EFFECTS OF PRENATAL ALCOHOL EXPOSURE AND OTHER DRUGS ON BRAIN DEVELOPMENT

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LEARNING OBJECTIVES

By the end of this presentation, the learner will be able to:

1. List two effects of prenatal alcohol exposure on fetal brain development
2. Describe potential long-term impact of prenatal alcohol exposure to infant and child development
3. Compare short-term and long-term effects of prenatal exposure of alcohol and other drugs
DISCLOSURES

• Dr. Onoye – no conflicts of interest reported
• Dr. Sorensen – no conflicts of interest reported

• The contents of this presentation are solely the responsibility of the authors and does not necessarily constitute or represent the views of any affiliated institutions or agencies.
A variety of developmental and behavioral problems noted in children and adolescents whose parents abuse alcohol and drugs.

Many women use alcohol and other drugs and do not know they are pregnant.

It is known that prenatal exposure of alcohol and other drugs directly impact the developing fetus as teratogens.

There may be significant short-term and long-lasting effects on brain development and subsequent behavior for children prenatally exposed.
BACKGROUND

- Alcohol and substance use and abuse during pregnancy still remains a significant and worldwide problem.
- Almost all drugs cross the placenta and can affect the fetus in multiple ways.
- Direct and indirect effects on fetus.

<table>
<thead>
<tr>
<th>Short-term effects/birth outcome</th>
<th>Nicotine</th>
<th>Alcohol</th>
<th>Marijuana</th>
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<td>Fetal growth</td>
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* Limited or no data available.

EPIDEMIOLOGY

• National Survey on Drug Use and Health (NSDUH) shows that among pregnant women aged 15-44 in 2012-2013
  • 9.4% reported current alcohol use and 2.3% reported binge drinking
  • 15.4% reported cigarette use in past month
  • 5.4% reported current illicit drug use

• Hawai’i Pregnancy Risk Assessment Monitoring System (PRAMS) 2009-2011 shows that among women who gave birth:
  • 51.5% reported drinking alcohol and 24.1% binge drinking in the 3 months prior to pregnancy
  • 6.9% reported drinking alcohol and 1.2% binge drinking in the last trimester of pregnancy
  • 20.9% reported smoking cigarettes in the 3 months prior to pregnancy
  • 7.5% reported smoking in the last trimester of pregnancy and 11.7% in early postpartum

ALCOHOL USE AND SMOKING MOST COMMON

• Majority of women who use alcohol/drugs during pregnancy, use more than one drug
• Alcohol and cigarettes are the most common substances used during pregnancy
• Rates of other illicit drugs may vary by type of drug and region
PSS DATA ON ALCOHOL, SMOKING, DRUG USE DURING PREGNANCY

• Perinatal Support Services (PSS) for at-risk women during pregnancy and postpartum

• Not representative for population but large sample of over 7000 unique cases (June 2007 – June 2012)

• Examine trimester data (1st, 2nd, and 3rd) for screen positive for alcohol, smoking, other drugs
ALCOHOL RATES BY TRIMESTER


SMOKING RATES BY TRIMESTER


ILLICIT/OTHER DRUG USE RATES BY TRIMESTER


FETAL ALCOHOL SPECTRUM DISORDERS (FASD)

- Individuals affected by prenatal alcohol exposure can have a range of serious, lifelong problems including physical, cognitive, behavioral, and social deficits
- FASD: an umbrella term describing the range of effects that can result from prenatal alcohol exposure—but not a diagnostic term
FETAL ALCOHOL SYNDROME (FAS)

• Estimated prevalence of FAS in US ranging from .2 to 1.5 per 1000 live births (CDC)


• One of the leading preventable causes of intellectual disability and physical disabilities
FETAL ALCOHOL SYNDROME (FAS)

- Diagnosis of FAS includes:
  - Documentation of facial abnormalities (smooth philtrum, thin vermillion border [upper lip], short palpebral fissures [eye openings])
  - Documentation of prenatal and postnatal growth deficits
  - Documentation of CNS abnormalities (structural, neurological, behavioral)

- Often, affected children have learning disorders and ADHD, and/or intellectual disability

FETAL ALCOHOL SPECTRUM DISORDERS

• FASD includes the spectrum of effects from prenatal alcohol exposure, many without the facial dysmorphism (alcohol-related birth defects [ARBD], partial FASD [pFAS], alcohol-related neurodevelopmental disorder [ARND])

• Estimated prevalence from community study using case ascertainment even higher (partial FAS 7.9 to 17.7 out of 1000 in early school aged children 1st graders)

• Combined prevalence of FAS and pFAS 10.9 to 25.2 per 1000 or 1.1-2.5%

IMPACT OF ALCOHOL ON THE DEVELOPING EMBRYO/FETUS

• Alcohol readily crosses the placenta
  • Fetal liver/organs unable to fully metabolize alcohol
  • Embryo/fetus exposed to similar BAC (blood alcohol concentrations) levels as mother

• Specific manifestations of prenatal alcohol exposure are affected by timing, dose, and other fetal/maternal factors

Source: http://sites.duke.edu/rise/programs/rise-program/
TIMING OF PRENATAL ALCOHOL EXPOSURE

• There are multiple critical periods associated with prenatal alcohol exposure:
  • 1st Trimester Drinking: risk for major morphological abnormalities, characteristic facial features, growth retardation, and neurological effects
  • 2nd Trimester Drinking: risk for spontaneous abortion, growth retardation, and neurological effects
  • 3rd Trimester Drinking: risk for growth retardation and neurological effects
PRENATAL ALCOHOL EXPOSURE DURING DEVELOPMENT

Figure 4.1. Critical Periods of Fetal Development

Period of the Embryo (in weeks)

Period of the Fetus (in weeks)

1-2 3 4 5 6 7 8 12 16 20-36 38

- Most common site of birth defects

Central Nervous System (CNS)

Heart

Arms

Eyes

Legs

Teeth

Palate

External Genitalia

Ears

Fetal Alcohol Spectrum Disorders Competency-Based Curriculum Development Guide for Medical and Allied Health Education and Practice.

Figure from Ch IV. Biological Effects on the Fetus, source: National Organization on Fetal Alcohol Syndrome (NOFAS), 2004; Adapted from Moore, 1993
TIMING OF PRENATAL ALCOHOL EXPOSURE

• Extent of damage to any brain area may be related to timing of alcohol exposure relative to developmental processes that are occurring in that brain region

• Animal studies also show neurobehavioral effects related to timing of prenatal alcohol exposure (Mantha et al, 2013. *Journal of Behavioral and Brain Science* 3[1]:15)
NORMAL BRAIN DEVELOPMENT

Source: http://sites.duke.edu/rise/programs/rise-program/
EFFECTS OF PAE ON FETAL BRAIN DEVELOPMENT

• Neurons and glia formed from stem cells (neurogenesis and gliogenesis)
• Alcohol kills neural stem cells, reducing neurogenesis
• Abnormal migration of cells
• Disrupts stabilization of functional synapses and pruning of unneeded synapses


Source: http://sites.duke.edu/rise/programs/rise-program
BUT FASD IS PREVENTABLE!

- Alcohol exposure at any time during pregnancy can cause damage to the fetal brain.
ETHANOL EXPOSURE AND NEUROTRANSMITTERS

• GABA neurotransmitter system affected during early development
• In fetal mouse model, ethanol exposure causes premature maturation of progenitor cells partly via GABA receptors (Sathyan et al, 2007)
• Low dose ethanol promoted premature migration of immature GABA interneurons in cerebral cortex (Cuzon et al, 2008)
• Suggests that daily consumption of small amounts of alcohol (e.g., glass of wine with meals) during 1st and 2nd trimesters could have significant effects on development of GABAergic neurons in the fetus

BRAIN REGIONS AFFECTED BY POTENTIAL NEUROTRANSMITTER SYSTEM ALTERATIONS FROM ALCOHOL

POTENTIAL LONG-TERM IMPACT OF PRENATAL ALCOHOL EXPOSURE: COGNITIVE AND BEHAVIORAL EFFECTS

• Potential long-term impact of PAE to infant and child development may result in cognitive or behavioral problems as a consequence of damage to specific brain areas

<table>
<thead>
<tr>
<th>Brain Region Commonly Affected</th>
<th>Function affected by PAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortex</td>
<td>Executive function, attention, memory, language</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>Motor tasks, coordination, attention</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Learning and memory</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>Cognition, movement, attention</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Motor control, coordination, time perception</td>
</tr>
</tbody>
</table>

Adapted from Source: http://sites.duke.edu/rise/programs/rise-program/
CEREBRAL CORTEX

- Involved in attention, memory, perceptual awareness, thought, language and consciousness
- Executive function – planning, self-control, abstract thinking – associated with prefrontal cortex
- Cortical connections being refined in 3rd trimester and into childhood & adolescence

Source: http://sites.duke.edu/rise/programs/rise-program/
CORPUS CALLOSUM

- One of most consistent structures found to be affected in FASD (malformed or absent)
- Typically heavily myelinated bundle of fibers crossing the midline between hemispheres
- Important in timing tasks, attention, motor tasks, and coordination

HIPPOCAMPUS

- Responsible for learning and memory along with other cortical areas
- Hippocampal formation begins early in 2\textsuperscript{nd} trimester with connections refined in late pregnancy

Source: http://sites.duke.edu/rise/programs/rise-program/
CAUDATE NUCLEUS AND CEREBELLUM

- Caudate nucleus important in understanding (cognition) and movement and carrying out tasks
- Works with the cerebellum, which is responsible for motor control and coordination (development into postnatal period)

Source: http://sites.duke.edu/rise/programs/rise-program/
NEUROBEHAVIORAL PROFILES

• Neurocognitive and behavioral deficits range on continuum (Mattson et al, 2011. Neuropsych Review 21[2]: 81-101), some examples:
  • General Intelligence – most common finding is diminished intellectual capacity more often in FAS
  • Executive Function – frontal-subcortical circuits vulnerable (Fryer et al, 2007; Mattson et al, 1996)
    • Problem-solving and Planning – perseverate on incorrect strategies, rule violations (Aragon et al, 2008; Green et al, 2009)
    • Concept Formation and Set-Shifting – difficulty identifying abstract concepts and shifting concepts (Carmichael Olson et al, 1998; McGee et al, 2008; Vaurio et al, 2008)
    • Inhibitory Control – require greater cognitive effort for behavioral inhibition as seen in ERP and fMRI studies (Burden et al, 2009; Fryer et al, 2007)
NEUROBEHAVIORAL PROFILES

- **Working Memory** — verbal (Green et al, 2009) and visual-spatial working memory (Green et al, 2009) deficits beyond IQ
- **Attention** — hyperactivity, higher rate of ADHD (Fryer et al, 2007), may be differential in visual and auditory modalities
- **Academic** — difficulties both verbal and mathematical (Carmichael Olson et al, 1992, Howell et al, 2006), may be dose-timing related to prenatal exposure (Goldschmidt et al, 1996)
- **Clinical and Behavioral** — range of maladaptive and clinically significant behavioral characteristics, e.g., social problems, aggressive behavior, behavioral emotional disturbances (Mattson & Riley, 2000), but conduct problems may be environmentally mediated while impulsivity and attention difficulties accounted by other related factors (D’Onofrio et al, 2007)
Change in total and white matter volume in the control and FASD groups.

x axes: age
y axes: white matter volumes

Regions: superior frontal; middle frontal; inferior frontal; superior parietal; inferior parietal; supramarginal; corpus callosum; and whole brain regions.

Status-by-age interactions were not significant for any region. For the supramarginal region, the FASD group had significantly smaller volumes but there were no significant age-related change in volume in either group.

ALTERED TRAJECTORY OF BRAIN DEVELOPMENT DURING CHILDHOOD & ADOLESCENCE

- MRI (diffusion tensor imaging/DTI) longitudinal scans (every 2-4 years) show neurodevelopment affected in FASD (n=17) compared to controls (n=27) aged 5-15 years.

- Both groups show increase of fractional anisotropy and decrease of mean diffusivity (MD) expected of typical development.

- However, FASD had greater reduction of MD between scans – shown to be correlated with reading and receptive vocabulary in FASD group.

- Steeper decrease of MD in superior fronto-occipital fasciculus and superior longitudinal fasciculus correlating with greater improvement in language scores.

- Volumetric analysis revealed reduced total brain, white, cortical gray, and deep gray matter volumes.

- DELAYED WHITE MATTER DEVELOPMENT DURING CHILDHOOD & ADOLESCENCE IN FASD, may underlie persistent or worsening behavioral and cognitive deficits during critical period.

GROWING UP WITH ALCOHOL BRAIN DAMAGE

- Learns a simple task but forgets quickly
- Difficulty developing any friendships
- Frequently does not attend to social / environmental stimuli
- Does not follow simple commands given once
- Strong reactions to routine/changes in environment
- Problems in fine and gross motor control
- Trouble with sequencing (counting, etc.)
- Difficulty controlling impulses
- Difficulty predicting consequences
- Severe temper tantrums or frequent minor tantrums
- Does not wait for needs to be met, wants things immediately
- Difficulties with toilet training
- Often frightened or very anxious
- Difficulty seeing sameness in daily living situations and in making generalizations
- Difficulty understanding abstract concepts
- Frequently unaware of surroundings and may be oblivious to dangerous situations
- Is very destructive
- Not afraid of strangers
- Strong need for bodily contact (patting, touching, etc.)
NICOTINE

• Nicotine concentrations higher in the placenta, amniotic fluid, fetal serum compared to mother
• Nicotine is only one of more than 4000 compounds to which the fetus is exposed through maternal smoking
• About 30 compounds associated with adverse health outcomes
• Adverse fetal affects likely related to hypoxia, undernourishment of the fetus and vasoconstrictor effects on the placenta and umbilical all play a part
• Significant damaging effects on brain development - alterations in brain development, brain metabolism and neurotransmitter systems and abnormal brain development
NICOTINE

• Linked to ADHD, reflect abnormal inhibitory control by the prefrontal cortex
• Prenatal nicotine exposure (PNE) impairs the proliferation of neural stem cells, leading to fewer glutamatergic neurons in the prefrontal cortex
• May heighten vulnerability to neurotoxic substances later in life

MARIJUANA

- Deleterious effects attributed to pharmacological actions on developing biological systems, altered uterine blood flow and maternal health behaviors
- Marijuana remains in body up to 30 days = prolonged exposure
- Smoking marijuana produces 5X carbon monoxide as cigarette smoking perhaps affecting fetal oxygenation
- In general, marijuana not associated with fetal growth restrictions
MARIJUANA

• Marijuana alters brain neurotransmitters and brain biochemistry
• Little evidence for negative effect of prenatal cannabis exposure on motor or cognitive development in early infancy
• Inconsistent findings for neurocognitive and behavioral effects

Huizink (2014). Progress in Neuropsychopharmacology and Biological Psychiatry, 52: 45-52
COCAINÉ

• Animal studies: teratogenic effects on developing fetus – morphological abnormalities in several brain structures

• Reduced neonatal total cortical gray matter (e.g., prefrontal cortex), areas of the brain regulate attention, executive functioning especially vulnerable to cocaine

• Intrauterine growth effects most consistent finding

COCAINE

• Arousal, attention and memory may be impacted

• Reported effects included irritability and lability of state, decreased behavioral and autonomic regulation, and poor alertness and orientation

• Behavior problems inconsistent findings – deficits in attention, processing, symptoms of ADHD

• Cocaine exposure does not predict overall development, IQ or school readiness

• Association with subtle language delays

METHAMPHETAMINE

• Stimulate the central nervous system

• Can have significant effects on fetus such as alteration in brain morphogenesis and neurotransmitter systems

• Limited literature but suggest involvement in subcortical structures (striatum), temporal lobe, frontal, and parietal regions associated with cognitive impairment in motor function (visual-motor integration), executive function, memory and attention

OPIATES

• Decrease brain growth and cell development
• Decrease cortical dendrite morphogenesis
• No clear teratogenic effect documented
• Neonatal abstinence syndrome (NAS) reported
• Long terms effects on growth not documented
OPIATES

• Hyperactivity and short attention span noted in toddlers; memory and perceptual problems noted in older children

• Animal model showed reduced tendency of exploration of objects in novel locations

• Longitudinal studies produced no consistent findings in development although developmental scores tend to be lower

## POTENTIAL EFFECTS OF PRENATAL DRUG EXPOSURE

<table>
<thead>
<tr>
<th></th>
<th>ALCOHOL</th>
<th>TOBACCO</th>
<th>MARIJUANA</th>
<th>STIMULANTS</th>
<th>OPIATES</th>
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</thead>
<tbody>
<tr>
<td><strong>Short-term</strong></td>
<td>Poor habituation</td>
<td>Excitability</td>
<td>Mild withdrawal symptoms</td>
<td>Cocaine</td>
<td>Abstinence syndrome</td>
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<td></td>
<td>Low level of arousal</td>
<td>Hypertonia</td>
<td>Delayed state regulation</td>
<td>Early deficits; orientation, state regulation, autonomic stability,</td>
<td>Strabismus</td>
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<td></td>
<td>Developmental delays</td>
<td>Stress abstinence signs</td>
<td>Increased startles and tremors</td>
<td>attention, sensory, motor asymmetry; jitteriness</td>
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<td></td>
<td>Sensory integration</td>
<td>Impaired orientation</td>
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<td></td>
<td>Attention</td>
<td>Autonomic regulation</td>
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<td></td>
<td>Learning &amp; memory</td>
<td>Muscle tone</td>
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<td></td>
<td>Global cognitive deficits</td>
<td>Language development</td>
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<tr>
<td><strong>Long-term</strong></td>
<td>Global cognitive deficits</td>
<td>Attention problems</td>
<td>Problem-solving requiring sustained attention</td>
<td>Cocaine</td>
<td>Possible delay in general cognitive function</td>
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<tr>
<td></td>
<td>Executive function</td>
<td>Impulsivity</td>
<td>Visual memory</td>
<td>Delayed information processing</td>
<td>Anxiety</td>
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<tr>
<td></td>
<td>Learning &amp; memory</td>
<td>Reduced IQ</td>
<td>Analytical</td>
<td>General cognitive delay</td>
<td>Aggression</td>
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<td></td>
<td>Language</td>
<td>Aggression</td>
<td>Reading, spelling difficulty</td>
<td></td>
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<tr>
<td></td>
<td>Social cognition</td>
<td>Some learning &amp; memory problems</td>
<td>Executive function impairment</td>
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<td>Substance use disorders</td>
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| Adapted from Behnke, M., et al. (2013). *Pediatrics* 131(3): e1009-e1024
# SHORT & LONG TERM EFFECTS OF PRENATAL DRUG EXPOSURE

**TABLE 2** Summary of Effects of Prenatal Drug Exposure

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IMPLICATIONS & FUTURE DIRECTIONS

• Prenatal alcohol exposure can affect fetal brain development in multiple ways

• The brain is developing throughout most of the perinatal period and therefore vulnerable throughout pregnancy – prevention is key

• Programs for screening and brief intervention and referral to treatment (SBIRT) may be a significant factor in preventing adverse impacts of prenatal exposure

• Taken together with the neurobehavioral effects, documentation of prenatal exposure helps to accurately diagnose affected infants and children and inform early and later intervention strategies

• More research is needed on the specificity and mechanisms of brain function and consequent behavior affected by prenatal exposure as well as trials for intervention and treatment
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Mahalo nui loa!