Treatment of Substance Use Disorders in the Perinatal Patient

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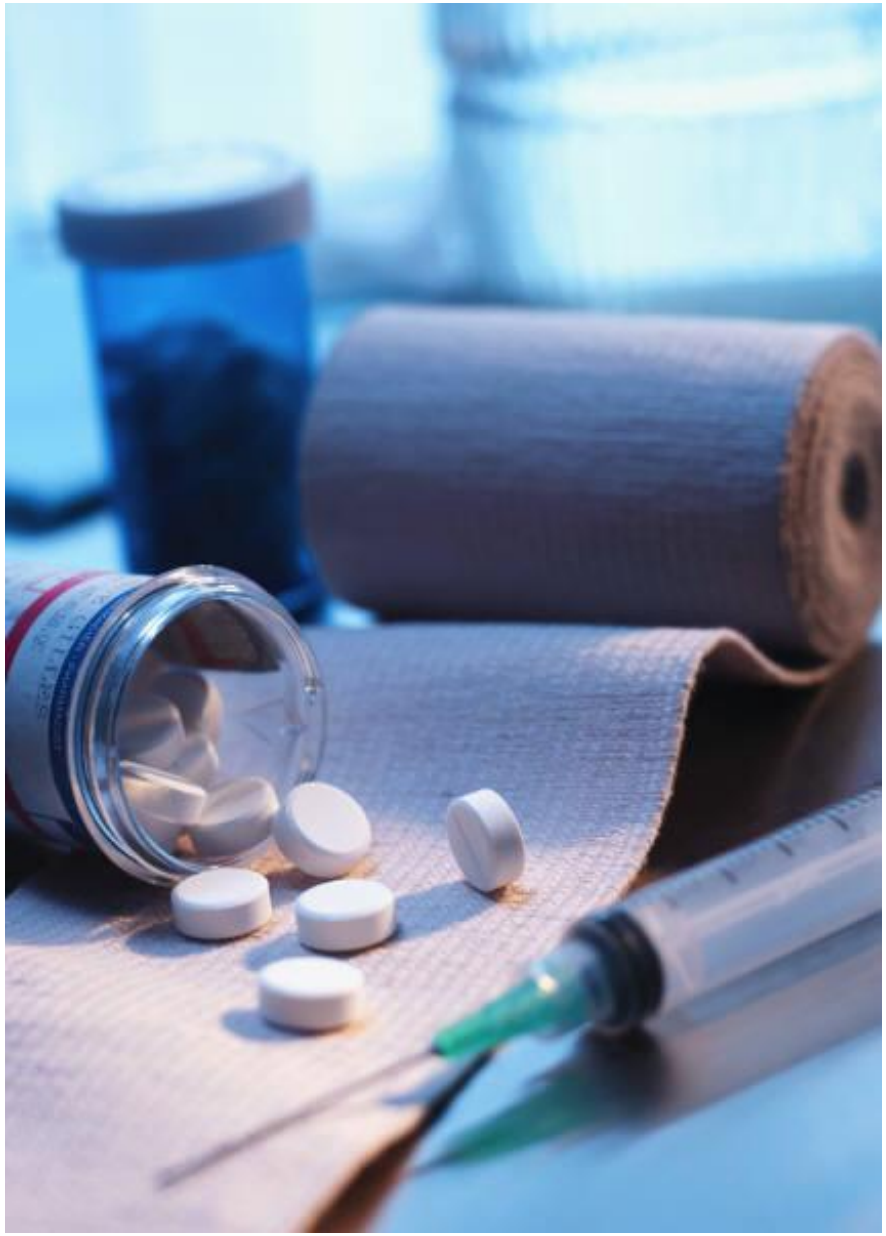

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Leena Mittal, MD, FAPM

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- Consultant, GLG Consulting
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Overview






“I was good for 51 yrs”

Ms C is a 52 yo woman, divorced 1.5 yrs ago, who was admitted to the medical hospital for treatment of pancreatitis

- Treated for alcohol withdrawal at the beginning of admission
- Alcohol use escalated after divorce
- Lost her job as a dental hygienist and nearly losing her home
- Declined referral for treatment

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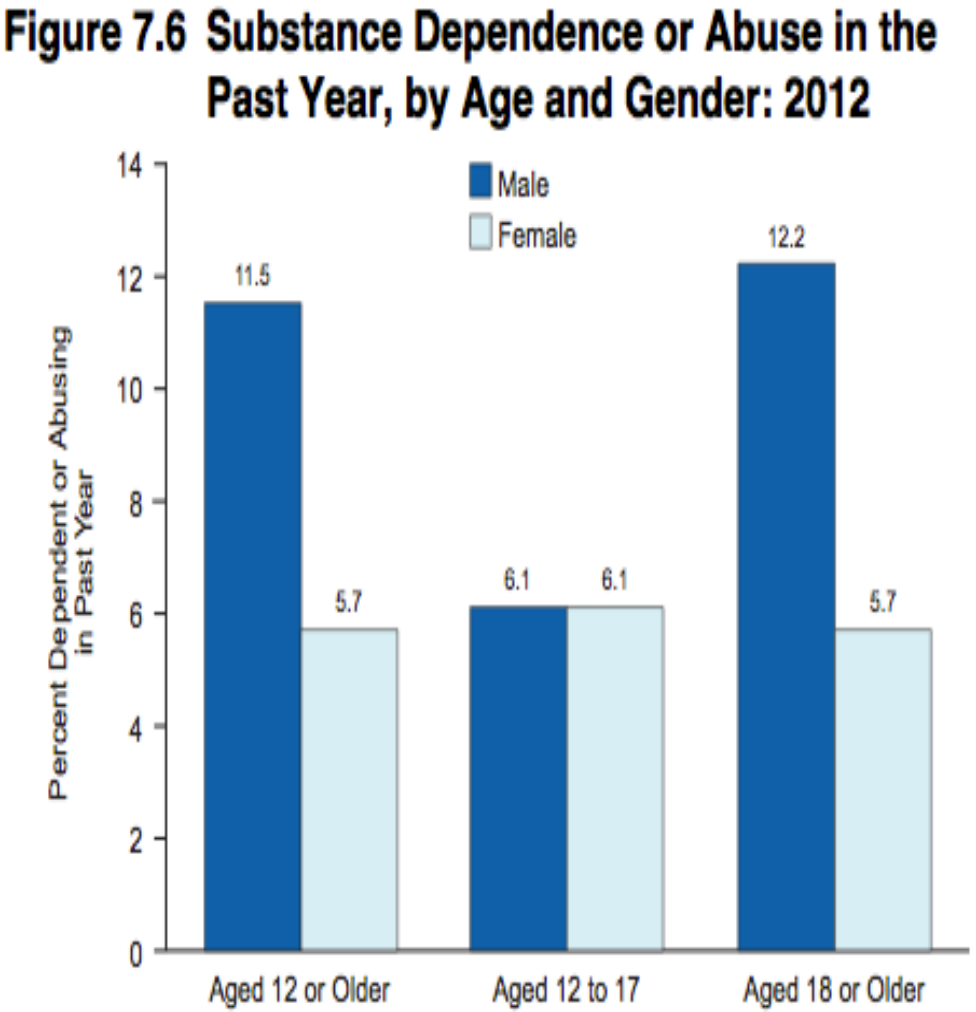
Sex based differences

- SUD are more common in men than women
  - The gap is closing
  - May be age related



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Sex based differences

- Different course/natural history
  - Telescoping – accelerated progression from initiation of use to onset of dependence and initiation of tx – seen with ETOH, opioids, cannabis
  - Interpersonal factors modulate progression (partners and children)

Sex based differences

- Biological
  - Menstrual cycle, pregnancy, aging and menopause
  - Ovarian sex steroids impact effects of cocaine, amphetamines, cannabis
  - Sex-based ETOH thresholds
- Psychiatric comorbidity
  - Mood disorders
  - Eating Disorders
  - PTSD

Women can benefit from gender specific treatment

- Childcare, prenatal care, integrated HIV care
- Women only treatment associated with lower rates of relapse and improved outcomes in some studies
- A minority of programs offer women-targeted treatment

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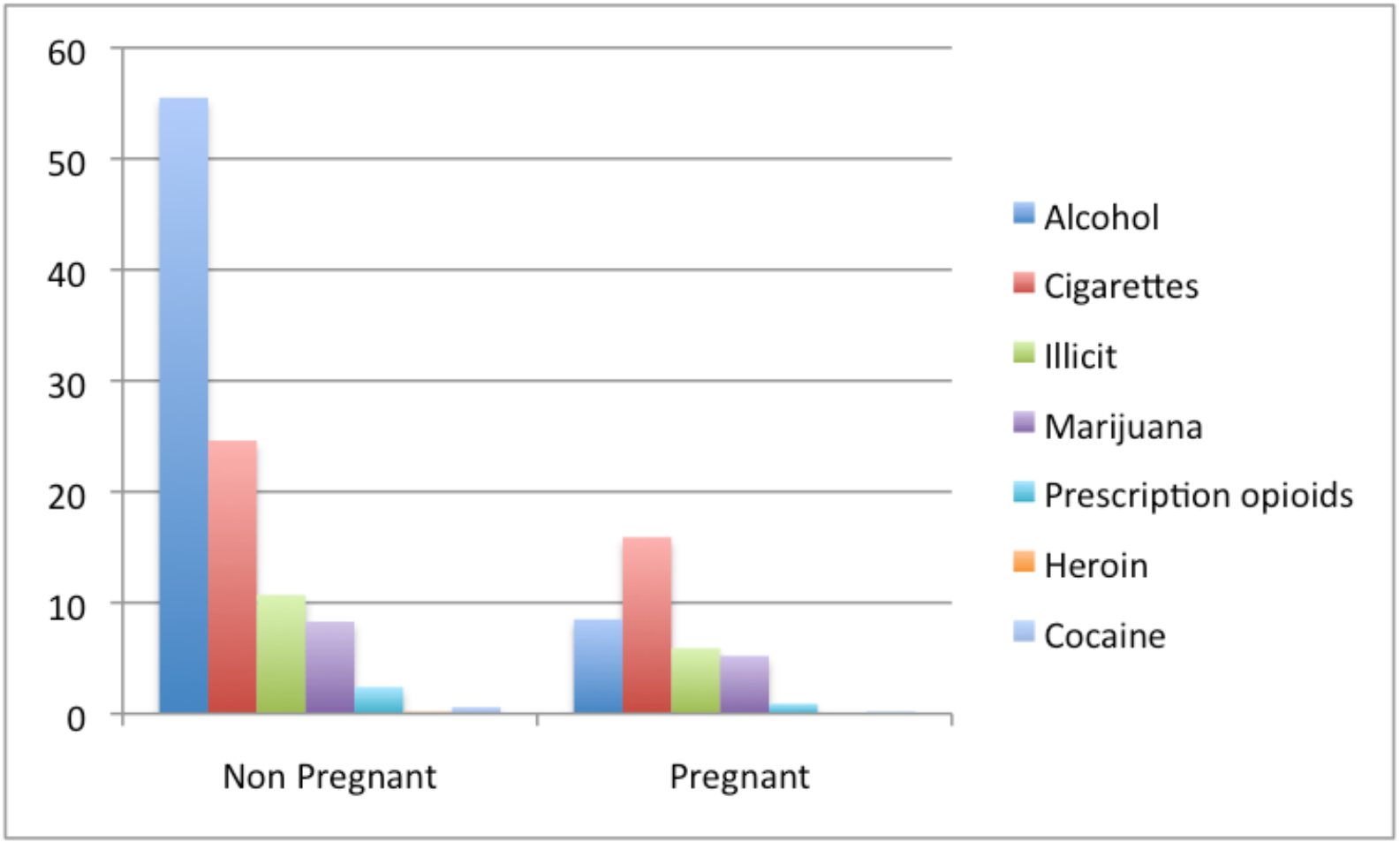
Greenfield Psychiatr Clin North Am. 2010
June ; 33(2): 339–355

What makes pregnancy different?

“I just can’t get it together”

- Christy is a 32 yo F who presented to Labor and Delivery reporting she had abdominal pain and was “around 7 months pregnant”
  - One prenatal visit - “smelled of alcohol”
  - Outreach calls from midwife found patient to have slurred speech
  - DV, unstable housing, loss of custody, poor access to food and health care
  - Drinking daily
  - Accepted referral for substance tx though did not show for appt

Drug Use in the past month, Females 15-44



NSDUH 2012

Substance Abuse during pregnancy – opportunities and challenges

- Pregnancy is a motivator for cessation
- Persistence of substance abuse during pregnancy may represent a particularly refractory and high risk subpopulation
- Higher levels of use prior to pregnancy correlate with continued use during pregnancy
- Most women return to pre-pregnancy rates of smoking and alcohol abuse within 6-12 months postpartum

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Havens JR et al. Drug and Alcohol Dependence 99 (2009) 89–95; NSDUH 2010; Harrison et al Matern Child Health J (2009) 13:386–394

Detection of Substance Use in Pregnancy – Red Flags

- Late presentation to prenatal care
- Acute intoxication
- Requests for controlled substances
- Positive toxicologic screen in mother or baby
- IUGR detected during antepartum testing
- Withdrawal suspected in the neonate

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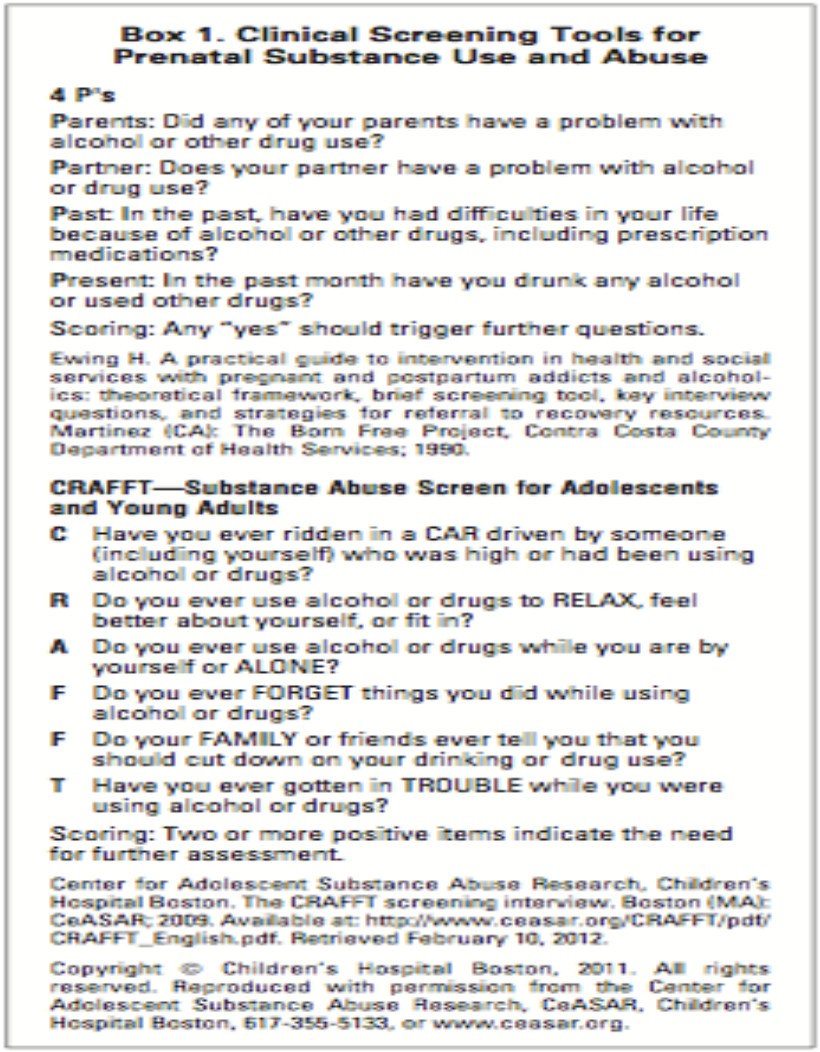
Detection - Screening

- 4 P's – Validated for screening in pregnancy and postpartum
- CRAFFT – validated for use in adolescents



Box 1. Clinical Screening Tools for Prenatal Substance Use and Abuse

4 P's

Parents: Did any of your parents have a problem with alcohol or other drug use?

Partner: Does your partner have a problem with alcohol or drug use?

Past: In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?

Present: In the past month have you drunk any alcohol or used other drugs?

Scoring: Any "yes" should trigger further questions.

Ewing H. A practical guide to intervention in health and social services with pregnant and postpartum addicts and alcoholics: theoretical framework, brief screening tool, key interview questions, and strategies for referral to recovery resources. Martinez (CA): The Born Free Project, Contra Costa County Department of Health Services; 1990.

CRAFFT—Substance Abuse Screen for Adolescents and Young Adults

C Have you ever ridden in a CAR driven by someone (including yourself) who was high or had been using alcohol or drugs?

R Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?

A Do you ever use alcohol or drugs while you are by yourself or ALONE?

F Do you ever FORGET things you did while using alcohol or drugs?

F Do your FAMILY or friends ever tell you that you should cut down on your drinking or drug use?

T Have you ever gotten in TROUBLE while you were using alcohol or drugs?

Scoring: Two or more positive items indicate the need for further assessment.

Center for Adolescent Substance Abuse Research, Children's Hospital Boston. The CRAFFT screening interview. Boston (MA): CeASAR; 2009. Available at: http://www.ceasar.org/CRAFFT/pdf/CRAFFT_English.pdf. Retrieved February 10, 2012.

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Obstetric and Gynecology Vol 119 No 5
May 2012

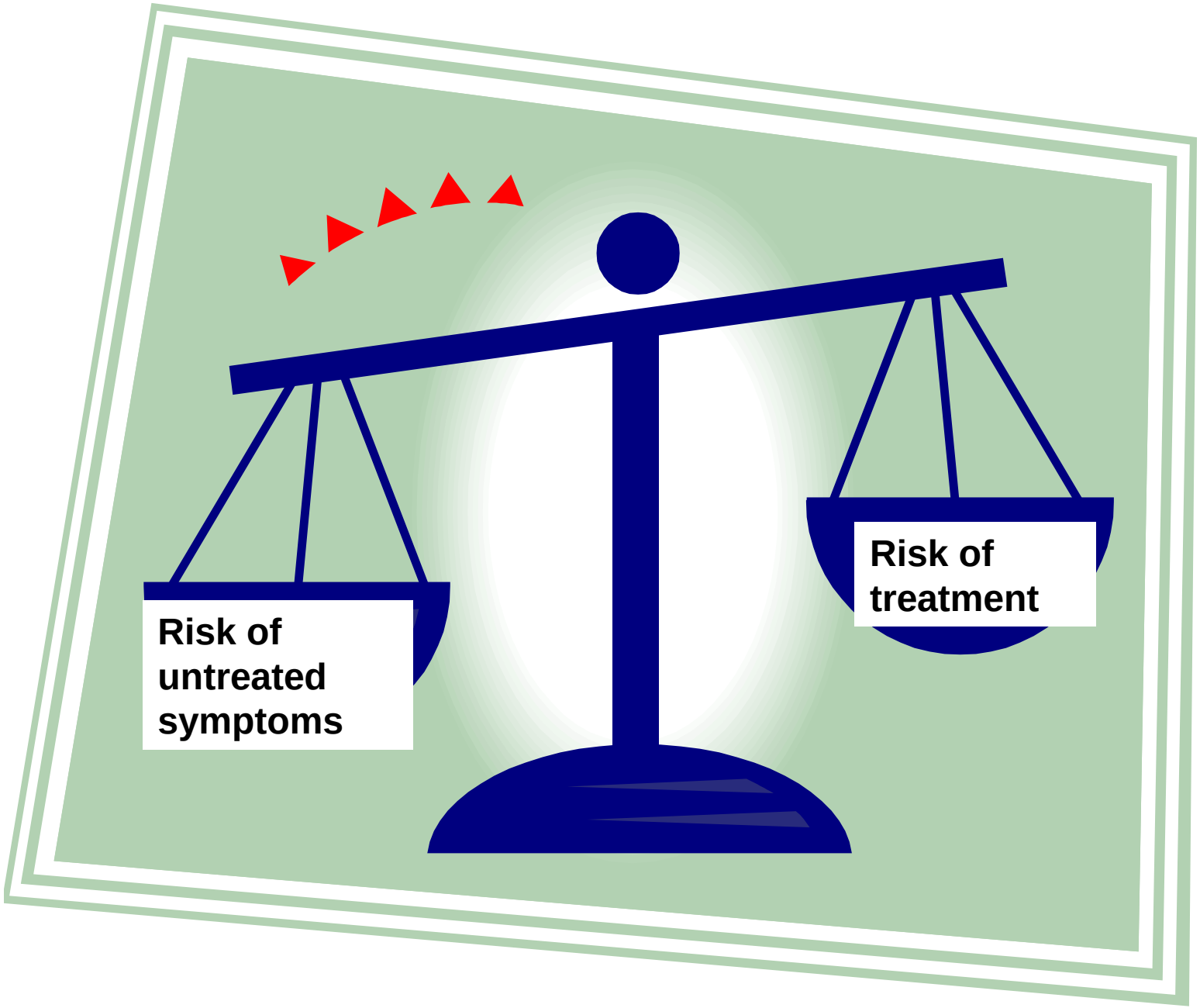
Detection - Toxicologic Screening

- Maternal screening
  - Prenatal and at the time of delivery
    - Universal toxicologic screen not recommended
    - Role of negative tests
- Neonatal screening
  - Serum/Urine reflect recent use
  - Hair/Meconium reflects use since 2nd trimester
  - Cord blood
- Consent

ostrea 2001

Substance use in pregnancy presents barriers to treatment engagement

- Stigma and shame
- Refractory illness
- Providers' own emotional reactions
- Concerns about DCF reporting
- Legal implications
- Access to treatment
- Time elapsed before recognition of pregnancy



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Opioid Use in Pregnancy

- Opioids are not likely directly teratogenic[1,2]
- Opioid dependence during pregnancy is associated with:
  - Intrauterine growth restriction
  - Intrauterine fetal demise and stillbirth
  - Preterm labor
  - Placental abruption
  - Postpartum hemorrhage
  - Reduced cognitive function in exposed children
- Risks related to peaks/troughs and intermittent w/d
- Lifestyle factors associated with use/relapse

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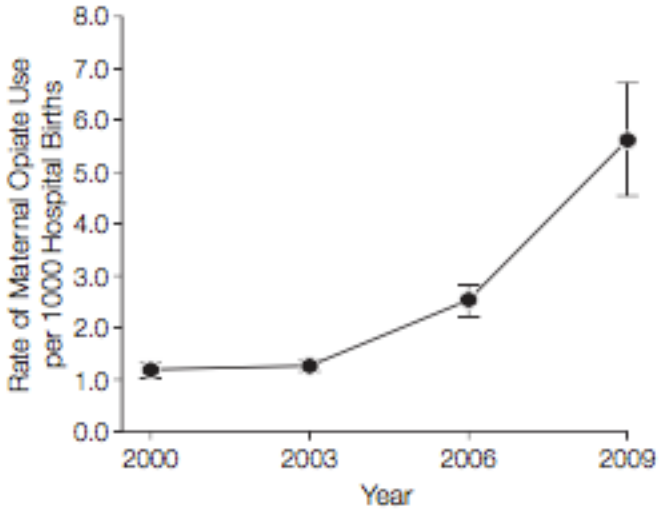
1. Kaltenbach et al. *Obstetrics and Gynecology Clinics.* 1998; 25: 139-51 2. Jick et al *JAMA*. 1981; 246: 343-6

Rates of Opioid Use in Pregnancy are increasing

Figure 2. Weighted National Estimates of the Rates of Maternal Opiate Use per 1000 Hospital Births per Year



Between 2000 and 2009, opioid use among women who gave birth increased in the United States from 1.19 to 5.63 per 1,000 hospital births per year

Patrick *JAMA* (2012)

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Medication treatment for OUD in Pregnancy

- No FDA approved treatment
- Mainstays of treatment include medication:
  - Methadone
  - Buprenorphine (single or combination)
- Withdrawal *MAY* present a risk to the fetus[1-5]
  - Risk of stillbirth, IUFD, preterm labor, meconium
- High risk of relapse after discontinuation of opioids[6]
- Neonatal Abstinence Syndrome

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1. Rementeria et al. *AJOG.* 1973; 2. Zuspan *AJOG*.. 3. Fricker *Arch of Pedi & Adol Med.* 1978 4 Luty *J of Sub Abuse Treat.* 2003 5.Towers et al AJOG 2015 6 Jones et al. *The American Journal on Addictions.* 2008

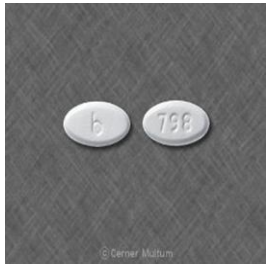
Benefits of medication in pregnancy

Maternal Benefits

- 70% reduction in overdose related deaths
- Decrease in risk of HIV, HBV, HCV
- Increased engagement in prenatal care and recovery treatment

Fetal Benefits

- Reduces fluctuations in maternal opioid levels; reducing fetal stress
- Decrease in intrauterine fetal demise
- Decrease in intrauterine growth restriction
- Decrease in preterm delivery



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Methadone – Pharmacodynamic Considerations During Pregnancy

- Administered through a federally licensed facility
- Breakthrough withdrawal symptoms may appear in the third trimester
- Doses typically 80-120 mg
  - may need to increase in 3rd trimester
- Split dosing should be considered
  - From daily to twice a day

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Park 2012

Methadone – Fetal considerations

- Decreased heart rate and heart rate variability
  - Greater at peak than trough
- Slower breathing movements on BPP
- Decreased fetal movements on BPP

Buprenorphine causes shorter duration and less severe NAS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Hendrée E. Jones, Ph.D., Karol Kaltenbach, Ph.D., Sarah H. Heil, Ph.D., Susan M. Stine, M.D., Ph.D., Mara G. Coyle, M.D., Amelia M. Arria, Ph.D., Kevin E. O'Grady, Ph.D., Peter Selby, M.B., B.S., Peter R. Martin, M.D., and Gabriele Fischer, M.D.

Buprenorphine is an office based treatment

•Buprenorphine is a ***high affinity partial agonist*** at the mu opioid receptor

•Buprenorphine has lower OD risk, fewer drug interactions, office based administration, less risk of sedation than methadone

•Use buprenorphine alone (not combined with naloxone) (Brand name: Subutex)

- theoretical risk of inducing maternal/fetal withdrawal
- animal data re teratogenicity

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Jones 2010, Blandthorn 2011, Park 2012

Buprenorphine is Effective in Pregnancy

- Similar to methadone in reduction of illicit drug use/relapse risk
- No apparent difference between buprenorphine and methadone for:
  - Maternal weight gain
  - Cesarean section
  - Abnormal presentation
  - Use of analgesia
  - Positive drug screen
  - Medical complications at delivery
- Implications for peripartum pain management

Jones 2012

Buprenorphine – Fetal effects

- In analyses of MOTHER participants buprenorphine exposed fetuses had
  - Less motor suppression
  - Lower incidence of non reactive Non Stress Tests
  - Clinical significance of these findings not clear

Naloxone should be prescribed to all opioid users

- Opioid overdose is a leading cause of death in the US
  - Suicide and OD leading causes of maternal mortality
- Fetal effects have been reported
- ***Risk of maternal death outweighs fetal risks in the case of overdose***

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Metz 2016

Naltrexone

- Limited human data
- Animal data suggests not teratogenic
- Induction onto naltrexone in pregnancy is not recommended
- For those already using extended release naltrexone/implantable naltrexone, maybe reasonable to continue during pregnancy

How do I choose?

- Methadone and Buprenorphine are both effective options
- In a patient stable on treatment, no need to switch
- In a patient new to treatment or who wishes to switch consider:
  - Patient preference
  - Access
  - Need for structured treatment
  - Methadone ->buprenorphine is difficult and not recommended

Neonatal Abstinence Syndrome

SIGNS

- Neurologic excitability
  - Tremor, seizure, inc muscle tone, yawning, sneezing, irritability
- GI dysfunction
  - Feeding diff, vomiting, diarrhea, poor wt gain
- Autonomic signs
  - Diaphoresis, fever/temp instability

IDENTIFICATION OF RISK

- Maternal history
- Onset depends on which agent/confounding agents
  - Not dose dependent
- Tox screens
- Validated scales
  - All are **subjective**
- **Unclear long term consequences**

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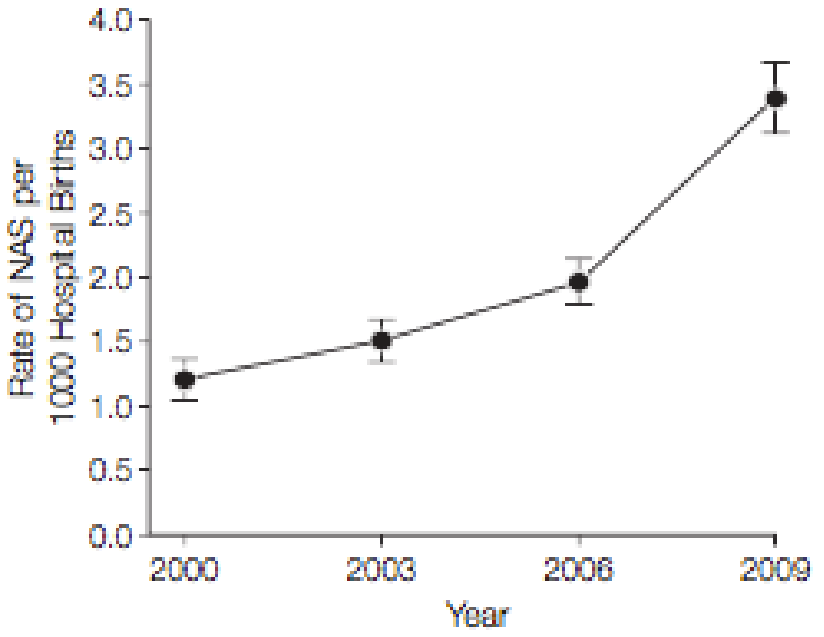
Rates of Neonatal Abstinence Syndrome have increased

Figure 1. Weighted National Estimates of the Rates of NAS per 1000 Hospital Births per Year



The incidence of NAS increased from 1.20 per 1,000 hospital births per year in 2000 to 3.39 per 1,000 hospital births per year in 2009

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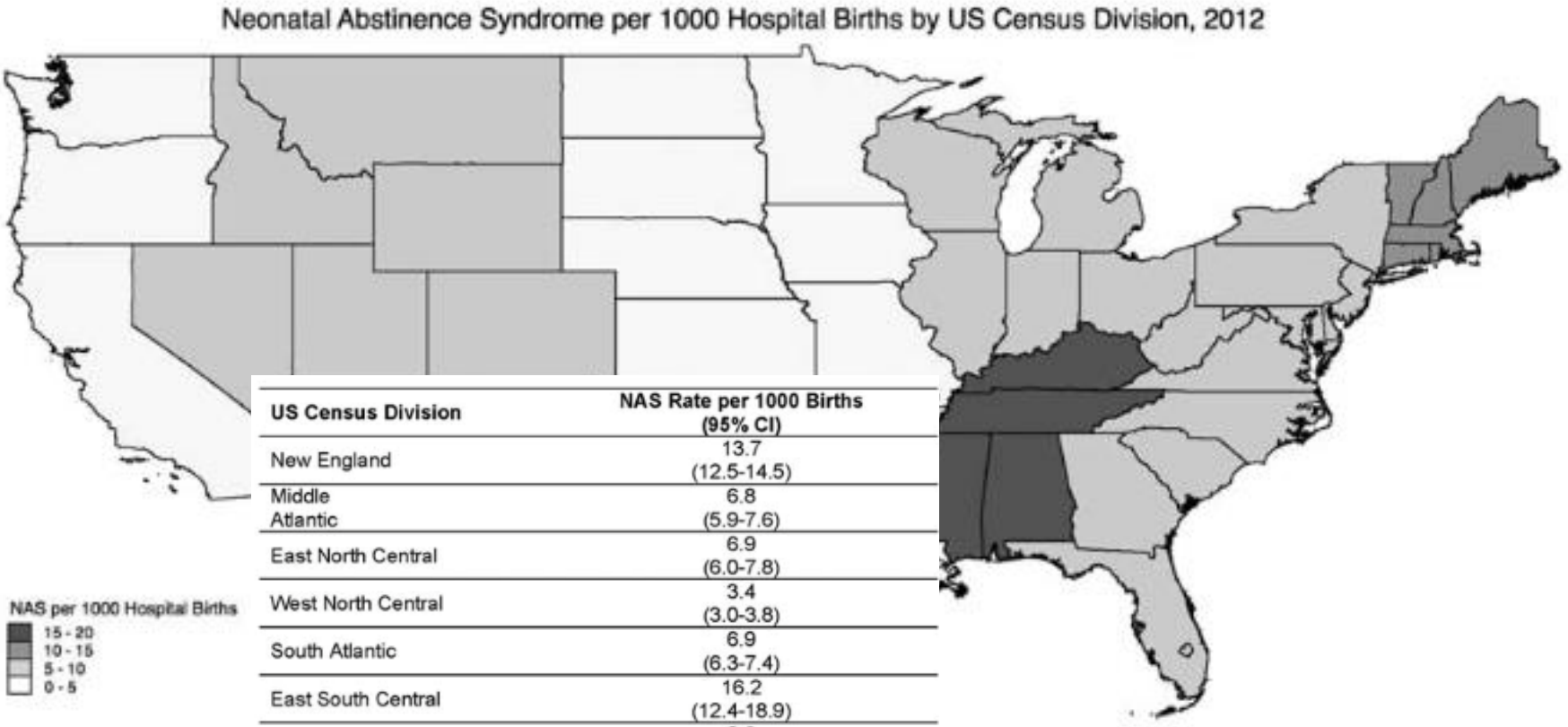
Patrick et al Journal of Perinatology (2015) 35, 650–655

New England has the second highest rate of Neonatal Abstinence Syndrome



US Census Division	NAS Rate per 1000 Births (95% CI)
New England	13.7 (12.5-14.5)
Middle Atlantic	6.8 (5.9-7.6)
East North Central	6.9 (6.0-7.8)
West North Central	3.4 (3.0-3.8)
South Atlantic	6.9 (6.3-7.4)
East South Central	16.2 (12.4-18.9)
West South Central	2.6 (2.3-2.9)
Mountain	5.1 (4.6-5.5)
Pacific	3.0 (2.7-3.3)

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Patrick et al Journal of Perinatology (2015) 35, 650–655

Neonatal Abstinence Syndrome is Costly

- Newborns with NAS were more likely to have
  - low birthweight
  - respiratory complications
- Mean hospital charges for discharges with NAS increased from $39 400 in 2000 to $53 400
  - Average LOS 16 days
  - $720 million in 2009

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Wiles 2014; Patrick 2012

Treatment of NAS

- NON Pharmacologic treatment is first line
  - Breastfeeding – low levels of opioids in BM
  - Rooming in, low stim enviro, swaddling, sucking
- Morphine
- Methadone
- Buprenorphine
- Adjunctive Medications
  - Phenobarbital, clonidine

Maternal Dose and NAS Severity

- No correlation between maternal opioid maintenance therapy dose and the duration or severity of NAS
- Women should be encouraged to report any symptoms of withdrawal through her pregnancy without fear a dose increase will affect her baby's hospital stay or need for NAS treatment
- Tobacco and SSRI use may worsen NAS

Cleary et al. 2010; Isemann et al. 2010;

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Mothers on MAT should be encouraged to consider breastfeeding

- Amount of methadone in breastmilk is low
  - 1-6% of weight adjusted maternal dose
- Amount of buprenorphine in breastmilk is low
  - 1-20% of maternal weight adjusted dose present in breastmilk
  - Poor oral bioavailability further limits exposure
- Can observe for neonatal sedation
- Enhance maternal infant bonding and Reinforce maternal role
- Improve NAS outcomes

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Pritham UA et al. *J Obstet Gynecol Neonatal Nurs.* 2012. ; Welle-Strand GK et al. *Acta Paediatr.* 2013.; Wachman EM et al. *JAMA.* 2013.; Abdel-Latif ME

Alcohol Abuse during Pregnancy is common and carries known risk

- Epidemiology
  - 12.2% of pregnant women reported alcohol use during the prior month
  - NO safe amount defined
  - New AAP statement on FASD Oct 2015
  - DSM5: Neurobehavioral DO assoc w Prenatal Alcohol Exposure (ND-PAE)
- Fetal effects
  - Spontaneous AB, PTL, stillbirth, IUGR
  - Ethnic variation, polymorphisms change risk for fetal effects
- Neonatal effects
  - 1st tri use – 12x risk of FASD
  - Intoxication and Withdrawal
  - SIDS
- Childhood effects
  - Learning DO, ADHD, executive dysfunction, anxiety DO, mood DO, SUD

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Bailey 2011 Alc Research; Hannigan Semin Neonatol 2000 ; Williams 2015 *Pediatrics*

Neurobehavioral DO associated with prenatal Alcohol Exposure (FASD)

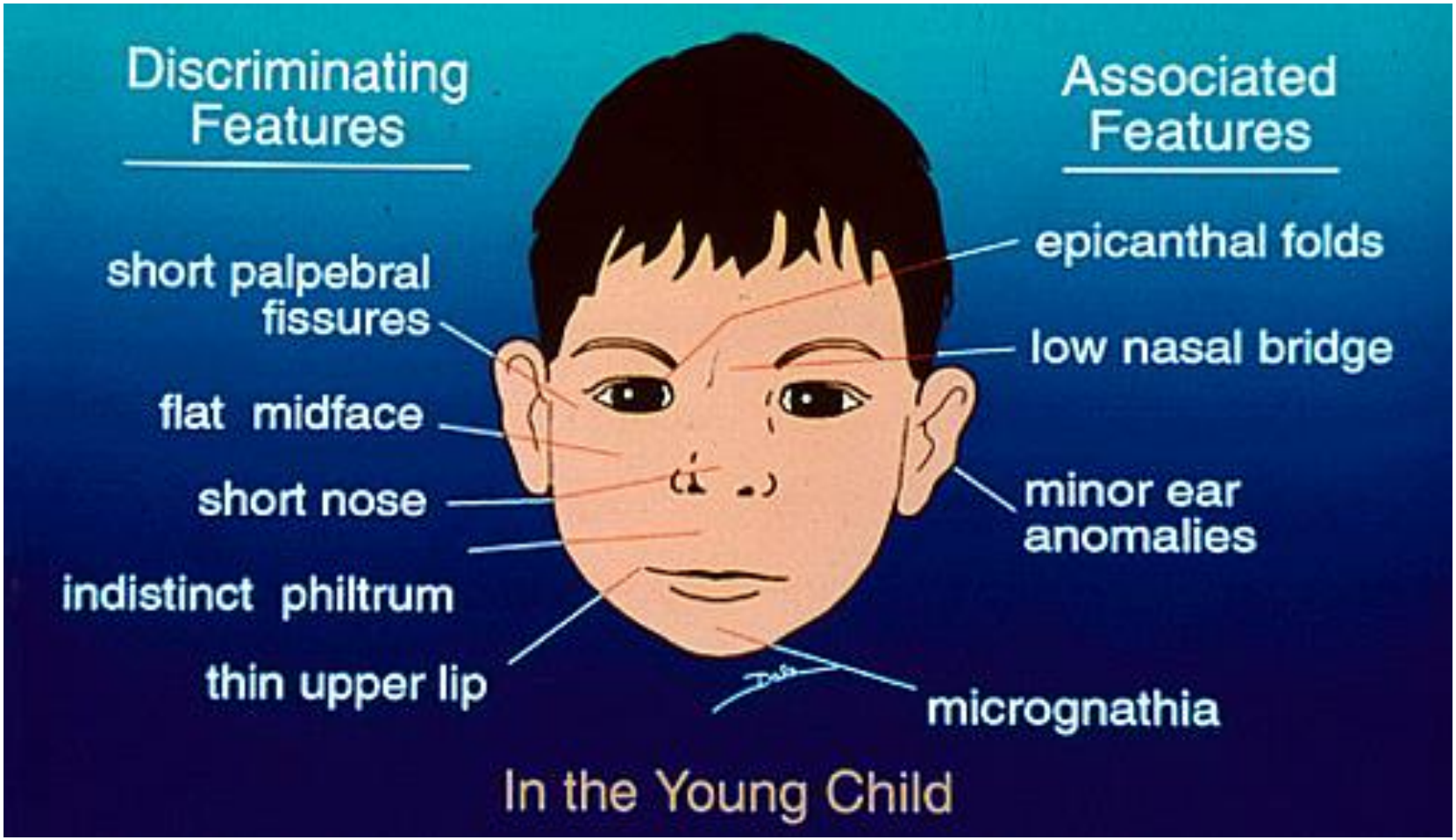

Figure 1. T-ACE and TWEAK for problematic alcohol use

T-ACE

T How many drinks does it take to make you feel high? (Tolerance)

A Have people annoyed you by criticizing your drinking?

C Have you felt you ought to cut down on your drinking?

E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (Eye-opener)

Scoring: T: 2 points if > 3 drinks; A,C,E: 1 point for each yes answer

A total of 2 or more points indicates patient is likely to have an alcohol problem.

TWEAK

T Tolerance

W Have friends or relatives complained about your drinking? (Worried)

E Eye-opener

A Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember? (Amnesia or black-out)

K Cut-down

Scoring: T: 2 points if > 3 drinks; W, E, A, K: 1 point for each yes answer

A total of score of 3 or more points indicates patient is at-risk drinking

Wong S et al. JOGC 2011; 33 (4) 367-84

Alcohol Withdrawal in pregnancy is managed with benzodiazepine taper

- Medically supervised withdrawal
  - Appropriate setting
  - Risk of withdrawal during pregnancy not well defined
  - Risk during labor and neonatal withdrawal
  - No RCTs to guide choice of medication
    - lorazepam or chlordiazepoxide

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Gopalan 2015; Devido 2015, Gopalan 2014

Brief Interventions can impact alcohol use in pregnancy

- Pregnant women are generally motivated to change
- Physician relaying information
- Motivational interviewing
- Goal setting and evaluation of triggers
- Education re potential harms

Floyd 2007

Alcohol may impact lactation

- Alcohol can *decrease* breastmilk volume and milk ejection reflex
- Alcohol equilibrates across membranes within 30-60 minutes – high exposure risk
- Infant effects on growth, motor and feeding/sleeping behavior
- Varying recommendations regarding “safe” amount to consume

Giglia 2006

Cannabis is the most commonly used illicit substance in pregnancy

- 48-60% of users continue during pregnancy
- Rates of use increase with low SES
- No consistent data regarding structural teratogenesis
- No described neonatal intoxication or withdrawal syndrome

ACOG 2015

But it's natural…

- THC in marijuana ↑ 25x since 1970s
- No compelling evidence that cannabis treats any condition
- Legalization and Medicalization make marijuana more accessible
- Not recommended in women of childbearing age or in nursing mothers.

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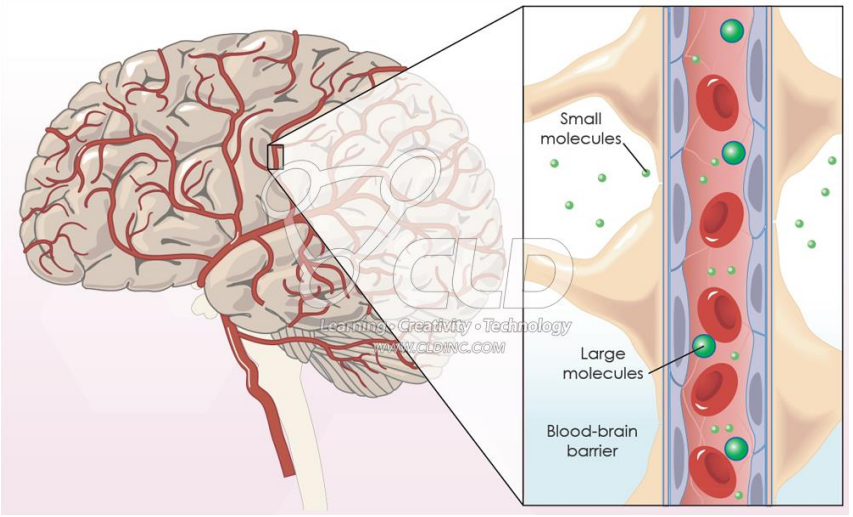
Cannabinoids are lipophilic

- Readily cross BBB, placenta and into breastmilk
- Half life: 20-36 h to 4-5 d (chronic users)
  - 5 half lives for complete excretion
- Fetal plasma levels can be 10% maternal levels
- Higher concentration in fetal tissue with chronic use (animal)
- Deposits in maternal fat



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Marroun et al (2009) JAACAP; Jacques Journal of Perinatology (2014

Cannabis use can impact pregnancy through many mechanisms

- Implantation
- Growth Restriction
  - Dose response – greater effect with continued use
  - Birthweight and head circumference
- Neural Development (CB1 receptors in fetal brain, 60% fat)
- THC decreases fetal folic acid uptake (risk of SpAb, NTD, LBW)

ACOG urges preconception and pregnant women to stop marijuana

- Fetus has endocannabinoid receptors
- Cannabinoid use may disrupt brain development (animal studies)
- Intrauterine growth restriction and Low birth weight
- Increased risk of stillbirth (limited evidence)
- Developmental risks: visual processing, attention, behavior, inc risk for MJ use
- Risks associated with smoking

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Marijuana use during pregnancy and lactation. Committee Opinion No. 637. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;126:234–8.

Cannabis use in lactation can result in significant exposure to the baby

- Lactation
  - Readily passes into breast milk
    - Regular consumption- 8x higher conc in BM!
  - May inhibit milk supply (inhib GRH, prolactin, TSH)
- Women should be advised to abstain

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Marroun et al (2009) JAACAP; Jacques Journal of Perinatology (2014

Cocaine

- Primary effects are due to vasoconstriction
  - Spontaneous abortion
  - Placental abruption
  - Placental insufficiency
- Increased risk for LBW, SGA, PTB
- Intoxication can mimic preeclampsia
- Not likely a structural teratogen
- Lasting effects on child growth and neurodevelopment

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Cressman et al JOGC 2014; Cain et al Clin OG 2013

Stimulants

- Need to distinguish therapeutic use vs abuse
- Abuse of amphetamines associated with risks associated with placental vasoconstriction
- Data suggest with therapeutic use both amp and mph :
  - Not likely teratogenic
  - Impact on fetal growth (?before week 28)
- During pregnancy - appetite suppression/low mat wt gain
- Lactation – Relatively low exposure
  - Methylphenidate: RID of <1%
  - Dextroamphetamine: RID 5.7%

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Bolea- Alamanac et al Br Journ Pharmac 2013; Freeman AJP 2014

Summary

- Women with SUD biological and social differences, especially in pregnancy
- OUD is a growing problem with emerging treamtents
- Buprenorphine and methadone are mainstays for OUD
- Alcohol Use requires screening and counseling in pregnancy
- Cannabis use is prevalent and not recommended during pregnancy
- Cocaine and stimulants carry significant risk when abused

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Education

855-Mom-MCPAP

Resources and Referral

Questions?

www.mcpapformoms.org

Call 855-Mom-MCPAP
(855-666-6272)

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Thank you!