

# 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

# 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

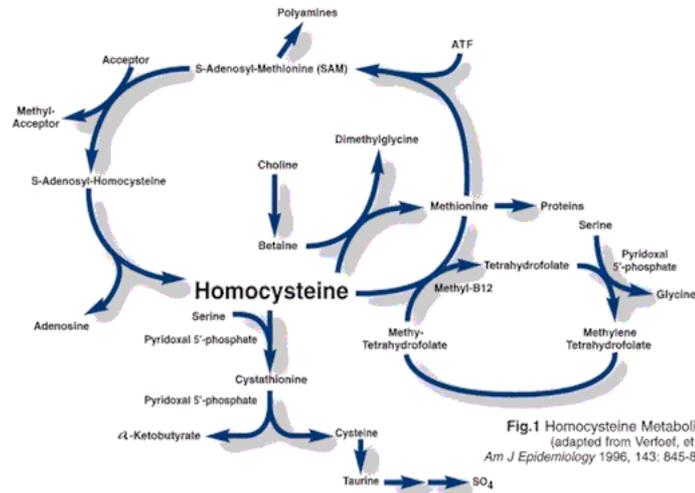


Fig.1 Homocysteine Metabolism  
(adapted from Verfoef, et al.,  
*Am J Epidemiology* 1996, 143: 845-859)

# 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

Maternal Lifestyle and Pregnancy Complications: The Generation R Study, Rachel Bakker

[http://www.mighealth.net/nl/images/2/22/Proefschrift\\_rachel.pdf](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)

Nigg J., Breslau N. Nigg JT, Breslau N. Prenatal smoking exposure, low birth weight, and disruptive behavior disorders. J Am Acad Child Adolesc Psychiatry. 2007 Mar;46(3):362-9.

# 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  
Broussard CS et al. *Am J Obstet Gyn* 2011 Apr; 204(4):314.e1-11.

# 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

**Hurt H et al.** School performance of children with gestational cocaine exposure. *Neurotoxicol Teratol* 2005; 27:513

# 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

Bennett DS et al. *Developmental Psychology*, Vol 44(4), Jul 2008, 919-928

# 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

Piper, B. Abnormalities in parentally rated executive function in methamphetamine/polysubstance exposed children. *Pharmacol Biochem Behav* 2011 May; 98(3):432-9

# 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

Gray, T et al. Identifying Prenatal Cannabis Exposure and Effects of Concurrent Tobacco Exposure on Neonatal Growth . Clin Chem 2010 Sept; 56(9): 1442-1450

# 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

Streissguth et al. Amphetamine abuse during pregnancy: environmental factors and outcome after 14-15 years J. Dev. Behav. Pediatr. 2004Aug;25(4):228-38

# Amphetamine-exposed adolescents

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

Eriksson M et al. Amphetamine abuse during pregnancy: environmental factors and outcome after 14-15 years *Scand J Public Health April 2000 vol. 28 no. 2 154-157*

# 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 3<sup>rd</sup> trimester “growth spurt”
- Increased free radicals, increased stress-related factors- glucocorticoids, prostaglandins

# Alcohol as a Teratogen

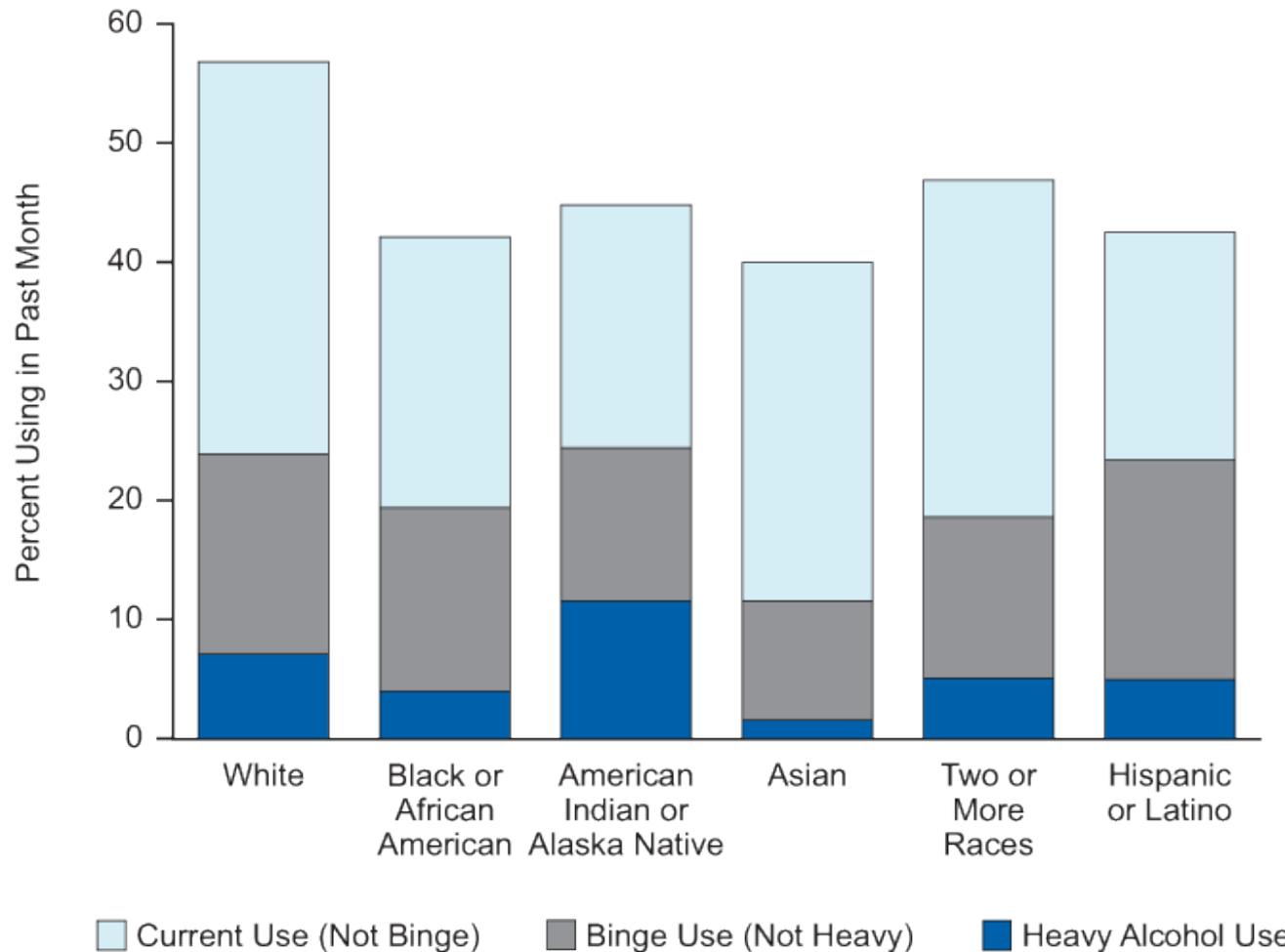
- Structural alterations to the shape, volume and surface area of the overall brain and particular brain regions
- Reduced white matter and increased grey matter densities in corresponding areas

Guerri, C et al. Foetal Alcohol Spectrum Disorders and Alterations in Brain and Behaviour *Alcohol and Alcoholism* (2009) 44 (2): 108-114.

# Alcohol: Indirect Teratogenicity

- Dehydration
- Erratic nutrition
  - Especially in critical embryonic stages
- high-risk behaviors
  - STD's
  - Other substance use
  - Injury

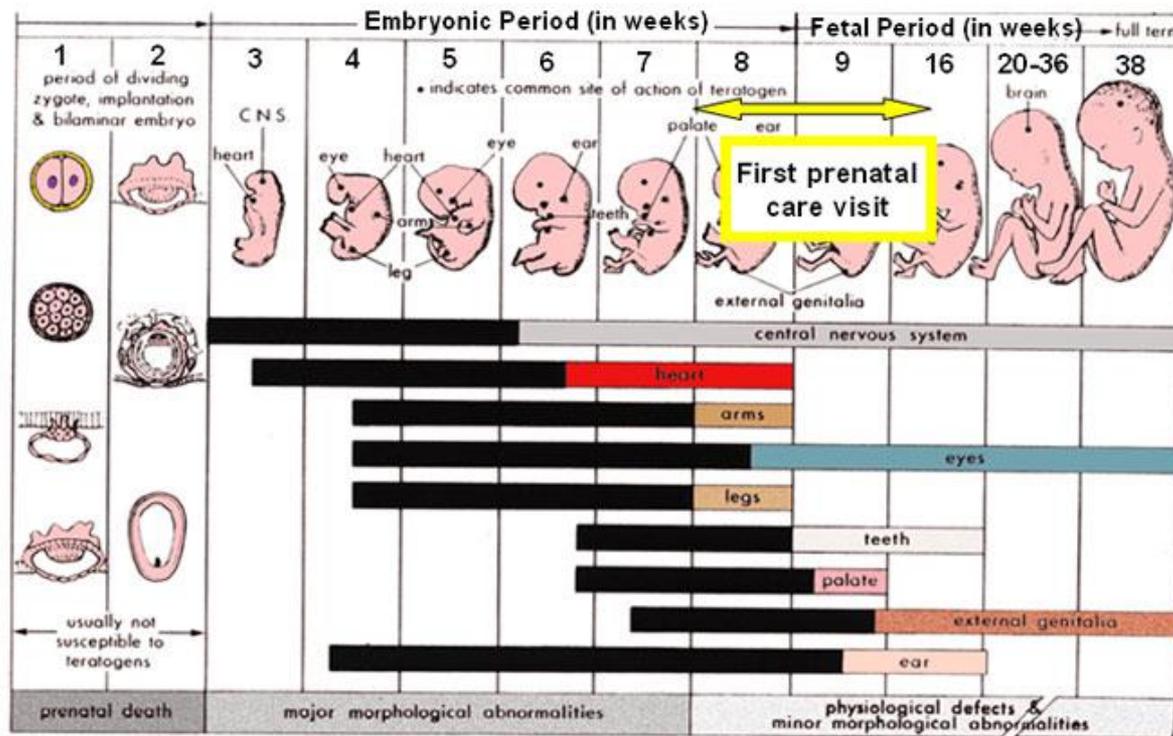
# Patterns of Alcohol Use



***2011 National Survey on Drug Use & Health: National Results***

# Important Milestones for the Embryo

## Embryonic Development



Developmental Progression & Susceptibility to Teratogens & Fetal Loss

(Modified from Keith Moore, *The Developing Human: Clinically Oriented Embryology*, 3rd Ed., W.B. Saunders Co.: Philadelphia, PA, 1983.)

# 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  $\geq$  25, gravidity  $\geq$  3, parity  $\geq$  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

# 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

# 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

# History of Fetal Alcohol Spectrum Disorders (*FASD*)

- In the first half of the 18<sup>th</sup> 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

**Lemoine P, Harousseau H, et al:** Children of Alcoholic Parents: Abnormalities Observed in 127 Cases, *Ouest Med.* 1968; 21: 476-482

**Jones KL, Smith DW, et al:** Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet.* 1973; 1:1267-1271

**Jones KL, Smith DW, et al:** Recognition of the fetal alcohol syndrome in early infancy. *Lancet.* 1973; 2:999-1001

# 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*

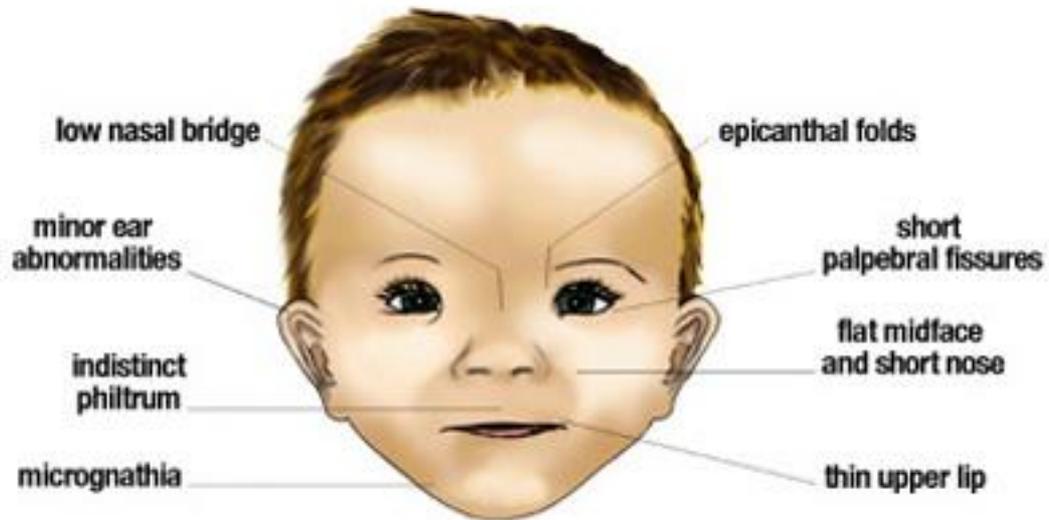
# Criteria For FAS diagnosis

- FAS diagnosis requires all three of these findings\*
  - Documentation of all three facial abnormalities- smooth philtrum, thin vermilion, 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.

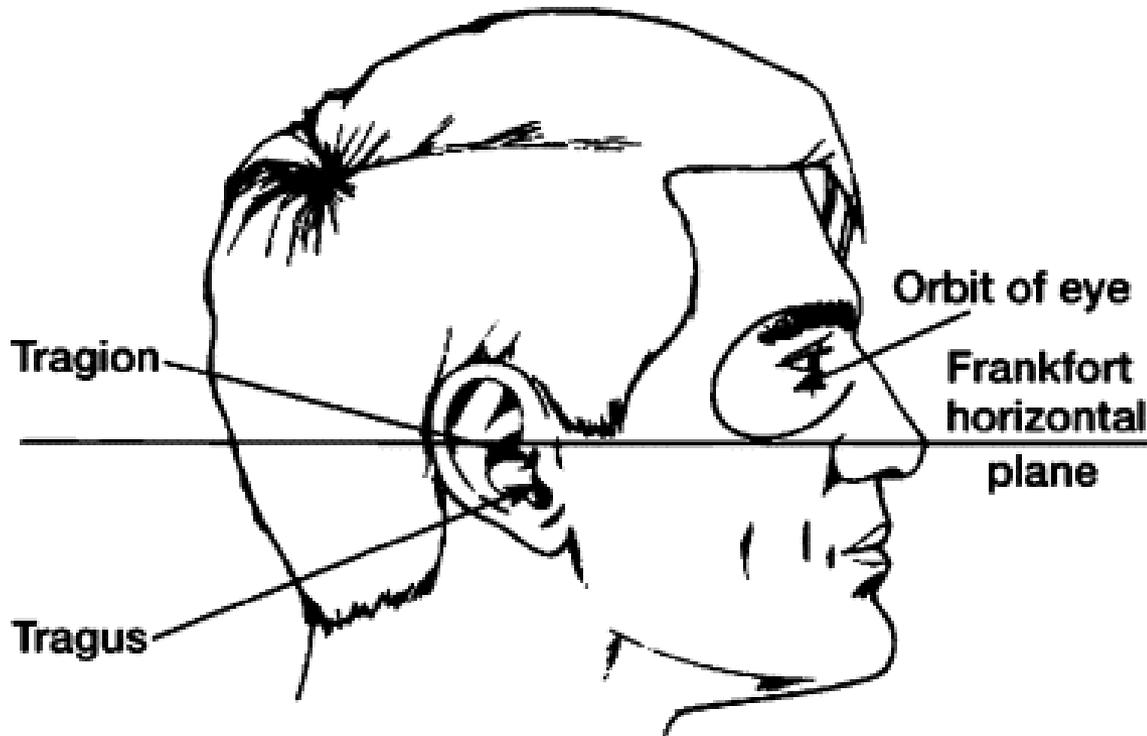
# Typical Facies in FAS

## FETAL ALCOHOL SYNDROME

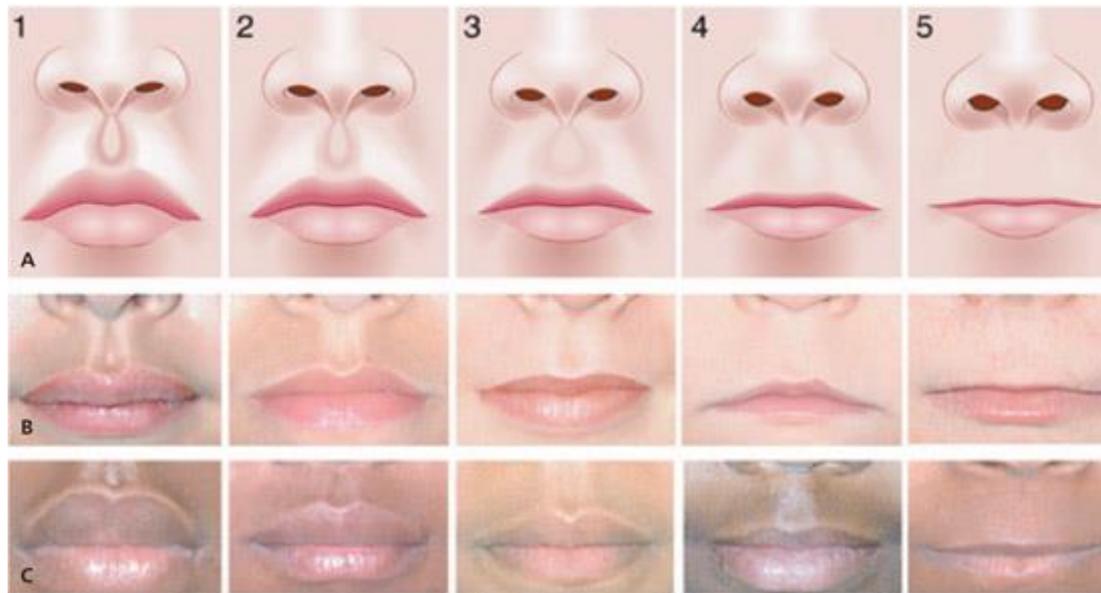


# Lip-Philtrum Assessment

- View the face along the Frankfort plane



# Lip-Philtrum 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

Fagerlund, Å et al. Risk factors for behavioural problems in foetal alcohol spectrum disorders. Acta Paediatrica (2011), 100: 1481–1488.

# 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

Fryer et al. Evaluation of Psychopathological Conditions in Children with Heavy Prenatal Alcohol Exposure. *Pediatrics* Vol. 199 No. 3 Mar 2007

# 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

# Learning and Behavior in ARND/FAS

- 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?”

# 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-philtrim guides available\*

\*<http://depts.washington.edu/fasdpm/htmls/lip-philtrum-guides.htm>

# 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>

# 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