Developmental Origins of Health and Disease: A new perspective on Fetal Alcohol Spectrum Disorder

JOANNE WEINBERG, PHD
DEPARTMENT OF CELLULAR & PHYSIOLOGICAL SCIENCES
UNIVERSITY OF BRITISH COLUMBIA

7TH NATIONAL BIENNIAL CONFERENCE ON ADOLESCENTS AND ADULTS WITH FASD
APRIL 6-9, VANCOUVER, BC
Learning Objectives

• Describe the adverse health outcomes in individuals with FASD

• Explain how prenatal alcohol exposure could act on the fetus to increase vulnerability to later life diseases/disorders

• Explain what types of interventions might be possible to attenuate some of the adverse health outcomes observed in FASD
Adverse effects of prenatal alcohol exposure on long-term health outcomes:

Clinical evidence and data from animal models
Dose-Response Curve for Teratogens

As dose increases, more fetuses at risk, effects more severe
(From Jacobson & Jacobson, Alcohol Health & Research World 18:30-36, 1994)

Figure 2. Ideal dose-response curves for four domains affected by toxic exposure during fetal development. As dose of a toxic substance increases, more fetuses are at risk of injury and effects become more severe, ranging from functional teratogenesis, which includes neurobehavioral outcomes, to fetal death.

1The LD50 represents the median lethal dose of a toxic substance at which half of the fetuses exposed will die.
Vulnerability at Different Developmental Periods
(From Coles, Alcohol Health & Research World 18:22-29, 1994)

<table>
<thead>
<tr>
<th>Period of the Ovum</th>
<th>Period of the Embryo (in weeks)</th>
<th>Period of the Fetus (in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>20-36</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>38</td>
</tr>
</tbody>
</table>

- **Central Nervous System (CNS)**
  - Heart
  - Arms
  - Eyes
  - Legs

- **Other Structures**
  - Teeth
  - Palate
  - External Genitalia
  - Ears

*Figure 1* Vulnerability of the fetus to defects during different periods of development. The red portion of the bars represents the most sensitive periods of development, during which teratogenic effects on the sites listed would result in major structural abnormalities in the child. The yellow portion of the bars represents periods of development during which physiological defects and minor structural abnormalities would occur.

SOURCE: Adapted from Moore 1993.

Of note, the brain develops throughout gestation and into postnatal life. Weinberg 2016
NIAAA Program Announcement:

- Fetal adaptations in response to adverse intrauterine conditions may increase the risk for diseases or disorders across the lifespan.
- At this time, the impact of prenatal alcohol exposure on the development of adult-onset disease and health conditions is largely unknown.
- Understanding how exposure of the embryo and fetus to alcohol may alter health and chronic disease later in life represents a significant public health concern and warrants investigation.

The DOHaD framework is relatively new to the FASD field. But it provides an extremely important approach for understanding later life outcomes and for developing appropriate interventions.
Data from clinical studies to date

- Numerous structural/functional abnormalities that will impact health and well-being\textsuperscript{1,2,3}
  - Cardiac anomalies
  - Urinary and kidney anomalies
  - Neural tube defects
  - Cleft lip with or without cleft palate
  - Gastrointestinal and genital abnormalities
  - Dental anomalies
  - Limb and joint abnormalities, scoliosis
  - Eye abnormalities - ptosis, strabismus, epicanthal folds, microphthalmia, myopia

- Increased risk of preterm birth\textsuperscript{4}

- Decreased immune cells counts (eosinophils, neutrophils) and response to stimulation\textsuperscript{5}

Weinberg 2016
Data from clinical studies to date

- Higher incidence of minor infections (recurrent ear and respiratory) and major/life-threatening infections (early-onset sepsis in very low birth weight alcohol-exposed newborns)\(^5,6\)
  - Likely due to deficits in immune function of both infant and mother
  - Level of alcohol intake important factor in predicting neonatal infection risk

- Increased incidence of certain types of cancer (neuroblastoma, leukemia) - possibly related to compromised immune status\(^7,8\)

- Alterations in maternal immune function with alcohol consumption\(^6,9,10\)
  - Programming effects on developing fetus:
    - Altered cytokine levels in maternal circulation (Chambers et al and the CIFASD, preliminary data) - implications for offspring brain, physiological, cognitive, behavioral, immune development

- Functional abnormalities of the kidney\(^11\)
  - Impairment in renal acidification and potassium excretion, defect in urinary concentrating ability, even in the absence of any structural abnormalities.

- Mental Health problems\(^12,13\)
  - Occur in ~ 94% of individuals with FASD
  - Depression (50%), ADHD/ADD (42%), anxiety/panic attacks (38%)
Causes of death for people with FAS\textsuperscript{14}

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>External causes of morbidity and mortality:*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Suicide</td>
<td>15</td>
<td>15%</td>
</tr>
<tr>
<td>- Accident</td>
<td>14</td>
<td>14%</td>
</tr>
<tr>
<td>- Poisoning by illegal drugs or alcohol</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>- Other external causes</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Diseases of the nervous system</td>
<td>8</td>
<td>8%</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>8</td>
<td>8%</td>
</tr>
<tr>
<td>Diseases of the digestive system</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Mental and behavioural disorders</td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Certain conditions originating in the perinatal period</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Certain infectious and parasitic diseases</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Endocrine, nutritional, and metabolic diseases</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Diseases of the genitourinary system</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Diseases of the blood and blood-forming organs</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>98</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Note that the sum may not be equal, due to rounding; **Of 113 deaths, 15 cases with missing causes of death were excluded.
Why Use animal models?

- Control of environmental variables
  - Dose, timing of exposure, other drugs, maternal nutrition and health, prenatal/postnatal environment

- Control of genetic variables
  - Genetic differences in vulnerability or sensitivity to the same dose of alcohol
  - Genetic differences in absorption, distribution, metabolism, elimination of alcohol
  - Separate genetic from environmental effects

- Insight into mechanisms of action can suggest strategies for intervention (pregnant females) and treatment (exposed offspring)
Cellular and molecular mechanisms of alcohol’s teratogenic effects

- The varying patterns observed in children with FASD suggest multiple mechanisms, likely activated at different stages of development or at different dose thresholds of exposure.

- Multilevel analyses needed as we collect data on adverse health outcomes in relation to FASD.
  - Can we get enough information on dose, timing, level of exposure?
  - Can we get good information on prenatal/early life environments?
  - Can we begin to separate effects of alcohol from effects of adverse early life environments?

- Understanding **mechanisms** can allow for targeted interventions and have policy implications.
  - Need to consider both **direct** (neuronal cell damage/death, inhibition of protein/DNA synthesis) and **indirect** (nutrition, placenta dysmorphismology, vascular, oxidative stress/free radicals, growth factors, hormones, cell signaling, cell adhesion, epigenetics [changes in gene expression]) effects.

Weinberg 2016
Data from animal models

- Many organ systems show adverse effect of prenatal alcohol exposure on structure and function
  - Pancreas abnormalities: structural changes, adiposity, glucose intolerance, pre-diabetic insulin insensitivity, insulin function\(^{15-18}\)
  - Heart problems – changes indicative of left ventricular hypertrophy following chronic low dose alcohol during gestation; adverse effects on heart muscle; smaller volume of heart cells; impaired neural control of heart rate\(^{19,20}\)
  - Changes in fetal and postnatal lung: impaired and delayed growth and development, decreased surfactant, cellular changes suggestive of pulmonary fibrosis, changes in immune cells in lung (disruption of alveolar macrophage activity - deficits in clearing infectious agent)\(^{21-25}\)
  - Adverse effects on offspring kidney and blood pressure: decreased nephron numbers – implications for cardiovascular health, blood pressure\(^{26-28}\)
Data from animal models

- Altered mammary gland development and increased tumor susceptibility, altered tumor phenotype\textsuperscript{29-33}

- Increased susceptibility to osteoarthritis\textsuperscript{34}

- Deficits in immune function and increased inflammation\textsuperscript{35,36}
  - Deficits in immune cell responses to stimulation (mitogens and alcohol)
  - Altered immune function in the neonatal period – a “pro-inflammatory” bias
  - Increased severity and duration of immune activity or inflammation in response to challenge in adulthood – increased severity and duration of arthritis, increased inflammation following “bacterial” challenge

- Increased vulnerability to depressive- and anxiety-like behavior\textsuperscript{37}
Insights from Animal models

- Animal models mirror many of the health problems, diseases and disorders seen in children with FASD

- If these health problems, diseases, disorders can be reproduced in an animal model under controlled conditions - dose, timing of exposure, other drugs, maternal nutrition and health, prenatal/postnatal environment, genetics
  - Then are these *secondary disabilities* as they have been called previously?
  - Or are they *primary problems*, or at least have a primary component, and based largely on the effects of alcohol?

- No doubt that problems may be exacerbated by adverse prenatal/early life environments, but they are not necessarily due to environmental causes

- In the real world, many children with FASD also experience early life stress and adversity, and stress/adversity may sometimes continue into childhood or adolescence.

- Early life stress/adversity can result in some of the same long-term deficits/problems/health issues as FASD. In those situations it may be difficult if not impossible to separate the effects of FASD from those of early life adversity

- Animal models can help us sort out these issues
Developmental Origins of Health & Disease (DOHaD)

Relationships between early environment and adult outcomes first published by David Barker and colleagues, who showed correlations between low birth weight and adverse health outcomes (eg., cardiovascular disease, insulin resistance/diabetes) – as birth weight decreased, incidence of disease/disorders increased.

Adapted from Barker 2000

Weinberg 2016
How can the intrauterine or early life environment influence development?

- Maternal Nutrition / Health
- Stress / Infection
- Alcohol / Drugs

Many things in the environment can influence the developmental trajectory and increase the risk for later life health problems.

Increased Risk for:
- Metabolic Disorders
- Cardiovascular Disease
- Immune Dysfunction
- Mental Health Disorders

Prenatal Development

Postnatal Development

Thank you to Parker Holman for slide animations!
Fetal Programming Hypothesis:

Early life events can program fetal/early life neurobiological/physiological systems, altering the developmental trajectory and increasing later life vulnerabilities.

Increased Risk for:
- Behavior
- Cognition
- Learning
- Memory
- Attention
- Emotion

Programming effects not only physical but also behavioral, cognitive, emotional

Programming or resetting of key hormonal systems by early experience is one mechanism linking early life events with long-term health consequences.
Implications for intervention

- Can we reverse or rescue the programmed phenotype? Evidence suggests that we should be able to intervene to change at least some outcomes.

- Direct mechanisms of alcohol damage - neuronal cell damage/death, inhibition of protein/DNA synthesis – may not be reversible.

- But if indirect mechanisms are involved in alcohol’s adverse effects – nutrition, placenta structure, vascular development, oxidative stress/free radicals, growth factors, hormones, cell signaling, cell adhesion, epigenetics – we might be able to attenuate these effects:
  - Nutrition
  - Drugs that target cell signaling pathways, altered cell adhesion molecules, epigenetic alterations, hormonal changes, inflammation, free radicals/oxidative stress:
    - Some treatments could act independently, some may be adjunctive treatments to boost the efficacy of current medication.
  - Behavioral interventions also very important - may attenuate adverse effects and improve outcome.
Acknowledgments
References

12. Streissguth
References, cont’d

33. Hilakivi-Clarke et al, Br J Cancer 90:2225-2231, 2004