Psychiatric Sequelae of Fetal Substance Exposure

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Objectives

• Review incidence of substance abuse in pregnancy
• Explore neuropsychiatric effects of fetal substance exposure
• Discuss management of substance-exposure-related behavioral issues
Introduction

• Maternal substance abuse is associated with multiple insults to children
  – Teratogenic effect of drug
  – Poor nutrition in pregnancy
  – Lack of prenatal care
  – Women who abuse substances have higher rates of other mental health problems, which can be heritable
  – Postnatal neglect, abuse
Incidence of Substance Use in Women (ages 15-44)

- Illicit drugs: 5.0% pregnant vs. 10.8% non-pregnant
  - Teens 4 x higher use in pregnancy
- Alcohol: 9.4% pregnant vs. 55.1% non-pregnant (binge use 2.6% vs. 24.5%, heavy use 0.4% vs. 5.3%)
- Tobacco: 17.6% pregnant vs. 25.4% non-pregnant

2011 National Survey on Drug Use & Health: National Results
Pregnant Teens are Different

– Pregnancy in teens is (in most cases) part of the **constellation of high-risk behaviors** that can include smoking, alcohol, and illicit drug abuse
– These girls use MORE substances than non-pregnant peers
– **20.9%** of pregnant teens use illicit drugs*

*2011 National Survey on Drug Use & Health: National Results
Tobacco Use in Pregnancy

- About one in six pregnant women reported smoking during the last month (NSDUH, 2011)
- Maternal smoking is by far the largest single cause of low birth weight (<2500 gm) in babies in the developed world
  - Responsible for around 30% of low birth weight
Low Birth Weight: Outcomes (< 2500 grams, or 5 lb. 8 oz.)

- Increased infant mortality
- Increased MR, CP, LD
- Increased asthma, ear infections
- Increased depression in female adolescents: 38% vs. 8.4%
- Increased risk of type II DM, heart disease, stroke, COPD
- Increased risk (rel risk= 1.7) of adult kidney disease (fewer, smaller nephrons)
  - American Journal of Kidney Diseases, August 2009

Costello EJ et al. Prediction from low birth weight to female adolescent depression. Arch Gen Psychiatry 2007; 64:338
Tobacco Use in Pregnancy

- Increased placenta previa, placental abruption, PROM, preterm labor and delivery
  - Effect higher in older and non-white mothers
- Relative risk of infant mortality is 1.2 -1.4 in smoking vs. non-smoking mothers, for SIDS, 2-4
- Increased risk of asthma, obesity, lymphoma, bladder Ca in later life
Possible Mechanisms of Toxicity

• Homocysteine levels higher in smokers
  – Dose-dependent
  – Increased homocysteine levels are associated with vascular, neurologic, genetic damage in adults
Physiology Review Slide

Fig. 1 Homocysteine Metabolism (adapted from Verhoef, et al., Am J Epidemiology 1998, 143: 840-850)
Folate supplementation

• Folate supplementation helps mitigate effect of maternal smoking
• If mothers can’t quit, cutting down helps
• Everyone should be on folate supplementation prior to conception
• Smokers should ESPECIALLY be on folate

http://www.mighealth.net/nl/images/2/22/Proefschrift_rachel.pdf
Tobacco: Behavioral Effects

• Increased adolescent drug dependency in girls
• Conflicting data re: slight decrease in IQ scores (2-3 points)

Wakschlag et al. Arch Gen Psychiatry 1997; 54:670
Batty et al. Pediatrics 2006; 118:943
Tobacco: Behavioral Effects

• Increased:
  – Oppositional defiant disorder
  – Conduct disorder in boys
  – ADHD (if birth weight low)

Opioid Use in Pregnancy

• Low birth weight
• Neonatal abstinence syndrome (NAS): acute opioid withdrawal
  – Tremors, irritability, high-pitched cry
  – Hypertonicity, increased DTR’s
  – Sweating, yawning
  – Seizures
Maternal Opioid Abuse

- No association with mental, motor, or behavioral deficits after controlling for low birth weight

Messinger et al. Maternal Lifestyle Study; Pediatrics Vol. 113 No. 6
June 2004
Medical Opioid Use and Birth Defects

- conoventricular septal defects (OR= 2.7)
  - May close spontaneously
- atrioventricular septal defects (OR= 2.0)
- hypoplastic left heart syndrome (OR= 2.4)
- spina bifida (OR=2.0)
- gastroschisis (OR= 1.8)

Maternal treatment with opioid analgesics and risk for birth defects
Maternal Cocaine Abuse

- Deceleration in growth with use late in pregnancy
- Low birth weight, head circ, length
- Neonatal symptoms
  - “Crack baby”: tremors, high-pitched cry, irritability
  - Transitory changes on EEG, autonomic instability in first week of life
Maternal Cocaine Abuse

• Cocaine-induced vasculopathy
  – Reduced efficacy of fetal blood-brain barrier (makes other teratogens more potent)
  – Higher risk of maternal-fetal HIV transmission

• Hyperthermia mediated by vasoconstriction
  – Placental compromise
Cocaine Exposure and Learning

- N=135
- Report card data, standardized tests, teacher and parent reports
- Mild impairment in attention
  - Boys appear more at risk than girls

Cocaine exposure and IQ

• N=231 (91 exposed, 140 not)
  – Ages 4, 6, and 9
• Alcohol, tobacco, and marijuana use also examined
• Cocaine-exposed boys had lower IQ’s
  – about 6 points
  – abstract/visual reasoning more affected than short-term memory and verbal reasoning

Children's cognitive ability from 4 to 9 years old as a function of prenatal cocaine exposure, environmental risk, and maternal verbal intelligence
Cocaine exposure and executive functioning

- N=66, 31 exposed, 35 not, ages 7-9
- Parent rating, various testing instruments
- Parents saw more problems with behavioral regulation
- Insignificant difference in IQ

Maternal Cannabis Use

• Birth weight, length, and head circumference were decreased in babies exposed to marijuana in the third trimester
  – BW decreased 500gm
  – Length decreased 2 cm
  – Head circ. decreased 1.4 cm

• This effect remained after controlling for concurrent tobacco use

Maternal Marijuana Abuse

• 417 mothers using only marijuana showed no association with prematurity or congenital anomalies
• Possible impairment in sustained attention, visual memory, analysis, and integration
• No effect on intelligence

Fried PA et al. Differential effects on cognitive functioning in 13 to 16 year-olds prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 2003; 25:427
Maternal Amphetamine Abuse

- Increased risk of prematurity, low birth weight
- Neonatal (intoxication) - irritability, shrill cry, myoclonic jerks
- Problems with verbal memory and sustained attention
  - Other drug use (EtOH and tobacco), malnutrition are confounding factors

Amphetamine-exposed adolescents

• 65 Swedish children followed from birth
• 15% were a grade behind
• 33% noted to have behavioral problems in school

Alcohol: Impact on Fetal Development

– Compounded by older maternal age, high parity, race (Native American, African-American)
– Binge drinking increases stakes
– Polymorphisms of ADH gene (alcohol dehydrogenase) can affect risk
  • Some are protective, some increase risk
Alcohol as a Teratogen

• Interferes with neuronal migration needed for proper brain structure formation
• Interferes with glial development especially in 3rd trimester “growth spurt”
• Increased free radicals, increased stress-related factors- glucocorticoids, prostaglandins
Alcohol as a Teratogen

• Structural alterations to the shape, volume and surface area of the overall brain and particular brain regions
• Reduced white matter and increased grey matter densities in corresponding areas

Alcohol: Indirect Teratogenicity

• Dehydration
• Erratic nutrition
  – Especially in critical embryonic stages
• high-risk behaviors
  – STD’s
  – Other substance use
  – Injury
Patterns of Alcohol Use

2011 National Survey on Drug Use & Health: National Results
Important Milestones for the Embryo

Embryonic Development

First prenatal care visit

Developmental Progression & Susceptibility to Teratogens & Fetal Loss
Risk factors for Fetal Alcohol Spectrum Disorders

• CDC 2004 data: 2 or more drinks per day OR 5 or more drinks per occasion
• Associated factors may enhance FASD expression
  – Very high EtOH levels in binge drinking
  – Poor diet
  – Stress, depression, poor prenatal care
  – Poverty (multifactorial)
FAS Risk Factors: Host

• Age ≥ 25, gravidity ≥ 3, parity ≥ 3
Higher rates of stillbirth/miscarriage
Infrequent practice of spirituality
Low education
Smokes cigarettes
Depression/psychological distress
Short stature, low weight, low BMI
Nutritional deficiency
Alcohol dehydrogenase polymorphisms

May, P et al. Maternal Risk Factors for Fetal Alcohol Spectrum Disorders: Not As Simple As It Might Seem Alcohol Research & Health, Volume 34, Issue Number 1
FAS Risk Factors: Agent

• High BAC from large quantities of EtOH
  Binge drinking (3+ per occasion)
  Length of drinking career
  Drinking outside of meals
  Beer is beverage of choice of a majority of
  FASD mothers in most populations
  Frequent smoker (lower birth weight)
  Polysubstance abuse in urban studies
  Change in gastric ADH activity
  Change in nutritional status during pregnancy
FAS Risk Factors: Environment

• Low SES
  Not married, but living with partner
  Culture accepting of heavy drinking
  Family of origin of heavy drinkers
  Partner is a heavy & frequent drinker
  Alcohol-centered recreation popular
  Social isolation from mainstream economy & society

Little or no knowledge or awareness of FASD

May, P et al. Maternal Risk Factors for Fetal Alcohol Spectrum Disorders: Not As Simple As It Might Seem Alcohol Research & Health, Volume 34, Issue Number 1
Mothers of Children with FAS Study

– All had alcohol use disorders, and 96% had one or more psychiatric diagnoses
  » 77%: PTSD
  » 59%: Major depressive episode
  » 34%: Generalized anxiety disorder
  » 22%: Manic episode/Bipolar disorder
  » 7%: Schizophrenia
– 95% had been physically or sexually abused during their lifetime
– 79% reported having a birth parent with an alcohol problem

80 Mothers of Children with FAS (Astley et al., 2000)
History of Fetal Alcohol Spectrum Disorders (FASD)

• In the first half of the 18th C, England’s gin consumption rose from 2 to 11 million gallons per year

• In 1865 Dr. E. Lanceraux, a French physician, noted:
  – “..bears the special characteristics: the head is small..., his physiognomy vacant [peculiar facial features], a nervous susceptibility more or less accentuated, a state of nervousness bordering on hysteria, convulsions, epilepsy...are the sorrowful inheritance a great number of individuals given to drink bequeath their children.”
History of Fetal Alcohol Spectrum Disorders (FASD)

• France 1968: Abnormalities observed in 127 children with alcoholic parents
• Lancet 1973: Pattern of malformation described in children and infants


Fetal Alcohol Timeline

• 1973: Fetal Alcohol Syndrome
  – Criteria standardized in 1980
  – Criteria revised 1989

• 1981: US surgeon general issues an advisory warning pregnant women to limit their alcohol intake
Evolution of FAS

• 1989: Alcohol-Related Birth Defects (ARBD) and Fetal Alcohol Effect (FAE)
  – ARBD: abnormalities attributable to known alcohol intake
  – FAE: alcohol is a possible cause of defects
    • “FAE” became widely used to describe all alcohol-related abnormalities not meeting criteria for FAS
FAS Timeline

• 1996: Alcohol-related neurodevelopmental disorder (ARND) and ARBD (other organs) replaced FAE

• 2005: Fetal Alcohol Spectrum Disorders (FASD) accepted as “umbrella term”

• 2005: US surgeon general issues an update recommending no alcohol intake for women who are pregnant or could become so
Fetal Alcohol Toxicity

• Incidence of full FAS:
  – All groups: 0.5 to 2 cases per 1000
  – Blacks, American Indians, and Alaska Natives: 3 to 4 per 1000 births
  – “Heavy” drinkers (defined as 5 or more drinks at a time, 5 or more times a month): 49 per 1000 births

Surveillance data from 4 states: Alaska, Arizona, Colorado, and New York
Criteria For FAS diagnosis

• FAS diagnosis requires all three of these findings*

  – Documentation of all three facial abnormalities- smooth philtrum, thin vermillion, small palpebral fissures
  – Documentation of growth deficits
  – Documentation of central nervous system/neurobehavioral disorders (structural, neurological and/or functional)

*Confirmed prenatal alcohol use can strengthen the evidence for diagnosis, but is not necessary in the presence of all findings listed above.
Typical Facies in FAS

FETAL ALCOHOL SYNDROME

- low nasal bridge
- epicanthal folds
- minor ear abnormalities
- short palpebral fissures
- indistinct philtrum
- flat midface and short nose
- micrognathia
- thin upper lip
Lip-Philtrim Assessment

- View the face along the Frankfort plane
Lip-Philtrim Assessment
FAS: Other Visible Markers

“railroad-track” upper ear

clinodactyly and “hockey puck” palmar crease
Growth Deficits in FAS/ARBD

- Small head
- Low birth weight
- Decelerating weight gain over time
- Low weight to height ratio
- Short stature
IQ and FAS

- Mental retardation in 25% of FAS cases, 10% of ARND cases
  - Alcohol is the largest PREVENTABLE cause of mental retardation
  - In some populations it is more common than Down’s syndrome (1:800)

- Remember - after the first trimester, facial structures remain normal despite alcohol exposure
A Normal Face is no Guarantee

• 73 children with FASD
• MORE behavioral problems were seen in LESS visibly affected children

FASD and Psychopathology

• 97% of children with FASD met criteria for one or more DSM-IV disorders

• Significantly more ADHD, depressive disorders, ODD, conduct disorder, phobias, and multiple diagnoses

Learning and Behavior in ARND/FAS

• Memory: encoding more impaired than retrieval
  – short-term memory deficits
• Verbal learning: FAS kids learn *fewer* words *more slowly*
• Visual-spatial: may recall which objects were on a table, but not their relative positions
Learning and Behavior in ARND/FAS

• Sequencing

• Impaired executive functions:
  – Planning, organizing
  – Set shifting/generalizing
  – Difficulty abandoning ineffective strategies (perseveration)
  – Poor suppression (impulsivity)

• Can look a lot like ADHD, but may not respond to the usual approaches
• Difficulty establishing routines
  – Seen in infants’ sleep and feeding schedules
  – Persists throughout life
  – VERY frustrating to parents and teachers
    • “He’s 16 years old, why can’t he brush his teeth without having to be reminded?”

Learning and Behavior in ARND/FAS
Educational Challenges with FAS

• Learning problems are spotty and inconsistent
• Failure to adjust ineffective behaviors (impaired set-shifting) can alienate peers and be interpreted as defiance by parents and teachers
• Poor sequencing and generalizing result in frequent lapses in “common sense”
What Happens to Kids with FAS?

- 61% ‘disrupted school experience’
- 60% trouble with the law
- 50% ‘confinement’ (jail, prison, institution)
- 49% inappropriate sexual behavior on repeated occasions
- 35% alcohol or drug problems

What Happens to Kids with FAS?

• What improves these outcomes?
  – Earlier diagnosis
    • May reflect better overall parental function, more availability of services
  – Stable environment most of life
    • Placement lengths average >2.8 years
    • Years 8 to 12 especially important
  – Never experiencing physical abuse

Prevention

• Birth control for teens with ANY high-risk behaviors
• Folate supplementation and drug screening in pregnancy
• Refer for drug/EtOH treatment as needed
• Reinforce small improvements
  – Reduction in use
  – Good nutrition
Optimizing Care

• Include maternal substance use in routine history-taking for children
  – Substance
  – Pattern (binge or chronic)
  – Timing (when during pregnancy)

• Check birth weight

• Include facial assessment in MSE
  – Lip-philtrum guides available*

Optimizing Care

- In children with MR, refer to your state’s department of developmental disabilities for case management and lifelong supportive services
- In children with near-borderline IQ, DDD services may still be obtained
  - Document diagnosis (FAS, ARND)
  - Demonstrate functional impairment (psycho-ed testing, neuropsychiatric testing)
  - Follow through
Optimizing Care

• Help parents to advocate for assessment and services in school
  – **Written** request for psycho-educational evaluation triggers federal IDEA* requirements

• Work with special ed. staff to develop effective behavioral interventions
  – In FASD, allow for poor memory, slow receptive language, poor sequencing

* [http://idea.ed.gov](http://idea.ed.gov)
Optimizing Care

• Expect some differences in medication response
  – ADHD symptoms in alcohol-exposed kids may respond better to guanfacine or an atypical antipsychotic than to stimulants

• Educate parents and older children about HIGH risk of substance use disorders

• Help prevent teen pregnancy