Long-Term Outcomes for Neonatal Abstinence syndrome: What We Know and What We Don’t

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Outline
1. Background and framing
2. Post-discharge utilization
3. Neurodevelopmental outcomes

Maternal Drug Use
• Maternal drug use does not occur in isolation
  – Poor health
  – Poor nutrition (food insecurity)
  – Poor prenatal care
  – Social stress
• Associated with poor obstetric outcomes
• Each common factors which could impact neurodevelopmental outcomes

Maternal Drug Use
• Commonly occurs with other substances
  – Among pregnant women misusing opioids in last year (compared to those who did not), in the last month:
    • 22.9% used marijuana (versus 2.6%)
    • 23.9% used alcohol (versus 8.1%)
    • 43.5% used tobacco (versus 14.5%)


Maternal Drug Use

Alcohol Exposure
• Alcohol is a frequently un- or under-recognized exposure
• Prenatal alcohol use is the chief preventable cause of developmental delay in children
• Alcohol use is common, especially among mothers with substance use disorder
• How do long-term developmental studies account for it?
Mechanisms

- Drug exposure can impact development through several mechanisms
  - Crossing placenta (most do) and have direct effect on fetus
  - Direct action on uterus or placenta
    - e.g. Alteration of placental blood flow
  - Secondary effects of fetus from maternal drug use
    - e.g. Maternal stress hormones

Readmission Risk

- Drug effects do not appear in isolation
  - Polysubstance use
  - Maternal clinical comorbidities
  - Maternal psychiatric conditions

Readmission Risk

- Protracted signs of opioid withdrawal
  - Well-described in adults
  - Case reports in neonates
- Readmission is a common quality metric
- Most NAS efforts have focused on birth hospital stay with little focus on readmission risk
- Are infants with NAS at increased risk of readmission?

What are health care needs after discharge home?
Readmission Risk

- Compared to term infants, 30-day readmission rates*
  - Late preterm OR 2.26 (95%CI 2.09-2.45)
  - NAS OR 2.49 (95%CI 1.75-3.55)
- 30-day reasons for readmission
  - NAS – (NAS – 26.8%)
  - Late preterm (Jaundice 34.5%)
  - Term (Jaundice 51.2%)

*Accounting for infant sex, birthweight, clinical comorbidities, insurance type and length of birth hospitalization

What about later in life?

- Large cohort from New South Wales, Australia
  - Infants followed from 2000-2011
- Reasons for care (compared to other infants)
  - Anxiety (aOR 3.77; 3.09-4.61)
  - Behavioral/emotional d/o (aOR 3.35; 3.02-3.72)
  - Stabismus (aOR 3.13; 2.72-3.59) and nystagmus (aOR 4.61; 3.43-6.20)
  - Drug poisoning (aOR 1.39; 1.17-1.66)
  - Maltreatment (aOR 3.38; 2.87-4.26)
  - Assault (aOR 4.20; 3.58-4.93)

Opioid-Exposure

- Illicit opioid use increases probability of:
  - Prenatal
    - Preeclampsia
    - Premature rupture of membranes
    - Placental insufficiency
    - Intrauterine growth restriction
    - Fetal demise
    - Birth defects
  - Postnatal
    - Low birth weight
    - Small head circumference
    - Withdrawal

Neurodevelopmental Outcomes

Behavior

- Rosen (prospective cohort)
  - Methadone maintenance - 61 infants from birth to 36 months (36% loss)
  - Comparison – 32 infants matched on races, SES, sex, birth weight and gestational age (28% loss)
  - Methadone group, more likely smokers, polysubstance users (15% heavy drinkers)
  - 36 months – no growth differences, but higher incidence of smaller head circumference among methadone-exposed
  - Increased rates of strabismus/nystagmus, otitis media

Behavior

- Rosen (prospective cohort)
  - 36 mo: Hypertonia, poor fine motor, delays in attaining developmental milestones, poor language development
  - 84 mo: “generally healthy,” higher prevalence:
    - Abnormal fine/gross motor coordination
    - Poor balance
    - Hyperactivity
    - Decreased attention
    - Speech/language delays
Behavior

• Rosen (prospective cohort)
  – “no uniform long-term effects”
  – “minor neurologic abnormalities”
  – Lower scores on developmental evaluations
  – Differences smaller as infants aged
  – Factors noted to improve outcomes at 36 months
    • Maternal education and family stability


Cognition

• Lifschitz (prospective cohort)
  – 25 heroin; 26 methadone maintenance; 41 with no documented substance use
  – Initial findings
    • Mean head circumference lower (heroin/MMT)
  – Long-term
    • Low-average to mild intellectual disability (heroin/MMT)
    • Adjusted analysis: Amount of prenatal care, prenatal risk, home environment all predictive of intellectual outcome and NOT drug use


Additional Studies

• NAS vs. controls, 6 months (McGlone 2015)
  – Developmental delay, visual difficulties
  – Analyses controlled for EtOH and smoking
• Norway, 50k infants, ~900 opioid pain reliever-exposed (Skovlund 2017)
  – No language differences
• Opioid-exposed vs. Control, n=23 (Walhovd 2015)
  – MRI: no structural differences
  – Differences in visual acuity


Achievement

• Oie (retrospective cohort)
  – New South Wales, Australia, infants born between 2000-2006
  – NAS vs. controls (matched on gestation, socioeconomic status, and gender)
  – Outcome: National Assessment Program: Literacy and Numeracy, in grades 3, 5, and 7


Comparing Test Scores

• Do infants with NAS really do that poorly?
• Does matching on 3 characteristics really account for confounding? Other exposures?
  – Mothers were older, control infants had higher birthweights, less likely to be in NICU.
  – Effect of alcohol exposure?
• Ongoing differences?
Summary of Outcomes

<table>
<thead>
<tr>
<th>Short-term Effects/Birth Outcomes</th>
<th>Long-term Outcome</th>
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<tbody>
<tr>
<td>Fetal growth Effect</td>
<td>Growth No effect</td>
</tr>
<tr>
<td>Anomalies No effect</td>
<td>Behavior Effect</td>
</tr>
<tr>
<td>Withdrawal Strong effect</td>
<td>Cognition No consensus on effect</td>
</tr>
<tr>
<td>Neurobehavior Effect</td>
<td>Language Limited or no data</td>
</tr>
<tr>
<td></td>
<td>Achievement Limited or no data</td>
</tr>
</tbody>
</table>

Substance Use as a Symptom

- More than ¾ women in treatment for substance use disorder report history of trauma or abuse
- Among inmates, physical abuse, sexual abuse, foster care involvement and caretakers who use drugs increase risk of substance use
- Trauma common, substance use often coping
- Is there a cycle?

Adverse Childhood Experiences

When you were growing up, during your first 18 years of life, did you experience:

- Physical abuse
- Emotional abuse
- Sexual abuse
- Domestic violence (mother treated violently)
- Substance abuse in home
- Mental illness in parent
- Lost parent due to separation or divorce
- Household member in jail

Credit: Ruth Ann Shepherd, MD

Life Expectancy

6 ACEs or more = 20 year decrease in life expectancy

ACES and Risk of Illegal Drug Use

<table>
<thead>
<tr>
<th>ACE Score</th>
<th>Lifetime Risk of Illegal Drug Use</th>
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<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>15.2%</td>
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<tr>
<td>3</td>
<td>22.3%</td>
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<tr>
<td>4</td>
<td>25.6%</td>
</tr>
<tr>
<td>5</td>
<td>28.8%</td>
</tr>
<tr>
<td>≥6</td>
<td>37.4%</td>
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Neonatologist Take Away?

- It appears that there are not substantial issues with development
- How can we modify developmental outcomes?
  - Avoid long weans, especially with phenobarbital
  - Helping family engage in treatment
  - Discharge plan
    - Child welfare when appropriate
    - Early intervention services
    - Communication/follow-up plans

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