EFFECTS OF PRENATAL EXPOSURES

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DISCLOSURES

• I have nothing to disclose.
DISCLAIMER

• Any views or opinions expressed are mine and are do not necessarily reflect the official views of the Indian Health Service, the Department of Health and Human Services or the United States Public Health Service.
OBJECTIVES

• Provide an overview of neonatal abstinence syndrome.
• Look at confounding exposures.
• Review of the Literature with regards to long term effects of prenatal opioid exposure.
• Why does it matter?
CURRENT STATE OF ILLICIT DRUG USE IN USA

• Nearly 25 million (9.2%) Americans aged 12 or older are current illicit drug users.
  • Marijuana, cocaine, heroin, hallucinogens, inhalants or prescription type psychotherapeutics used nonmedically.
• 24 million Americans > 12 years old had used a pain reliever non-medically at least once in their lifetimes
• Illicit drug use among pregnant women 15-44 has remained constant at 5.9%
PREVALENCE FOR PRENATAL SUBSTANCE USE

• Estimates vary widely due to:
  • Use of different sampling methods
  • Use of different drug-detection methods
  • Screening women in different settings
  • Obtaining data at different points in time.
### Prevalence for Prenatal Substance Use 2009-2010 Ages 15-44

<table>
<thead>
<tr>
<th></th>
<th>% Pregnant Women</th>
<th>% Nonpregnant Women</th>
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<tbody>
<tr>
<td>Illicit Drug Use</td>
<td>4.4</td>
<td>10.9</td>
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<tr>
<td>Alcohol Use</td>
<td>10.8</td>
<td>54.7</td>
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<tr>
<td>Binge Drinking</td>
<td>3.7</td>
<td>24.6</td>
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<tr>
<td>Cigarette Use</td>
<td>16.3</td>
<td>26.7</td>
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# Prevalence for Prenatal Substance Use

<table>
<thead>
<tr>
<th>Illicit drug use</th>
<th>% Pregnant Women</th>
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<tbody>
<tr>
<td>15-17 year olds</td>
<td>16.2</td>
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<tr>
<td>18-25 year olds</td>
<td>7.4</td>
</tr>
<tr>
<td>26-44 year olds</td>
<td>1.9</td>
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DIFFICULTIES IN SORTING OUT THE CAUSE

• The addition of environmental stress may further affect child health and development.
  • Chaotic home environment,
  • parental dysfunction,
  • poverty,
  • malnutrition.
FETAL DEVELOPMENT: MECHANISMS OF EFFECT

• If the drug crosses the placenta then it can act directly on its molecular target in the fetus.

• Direct effect on the uterus or placenta.
  • Would include altering placental secretory activity
  • Uteroplacental blood flow

• Effects on the mother’s physiology that may affect the fetus
  • Increased secretion of stress hormones
  • Altered maternal health behaviors attributable to the mother’s addiction.

• Paternal exposures
  • Cocaine can influence offspring brain development (in animal models)
NICOTINE

• Only 1 of more than 4,000 compounds presenting to fetus with smoking.
• Exact mechanisms of adverse effects not known.
• Probable effects:
  • Hypoxia
  • Undernourishment of the fetus
  • Direct vasoconstriction of placental and umbilical vessels.
• Definite effects demonstrated resulting in abnormal brain development.
ADDITIONAL TOXICITY

• From compounds such as cyanide and cadmium in the smoke.
ETHANOL

- Easily crosses the placenta
- Direct teratogenic effects
- Toxic effects on placenta
- Altered prostaglandin and protein synthesis
- Hormonal alterations
- Nutritional effects
- Altered neurotransmitter levels
- Altered brain morphology and neuronal development
- Hypoxia
MARIJUANA

• Placenta appears to limit fetal exposure to some degree
• Alters brain neurotransmitters and brain biochemistry.
  • Results in decreased protein, nucleic acid and lipid synthesis.
• Ability to remain in the body up to 30 days prolongs the effect.
• Produces 5 times the amount of CO as compared to cigarettes.
OPIATES

• Rapidly cross the placenta.
• Decrease brain growth and cell development in animals.
• Studies on their effects on neurotransmitter levels and opioid receptors have produced mixed results.
COCAINE

• Easily crosses the placenta and blood brain barrier.
• Significant teratogenic effects.
• The development of areas of the brain that regulate attention and executive functioning appear particularly vulnerable.
METHAMPHETAMINE

• Readily passes through the placenta and the blood-brain barrier.
• Effects thought to be from interaction and alteration in the neurotransmitter systems as well as alterations in brain morphogenesis.
OPIATE MAINTENANCE THERAPIES

• Recommended by both the AAP and ACOG as first line treatment for opioid dependency during pregnancy.
• Untreated illicit opiate use is associated with poor prenatal care, nutrition, and fetal health.
• Facilitates better prenatal care, decreased illicit use of opiates and other drugs and prevents maternal/fetal withdrawal.
• Long-acting full mu opioid receptor agonist
  • Activation of the μ-opioid receptor by an agonist such as morphine causes analgesia, sedation, slightly reduced blood pressure, itching, nausea, euphoria, decreased respiration, miosis (constricted pupils), and decreased bowel motility often leading to constipation.
**METHADONE**

- Can lead to increased risk of premature birth
- Decreased birthweight
- Smaller head circumference
- Increased incidence of respiratory insufficiency at birth
- Altered QTc during the first postnatal week.
- Postnatal hyperphagia
- Disrupted auditory event related potentials
- Myelination deficits
METHADONE

• Prevalence of cognitive impairments is uncertain because of conflicting study results.
BUPRENORPHINE

• Partial mu opioid receptor agonist
  • Activation of the μ-opioid receptor by an agonist such as morphine causes analgesia, sedation, slightly reduced blood pressure, itching, nausea, euphoria, decreased respiration, miosis (constricted pupils), and decreased bowel motility often leading to constipation.

• Kappa opioid receptor antagonist
  • May have a role in inhibiting stress-induced relapse to cocaine and alcohol seeking
  • May have antidepressant properties
  • Has long durations of action
BUPRENORPHINE:

• May produce fewer neurobehavioral problems.
• May result in higher birthweights as compared to methadone.
• May result in larger head circumferences as compared to methadone.
• Results in a shorter, less severe neonatal abstinence syndrome.
BUPRENORPHINE NEGATIVE EFFECTS OBSERVED:

- Hyperactivity
- Visual/motor impairment
- Memory problems
- Altered myelination
NEUROBEHAVIOURAL DEVELOPMENT OF PRESCHOOL-AGE CHILDREN BORN TO ADDICTED MOTHERS GIVEN OPIATE MAINTENANCE TREATMENT WITH BUPRENOORPHINE DURING PREGNANCY.
METHODS

• 28 children, whose 21 opiate addicted mothers were treated with buprenorphine during pregnancy.

• 25 of these children were administered a battery of neurobehavioral tests at age 5-6.
RESULTS

• Evidence of:
  • Serious visual motor and attention problems.
  • Major problems in the field of motor skills and memory abilities.
  • Significantly elevated levels of hyperactivity, impulsivity and attention problems.
CHILDHOOD HEALTH AND DEVELOPMENT IN A COHORT OF INFANTS EXPOSED PRENATALLY TO METHADONE OR BUPRENORPHINE
In a longitudinal study from Norway of 72 children with prenatal opioid and polysubstance exposure, both boys and girls had lower intelligence quotient (IQ) scores at eight years of age than the unexposed group after controlling for earlier cognitive abilities, and for children who were permanently placed in adoptive/foster homes before one year of age.
OPIOID MAINTENANCE THERAPIES: SUMMARY

• Not without risk.
• Incidence, peak severity score, duration, and length of hospital stay due to NAS are less severe in neonates born to women following medically controlled maintenance therapies compared to near-term mothers still using illicitly.
• Accumulating data indicates mothers and fathers who continue in maintenance therapy programs maintain more stable lives.
NEONATAL ABSTINENCE SYNDROME
NAS

• Variable, highly complex spectrum of signs of neonatal behavioral dysregulation.
• Not completely understood.
• Opioid exposure most common cause.
• Other substances such as nicotine are associated as well.
• May be accentuated by substances such as benzodiazepines, SSRI’s and cigarettes.
OPIOIDS: DEFINITION

• Natural and synthetic substances with morphine-like activities that activate mu-opioid receptors in the central nervous symptoms and gastrointestinal tract.
  • Examples:
    • morphine
    • codeine
    • heroin
    • methadone
    • fentanyl
    • hydromorphone
    • buprenorphine
RISING INCIDENCE OF NAS

• Maternal use of opioid pain relievers has increased.
  • One study documented a rise from 1.9 to 5.63 per 1000 hospital births (2000-2009)
• NAS
  • Incidence increased from 1.2 to 5.8 per 1000 hospital births (2000-2012)
  • NAS admissions to NICUs rose from 7 to 27 cases per 1000 admissions (USA).
PATHOPHYSIOLOGY OF NAS

• Not completely understood, altered levels of neurotransmitters are presumed to play a role such as:
  • Norepinephrine
  • Dopamine
  • Serotonin

• Similar to adult data showing variability in opioid dependence, genetic variations appear to affect the need for pharmacotherapy and length of stay in neonates with prenatal opioid exposure.
CLINICAL MANIFESTATIONS

• Varies widely
  • in timing of onset
  • Severity
  • Types of signs
VARIABILITY IN PRESENTATION DUE TO:

- Maternal exposures
  - Substances used
  - Concurrent use of prescribed medications
  - Timing of exposure during pregnancy
  - Polysubstance use (including alcohol and nicotine)
  - Frequency
  - Type – oral vs IV
  - Dose
VARIABILITY IN PRESENTATION CONTINUED:

• Maternal factors:
  • Nutrition
  • Infections
  • Stress
  • Comorbid psychiatric conditions
VARIABILITY IN PRESENTATION CONTINUED:

• Placental opioid metabolism
• Genetics
• Infant factors
  • Prematurity
  • Comorbid infections
  • Rate of drug metabolism and excretion
  • Other conditions in the baby
  • Medications prescribed
VARIABILITY IN PRESENTATION CONTINUED:

• Environmental factors
  • Response of care givers to infant cues
  • Physical environment
    • NICU vs rooming in vs regular nursery.
SIGNS OF NAS

- High-pitched crying and irritability
- Sleep and wake disturbances
- Alterations in tone or movement:
  - Hyperactive primitive reflexes
  - Hypertonicity
  - Tremors
- Feeding difficulties
- Vomiting and loose stools
SIGNS OF NAS CONTINUED

• Autonomic dysfunction
  • Sweating
  • Sneezing
  • Mottling
  • Fever
  • Nasal stuffiness
  • Yawning
• Failure to thrive
ADDITIONAL FINDINGS

• Seizures
  • Reported in 2-11%
  • Cause of NAS related seizures is unknown.
  • EEG abnormalities have been reported in >30% of neonates withdrawing from opioids.

• Small for gestational age (SGA)

• Respiratory complications
TIMING OF WITHDRAWAL

- Dependent upon the timing of maternal drug use and the half-life of the drug.

- Drugs with short half-lives such as heroin:
  - Withdrawal signs start within 24 hours of birth.

- Drugs with longer half-lives such as methadone or buprenorphine:
  - Withdrawal signs usually starts from 24-72 hours after birth.

- However, for both groups withdrawal can be delayed for 5 days or longer. (Late Onset NAS)
TIMING OF WITHDRAWAL CONTINUED

• If mom’s last use of opioids was one week or greater prior to delivery, the risk of acute signs of neonatal withdrawal is low.
  • There is still the possibility of late onset NAS.
TIMING OF WITHDRAWAL CONTINUED

- Narcotics: birth/pk 3-4 days, abn reflexes can last up to 8 mos
- Barbiturates: 4-7 days, can last 4 mos
- Cocaine/Methamphetamine: 1st wk due “toxicity”
- Depressants/Sedatives: ETOH 3-12 hrs / 2-3 wks
- Selective Serotonin Reuptake Inhibitors-SSRIs : 48 hrs with resolution by 4 days
- Alcohol: first 3-12 hours after delivery.
MANAGEMENT GOALS

• To Establish consistent weight gain.
  • Requires adequate sleep and nutrition

• To allow the infant to successfully integrate into his or her environment by:
  • Enabling infant to communicate with caretakers.
  • To manage stimuli.
MANAGEMENT APPROACH

• Supportive nonpharmacologic care.
• Pharmacologic therapy.
  • Typically determined by abstinence scoring systems and the response to nonpharmacologic measures.
ABSTINENCE SCORING METHODS

- Lipsitz tool
- Finnegan Neonatal Abstinence Scoring System
- Neonatal Withdrawal Inventory
ENVIRONMENTAL MEASURES

• Learn infant’s cues
• Remain calm
• Reduce environmental stimulation
• Offer pacifier
• Do not overdress infant
• Gradually (re)introduce stimuli
• Use soft music and relaxation baths
THERAPEUTIC HANDLING

• Minimize “hands on” time
• Provide cluster care
• Hold infant firmly and closely
• Gently rock infant
• Use infant swing or vibration seat
• Swaddle infant
• Use sleep sack
• Encourage skin-to-skin contact (Kangaroo care)
NUTRITION/FEEDINGS

• Increase calories for satiety
• Feed on early hunger cues
• Consider simethicone drops
• Burp frequently
• Monitor stooling pattern...use barrier creams for diaper rash
• Support breastfeeding, when appropriate
BREASTFEEDING WHEN MOM ON MAINTENANCE

• Methadone maintained mothers
  • Concentrations low in breast milk and appear not to be related to the maternal dose of methadone.
  • May reduce the severity of NAS.
    • Low concentrations unlikely to be the source of this reduction and may be related to other factors associated with breastfeeding.

• Buprenorphine maintained mothers
  • Low concentrations in breastmilk.
  • Appears safe.
PHARMACOLOGIC THERAPY

- Opioid Therapy is first line therapy.
  - Morphine or Methadone most commonly used drugs.
- Second line drug therapy
  - For those infants with severe NAS
  - Clonidine or phenobarbital most commonly used.
LONG-TERM EFFECTS OF OPIOIDS

• Difficult to isolate effects due to confounding variables such as
  • Prenatal:
    • Other drug exposures
    • Prematurity
    • Low Birth Weight
    • IUGR
  • Postnatal:
    • Continued maternal drug use
    • Domestic violence exposure
    • Socioeconomic level
    • Educational level
MECHANISMS OF ACTION OF DRUGS ON THE FETUS

• Early in gestation during the embryonic stage:
  • Can have significant teratogenic effects.

• Later in pregnancy (2\textsuperscript{nd} – 3\textsuperscript{rd} Trimesters)
  • More subtle effects:
    • Abnormal growth
    • Alterations in neurotransmitters
    • Brain organization
  • Indirect effects
    • Maternal effects
    • Placenta insufficiency
    • Altered maternal behavior
REHOSPITALIZATION IN CHILDREN WHO HAD NAS

• Population-based study of all children registered in NSW, Australia.
  • Looked at births, hospitalization and death records of all children between 2000-2011 to a maximum of 13 years.
  • Infants with NAS (n=3842) were compared to 1,018,421 infants without a diagnosis of NAS.
REHOSPITALIZATION IN CHILDREN WHO HAD NAS

• Infants are more likely to be admitted to higher level nursery care and have longer stay (10 vs 3 days)

• Children were more likely to:
  • Require hospitalization. (twice as likely).
  • To die in the hospital. (three times as likely)
  • Be admitted for maltreatment (up to 36 times more likely for unspecified causes)
  • Be admitted for strabismus and nystagmus (12 fold higher).
  • mental and behavioral problems (18 times higher).
REHOSPITALIZATION IN CHILDREN WHO HAD NAS

• Conclusions
  • Children with NAS are more likely to be rehospitalized during childhood for maltreatment, trauma, and mental and behavioral disorders even after accounting for prematurity.
  • This continues to adolescence and emphasizes the critical need for continued support of this vulnerable group after resolution of NAS.
CDC STUDY IN TN: CHILDREN WITH NAS

• 1,800 children with a history of NAS.
• Compared to 5,400 control children.
• All children were born between 2008 and 2011.
• Current report followed them until they reached school age.
• TN had a 15 fold increase in NAS from 2002 to 2012.
CDC STUDY IN TN: CHILDREN WITH NAS

- Study attempted to control for the following:
  - Parental education status
  - Maternal smoking
  - Regional differences
  - Low birth weight
CDC STUDY IN TN: CHILDREN WITH NAS

• 44% more likely to be referred for evaluation of developmental delay.
• 36% more likely to meet their state’s criteria for educational disability.
• 37% more likely to receive help with educational and developmental difficulties.
CDC STUDY IN TN: CHILDREN WITH NAS

• Conclusion:
  • “They should be enrolled in or at least evaluated for early intervention services through age 3, to determine if they show any signs of early developmental delays. They should have ongoing close monitoring to make sure there’s no evidence they need additional therapies or services.”
NEONATAL ABSTINENCE SYNDROME AND HIGH SCHOOL PERFORMANCE

• Pediatrics February 2017, Volume 139/Issue 2
• Ju Lee Oei, lead author
• New South Wales, Australia
• The first report of academic outcomes at a population level for children with a history of NAS.
METHODS

• Linked analysis of health and curriculum-based test data
  • For all children born in New South Wales between 2000-2006

• Children with NAS compared with a control group
  • NAS n = 2234
  • Controls n = 4330

• Matched for:
  • Gestation
  • Socioeconomic status
  • Gender

• Compared with other NSW children: n = 598,265
NATIONAL ASSESSMENT PROGRAM

• Literacy and Numeracy results in grades 3, 5, and 7
RESULTS

• Mean test scores for children with NAS
  • Significantly lower in grade 3
    • 359 (NAS) vs control: 410 vs general population: 421

• Deficit was progressive
  • By grade 7, children with NAS scored lower than other children in grade 5
WHY DOES IT MATTER?
CHILDREN WHO FAIL AT SCHOOL ARE AT RISK FOR MANY POOR ADULT OUTCOMES:

- Psychiatric illness
- Physical Illness
- Unemployment
- Delinquency
- Crime
- Drug Use
SUMMARY

• Gave an overview of neonatal abstinence syndrome.
• Looked at confounding exposures.
• Review of the Literature with regards to long term effects of prenatal opioid exposure.
MIIGWECH
QUESTIONS?
REFERENCES


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