
 School of Medicine and Public Health
UNIVERSITY OF WISCONSIN MADISON

 MERITER
UnityPoint Health

In utero drug exposure; what are the long term outcomes for children?

Dr. Michael Porte
University of Wisconsin- Madison
Pediatrics- Neonatology

Disclosure Information for:
Dr. Michael Porte
In utero drug exposure; what are the long term outcomes for children?

- There are no relevant financial relationships related to this presentation/program
- There is no sponsorship/commercial support of this presentation/program
- The content being presented will be fair, well-balanced and evidence-based
- Learners who wish to receive Continuing Education Credit (CME/CLE/CE) must complete and turn in evaluations to successfully complete this program

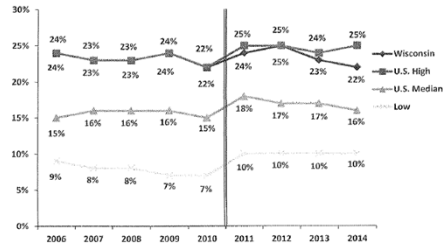
In utero fetal exposure to tobacco, alcohol and illegal drugs: What is the scope of the problem?

- Maternal Tobacco use in Pregnancy: 15.4%
- Alcohol Use in Pregnancy: 9.4%
- Illicit Drug use 5.4% (includes Opiates, Marijuana, Cocaine, Methamphetamine)
- Illicit Drug use 15 - 17 y/o: 14.6%, 18 - 25 y/o 8.6%, 26 - 44 y/o 3.2%.
- Federal study relying on maternal questionnaire.

Wisconsin data for maternal use of alcohol in pregnancy

- Overall binge drinking among Wisconsin adults 18 and older was 22%
- US median is 16%, high is 25%
- We are no longer # 1 in binge drinking! (now # 3)
- US binge drinking rate is 2.6%

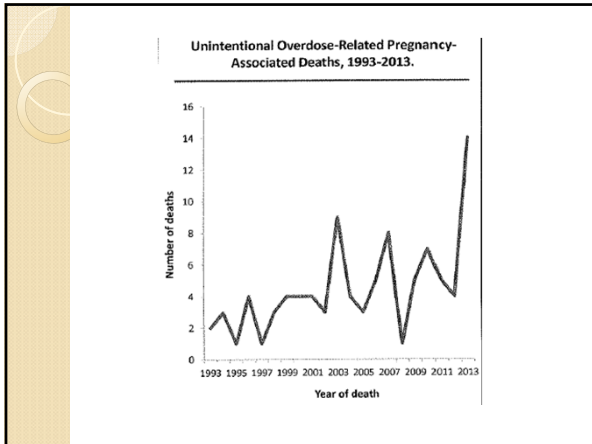
Figure 32. Adult binge drinking, range of state estimates: low, high, and U.S. median, 2006-2014



Source: Behavioral Risk Factor Surveillance System, Division of Public Health, Wisconsin Department of Health Services/Centers for Disease Control and Prevention.
 Note: The median is the midpoint of the range of estimates for all U.S. states and territories. Differences between groups and time periods may not be statistically significant. Double line indicates trend break due to methodological changes.

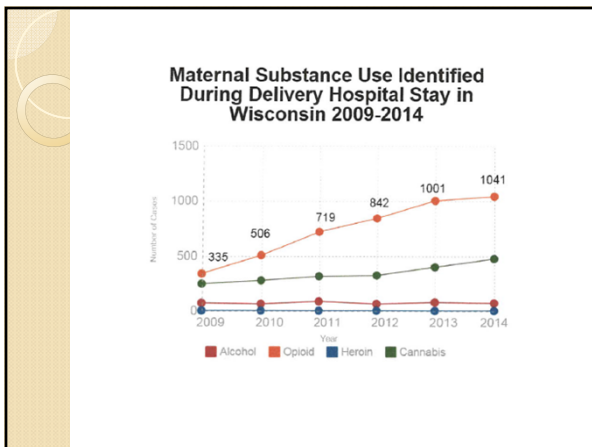
Wisconsin data for opioid use in pregnancy

- Includes illicit opioids (Heroin) and legally prescribed (Methadone, Hydrocodone, Oxycodone)
- 66,000 babies born per year in WI
- 1041 women tested positive for opioid use at time of delivery. (will miss those not tested)
- 16.4/1000 pregnancies identified as risk for infant NAS (Neonatal Abstinence Syndrome)
- 8/1000 infants are diagnosed with NAS.



Wisconsin data for overall use of maternal use of illicit drugs

- 1600/66000 deliveries test positive for opioids, alcohol, heroin, cannabis, 2014.
- 3 fold increase in cases from 2009.
- Data does not include Amphetamine drugs (prescription amphetamine, methamphetamine)



Polydrug use in pregnancy

- Mothers with heavy use of alcohol in pregnancy (often defined as 4 - 5 drinks/day minimum) have a 2 x increased risk of opioid use and 3 x increased risk of use of amphetamines.
- Data may well underestimate polydrug use as many studies rely on questionnaires.

Illicit or abuse of legal drugs used in pregnancy, most common to least common

- Marijuana: Now legal in several states.
- Prescript psychotherapeutics: Narcotic, eg Oxycodone, Benzodiazepine, eg Xanax, SSRI, Prozac
- Cocaine: Including Methamphetamine
- Hallucinogens

Questions?

Problems with surveys for drug or alcohol use in pregnant women:

- Denial or fear of discovery is a barrier to obtaining accurate data.
- Maternal concerns for having reputation destroyed, or provider recrimination.
- Maternal concern for having caused harm to fetus
- Maternal fear of being charged with child abuse; less of a concern now.

Substance Use, Abuse, Dependence, Addiction definitions (modified from Chang, UTD, Hopkins)

- Use--Sporadic consumption of alcohol or drugs
- Abuse--Adverse consequences are experienced by user
- Dependence--Need for specific psychoactive substance for benefit, or avoid withdrawal
- Addiction--Pathologic pursuit of drug for benefit or avoidance of withdrawal; patient is unable to recognize personal abnormal behavior; cycles of relapse by history.

Identification of maternal substances of use/abuse in pregnancy: CRAFFT screen

- **C**--Have you ever ridden in a **CAR** driven by someone (or you) who was high on alcohol/drugs?
- **R**--Do you ever use alcohol or drugs to **RELAX**?
- **A**--Do you ever use alcohol or drugs **ALONE**?
- **F**--Do you ever **FORGET** things you did while using alcohol or drugs?
- **F**--Do your **FAMILY** or **FRIENDS** ever tell you, you should cut down your drinking or drug use?
- **T**--Have you ever gotten in **TROUBLE** while you were using alcohol or drugs?

Screening for Drug Use: Laboratory urine screen most commonly used for pregnancy.

- DOA (drugs of abuse) screen, most commonly used Immunoassay
- Antibodies specifically recognize a drug or metabolite
- Amphetamine (including Methamphetamine)
- Cocaine
- Marijuana
- Opioids
- PCP
- Other drugs may be included: Barbiturates, Synthetic opioids eg fentanyl, LSD

Problems with DOA Immunoassay: False positive results

- Amphetamines: Pseudoephedrine (Sudafed), Phenylephrine, Beta Blocker (Propranolol)
- Opioids: Poppy seed ingestions (bagels)
- Canniboids: Hemp containing food products.

Testing Period for positivity with DOA Immunoassay:

- Amphetamines: 1 - 3 days
- Cocaine: 1 - 3 days
- Opioids: 1 - 3 days, Heroin, short acting opioids. Methadone 3 - 10 days.
- Marijuana: Days to Months; far more concentrated in fetus.
- Benzodiazepines: 1 - 7 days, some greater.

Alternative to Immunoassay DOA: Chromatography

- Physical separation of substances with unique peaks in stationary and mobile phases.
- Gas-chromatography/mass spectrometry is the most accurate test
- Not practical and not available in the vast majority of hospitals.
- Refer to Addiction specialist if in doubt.

Treatment of mother with drug use/abuse problem

- Counseling: essential. Goal should be zero tolerance of tobacco, alcohol, illicit drugs, prescription drugs, when not medically indicated. Enroll in drug treatment program when indicated.
- Methadone treatment program will put infants at risk for NAS, but have so many benefits.
- Most women are highly motivated to quit/reduce drugs or alcohol to help their babies.
- Nearly 60% of women eliminate illicit drugs and alcohol during pregnancy. (90%, Terplan)

- Treat all patients with respect, regardless of drug and alcohol use in pregnancy
- Sadly, many relapse after the baby is born
- Addiction Specialist referral

Impact of Tobacco on the Fetus and Newborn:

- Reduction in placental capillary volume
- Increased thickness of placental villous membranes.
- Nicotine induced placental vascular constriction/vasospasm.
- Nicotine induced reduction in uteroplacental flow
- Carbon Monoxide binding to Fetal Hemoglobin reducing O2 delivery.

Tobacco use in Pregnancy: Adverse associations with Fetus and Newborn

- Spontaneous Abortion, RRR 1.23, dose related.
- Placental Abruption RRR 1.4 - 2.5, dose related.
- Birth Asphyxia/Stillbirth/Neonatal Death
- Increased risk of Stillbirth by 50%, and Neonatal Death 25%

- Premature Rupture of Membranes RRR 1.9 - 4.2
- Preterm Labor and Delivery 1.3 - 2.5 x risk < 32 weeks
- Intrauterine Growth Restriction (IUGR)-> 280 gram mean loss (100- 300 g)
- Small for Gestational age (< 2500 grams in full term infant, < 10%) 1.5- 3.5x)

- Birth Defects, including Cleft Lip and Palate, Gastroschisis, Anal Atresia, Limb
- Reduction, Finger Anomalies, Renal anomalies including Hypoplasia/Agenesis
- 2500 Chemicals found in cigarettes.
- Nicotine use may result in vascular disruption/constriction in organ formation
- Smaller lung volumes

Tobacco use in Pregnancy :Adverse associations with Children

- Increased risk for SIDS, (both prenatal and postnatal exposures), 2-4 x increase
- Otitis Media, Pneumonia, Colic, Asthma, Atopy
- Shorter Stature
- Worse school performance, ADHD, Obesity (also related to SGA/Preterm)
- Cofounding factors include social/economic issues.
- Smaller frontal lobes and cerebellar volumes.

Tobacco use in Pregnancy: Neonatal issues

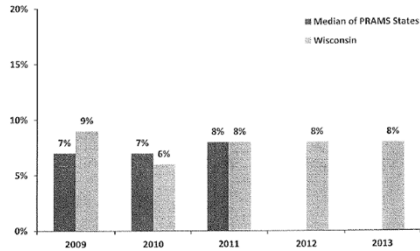
- Withdrawal/Abstinence: generally seen first few days:
- Irritability, tremor, and hypertonicity
- Nicotine withdrawal, also may be tied into polydrug exposure
- Breast feeding: Recommend, but baby urinary cotinine levels are 50x increased

- Mothers who continue to smoke have decreased breast milk production/failure.
- Increased infant irritability in mothers who continue to smoke postnatally.
- Counsel that smoking around baby is a risk factor for SIDS.

Alcohol use in Pregnancy: Impact on Fetus

- 8% of pregnant Wisconsin women drink in 3rd trimester. US data similar
- Alcohol is a true Teratogen. More potential for injury than cigarettes or illicit drugs.
- Alcohol readily crosses the placenta and in 1st trimester can cause organ damage.

Figure 40. New mothers who consumed alcohol in the last three months of pregnancy, Wisconsin and PRAMS states, 2009-2013



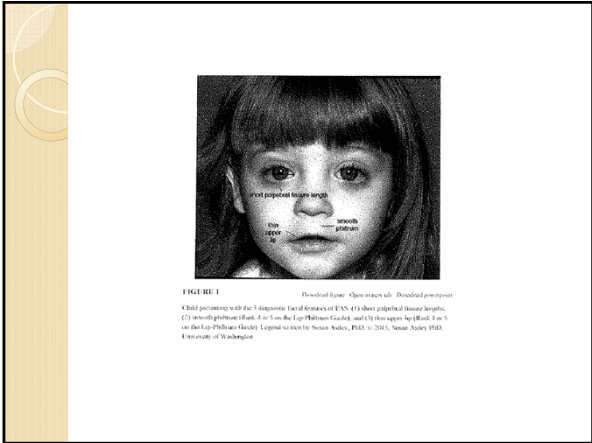
Source: Pregnancy Risk Assessment Monitoring System (PRAMS), Division of Public Health, Wisconsin Department of Health Services/Centers for Disease Control and Prevention.
Note: Data for U.S. was not available for 2012 and 2013. Not every state collects PRAMS data.

Alcohol use in Pregnancy: FASD: Fetal Alcohol Spectrum Disorders

- FAS: Fetal Alcohol Syndrome
- pFAS: partial Fetal Alcohol Syndrome
- ARND: Alcohol-Related Neurodevelopmental Disorder
- ARBD: Alcohol-Related Birth Defects

Alcohol use in Pregnancy: FAS: Fetal Alcohol Syndrome, the worst expression: 3 criteria

- Facial abnormalities including smooth philtrum, thin upper lip, and small palpebral fissures
- Fetal Intrauterine Growth Retardation, Small for Gestational Age (Birth weight <10%)
- Central Nervous System Abnormalities including learning difficulties, ADHD, cognitive disabilities



- Microcephaly may be seen. Visual and Hearing loss are associated.
- CNS delays and abnormalities can be seen without physical features. (ARND)
- Other organ system involvement besides CNS: Heart (ASD, VSD), Kidney

Alcohol use in Pregnancy: Dose and Mechanism of Injury

- Dose for fetal injury is unpredictable, dependent on maternal hepatic detoxification.
- Fetal Alcohol dehydrogenase (ADH) activity is variable but typically < 10% of maternal.
- Ethanol, Acetaldehyde disrupt DNA and protein synthesis, cell differentiation, and cell migration.

- Ethanol, disrupts transfer of nutrients and O₂ transplacentally.
- Risk of Fetal IUGR is increased even with 1 drink/day. (1.5 oz spirits, 5 oz wine, 12 oz beer)
- Independent increased risk of still birth, abruption, preterm labor.

Alcohol use in Pregnancy: Incidence and Long Term implications:

- FAS incidence is estimated at 1/1000
- FASD incidence is estimated at 1:100
- These are likely underestimates. One cohort of adopted children suggested 6.4%

Conclusion:

- Fetal Alcohol Spectrum Disorder is the most commonly identifiable cause of Developmental Delays and Intellectual Disabilities. It is under-recognized. It is completely preventable.
- The long term costs for cognitive, behavioral, and medical difficulties is enormous.
- There is no safe level of alcohol intake in pregnancy. Zero is the goal.

Questions?

Marijuana use in Pregnancy: Increasing maternal use

- Marijuana is the most common illicit drug use in pregnancy.
- Legalization in increasing # of states may have made Marijuana more appealing, use increases.
- Use in pregnancy increases from 2.37% to 3.85% from 2002 - 2014,, 62% increase.
- Touted on Internet and elsewhere as good treatment for nausea with minimal risk.
- Public accepts Marijuana as OK for medical illness.

Marijuana use in Pregnancy: Effect on Fetus

- Of women using in pregnancy, 16% report daily use.
- Passes transplacentally, and binds to emerging fetal cannabinoid system.
- THC (Delta 9 Tetrahydrocannabinol) interrupts nerve synapses, neuronal growth

- THC interrupts neurotransmitter binding, likely in dopamine pathways.
- THC downloads tyrosine hydroxylase activity involved in dopamine synthesis.
- Probable impact on serotonin and even opioid pathways.

Marijuana use in Pregnancy: Increasing concentration THC, causing increasing fetal drug exposure

- Mean concentration of Marijuana THC rises from 3.4% - 8.8%, even up to 12%.
- Synthetic Marijuana preparations, (hash oil, K2, Spice) have over 20% THC.
- Difficult to regulate these drugs as their chemical constituents remain 1 step ahead of the law.

- Ammonia, content is 20 x that of cigarette smoke.
- I have taken care of a baby whose mother presented with seizures. The child had no brain function following emergency delivery.

Marijuana use in Pregnancy: Risk to Fetus:

- Increased risk for stillbirth (OR 2.34, CI 1.13-4.81)
- Increased risk for Small for Gestational Age (OR 2.2, CI 1.8-2.7)
- Netherlands: Growth reduction of 14.4 grams/week and Head Circumference .21 cm/week)
- Smoking through 20 weeks results in 5 fold risk for preterm birth adjusting for cigarettes, EtOH.

Marijuana use in Pregnancy: Impact on Neonate and Child

- Withdrawal/toxicity in Neonate has been reported.
- Exaggerated startle, high pitched cry, poor habituation, sleep-wake cycles.
- Delayed acquisition of visual perceptual skills, language, ADHD, learning difficulties.
- Lower scores Welscher Individual Achievement Test at 14 y/o.
- Increased risk of children using marijuana as adolescents

Marijuana use in Pregnancy: Impact on Breast Feeding

- THC in Breast Milk is concentrated up to 8 x above maternal levels. This is absorbed by baby.
- THC is highly lipid soluble and is stored in brain, adipose tissue and bile for weeks to months.
- Adverse baby effects include: increased tremor, poor sucking, decreased feeding time, slow weight gain, change in visual responses, and delayed motor development.
- Older studies suggest there is no conclusive evidence that breast feeding affects outcome.

- These studies may be flawed because THC concentrations were much less in these studies.
- AAP guidelines recommend cessation of Marijuana use
- Risk versus benefit must be discussed.

Give your baby the healthiest start in life. Choose to breastfeed and DON'T use marijuana.

MERITER
UnityPoint Health

The point of everything we do is you.

meriter.com

MERITER
UnityPoint Health

Using marijuana if you breastfeed is NOT healthy for your baby and it is NOT recommended.
(American Academy of Pediatrics and The Academy of Breastfeeding Medicine)

What are the risks?

- THC, the active ingredient in marijuana, gets into your breast milk and your baby.
- When you use marijuana, the THC stays in your body fat, blood, and breast milk for up to 30 days. This means it can build up in your baby's body over time. Your baby could also test positive for THC.
- Using marijuana may create feeding problems. It can lower your milk supply. It can also make your baby less willing to eat. This could lead to slow weight gain or failure to thrive.
- Some studies show that babies exposed to THC in breast milk may have an increased risk for Sudden Infant Death Syndrome (SIDS).

The benefits of breastfeeding!

- When you choose to breastfeed you are investing in your baby's future. Breastfeeding allows you to make the food that is perfect for your baby.
- Breast milk protects your baby against illnesses like ear infections and colds.
- Breastfeeding helps lower the chance that your baby will have allergies, asthma, obesity, some childhood cancers, and type 2 diabetes.
- Mothers who breastfeed heal from childbirth more quickly and easily.
- The hormones released while breastfeeding can help you feel less stressed and anxious.
- Women who breastfeed have lower rates of breast and ovarian cancer and type 2 diabetes later in life.
- Breastfeeding is free and without the hassle of using bottles or mixing formula.

Still have questions?

Talk to your baby's health care provider about the risks of marijuana use compared to the benefits of breastfeeding. This will help you make the best decision for you and your baby.

Do you need help quitting?

Reaching out for help is a sign of strength. For more information, call the Meriter NewStart at (608) 437-3366 or go to meriter.com/newstart.

Advice to Mothers who Smoke Marijuana and Want to Breastfeed: EPIC EHR.

I have discussed the risks to the baby of continued marijuana exposure via breast milk and in the environment. These risks include but are not limited to poor feeding by the infant, decreased breast milk production, increased risk of Sudden Infant Death Syndrome (SIDS) from smoking exposure and potential increased risk of abnormal future neurodevelopmental outcomes. I've discussed that tetrahydrocannabinol (THC, an active constituent of cannabis) is highly concentrated in breast milk secondary to its lipophilic nature. I have strongly recommended that any use of marijuana be immediately discontinued. Should there be continued use of marijuana, I strongly recommended that any smoking be outside of the home and away from the infant. Parents had all of their questions answered during this discussion.

Marijuana use in Pregnancy:

- There is morbidity to babies from preterm labor to subtle behavioral and learning deficits.
- Of concern, is the risk from breast feeding, and the inadvertent downside of increasing acceptance of Marijuana use and legalization.
- Toddler ingestion of parental marijuana, more likely to be left out has been reported in CO.
- There is 2 - 3 x risk of child abuse/neglect with ongoing parental marijuana use.
- The AAP opposes legalization of Marijuana.

Questions?

Use of Opiates in Pregnancy: Maternal use in Pregnancy:

- As noted, in WI, mothers have positive urine screen for opiates in 16/1000 deliveries, 1.6%.
- True incidence is likely > 6%.
- Opioid use includes street drugs and prescriptive drugs.
- Includes Heroin, Morphine, Fentanyl, Codeine, Methadone, Oxycodone, and Buprenorphine.
- Encourage enrollment of pregnant mothers to enter drug treatment programs.

Use of Opiates in Pregnancy: Effect on Fetus

- Opiates readily cross the placenta and occupy mu-opioid receptors in the fetal brain.
- Opiates also occupy catecholamine receptors with impact on norepinephrine, dopamine and serotonin neurotransmitters.
- Genetic variations in mu receptors and catechol methyltransferase enzymes impact on severity of NAS in the newborn.

Wadhwan et al, J. Pediatric, 2014, 165:472.

Use of Opiates in Pregnancy: Effect on Newborn: Neonatal Abstinence Syndrome has increased

- Newborn is at risk for NAS; risk of NAS is at least 50% of opiate exposed mothers.
- Admission to the NICU for NAS increased from 1.2 to 5.8/1000 hospital births 2000 - 2012.
- NICU NAS admissions rose from 7 to 27/1000 admissions from 2004 - 2013, in 299 US NICU's.
- Average range of hospital stay is 13 - 19 days.

Ko, PMW, 2016, 65:799. Patrick et al, J. Perinatol, 2015, 35:650. Taha, N Engl J Med, 2015, 372:2118.

Use of Opiates in Pregnancy: Signs of NAS:

- High Pitched Cry
- Irritability
- Sleep Wake cycle disturbance; Often will not sleep.
- Hypertonia (stiff joints)
- Jitteriness and Clonus.
- Hyperphagia, and yet may have poor weight gain
- Diarrhea
- Sweating
- Fever

Use of Opiates in Pregnancy: Timing of withdrawal:

- Heroin (short acting) occurs in first 24 hours.
- Tobacco, may have withdrawal in first 24 hours.
- Reaction to Maternal SSRI usually occurs in first 24 hours.

- Methadone and Buprenorphine begins after 24 hours, up to 5 days.
- Happy to have Moms in treatment programs, but NAS may be worse in babies.
- Preterm babies < 35 weeks tend to have lesser degree of NAS. Less accumulation, less fat.

Use of Opiates in Pregnancy: Criteria for admission to NICU

- Failed non-pharmacologic treatment.
- Severe feeding problem.
- High scores on the Finnegan scale, designed to quantify degree of NAS.

Drug testing:

- We are making transition to Umbilical cord testing for drug testing of baby. Rapid results.
- Urine and Meconium are still used. Results may come in many days later. Hinders decisions.
- Some drugs are stored in meconium for many weeks, so timing of exposure can't be determined.

Use of Opiates in Pregnancy: Non-pharmacologic treatment

- Involve Mother and family, counsel and educate. Treat family with respect.
- Swaddle in blankets. Low lighting in room. Soft voices, minimize noise.
- Feed frequently as needed.

- Encourage breast feeding if not contraindicated (Cocaine, Methamphetamine, HIV, IV drugs, relapse, refusal to enter drug treatment program).
- Methadone and Buprenorphine are safe for breast feeding.
- Mamaroos and other positional devices to help hypertonicity and irritability.

Use of Opiates and Pregnancy: Pharmacologic treatment

- Continue non-pharmacologic treatment
- Morphine or Methadone as first line treatment. Ongoing studies with Buprenorphine.
- Clonidine or Phenobarbital as second or third line drugs.
- Wean slowly, 10% - 20% Q 24 - 72 hours.
- Ongoing family support.

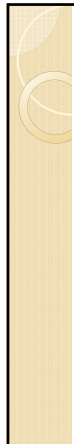
Jansson et al. Up to date, www.uptodate.com 2017.

Use of Opiates and Pregnancy: Long term child outcomes.

- Variable at best. No increased risk for severe cognitive delays
- Outcomes for all drug exposed babies is dependent on multifactors:
- Other maternal drugs, socioeconomic status, social problems, are all issues.
- Poor maternal nutrition may result in small for gestational age babies independent of drugs.
- Maternal behavioral difficulties, and child abuse and neglect by family members also influence.

Other drugs such as Methamphetamine or Cocaine also have a negative influence:

- Fetal growth, and fetal nervous system may be significantly impacted
- Maternal nutrition and behavior are impacted.
- Studies are conflicting about long term outcome, but many show behavioral and cognitive delays



Final Questions?
