Substance Use, Abuse and Breastfeeding: What is Known and Still to Know?

Kathleen A. Marinelli MD, IBCLC, FABM, FAAP
Associate Professor of Pediatrics, Univ. of CT School of Medicine
Neonatology and CT Human Milk Research Center, Connecticut Children's Medical Center
Kathleen.marinelli@cox.net

Faculty Disclosure Information

- I have no financial relationships to disclose.
- I will not discuss “off label” and/or investigational use in my presentation.

Kathleen A. Marinelli MD, IBCLC, FABM, FAAP
I am however quite biased toward breastfeeding and the use of human milk...

Objectives

- Enumerate factors affecting drug transport into human milk
- Articulate the epidemiology of drug use in pregnancy and lactation
- Discuss current knowledge of individual drugs of addiction in relationship to lactation and Neonatal Abstinence Syndrome
- Determine drug compatibility with lactation
Slide 1: What We Know About Drugs and Human Milk

- Most drugs pass into human milk
- Almost all medication appears in only small amounts in human milk - usually less than 1% of the maternal dose
- Very few drugs are contraindicated for breastfeeding women (Dr. Jennifer Thomas)
  - Drugs that make you “glow”
  - Drugs that treat cancer
  - Drugs that get you arrested

Problems

- “Authorities” often recommend weaning when a medication is known to pass into milk
- Many reports on lactation and drugs are single case studies
- Many physicians do not have knowledge of drugs in lactation
  - easier & less threatening to recommend weaning
  - “Temporary” wean may become permanent

Passage of Maternal Drugs to Breastfeeding Infants

- Amount of drug transported into human milk and available to the baby depends on:
  - Characteristics of the drug
  - Maternal factors
  - Infant factors
  - Human milk characteristics
Drug Characteristics Influencing Concentration in Human Milk

- Bioavailability
- Acid-base properties (pH)
- Ionization
- Molecular weight
- Plasma protein binding
- Lipid solubility
- Half life (t½)
- Secondary drug-specific factors
- Metabolic profile

Bioavailability

- Defined as the percentage of administered dose that is systemically absorbed
- Bioavailable drug is transferred into human milk via passive diffusion and by active transport mechanisms
- Passage is greatest into colostrum due to “open” intracellular junctions (but milk volume low so dose may be insignificant)

Day of delivery until day of life 4
Colostrum

Thanks to Jennifer Thomas, MD
Kathleen Marinelli MD

March 2016
Day 4 - closure of gap junctions
Establishment of blood:milk barrier

Thanks to Jennifer Thomas, MD

Closed gap junctions

- When gap junctions close, medications need to penetrate 2 lipid bilayers to get into milk
- Similar to the blood-brain barrier


Thanks to Jennifer Thomas, MD

Kathleen Marinelli MD

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Acid-base Properties

- Blood pH 7.4, milk pH 6.8-7.3 (colostrum pH=blood)
- Basic (unionized) drug passes into milk, becomes ionized and is trapped
  - Erythromycin, antihistamines, isoniazid
- Acidic (ionized) drug passes minimally into milk and back diffuses into blood
  - Barbiturates, sulfonamides, penicillin, diuretics
**Molecular Weight**

- <200 Daltons: freely pass through aqueous pores
- 200 to 500 Daltons: concentration and pH dependent access
- >500 Daltons: little to no passage (e.g. heparin)

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**Plasma Protein Binding**

- The greater the degree of protein binding, the less free drug to cross into milk
- Examples of highly protein bound drugs: paroxetine (Paxil), propranolol (Inderal)

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**Lipid Solubility**

- The more lipid soluble a medication, the greater the quantity of medication transferred into human milk
- Medications with low lipid solubility pass slowly into milk.
Metabolic Profile

- Consider inactive vs. active metabolites

Example:
- Codeine is metabolized via CYP2D6 to morphine (5%), norcodeine (15%), and further to codeine-6-glucuronide (80%) and morphine-6-glucuronide by UGT2B7
- Codeine itself has very weak analgesic activity
- The morphine and codeine-6-glucuronide metabolites are responsible for codeine's analgesic properties

Secondary Drug Specific Factors

- Time to peak serum concentration
- Half-life (t½) of drug and metabolites
  - Half-life: how fast drug leaves body
  - Determined by absorption, metabolism and excretion
- Non-dose-related toxicities such as sensitization


Maternal Factors

- Amount of medication taken
- How often and when the medication is taken
  - Drugs taken 30-60 minutes before a feed are at maximum maternal serum levels during that feed
  - Taken right after breastfeeding, has maximum time to clear maternal blood
- The route of administration
  - IV>intramuscular>oral>topical
- Maternal kidney and liver function
**Infant Factors**
- Age and maturity of infant
- Immature renal and hepatic and systems
- Immature detoxification systems
- Volume of distribution
- Frequency of feeds and volume of human milk consumed
- Absorption from infant’s GI tract
  - Some drugs not absorbed (gentamicin, tetracycline, magnesium salts, radiocontrast agents, morphine)

**Human Milk Factors**
- Timing of dose to human milk manufacture
- Human milk composition
  - Colostrum versus mature milk
  - Foremilk versus hindmilk


**Relative Infant Dose**
- \[ \text{RID} = \frac{\text{Infant dose (mg/kg/day)}}{\text{Maternal dose (mg/kg/day)}} \]
- A Relative infant dose of < 10% is generally considered safe

Hale 2014
Drugs Commonly Used by the Breastfeeding Mother

- NSAIDs
- Narcotic Analgesics
- Anticoagulants
- Anticonvulsants
- Antidepressants
- Antihistamines
- Antimicrobials
- Bronchodilators
- Anti-hypertensives
- Calcium channel blockers
- Contraceptives
- Cough and cold
- Diuretics
- Steroids
- (Drugs of abuse)

Why is this important?

- Virtually all lactating mothers will take at least one or more medications/drugs during the course of time they lactate!!
Slide 2: Guidelines for Medication/Drug Use in the Breastfeeding Mother

- Use medication only if absolutely necessary
- If possible, delay starting medication until infant more mature
- Take lowest dose possible
- For most drugs, relative infant dose of <10% maternal dose is safe (Hale 2014)
- Avoid sustained release preparations
- Take the medication so that lowest amount gets into milk—short half life, high protein binding, low oral bioavailability
- Watch for adverse reactions (fussiness, rash, changes in feeding or sleeping behaviors)
- **A very small number of drugs are unsafe under any circumstances**

What about illicit drug use and licit substance abuse?

- A significant problem among women of childbearing age in the US
- 2012 National Survey on Drug Use and Health
  (http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm#ch2.6)
  - Among pregnant women aged 15 to 44 years, 5.9% used illicit drugs averaged across 2011 and 2012
  - This rate was significantly lower than the rate among women in this age group who were not pregnant (10.7 percent)

Retrospective cross-sectional analysis of hospital births from 2000 to 2009 (Patrick 2012)
- Neonatal Abstinence Syndrome increased from 1.2 to 3.39 per 1,000 births
- Antepartum maternal opioid use rose from 1.19 to 5.63 per 1,000 hospital births
- ~ 1/3 of women of reproductive age filled a prescription for opioids each year between 2008 and 2012 (CDC 2015)
Neonatal Abstinence Syndrome (NAS)

- Infants chronically exposed to opiates in utero
  - 55-94% of neonates with in utero narcotic exposure develop NAS
- Constellation of S/S:
  - Neurologic excitability (tremors, irritability, increased wakefulness, high pitched crying, increased muscle tone, hyperactive reflexes, seizures, frequent yawning/sneezing)
  - Gastrointestinal dysfunction (poor feeding, uncoordinated and constant sucking, vomiting, diarrhea, dehydration, poor weight gain)
  - Autonomic signs (increased sweating, nasal stuffiness, fever and mottling of skin)

Withdrawal signs and symptoms typically present within 48 to 72 hours of birth following in utero opioid exposure

- Can manifest up to 4 weeks later in some infants
- Infants with significant NAS Sx can have difficulties with breastfeeding mechanics impacting their ability to breastfeed
- Increasing evidence to support methadone exposed infants may benefit from breastfeeding and/or EMM
  - Less likely to have severe NAS

Narcotic use

- Primary circumstances under which pregnant women use narcotics:
  - Illicit drug abuse
  - Prescribed narcotic maintenance as treatment for abuse
  - Treatment of chronic pain conditions
What about narcotic analgesics?
- In general population, lower doses
  - Used short-term, no probable affects
  - Long-term use, monitor infant for drowsiness, poor breastfeeding and weight loss
- Newborn infants seem to be particularly sensitive to effects of even small dosages of narcotic analgesics
  - particularly in the first week of life

Narcotic analgesics
- Newborn's dosage limited by small volumes of colostrum in the first 2-3 days postpartum
- For non-addicted mothers:
  - Once the mother's milk becomes copious (Lactogenesis II) it is best to use non-narcotic analgesic and limit the maternal dosage and duration of treatment with narcotics
- Rx narcotics are also abused

SPECIFIC DRUGS....
Methadone: Summary of Use During Lactation

- Expert opinion: women stable on methadone maintenance during pregnancy should be encouraged to breastfeed their infants
  - Low concentrations in milk regardless of dose (well-studied)
  - Breastfeeding decreases NAS symptoms in infants (Wachmann 2015, Ordean 2015, Pritham 2013, Welle-Strand GK 2013)
  - May require additional treatment for withdrawal
  - Recent concerns about motor delays at 9 months compared to matched non-exposed infants (Logan 2013)

Methadone—drug levels

- Methadone is metabolized to inactive pyrrolidine and pyrroline metabolites
- In adults, methadone oral bioavailability 80-95%
- In newborns of opiate-dependent mothers, used to treat neonatal abstinence syndrome
  - usual infant dose: 50-100 mcg/kg every 6-12 hours

Buprenorphine (Buprenex, Subutex)

- Potent long-acting narcotic analgesic & partial opioid agonist
- Recently approved for rx opiate dependence
- T ½ sub-lingual 23-30 hours; RID 1.93%
- Acceptable for use in lactation
  - Low levels in human milk; poor oral bioavailability in infant; low conc infant serum and urine
  - Monitor infant for drowsiness, weight gain, developmental milestones
  - Less severe NAS; less likely to require pharmacological rx (O’Conner 2013, D’Apolito 2013)
Possible Advantages Of Buprenorphine over Morphine for NAS

- Buprenorphine has longer duration of action and resides on the mu opioid receptor longer
- May decrease sudden shifts in receptor antagonism and thus, reduce withdrawal symptoms
- Higher up-titration of buprenorphine vs morphine (25% vs 10%) may result in more rapid attainment of symptom control
- 10% per day weaning schedule used for both drugs, however, buprenorphine is discontinued sooner, within 10% of starting dose, morphine to 0.15mg/kg/D

Buprenorphine (B) + Naloxone (N) (Suboxone)

- Sublingual tablet containing a partial opioid agonist (B) and an opioid antagonist (B) 4:1
- B reduces craving for opioids; N discourages use of other opioids by blocking opiate receptor
- N poorly absorbed orally; B only 31% absorbed; human milk levels insignificant

Hydrocodone (Vicodin w/ acetaminophen)

- Commonly used in lactation, although metabolized to 6 active metabolites
- Milk levels low
- Monitor babies for lethargy, poor feeding

(Debelak K 2013)

Anderson 2007
Hydromorphone (Dilaudid)
- Potent semisynthetic narcotic analgesic
  - 7-10 times more potent than morphine
- T ½ 10.5 hrs
- RID 0.52%
- Although milk levels low, caution in preemies or after prolonged use

Narcotic analgesics
- Percocet, Percodan, Demerol, Darvon
  - Used short-term, no probable affects
  - Long-term use, monitor infant for drowsiness, poor breastfeeding and weight loss

Codeine—Deal or no deal???
- Considered a mild opiate analgesic
- RID 8%; t ½ 2.9 hrs
- Maternal dosages as low as 0.63 mg/kg (about 40 mg) daily have caused infant drowsiness in a breastfed infant
- Maternal dosages of 1.6 mg/kg (about 100 mg) daily are likely to cause drowsiness in many breastfed infants
**Codeine metabolism**

- Metabolized via CYP2D6 to:
  - morphine (5%) and norcodeine (15%)
  - and further to codeine-6-glucuronide (80%) and morphine-6-glucuronide by UGT2B7
- Codeine itself has very weak analgesic activity
  - The morphine and codeine-6-glucuronide metabolites are responsible for codeine's analgesic properties
- CYP2D6 and UGT2B7 subject to genetic variability which can alter the amount of active narcotic excreted into milk.

**Codeine—BIG DEAL!!!!!**

- Has been associated with otherwise unexplained cases of neonatal apnea, bradycardia, cyanosis and lethargy
  - One neonatal death whose mother was found to be an *ultrarapid metabolizer* of codeine (rare) who excreted very large amounts of morphine into her milk (Koren 2006, Madadi 2007)
    - Being disputed as general recommendation (Halder 2015)
  - Codeine can be considered a definite cause of CNS depression in some breastfed infants
  - Pharmacogenetics is an important predisposing factor

**Oxycodone** *(Tylox, Percodan, OxyContin)*

- Similar to hydrocodone
- Metabolized to the active metabolites
  - noroxycodone and oxymorphone
- Max oxycodone dosage of 30 mg/d suggested
- Oxycodone elimination is decreased in young infants
- Much inter-individual variability exists
- RID 3.9%; T ½ 3-6 hrs
- Monitor infant for drowsiness, wt gain, developmental milestones, esp in younger, exclusively breastfed infants
Cannabis (Marijuana)

- Legal issues and health issues
- Potency has been steadily increasing
  - 3% in the 1980s to 12% in 2012 (Volkow 2014)
- Relevancy of data from previous studies?
- Risks of not breastfeeding in this population
- Concern expressed:
  - Should not be used by nursing (any) mothers
  - Maternal inability to safely care for her infant while directly under its influence—opinion, no data

Delta 9 tetrahydrocannabinol (THC)

- Active ingredient delta 9 tetrahydrocannabinol (THC)
- Very lipid soluble; released slowly over time
- Present in human milk up to 8X maternal plasma levels
- Metabolites found in infant feces (Perez-Reyes 1982)
- absorbed and metabolized by the infant
- Long half-life (25–57 hours); stays positive in the urine for 2–3 weeks
- occasional versus a chronic user
- Few women have isolated use during breastfeeding in the absence of prenatal use of marijuana

Cannabis

- Concern expressed:
  - Infant sedation
  - Possible effects on neurotransmitters, nervous system development and endocannabinoid-related function (Astley 1990, Tennes 1985, Volkow 2014, Campolongo 2009)
    - Data are from random milk screening
  - Should not be smoked in the vicinity of infants
    - Infants can be exposed by inhaling the smoke
  - Some evidence indicates that paternal marijuana use increases the risk of sudden infant death syndrome in breastfed infants (Klonoff-Cohen 2001)
Growing concern...

- With increasing ability to obtain “legal medical marijuana” and states making recreational marijuana legal...
- Any estimates of numbers of mothers who use now are underestimates
- “Because breastfeeding can mitigate some of the effects of smoking and little evidence of serious infant harm has been seen, it appears preferable to encourage mothers who use marijuana to continue breastfeeding while minimizing infant exposure to marijuana smoke and reducing marijuana use.” LactMed http://toxnet.nlm.nih.gov/

Heroin

- Transfers into milk, converted to morphine
- Causes infant drowsiness, difficulty breastfeeding, breathing difficulties, limpness, central nervous system depression and even death.
- Not compatible with breastfeeding!!

D’Apolito 2013

Cocaine

- Cocaine should not be used by nursing mothers or smoked (“crack”) by anyone near infants
- Infants may be exposed by inhaling the smoke
- Mother of an 11-day-old infant applied cocaine powder to nipples for pain relief
  - Breastfed infant using breast shield—developed seizures
- Newborn infants are extremely sensitive to cocaine
  - have not yet developed the enzyme that inactivates it
- Cocaine and its metabolites are detectable in breastmilk
  - data are from random breastmilk screening
Cocaine
- Cocaine breastmilk concentrations have varied over 100-fold in reports
  - Due to its chemical nature (lipid soluble), high concentrations of cocaine are usually expected in milk
  - Serious adverse reactions have been reported in newborn infants exposed to cocaine via breastmilk
    - marked irritability, dilated pupils, vomiting, diarrhea, tremulous, frequent startle after minimal stimulation, high-pitched crying, hyperactive reflexes, mood liability, hypertension, tachycardia, shallow breathing, hypothermia and status epilepticus (Chasnoff 1987, Jones 2015)

Alcohol Consumption in the Breastfeeding Mother
- Alcohol passes freely into mother's milk (Haastrup 2014)
  - Milk alcohol levels closely parallel blood alcohol levels
  - Peaks at 30-60 minutes after consumption (60-90 minutes with food)
  - RID 16%
  - Wait 2-2.5 hours/drink consumed before breastfeeding
  - Nursing after 1 or 2 drinks can decrease infant's milk intake by 20-23%; cause infant agitation and poor sleep patterns (Mennella 1991, Haastrup 2014)

Alcohol
- Long-term effects of daily use of alcohol on the infant are unclear (Haastrup 2014)
  - Some evidence that infant growth & motor function may be negatively affected by 1 drink or more daily
    - Other studies have not confirmed these findings
  - Heavy maternal use may cause excessive sedation, fluid retention, and hormone imbalances in breastfed infants
  - Casual use (1 glass of wine or beer/day) unlikely to cause short- or long-term problems in the infant
  - Daily heavy use of alcohol (>2 drinks daily) appears to decrease duration of breastfeeding
Smoking and the Breastfeeding Mother

- Smoking linked to earlier weaning, fussiness, lower milk production, interference with letdown
  - ↓ prolactin levels
- Nicotine half life: 95 minutes
- Benefits of breastfeeding far outweigh risks of smoking on breastfeeding
- If must smoke:
  - Smoke immediately after breastfeeding to decrease amount of nicotine in human milk  
  - Avoid smoking in same room as baby

Nicotine Patches

- Nicotine and its metabolite cotinine both present in milk
- Patches 21 mg; 14 mg; 7 mg
  - 21 mg=17 cigarettes/day
  - Weaning on patches decreases exposure by 70% when go from 21mg to 7 mg
  - Safer option than smoking!!!
So...what can we do??

...throw up our hands...

...and just say NO!!??

Comprehensive Substance Abuse Treatment

Ideally, drug dependent women delivering an infant and desiring to breastfeed should engage in comprehensive substance abuse treatment.

Substance abuse treatment for this population of women is often not available, gender specific, or comprehensive.

- Force the perinatal provider to rely on maternal self-report, “best guess” at adequacy of services, compliance to treatment, length of “clean” time, community support systems, etc.

Comprehensive Substance Abuse Treatment

Choice to breastfeed may appear to indicate mother less or not likely to abuse substances.

- Research disproves this.
- Data from the 1988 US Maternal and Infant Health Survey indicates that heavy alcohol, marijuana and hashish use, and moderate cocaine use did not significantly deter women from choosing to breastfeed their infants.
Opioid dependency

- Opioid dependent pregnant/pp women in rx, methadone maint is treatment of choice in US
  - In contrast to other substances, conc of methadone in HM and effects on infant have been studied
  - Concentrations of methadone found in HM low
  - Women stable on methadone maintenance should be permitted to breastfeed if desired and irrespective of maternal methadone dose
  - No apparent short term or long term effects of methadone in HM on neurodevelopment

www.bfmed.org

ABM Clinical Protocol #21:
Guidelines for Breastfeeding and Substance Use or Substance Use Disorder, Revised 2015

Sarah Piece-Santiago, Kathleen A. Marinelli and The Academy of Breastfeeding Medicine

A central goal of The Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Purpose

The current document was developed by a team of experts in the care of pregnant and newly postpartum women with a history of past or recent drug/alcohol abuse or legal substance use or misuse to address the challenges of use of other harmful legal substances, including tobacco and alcohol. The drug is the drug(s) isolated and mentioned, and its type.

Recommendations from ABM Protocol 21:
Guidelines for breastfeeding and the drug-dependent woman

- Prenatal plan preparing mother for parenting, breastfeeding and post partum substance abuse treatment formulated for each woman
  - should include instruction in consequences of relapse to drug or alcohol use during lactation
  - teaching regarding donor milk, formula preparation/bottle care should breastfeeding be contraindicated
**Perinatal period**

- Each mother-infant dyad carefully/individually evaluated prior to breastfeeding
  - maternal drug use and substance abuse tx hx
  - medical and psychiatric status and medication needs
  - infant health status (include ongoing evaluation for NAS and impact on breastfeeding)
  - presence or absence and adequacy of family, community support systems, plans for pp health care, psychiatric care (if needed) & substance abuse rx for the mother & pediatric care for child

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**Supported in their decision to breastfeed their infants**

- Women engaged in substance abuse treatment who have provided their consent to discuss progress in treatment and plans for post partum treatment with substance abuse treatment counselor
- Women whose counselors endorse that she has been able to achieve and maintain sobriety prenatally; counselor approves of client’s plan for breastfeeding
- Women who plan to continue in substance abuse treatment in the post-partum period
- Women who have been abstinent from illicit drug use or licit drug abuse for 90 days prior to delivery and have demonstrated the ability to maintain sobriety in an outpatient setting

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**Supported in their decision to breastfeed their infants**

- Women who have a negative maternal urine toxicology testing at delivery except for prescribed medications
- Women who received consistent prenatal care
- Women who do not have medical contraindication to breastfeeding (such as HIV)
- Women who are not taking a psychiatric medication that is contraindicated during lactation
- Stable methadone maintained women wishing to breastfeed should be encouraged to do so regardless of maternal methadone dose
Discouraged from breastfeeding

- Women who did not receive prenatal care
- Women who relapsed into illicit drug use or licit substance misuse in the 30 days period prior to delivery
- Women who are not willing to engage in substance abuse treatment or who are engaged in treatment but are not willing to provide consent for contact with counselor
- Women with positive maternal urine toxicology testing for drugs of abuse or misuse of licit drugs at delivery
- Women who do not have confirmed plans for post partum substance abuse treatment or pediatric care
- Women who demonstrate behavioral qualities or other indicators of active drug use

Where does this leave us in 2016?

- The drug dependent woman who has successfully instituted breastfeeding should be carefully monitored, along with her infant, in the post partum period.
- Ongoing substance abuse treatment, post partum care, psychiatric care when warranted, and pediatric care are important for this group.
- Lactation support is particularly important for infants experiencing NAS.
- Communication between providers should provide an interactive network of supportive care for the dyad.
- As always—we need more research!!!!

Resources for Medications and Breastfeeding

- **Medications and Mother’s Milk**, Thomas Hale; 2014
- The Breastfeeding and Human Lactation Study Center 716-275-0088
- Dr. Philip Anderson, UCSD 900-285-3784
- [http://www.e-lactancia.org/ingles/inicio.asp](http://www.e-lactancia.org/ingles/inicio.asp)
- The Infant Risk Center, Texas Tech 806-352-2519
Thank you!!
kathleen.marinelli@cox.net