Substance Use During Pregnancy

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I have no conflicts of interest or relevant financial relationships with any commercial entities.

Use of Hazardous Substances in Pregnancy is Common

- 5.9% of pregnant women use an illicit substance
  - 375,771 of offspring are exposed in utero to illicit substances each year
- 10-12% of pregnant women use alcohol
  - 764,280 offspring are exposed in utero to alcohol each year
- 13-16% of pregnant women smoke
  - 1,019,040 offspring exposed in utero to nicotine

National Survey on Drug Use and Health, 2012
CDC, NCHS Data Brief, No. 136, December 2013

Alcohol & Illicit Substance Use In Pregnancy: Results of Routine Urine Testing (n=715)

- Self report under estimates use!

Chasnoff et al, NEJM, 322; 1202-1206; 1990
The Economic Costs Associated with Treating Drug Exposed Neonates

- ~30% of neonates with in utero cocaine or heroin exposure will require NICU treatment.
- Several studies find a mean length of NICU stay of ~11 days.
- The cost per infant is approximately $13,000-$14,000.
- One treatment study found a cost savings of ~$4600 per mother-infant pair with maternal inpatient treatment.

Svikis et al. Drug and Alcohol Dependence, 45, 105-11, 1997

Maternal Mortality Associated with Hazardous Substance Use

Consequences of Hazardous Substance Use in Pregnancy

- Nearly 3-fold increase of fetal death among amphetamine users.
- Between 2 ½ to 3 fold increase in neonatal death among amphetamine, cocaine and polydrug users.
- Between 3 ½ to 5 fold increase in postneonatal death in amphetamine, cocaine and polydrug users.

Wolfe et al, J of Perinatology, 25; 93-100; 2005

The Good, Bad and Ugly

- **The good**: hazardous substance use decreases throughout pregnancy.
- **The bad**: > 80% of postpartum women relapse to drug or alcohol use after delivery.
- **The ugly**: illicit substance and heavy alcohol use have physical & cognitive effects on offspring. They influence optimal maternal care; 2nd hand smoke is a hazard to children.
Abstinence Rates for Illicit Drugs and Alcohol Increase by Trimester

Ebrahim and Gfroerer, Obstetrics and Gynecology, 2003, 101, 374-379

Drug Use in Pregnancy and After Delivery (n=184)

Yonkers et al unpublished data

Cigarette Smoking in Pregnancy

- 23-25% women age 18-44 smoke daily
- ≥13% pregnant women self-report cigarette smoking although studies using cotinine find higher rates
- Most who quit smoking during pregnancy resume within 6 months postpartum.
- Rates are highest among women with high school or less education.
- Racially: 20% of pregnant Native Americans or Alaskan natives, 16% of pregnant Caucasians, 9% of pregnant African Americans and 4% of pregnant Hispanics smoked in 2002

Maternal-Fetal Risks Associated With Maternal Nicotine Use During Pregnancy

- Fetal growth restriction- complicated by poor maternal weight gain among smokers
- Ectopic pregnancy (1.5-2.5 greater risk)
- Placental disorders: abruption (1.4-2.4 increased risk) and previa (1.5-3.0 increased risk)
- Fetal or infant death- perhaps enhanced by fetal growth restriction- including SIDS (specific odds ratio 2.0-3.0, unknown if linked to prenatal or postnatal exposure)


Cigarette Smoking is a Major Contributor to SGA Delivery

Quesada, J Maternal Fetal Medicine, 2012
Behavioral Interventions

- Behavioral counseling is recommended for pregnant smokers, although overall has small effects- increasing quit rates by 6% to 10% over usual care

- Motivation and Problem-Solving (MAPS) therapy showed a medium effect size compared to usual care: abstinence was 42% for MAPS vs. 28% in usual care at 8 weeks, and 23% vs. 16.5%, respectively, at 28 weeks

Reitzel et al., Nicotine Tob Res, 2010

Contingency Management (CM)

- Efficacy of voucher-based CM for smoking cessation in pregnant women (n=166):
  - Abstinence was greater in the contingent than non-contingent condition, with late-pregnancy abstinence being 34.1% versus 7.4% (P < 0.001).
  - Infants born to mothers in the contingent condition had greater mean birth weight (3295.6 ± 63.8 g versus 3093.6 ± 67.0 g, P = 0.03), and lower percentage of low birth weight (<2500 g) deliveries (5.9% vs. 18.5%, P = 0.02) than infants born to mothers in the non-contingent condition

Higgins et al., Addiction, 2010

Pharmacological Treatments

- The efficacy and safety of anti-smoking medications are not yet established in pregnant and postpartum smokers

- Many have concerns about the use of these treatments in pregnant and breastfeeding women

Nicotine-replacement Therapy

- Coleman et al. study: Pregnant smokers randomized to behavioral counseling + nicotine patches (15mg/16hrs) or placebo
  - Quit rates at 4 wks were higher in NRT group vs. placebo group, but prolonged quit rates (to the end of pregnancy) were similar 9.4% and 7.6%, respectively
  
- To date, all placebo-controlled trials of nicotine-replacement therapy (NRT) in pregnancy have been negative

Coleman, et al., NEJM, 2012
Silver lining: there seems to be a dose response, so even reducing the number if cigarettes smoked daily improves the chances of a healthier pregnancy and baby.


Marijuana Use During Pregnancy

Caveats in Assessing the Effects of Hazardous Substance* Use In Pregnancy

- Polysubstance use is more the rule than the exception and one must account for multiple possible drug effects
- Those that are heavy users of a substance are more likely to use multiple hazardous substances
- Self reports of alcohol and illicit substance use in pregnancy are not always reliable

The Effects of Marijuana on Fetal Growth Using Urine Assays

<table>
<thead>
<tr>
<th></th>
<th>Non use</th>
<th>Marijuana Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight* (g)</td>
<td>3260</td>
<td>2980</td>
</tr>
<tr>
<td>Length* (cm)</td>
<td>49.8</td>
<td>48.3</td>
</tr>
<tr>
<td>Head circum.* (cm)</td>
<td>34.3</td>
<td>33.4</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39.2</td>
<td>38.9</td>
</tr>
</tbody>
</table>

Zuckerman et al, NEJM, 320, 762-768, 1989; * significant at p<.001

* This is especially true for illicit substance users
Cognitive Effects of Heavy Prenatal Marijuana Use: Outcomes at 10 Yrs

- 1st trimester is associated with inattention among offspring
- Inattention symptoms are associated with delinquency suggesting an indirect effect
- Offspring exposed to 3 joints per week prenatally have an increased rate of externalizing behavioral problems

Maternal Health Practices & Child Development Project

Depressive Symptoms in 10 Year Olds Exposed to Prenatal Marijuana

<table>
<thead>
<tr>
<th></th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
</tr>
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<tbody>
<tr>
<td>Abstain</td>
<td>25</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Light</td>
<td>30</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Moderate</td>
<td>35</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Heavy</td>
<td>40</td>
<td>35</td>
<td>30</td>
</tr>
</tbody>
</table>

% with scores ≥ 13 on CDI

*CDI= Children's Depression Inventory
Gray et al, Neurotoxicology & Teratology, pp 439-448, 2005

Summary: Prenatal Exposure to Marijuana

- Effects of marijuana often seen in conjunction with other hazardous substances
- Effects are most pronounced in heavy users
- Effects are rather subtle early on but include decrements in growth
- Later effects include inattention, impulsivity, delinquency and depressive symptoms

Cocaine Use During Pregnancy
**Prenatal Cocaine Use**

- Controversy about the magnitude of effects since the early descriptions of “crack babies”
- It is now thought that some of the deleterious effects are the consequences of poverty and other hazardous substance use
- Nonetheless, a number of deficits in offspring are specifically associated with prenatal cocaine use

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**Possible Mechanisms Underlying The Effects of Prenatal Cocaine**

- Monoamines and their receptors are critical in determining cellular architecture
- Cocaine inhibits the reuptake of monoamines and may influence cortical structure and function leading to specific deficits
- Cocaine leads to vasoconstriction and hypertension and may cause placental hypoperfusion leading to more global deficits

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**The Effects of Cocaine on Fetal Growth Using Urine Assays**

<table>
<thead>
<tr>
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<th>Non use</th>
<th>Cocaine Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight* (g)</td>
<td>3254</td>
<td>2947</td>
</tr>
<tr>
<td>Length* (cm)</td>
<td>49.7</td>
<td>47.7</td>
</tr>
<tr>
<td>Head circum.* (cm)</td>
<td>34.3</td>
<td>33.0</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39.3</td>
<td>38.8</td>
</tr>
</tbody>
</table>

*significant at p<.001

Zuckerman et al, NEJM, 320, 762-768, 1989

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**Cocaine Use Predicts Preterm Birth**

Quesada, J Maternal Fetal Medicine, 2012
Cocaine Immediately After Birth

- May be residual toxicity from cocaine rather than a “withdrawal” syndrome
- Frequently occur on postnatal days 2-3
- Reports include:
  - Jitteriness -- Abnormal EEG & Seizures
  - Hyperactive Moro -- Poor habituation
  - Excessive sucking -- Hyperreflexia
  - Hypertonicity -- Sleep disturbances

Committee on Drugs, Pediatrics, Vol 101, 1079-1086, 1998
Chiriboga et al, Pediatrics, Vol 96, pp 1070-1077, 1995

Neonatal Effects of Maternal Cocaine Use

- Cocaine exposed neonates have lower arousability\(^3\) and are more excitable\(^1,3\)
  - Lower dosages are associated with lower arousability
  - Higher doses are associated with greater difficulties with excitability and non-optimal reflexes\(^3\)
- Motor skills are lower in cocaine-exposed infants and this has a dose-related effect\(^2\)

\(^1\) Tronick et al, Pediatrics, 76-83, 1996; \(^2\) Miller-Loncar et al Neurotoxicology & Teratology, 213-220, 2005; \(^3\) Lester et al, Pediatrics, 1182-1192, 2002

Longer Term Effects of Prenatal Cocaine on Children

- Dose-related difficulties in attention control
- Diminished response inhibition
- Deficits in learning, among others
- Dose-related reductions in expressive language
- Generally, difficulties in the frontal-striatal system
- Effects may be influenced by postnatal environment!

Morrow et al, J Pediatric Psychology, 543-554, 2004
Mayes, Development and Psychopathology, 2005

Voucher Incentives & Cocaine Use in Methadone Maintained Gravidas

![Graph showing % Drug Positive Urines](image)

Contingency Management & Community Reinforcement vs 12-Step Facilitation

- Subjects were pregnant and parenting women (n=145)
- As compared to voucher controls, use of contingency management increased:
  - duration of cocaine abstinence
  - proportion of cocaine negative urines
- Community reinforcement was equivalent to 12-step facilitation

Schottenfeld et al, Drug and Alcohol Dependence, 2011

Gonadal Hormones and Cocaine: Preclinical Data

- β-estradiol promotes cocaine self administration in rats and monkeys
- β estradiol increases behavioral response to cocaine such as ambulation, rearing activity, conditioned placement preference and seizures
- Progesterone has the opposite effects and reverse the effects of β estradiol

PROG as a Neurosteroid

- PROG is also synthesized in the CNS and modulate multiple CNS functions (neurosteroid).
- PROG is neuroprotective, increased levels during pregnancy protects fetus
- PROG may be useful for CNS injuries like stroke or TBI
- PROG and its metabolites, allopregnanolone and pregnanolone, interact with GABA, glutamate, sigma, and nicotinic receptors

Days of Cocaine Use by Group

**Summary**

- There may be an acute intoxication syndrome
- Longer term effects include inattentiveness and impulsivity
- Treatments for pregnant cocaine users are understudied but short term use of vouchers has been found effective
- Progesterone is a promising intervention for postpartum women with a cocaine use disorder

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**Risk of Relapse After Delivery**

- **Figure 3:** Survival analysis for participants who were not using cocaine at study intake
- 41 participants were not using cocaine at study intake; 12 participants relapsed during the 12-week trial period, nine in the placebo group and three in the progesterone group. HR: hazard ratio.


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**Opiate Use During Pregnancy**

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**Fetal Weight Reductions Associated with Prenatal Opiate Use**

- **Hulse et al, Addiction, Vol 92, 1571-1579, 1997**

![Graph showing fetal weight reductions](image)
**Longer Term Issues for Neonates Born to Mothers Who Abused Opiates**

- Physical abuse and neglect associated with drug using live style of mother
- Studies find that 40% to over 90% of offspring are raised by adults other than their natural parents
- Children may fare better if placed in alternative care by 36 months
- Chaotic neonatal environment has a strong impact on child development


**Neurodevelopmental Outcome in Offspring Exposed to In Utero Opiates**

- Findings limited by difficulties in following up cohorts; most research relates to methadone use
- Intellectual deficits in preschool aged children, including mental retardation
- Impaired motor development in preschool aged children
- Intellectual deficits in some improve over time


**Neonatal Abstinence Syndrome**

- Occurs in 30%-80% of exposed offspring
- Mothers study and many cohort studies averaged at 50% of neonates
- May be associated with higher doses of opiates
- May be predicted by lower cord blood levels of methadone and norbuprenorphine

Committee on Drugs, Pediatrics, Vol 101, 1079-1086, 1998
Kuschel et al, Arch Dis Child Fetal Neonatal Ed, 89, 390-393, 2004

**Neonatal Abstinence Syndrome**

- Generally within 3-12 hours post delivery for heroin and 48-52 hours post maternal dose for methadone
- Occurs in 60%-90% of women

- **Central Nervous System Irritability**: increased wakefulness, disorganized sleep, hyperreflexia, high pitched cry, irritability, hypertonia, tremors, seizures
- **Gastrointestinal Dysfunction**: poor feeding, vomiting, uncoordinated sucking, diarrhea, dehydration
- **Autonomic Signs**: diaphoresis, nasal stuffiness, fever, mottling, temperature instability

Committee on Drugs, Pediatrics, Vol 101, 1079-1086, 1998
Neonatal Withdrawal Scale

Typical treatment is morphine drops

Treatment of Opiate Addiction During Pregnancy

- There is general agreement that opiate addicted gravidas should remain on maintenance treatment (methadone, buprenorphine, naltrexone)
- Some consensus that total withdrawal from opiates should be limited to 2nd trimester
- Goals of treatment address both maternal and child well being

Benefits of Opioid Agonist Treatment in Pregnancy

- Maintenance treatment increases use of prenatal care
- Associated with increases in birthweight compared to no agonist treatment
- Decreases craving for other street drugs

Methadone In Pregnancy

- μ-opioid agonist; and thus protects against maternal & "fetal withdrawal"
- 90% bioavailable but half life decreases across pregnancy
- May need to be increased in the 3rd trimester

Jones et al. Addiction; Supp S1, 2012
Buprenorphine for Opiate Addiction During Pregnancy

- It is a partial µ agonist and κ antagonist
- At least as well tolerated as methadone for acute treatment among heroin users
- Has lower intrinsic activity than methadone and lower subjective and physiological effects (e.g., useful at lower levels of opiate abuse)
- Higher receptor affinity than methadone and longer duration of action
- Less risk of withdrawal than heroin or methadone
- Adjustment across pregnancy needed


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.

N Engl J Med
Volume 363(24):2320-2331
December 9, 2010

Mothers Study

- Buprenorphine attrition (33%) was higher than methadone (18%)
- Buprenorphine was associated with shorter length of stay for neonates
- No differences in neonates who required treatment for NAS, peak NAS score
- No difference in substance use outcomes

Post-natal Consequences of Buprenorphine Exposure

- Buprenorphine neonates may be less excitable, less aroused and less hypertonic (MOTHERS study)
- Visual evoked potentials of 4 months of age in exposed (n=40) similar to non-exposed comparators

Jones et al. Addiction; Supp S1, 2012

Buprenorphine vs Morphine for Treatment of NAS

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Morphine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Length of treatment (days)</td>
<td>23 (SD 12)</td>
<td>38 (SD 14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>32 (SD 24)</td>
<td>42 (SD 13)</td>
<td>0.05</td>
</tr>
<tr>
<td>Phenobarbital adjunctive therapy (patients)</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>


Naltrexone Implants vs Methadone in Pregnancy: Birth Outcomes

![Bar chart showing preterm delivery and low birth weight percentages for Naltrexone Implant, Methadone, and Australian Norm.]

Hulse et al, Int J. Gynecology & Obstetrics, 85, 170-171, 2004

Summary: Prenatal Opiate Use

- Few women who are opiate dependent achieve abstinence during pregnancy
- Maintenance treatment during pregnancy is usually required
- Neonatal abstinence syndromes are common
- Long term outcome of offspring is confounded by environmental factors but diminished intelligence & motor deficits have been noted
Summary

- The adverse effects of hazardous substance use in pregnancy are well established
- Women tend to use less drugs or alcohol in pregnancy but use accelerates after delivery
- More controlled investigation is needed to assess the efficacy of outpatient interventions for pregnant, hazardous substance users
- It is hoped that this will lead to improved maternal and fetal outcomes