td>
<td>25%</td>
</tr>
<tr>
<td>Witness to IPDV</td>
<td>33%</td>
<td>No Data</td>
<td>100%</td>
</tr>
<tr>
<td>Multiple Caregiver Change</td>
<td>69%</td>
<td>Yes</td>
<td>100%</td>
</tr>
</tbody>
</table>
CRDC: Goals

- Articulate developmental/functional deficits and mental health profiles.
- Articulate cumulative risk/exposure (causative factors) and subsequent diagnostic profiles when applicable (including FASD).
- Collaborate in cross-sectional service planning and case management.
Two Children’s Stories

- **Cindy, Age 6**
  - Referred for an FASD Assessment
  - Maternal Prenatal Stress
  - Pre-natal Substance Use
  - Multiple Moves
  - Rage, inconsolable, disrupted sleep and developmental delays
  - Generational story – mom has FASD

- **Dustin, age 15**
  - Prenatal exposure – alcohol and drugs
  - Little to no pre-natal care
  - Family history of serious mental illness
  - Multiple losses
  - Significant neglect 0-3
  - Multiple caregivers/placements
  - FSIQ – 77, limited functional skills for adulthood
Is FASD (any single category) the Only Lens for Understanding Outcome?
What if....

- We only looked at the prenatal alcohol exposure....

- We ranked the pre-natal exposure as the most important (or only) exposure....

- The interventions were guided only by the FASD story....
Background:
PAE is an Important Exposure

• Individuals with FASD have:
  – Multiple Deficits
  – Cross Many Different Cognitive Domains
  – Include Significant Mental Health Symptoms
Background: Attribution in FASD

• Features of FASD are complex and multifaceted
  – originating with organic brain damage caused by alcohol
  – but interacting with genetic and other influences
• Over the lifespan features may be exacerbated or mitigated by experience
Background: Heterogeneity of Outcome

• A universal finding in groups of children exposed to multiple adverse experiences or risk factors (Rutter, 2007).

• Not all children exposed to risk have adverse outcomes
  – A proportion of children show resilience?
Background: Psychiatric Disorders in FASD

• No unique psychiatric disorders in children with FASD
  – Rates of any psychiatric disorder increased over baseline population rates

• Primary disability related to prenatal alcohol exposure versus related to other cumulative risk factors?

• Psychiatric morbidity often major contributor to functional impairment
Models of Risk, Resilience and Outcome

- Frame attribution, trajectories and prognosis
- Guide prevention and intervention
- Linear Causality Models:
  - Prenatal Alcohol Exposure
  - Maltreatment
  - Adverse Outcomes/FASD
  - Attachment Disorders
Integrating Evidence: Prenatal Alcohol Effects on Child Outcomes

- Institute of Medicine (1996)
- DSM5 Neurobehavioral Disorder associated with PAE (2013)
- Canadian Guidelines (2016)
Integrating Evidence: Postnatal Effects on Child Outcomes

- Adverse Childhood Experiences Study (1995)
- Harvard University Center on the Developing Child (2006)
- Alberta Family Wellness Initiative (2007) and the Frameworks Institute (2009): the “Core Story” of Brain Development and Metaphors for Child Development
Integrating Evidence: Prenatal AND Postnatal Effects on Child Outcomes

Single Risk
- Rutter
- Sameroff
- Greenspan

Multiple Risk Models (1979)
- Bronfenbrenner’s Ecological Model (1979)
- Rutter
- Sameroff
- Greenspan

Allostatic Load Models (1998)
- Cicchetti (1989)
- Sroufe and Colleagues (2005)

Developmental Psychopathology
- Cicchetti (1989)
- Sroufe and Colleagues (2005)

THE DEVELOPMENT OF THE PERSON
L. Alan Sroufe, Byron Egeland, Elizabeth A. Carlson, and W. Andrew Collins
• Are there ways to understand complex stories in the lives of individuals with multiple-risks?
• Moving forward with research related to multiple risks . . .
Risk Models

- Cumulative Risk:
  - Total number of risk exposures predicts maladaptation, regardless of the specific risks
  - Linear and threshold models
  - The number of factors carries more importance than the experience of any one exposure
  - e.g. Adverse Childhood Experiences (ACE) Research
- Dimensional Risk: e.g. threat versus harm
- Timing of Risk: early versus late
- *Case definition for exposures or combinations of exposures has been a challenge.*
Characterizing adverse prenatal and postnatal experiences in children

Catherine A. Lebel1,2,3 | Carly A. McMorris2,4 | Preeti Kar2,3 | Chantel Ritter2,4 | Quinn Andre2,3 | Christina Tortorelli5 | W. Ben Gibbard2,6
Research Exposure Reporting and Ranking Framework

- Integrates **cumulative risk** and **dimensional risk** models

**Dimensional risks** categorized into:
- Prenatal alcohol
- Prenatal other substance exposure
- Prenatal toxic stress
- Threat: harm or threat of harm
- Deprivation: failure to meet basic needs

**Timing of Risk:** early (before 2-years) versus late

**Cumulative model:** a 4-digit ranking system similar to that used for diagnosing FASD (Astley, 2004)
Research Exposure Reporting and Ranking Framework

- Seven exposure variables overall:

- **Adverse Prenatal Exposures:**
  - PAE
  - Other Prenatal Substance Exposure
  - Other Prenatal/Maternal Toxic Stress

- **Adverse Postnatal Exposures:**
  - Early Postnatal Threat
  - Early Postnatal Deprivation
  - Late Postnatal Threat
  - Late Postnatal Deprivation
# Exposure Case Definitions and Criteria

<table>
<thead>
<tr>
<th>Exposure type</th>
<th>Description</th>
<th>Rank 3</th>
<th>Rank 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal alcohol exposure</td>
<td>Consumption of any form of alcohol during pregnancy</td>
<td>Exposure to prenatal alcohol not meeting criteria for a score of 4 or confirmed exposure of unknown amount</td>
<td>High exposure of ( \geq 7 ) drinks/week or ( \geq 2 ) binge episodes (( \geq 4 ) drinks on one occasion) at some point in pregnancy</td>
</tr>
<tr>
<td>Other prenatal substance exposure</td>
<td>Exposure to harmful substances including marijuana, nicotine, cocaine, methamphetamines, and opioids during pregnancy.</td>
<td>Exposure to nicotine or marijuana of any amount; low frequency use of other substances, or confirmed use of unknown amount</td>
<td>High frequency use (( \geq 5 ) times in pregnancy) of an illicit substance (cocaine, methamphetamines, opioids, etc.)</td>
</tr>
<tr>
<td>Other prenatal toxic stress</td>
<td>Harm or threat of harm to the mother and fetus during pregnancy; lack of prenatal care, housing, food, or income to meet needs; maternal mental health problems.</td>
<td>Symptoms of a mental health problem (undiagnosed), lack of prenatal care, housing/food/income insecurity &lt;3 months, OR a single instance of domestic violence or sex trade work</td>
<td>DSM 5 diagnosis of mental health disorder, domestic violence or sex trade work at least twice during pregnancy, housing/food/income insecurity ( \geq 3 ) months, or multiple exposures</td>
</tr>
<tr>
<td>Early postnatal deprivation (&lt;24 months)</td>
<td>The basic needs of the child not being met or a risk of needs not being met, including attachment needs.</td>
<td>One care transition (excluding from hospital), housing/food/income insecurity, or loss of caregiver (e.g., death, incarceration)</td>
<td>Multiple care transitions (( \geq 2 )), neglect, or multiple exposures</td>
</tr>
<tr>
<td>Late postnatal deprivation (( \geq 24 ) months)</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Early postnatal threat</td>
<td>Harm or threat of harm, including physical, emotional, sexual abuse; or witnessing violence, substance abuse, or criminal activity in the home.</td>
<td>Witnessing substance use or domestic violence, caregiver with mental illness</td>
<td>Abuse of any kind, or multiple exposures</td>
</tr>
<tr>
<td>Late postnatal threat (( \geq 24 ) months)</td>
<td>Same as above</td>
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Our Research Study Cohort

• Applied to 77 children:
  – aged 2.8-15.9 years; 43 male/34 female
  – Recruited from: 1) Calgary and Region Child and Family Services; 2) FASD parent support groups; and 3) the Cumulative Risk Diagnostic Clinic (CRDC)

### DOCUMENTATION ON RISKS
- Pre- and post-natal risks
- Variety of records: birth, legal, adoption, and child and family services
- Self-report

### COMPREHENSIVE ASSESSMENTS
- Cognitive functioning/IQ
- Academic ability
- Executive functioning
- Memory
- Mental Health

### BRAIN IMAGING
- Diffusion MRI (dMRI)
- Resting state fMRI (rs-fMRI)
- Anatomical imaging (T1-weighted)
Prenatal Exposures

Lebel et al, Birth Defects Research, 2019
Postnatal Exposures

Lebel et al, Birth Defects Research, 2019
Overlapping Exposures

Lebel et al, Birth Defects Research, 2019
Mental Health in Individuals with PAE: Role of Neuropsychological Processes
Mental Health in Individuals with PAE

- Over 90% of individuals with FASD have co-occurring mental health issues (Pei et al., 2011)

- Internalizing and externalizing issues
  - Hyperactivity and depression most common
  - At risk for suicide and substance use

- Problems that emerge in childhood don’t disappear with age
  - Lay the foundation for the development of later, more severe issues in adulthood
Neurobehavioural Outcomes

- Individuals with FASD often display various, yet heterogeneous, neurobehavioural impairments (Kodituwakku et al., 2009)

- Executive functioning (EF) is an area of significant impairment (Rasmussen et al., 2013)

- Poor performance on tasks involving processing of complex information & integration of information (Mattson et al., 2011)
MH and Neurobehavioural Outcomes

Changes in brain function and development

Simple cognitive functions (Attention)

Complex cognitive functions (Social cognition)

Social and Behavioural Problems

Adapted from Kodituwakku & Kodituwakku (2014)
Role of Postnatal Risks

• Difficult to disentangle neurodevelopmental impact of PAE exposure from other postnatal risks

• Few studies have examined the interaction of both exposures (Price et al., 2017)
  – Exposure to both PAE and maltreatment is associated with higher risk of neurodevelopmental deficits than either exposure alone
  – Compounding relationship
Objectives

1. Investigate the association between mental health symptoms and neuropsychological processes

1. Determine if and how postnatal risks impact this relationship
MH and Neurobehavioural Outcomes

Changes in brain function and development

Simple cognitive functions (Attention)
Complex cognitive functions (Social cognition)

Postnatal risks

Social and Behavioural Problems

Adapted from Kodituwakku & Kodituwakku (2014)
Our Research Study Cohort

• Applied to 77 children
  – aged 2.8-15.9 years; 43 male/34 female
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**DOCUMENTATION OF RISKS**
- Pre- and post-natal risks
- Variety of records: birth, legal, adoption, and child and family services
- Self-report (when available)

**COMPREHENSIVE ASSESSMENTS**
- Cognitive functioning/IQ
- Academic ability
- Executive functioning
- Memory
- Mental Health

**BRAIN IMAGING**
- Diffusion MRI (dMRI)
- Resting state fMRI (rs-fMRI)
- Anatomical imaging (T1-weighted)
Sample

- 29 youth with documented PAE
- 7.9yrs – 15.9yrs ($M=10.4$, $SD=2.33$)
- 18 males/11 females
- FSIQ 87.07 (59-106; Low average range)
  - Verbal Comprehension 85.90 ($SD=12.68$)
  - Perceptual Reasoning 93.07 ($SD=14.19$)
- 48.3% ($n=14$) FASD dx
- 62% ($n=18$) youth experienced postnatal risks
### Methods

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<tr>
<th>Visit Type</th>
<th>Assessing</th>
<th>Measure(s)</th>
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<td>IQ</td>
<td>WASI-2</td>
</tr>
<tr>
<td></td>
<td>Academic functioning</td>
<td>WIAT-III (math, reading &amp; spelling)</td>
</tr>
<tr>
<td></td>
<td>Executive functions</td>
<td>NEPSY-II (selected subtests); BRIEF</td>
</tr>
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<td></td>
<td>Memory</td>
<td>CVLT-C</td>
</tr>
<tr>
<td></td>
<td>Behavioural &amp; Social-Emotional Functioning</td>
<td>BASC-2, CDI-2, MASC-2, DERS (self-report + caregiver)</td>
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<td>Phone Interview</td>
<td>Mental Health</td>
<td>K-SADS-PL</td>
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<td>(Caregiver)</td>
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Preliminary Findings: Mental Health Symptoms

BASC-2 PRS T-Scores

Externalizing: 66.38
Internalizing: 57.97
Hyperactivity: 67.72
Aggression: 62
Conduct: 64.66
Anxiety: 51.69
Depression: 61.1
Somatization: 56.31
Preliminary Findings: Neuropsychological Outcomes

• Academic Abilities
  – Average performance on subscales related to reading
  – Below average performance on subscales related to math

• Executive functioning
  – NEPSY-II: Average to below average on comprehension of instructions, speeded naming and narrative memory
Preliminary Findings: Neuropsychological Outcomes

BRIEF PRS T-Scores

Inhibit: 69.86  
Shift: 63.62  
Emotional Control: 60.48  
Initiate: 64.39  
WM: 69.45  
Plan: 65.28  
Org Materials: 56  
Monitor: 64.54  
GEC: 69.55
Preliminary Findings

• Age, IQ, and academic functioning not related to mental health symptoms

• Females ($M = 66.82$) more likely to experience internalizing mental health symptoms than males ($M = 52.56$), $F(1,27) = 5.06, p \leq .033$.

• Executive functions (BRIEF PRS) significantly predicted mental health symptoms, all $ps < .05$.
  – Except anxiety
### Preliminary Findings

#### Externalizing Issues
- Inhibiting
- Working memory
- Monitoring
- Planning

#### Internalizing Issues
- Emotional control
- Shifting
- Monitoring
- Global executive composite
Preliminary Findings

• Exposure to both pre- and postnatal risks did not predict severity of mental health symptoms, all $p$s > .05.
  – BUT some interesting trends related to MH and neuropsychological outcomes
Conclusions

• Mental health symptoms are common in children and youth with PAE

• Deficits in executive functions are associated with mental health symptoms
  – Emotional control and depression

• Youth who have been exposed to pre- and postnatal risks may experience more severe mental health symptoms
  – BUT fewer neuropsychological deficits
Brain Alterations
MRI

- 3T research-dedicated MRI scanner at ACH

- 77 children 2-16 years
  - 45 young: 2-7 years
  - 32 youth: 7-16 years
Water Diffusion
Diffusion in Brain White Matter

- White matter creates barriers to diffusion
  - Water follows path of least resistance

Perpendicular to Tract
- Slower water diffusion

Parallel to Tract
- Faster water diffusion
Tractography
Neuroimaging in FASD

- Altered corpus callosum
- Structural brain abnormalities are widespread
- Include areas known to be implicated in internalizing and externalizing disorders
- Frontal/temporal regions

Lebel et al, 2008; Wozniak et al, 2009
Neuroimaging in FASD

- Altered corpus callosum
- Structural brain abnormalities are widespread
- Include areas known to be implicated in internalizing and externalizing disorders
  - Frontal/temporal regions
- Studies focus on 8 years +
- Do not consider postnatal exposures

Lebel et al, 2008; Wozniak et al, 2009
Our Population

• 45 young children with PAE: 2-7 years
  – 80% with postnatal exposures (abuse, neglect, etc.)
  – Matched unexposed controls

• 32 older children/adolescents with PAE: 7-16 years
  – 50% with postnatal exposures
  – Matched unexposed controls

• Diffusion tensor imaging
Young Children with PAE

Fractional Anisotropy ($10^{-1}$)

![Graph showing fractional anisotropy for different brain regions with and without prenatal alcohol exposure.](image)

Controls

Prenatal Alcohol Exposure
Young Children with PAE
Young Children with PAE

• Higher FA, lower MD
  – More myelin, more densely packed white matter

• FA increases, MD decreases with age
Brain Structure in Youth with PAE
Typical Brain Development

Cingulum

Uncinate
Altered Brain Development

- Trajectories are altered by PAE
- Different profiles at different times
Cortical Development in FASD

Lebel et al., J Neurosci, 2012
Mental Health Symptoms in Youth

![Graph showing externalizing T-score comparison between PAE-, PAE+, and Controls groups.](image-url)
Brain Structure – Mental Health Relationships

- Left Superior Frontal Gyrus Volume (mm$^3$)
- Right Superior Frontal Gyrus Volume (mm$^3$)
- Left Middle Frontal Gyrus Volume (mm$^3$)

Graphs showing the relationship between brain structure and mental health.
Brain Findings in PAE

• Higher FA in young children
• Lower FA in youth (moderated by postnatal exposures)
• Suggests altered development trajectories
  – Premature development with early plateau?
• Related to mental health symptoms dependent on postnatal exposures
Implications for Policy & Practice
Implications for Assessment

• Multiple exposures beyond PAE are common and important.
• Heterogeneity of exposure and outcome requires assessment across functional areas in development, behavior and mental health.
• Diagnostic processes must take into account other relevant exposures and a comprehensive multidimensional exposure review is required.
Implications for Assessment

• Clinicians must expect complexity regarding exposures and associated outcomes, but also tolerate ambiguity as to which factors explain outcomes.

• Collaboration between clinicians is key to integrate assessment findings related to individual profiles of risk, protective factors and outcomes.

• Collaboration with other information sources such as Child Welfare will better inform the process.

• Recommendations must be individualized to the child/youth’s personal story.
Implications for Assessment

- Recognize the priority for functional / developmental and mental health assessment.
- Acknowledge individual multiple exposure profiles, and the effect that other adverse exposures together have on child outcomes.
- Acknowledge the service need intensity for this population.
- Disseminate findings to all child-serving sectors to enhance understanding and service provision.
- Importance of knowledge translation to inform funding and policy.
Summary

• PAE matters
• Other prenatal and postnatal exposures matter
• The mental health story matters
• Environment matters
• Resilience matters

Ask more questions, gather more information, more fully tell the story, improve outcomes
Upcoming Project

- CIHR-funded project to support continued research collaboration
- Mental health and brain abnormalities in youth with FASD
  - 120 FASD, 120 controls across Alberta
  - Comprehensive mental health and neurocognitive assessments
  - Structural and functional MRI scans
- Recommendations for provision of care
More Info

• **Posters:**
  • P02: The relationship between brain structure and mental health problems in children and adolescents with prenatal alcohol exposure
  • P22: White matter microstructure in young children with prenatal alcohol exposure
  • P39: The impact of placements on mental health outcomes in children exposed to alcohol prenatally
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• Preeti Kar
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• Alberta Ministry of Children’s Services
“The answers you get depend on the questions you ask!”

• Thomas Kuhn

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