Born on Opioids

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Neonatology

Opioid Exposed Infant

- Screening to identify at risk infants
- Objective scoring FNASS/ESC
- Interventions: non-pharmacologic & pharmacologic
- Post discharge plan of care: maternal support, infant support
- Psycho-social support
- Long term infant interventions throughout school

Current Epidemic of Opiates

On the left, a lethal dose of heroin; on the right, a lethal dose of fentanyl.
New Hampshire State Police Forensic Lab

By Centers for Disease Control and Prevention.
Current Epidemic of Opiates

“We lose a Vietnam War every single year to drug overdoses…”

Tom Price Secretary of Health and Human Services

Common Drugs of Abuse

- Opiates
- Tobacco/Nicotine
- Cannabis
- Alcohol
- Cocaine
- Methamphetamine

Brain images:

- Adult
- 36 weeks gestation
- 32 weeks gestation
- 22 weeks gestation
Dependence, Withdrawal, Tolerance and Addiction

- **Dependence** occurs as a result of physiological adaptations to chronic exposure to a drug. It is often a part of addiction, but they are not equivalent.

- Those who are dependent on a medication will experience **withdrawal** (unpleasant physical symptoms) when they abruptly reduce or stop use of the drug.

- **Withdrawal** symptoms can be mild to severe (depending on the drug) and can usually be managed medically or avoided by slowly tapering down the drug dosage.

- **Tolerance**, or the need to take higher doses of a medication to get the same effect, often accompanies dependence.

- **Addiction** involves other changes to brain circuitry and is distinguished by compulsive drug seeking and use despite negative consequences.

Teratogen

- An agent or factor that causes malformations of an embryo.

- Alteration of gene expression; turning genes off or on at the wrong time.
Plasticity

“Brain plasticity refers to the ability of the brain to persistently change its structure and function according to genetic code in response to environmental changes.”

Maquet, Smith, Stickgold

Plasticity

• The brain is shaped by the environment is experiences
• Gene expression is influenced by the environment

Long Term Impact of Maternal Substance Abuse on Babies

• In utero effects on fetal development
• Environmental effects on infant/childhood development
  • Family structure
  • Socio-economic status

In Utero

• Maternal health: comorbidities, mental health, complications of pregnancy
• Hostile in utero environment
• Toxic metabolites impact brain development
• Altered gene expression in the brain

Home Environment

• Life style: chaos, support, isolation, poverty
• IQ/verbal abilities
• Psychopathology
• Will the environment exacerbate or mitigate the behavioral disorders that arise from the in-utero CNS injury?

Opiates

• Increase stillbirths
• Risk of certain heart defects and spina bifida with 1st trimester exposure
• Prematurity
• Decreased Birth Weight, length, head circumference
• NAS
• SIDS
• Strabismus
Neonatal Abstinence Syndrome

- Clinical symptoms of withdrawal after delivery due to fetal exposure to maternal opiate use during pregnancy
- Maladaptation to extra-uterine life
- Symptoms assessed by using Finnegan scoring
- Treatment based on scores:
  - <8 non-pharmacologic
  - >8 medications
  - morphine vs methadone vs clonidine vs buprenorphine

Eat, Sleep, Console

- ESC an alternative to FNASS
- Yale New Haven Children’s Hospital
- Grossman et al; Hospital Pediatrics Jan 2018, Vol 8/Issue 1
  - ESC 6 infants (12%) were treated with morphine vs
  - 31 infants (62%) predicted to be treated by FNASS
  - ESC started or increased morphine on 8 days (3%) vs
  - 76 days (26%) predicted by FNASS
  - p<0.001
  - No readmissions or adverse events reported

Opiates

- Appears to be a pattern linking prenatal exposure to behavioral problems, including
  - Anxiety/Feelings of rejection
  - Aggression
  - ADHD disruptive/inattentive behavior

Opiates

- Most research based on heroine usage (usually intermittent/inconsistent) versus prescription opiate (more consistent)
- Limited outcomes research after treatment with methadone or buprenorphine
- Long term effects of opiate exposure in NICU?

Opiates

- Conflicting outcomes long term:
  - Delayed cognitive function at 3 years; Wilson et al., 1979
  - No cognitive delay 6–13 years; duCubas & Field, 1993
  - At 1 year infants prenatally exposed to opiates are at risk for mild psychomotor developmental impairment
    - Eur J Pediatrics 1998 Bunkowski et al
  - At 5.5 years infants of drug dependent mothers their care givers need extra support in order to improve early communication and cognitive development
    - Acta Paediatric 1994, van Daar et al
Maternal Interventions

- Placement: Home vs Family vs Foster
- Intensive home-based services
- Mental health treatment
- Substance use treatment

Child Interventions

- Specific individual therapy
- Speech/language
- Occupational
- Behavioral
- Early intervention/enrichment
- Ongoing cognitive & behavioral assessments

References

- Li K et al. Connectomics signatures of prenatal cocaine exposure affected adolescent brains. Hum Brain Mapp 2013 Oct 34(10) 2494-510

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In nature there are neither punishments nor rewards -- there are consequences.

Ingersoll
Tobacco

- Nicotine (1 of 4000+ compounds cigarette smoke)
- Nicotine levels: fetal compartments > maternal serum
- Preterm birth
- Low birth weight
- Abruption
- Increase risk of SIDS x5

Tobacco

- Deficits in self-regulation (soothe/calming self)
- Lower IQ
- MRI: reduced cortical gray matter/parenchymal vol
- ADHD
- Conduct disorders
- Depression/anxiety (childhood - adolescence: substance abuse)
- Aggression
- Impulsivity

Gene expression

- Smoking exposure during the prenatal period was directly associated with differential expression of 14 genes; in contrast, during adulthood, despite a much larger sample size, only two genes showed significant differential expression.

Tobacco

- US 2017
- 4,000,000 births
- 1 in 14 women smoked during pregnancy (7%)
- 280,000 newborns exposed

- 1,315 genes showed significantly different exposure effects between maternal smoking during pregnancy and direct exposure in adulthood
- these differences were largely driven by prenatal differences that were enriched for pathways previously implicated in addiction and synaptic function.
**Cannabis**
- Mild withdrawal symptoms
- Delayed state regulation
- Reading, spelling difficulty
- Executive function impairment: problem solving, memory, planning, impulsivity, attention

**Cannabis**
- Increased depressive symptoms
- Increase risk of tobacco/cannabis use
- fMRI altered neural functioning

**Alcohol**
- Teratogen with irreversible CNS effects
- Fetal elimination rate 3-4% of maternal rate
- Toxic metabolite acetaldehyde product of maternal and fetal metabolism
- Heterogeneity in symptom severity and presentation

**Alcohol**
- Fetal Alcohol Syndrome (FAS) 0.3/1000 7-9 year old children in USA (2015)
- Low IQ
- Impaired executive function
- Memory process and attention
- ADHD: hyperactivity and impulsivity
- Speech/language difficulties

**Alcohol**
- Secondary conditions
  - Mental health disorders: conduct disorder, depressive disorder, oppositional defiant disorder
  - Difficulties in school including withdrawal/suspension
  - Involvement with justice system, deviant sexual behavior, substance abuse
  - Employment challenges (rampant workplace drug screens)

**Alcohol**
- Prenatal Alcohol Exposure and Childhood Behavior at Age 6 to 7 Years, I. Dose-Response Effect (Sood et al.; Pediatrics 2011; August)
  - Maternal alcohol consumption even at low levels was adversely related to child behavior
  - A dose-response relationship was identified, effect observed at average levels even as low as 1 drink/week
  - Children with any exposure were 3.2 times as likely to have Delinquent behavior scores in the clinical range
Alcohol

- The Association Between Prenatal Alcohol Exposure and Behavior at 22 Years of Age (Day et al; Alcohol Clin Exp Res 2013 Jul)
- Prenatal alcohol exposure (PAE) effects are dose dependent and significant at each trimester
- Binge drinking did not predict more problems than non-binge drinking
- PAE, even at low to moderate levels extends into young adult

Alcohol

- No gold standard for treatment of FASD (Singal et al; BMJ Open 2018;8:e013775)
- Treatment pharmacologic and behavioral as dictated by symptoms

Sympathomimetic

- CNS stimulants
- Vasoactive: vasoconstriction
- Elevate heart rate
- Decrease placental blood flow
- Abruption
- Preterm labor

Cocaine

- IUGR/SGA
- Microcephaly
- Symptoms present 48-72 hours
- Neonatal CNS: irritability, tremors, excess suck, episodes apnea or tachypnea
- Cerebral infarctions

Cocaine

- Early studies limited by confounding variables: such as psychosocial factors, prenatal exposure to other drugs, prematurity, IUGR
- Mythology of “Crack Baby”

Cocaine

- Childhood
- Slower head & wt trajectories from 1-10 years
- Lower nonverbal perceptual reasoning
- Attention problems; poor school performance
- Disruptive behaviors/rule breaking; lack of self-regulation
- Structural changes of brain with MRI
Cocaine

- Singer et al (J Peds 2008)
  - "There were persistent teratologic effects of CE on specific cognitive functions…"
- Ackerman et al (Pediatrics 2010)
  - Environmental variables play a key role in moderating effects of PCE; with covariate control, PCE had a significant negative associations with sustained attention and behavioral self regulation

Methamphetamine

- Infant, Developmental, Environmental and Lifestyle Study (IDEAL) 2014 Diaz et al
  - Large scale, well control study of prenatal methamphetamine
  - 412 mother-infant pairs (204 methamp exposed/208 unexposed
  - 151 children exposed/141 comparisons at 7.5 years
  - After adjusting for covariates prenatal exposure was associated with increase cognitive problems

- Infant, Developmental, Environmental and Lifestyle Study (IDEAL) 2015 Smith et al
  - A neonatal abstinence syndrome was not observed
  - Somatic growth was significantly decreased
  - Increased emotional reactivity in young children

- Follow Up IDEAL 2016 Eze et al
  - At 7.5 years, prenatal methamphetamine exposure (PME) is associated with behavior problems; early adversity may be a strong determinant of behavioral outcomes
  - No difference in cognition at 5.5 years