Treatment for Pregnant and Parenting Women with Opioid Use Disorder: Considerations for Mother and Child

Karol Kaltenbach, PhD
Emeritus Professor of Pediatrics
Sidney Kimmel Medical College at Thomas Jefferson University

Outline

- Use of Medication in the Treatment of Opioid Use Disorder
  - Differences between methadone, buprenorphine, and naltrexone
- Mediation Assisted Withdrawal during Pregnancy
  - Risks and benefits
- Neonatal Abstinence Syndrome
  - Contexts and new treatment research

Pregnant and Postpartum Women and Their Infants

- Two major focal points:
  - Antenatal focus is on mother and the pharmacological management of her opioid use disorder during pregnancy
  - Postpartum focus is on the infant and the management of neonatal abstinence
- However, these must be placed in context of the complex bio-psycho-social problems associated with maternal substance use disorders with the focus on how we can obtain optimal outcomes for the mother/infant dyad.
We must always keep a mother in mind in order for her to keep her child in mind.

**Terminology: Language Matters**

- Pregnant women with opioid use disorders or women with opioid use disorders who are pregnant
  - Disorder is not specific to pregnancy
  - Ignores experiences that contributed to their disorder
  - Leads to marginalization and stigma
- Medication assisted treatment or medication for addiction treatment (MAT)
  - Suggests that rather than being efficacious is a treatment that assists something else.

**Guidelines**

- Medication Assisted Treatment for Opioid Addiction in Opioid Treatment Programs, TIP 43, SAMHSA, 2005
- Substance Abuse Treatment: Addressing the Specific Needs of Women, TIP 51, SAMHSA, 2009
- Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants, SAMHSA, 2016
Guidelines

Opioid Use and Opioid Use Disorder in Pregnancy. Committee Opinion No 711. American College of Obstetricians and Gynecologists, 2017

(Concept of Trauma and Guidance for a Trauma Informed Approach, SAMHSA, 2014)

All are available online

Medication for Addiction Treatment (MAT)

- The well being of the infant is improved with the well being of the mother

Maternal opioid use disorder and medication for addiction treatment

MAT

Medication for addiction treatment is the use of FDA approved medications in combination with evidence based behavioral therapies to provide a whole-patient approach to treating a substance use disorder
MAT

Medications used to treat opioid use disorders
- Methadone
- Buprenorphine (mono and combination products)
- Naltrexone (currently not recommended for use during pregnancy)

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MAT

Naltrexone
- Opioid antagonist medication for addiction treatment
- Information regarding its use in pregnancy is limited to small case studies and case reports
- Induction during pregnancy is difficult
- Decision to continue naltrexone treatment in women who become pregnant requires careful consideration of limited safety data vs. risk of relapse

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Historical Context of Treatment Principles

Methadone maintenance has been recommended for women with opioid use disorder who are pregnant since the early 1970’s

Over the past 40 years, the literature has established that methadone administered in appropriate doses, combined with counseling, psychiatric care and support services is an effective treatment

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Historical Context

The recognition of methadone as the standard of care in the United States can be traced historically through multiple federal publications:
- State Methadone Treatment Guidelines, CSAT, US DHHS, 1993

Buprenorphine has been used in Europe since the 1990’s. It was approved for use in the United States in 2002 and it is widely used in the US.

2012 Committee Opinion: American College of Obstetricians and Gynecologists and the American Society of Addiction Medicine recommend the use of methadone or buprenorphine for pregnant women with opioid use disorder

MAT during Pregnancy

Prevents erratic maternal opioid levels and protects the fetus from repeated episodes of withdrawal

Associated with improved obstetrical care, increased growth, and reduced fetal and neonatal morbidity and mortality

Supports and sustains recovery
Methadone and Buprenorphine

- Basic tenets of treatment are the same
  - Pharmacologically different
  - Schedule II vs. Schedule III
  - Different systems of care
  - Cost

MAT with Methadone

- Issues Specific to Methadone
  - Regulatory Schedule II Drug (may only be prescribed for MAT within an OTP except for hospitalization for medical condition)
  - Induction
  - Dose

Methadone Induction

- USA Regulatory Issues (42CFR 8.12)
  - Documented opioid dependence for a minimum of 1 year; pregnant women are exempt but must certify pregnancy
  - First dose ≤ 30mg
  - If withdrawal symptoms persist after 2-4 hours, initial dose can be supplemented with another 5-10mg
  - Maximum daily dose 40mg unless documented by physician that dose was insufficient to control withdrawal
**Methadone Induction**

- Difference in outpatient and hospital induction
- Inpatient allows for medical monitoring and comprehensive approach
- Outpatient often a practical necessity
  Twice daily observation until patient is stabilized

**Methadone Dose**

- Dose should be based on the same criteria as non-pregnant patients
- Pregnant women may develop symptoms of withdrawal as pregnancy progresses and may require dose increase in order to maintain the same plasma level
- Split dose regimen may be used to facilitate steady state maintenance (often difficult to implement)
- Increasing the daily medication regimen (2-6 doses per day) has been found to reduce the need for NAS treatment significantly to 29% (McCarthy et al., J Addict Med 2015)

- Dose should not be reduced during pregnancy to avoid NAS
- No clear evidence of association between maternal dose and severity of NAS
- Non-therapeutic maternal dose may promote supplemental drug use and increase risk to fetus
Medication Assisted Treatment

- Issues Specific to Buprenorphine
  - Regulatory Schedule III Drug
  - Transition from methadone to buprenorphine
  - Induction

Buprenorphine and DATA 2000

- Drug Addiction Treatment Act of 2000
  Qualifying physicians in medical offices outside the OTP system may prescribe and/or dispense Schedule III, IV, and V opioid medications for the treatment of opioid use disorders if such medications have been specifically approved by the FDA for that indication

Buprenorphine Induction

- Does not have the same regulatory restrictions
- Typically takes place over a 3 day period, beginning with 2mg or 4mg, with a maximum dose of
  - 8 mg Day 1
  - 12 mg Day 2
  - 16 mg Day 3
Buprenorphine Induction

- Dependence on short-acting or long acting opioids is issue
- Short-acting: minimum of 12-24 hrs between use and buprenorphine administration and exhibit early signs of withdrawal
- Long-acting: taper to ≤30mg for a minimum of 1 week. Last dose of methadone 24hr before buprenorphine and experiencing withdrawal
  - As such transition from methadone is especially difficult in pregnant women

Methadone or Buprenorphine?

- Both have maternal benefits and disadvantages
  - Buprenorphine: easier access to treatment,
  - Buprenorphine: behavioral treatment not always provided, ceiling effect, cost
  - Methadone: easier induction, lower cost, better treatment retention
  - Methadone: restrictive regulations, access to treatment often limited

Methadone or Buprenorphine?

- Buprenorphine has advantages for the infant
  - Systematic review and meta analysis of 12 studies (including MOTHER) had better neonatal outcomes for buprenorphine exposed infants compared to methadone exposed infants for treatment duration, morphine dose, birth weight, length and head circumference
  - No difference in need for treatment

(Brogly et al., 2014)
Methadone or Buprenorphine?

- Opioid dependent women naïve to agonist treatment may be a good candidate for buprenorphine. If she does not respond to buprenorphine, transfer to methadone can easily be initiated.
- Women stabilized on buprenorphine or methadone who become pregnant should remain on their current medication.
- Each woman’s medical, psychological and substance use history must be considered in any treatment decision.

Medication Assisted Withdrawal during Pregnancy

- Medication assisted withdrawal/detoxification used to provide transition from illicit opioids to drug free state.
- Taper is a gradual transition from maintenance to a drug free state.

Withdrawal during Pregnancy

- Historically, recommendations have been for withdrawal to be conducted only within the second trimester.
- Recommendations based on 2 events that occurred in the early 1970’s that identified safety issues with detoxification in pregnancy.
- However, there are no systematic studies on whether withdrawal should only be initiated during this time period.
- Data in 1994 indicated that with monitoring, withdrawal can be conducted safely in any trimester (Jarvis and Schnoll).
Medically Supervised Withdrawal in Pregnancy: Contemporary Data

- Dashe et al., *Obstetrics and Gynecology*, 1998
  - Small study of 34 women
  - 20 (59%) were successful, i.e. no drug use at delivery
  - 12% late preterm delivery
  - Safety established; high relapse rate, no follow up data postpartum

  - N=95
  - No fatal distress or demise
  - 44% relapse rate
  - Only followed to delivery

  - Group 1: 108 incarcerated patients who underwent acute detoxification 2 fetal demise (R=23.1%)
  - Group 2: 23 patients received inpatient medical detox, intense behavioral health follow-up (R=17.4%)
  - Group 3: 77 patient received inpatient medical detox, no behavioral health follow-up (R=74%)
  - Group 4: 93 patients received slow outpatient taper, continued behavioral health follow-up (17.2%)
Medically Supervised Withdrawal in Pregnancy: Contemporary Data

- Jones et al., *Journal of Substance Abuse Treatment*, 2008

**Medication-Assisted Withdrawal**

Chart review of 5 groups of patients:
- 3-day methadone-assisted withdrawal (MAW) alone (n=67)
- 3-day MAW followed by methadone maintenance (MM) (n=8)
- 7-day MAW alone (n=28)
- 7-day MAW followed by MM (n=20)
- Continuous MM (n=52)

**Days Retained in Treatment**

**Urine-positive Drug Screen Percentage at Delivery**

Patients in the three MM groups:
- remained in treatment longer
- had fewer positive urine drug screening test results
- attended more obstetrical visits
- more often delivered at the program hospital than patients in the two MAW alone groups.

Medically Supervised Withdrawal

- Women can be safely withdrawn during pregnancy
- Question is whether it should be done
  - Very high rate of relapse in opioid dependent women
  - Relapse places fetus at additional risk
Medically Supervised Withdrawal

- Medication assisted withdrawal:
  Need to provide counseling and education on risk/benefits of maintenance.
- Taper:
  A thorough assessment is essential to determine if woman is appropriate candidate
- Should be conducted under supervision by physician accompanied by fetal monitoring
- Important to provide prenatal and postpartum behavioral health treatment

MAT vs. Withdrawal or Taper

- Recommendations in support of treatment rather than withdrawal
  - American College of Obstetricians and Gynecologists and American Society of Addiction Medicine Joint Opinion 2017
  - Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants, SAMHSA, 2016
  - WHO 2014 Guidelines
  - Treatment Improvement Protocol, US Department of Health and Human Services 2005

MAT and Concomitant Use/Misuse of Drugs

- Illicit drug use and prescription misuse
- Methadone and buprenorphine have no direct pharmacological effect on non-opioids
- Misuse of other drugs such as cocaine, marijuana, alcohol, and/or benzodiazepine must be treated as a separate problem
- Benzodiazepine misuse is the most difficult problem
**Benzodiazepines**

- Benzodiazepines are one of the most widely prescribed medications to women.
- Generally used to treat insomnia and anxiety.
- Women more likely than men to be prescribed benzodiazepines when presenting for symptoms such as stress or life changes.
- Women are more likely to be prescribed benzodiazepines for a longer period of time.
- Women with opioid use disorders have rates of anxiety up to 78% (Green et al. 2009).

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**Special Challenges**

- Not all use/misuse is the same and requires different management strategies.
- Benzodiazepine use may be:
  - Prescribed and used appropriately.
  - Prescribed and misused.
  - No prescription/ buys off the street.
- These three categories are not always mutually exclusive.

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**Special Challenges**

- Benzodiazepines taken with methadone or buprenorphine can cause overdose (BZDs were present in 50% of PA’s drug-related deaths in 2014).
- Prescription Drug Monitoring Program (PDMP).
- Medical withdrawal not often available to pregnant patients.
- Slow taper is recommended to avoid withdrawal and/or exacerbation of psychiatric symptoms.
- Medical assessment is needed to determine appropriate medication, e.g. Klonopin/SSRI, and/or non medication options, e.g. Mindfulness, etc.
Opioid medications such as methadone and buprenorphine can be successful components in treating opioid use disorder, both in the general population and in pregnant women. Opioid medications are best provided in the context of a comprehensive treatment plan that includes behavioral treatment like individual counseling. A comprehensive treatment plan is developed following an assessment that determines which life areas have been affected by drug use and to what extent they have been affected. The patient and provider then develop specific goals for improved life functioning in each life area and a plan for how and when the goals will be met. Part of the plan may eventually include wellness indicators of when patients can taper off of their medication.

Neonatal Abstinence Syndrome

- The well being of the infant is improved with the well being of the mother

Neonatal Abstinence Syndrome

- NAS was first described in the 1950’s as the narcotic abstinence syndrome
- NAS is the occurrence of opioid withdrawal at birth after the discontinuation of opioid exposure in-utero
- Concomitantly, as treatment for opioid dependent pregnant women emerged, so also did treatment for NAS
Neonatal Abstinence Syndrome

- Central nervous system hyperirritability
  - hyperactivity, irritability, sleep disturbance, tremors
- Gastrointestinal dysfunction
  - uncoordinated sucking/swallowing, vomiting
- Autonomic Signs
  - fever, sweating, nasal stuffiness

Treated baby

Neonatal Abstinence Syndrome

- Due to the significant increase in prescription opioid use and misuse over the past decade, there has been an unprecedented focus on NAS in the past 5 years.
- Policies often reflect a lack of understanding of the factors that impact both the presentation and severity

Contexts of NAS

- NAS is an easily identifiable and treatable condition
- Has not been found to be related to adverse developmental consequences
  - Research has shown that infants with withdrawal that requires treatment and infants with mild withdrawal do not differ in developmental outcome at 6 months of age and function well within the normal range of development throughout 3 year of age.
    (Kaltenbach and Finnegan, 1986; Kaltenbach et al. 2018)
Context of NAS

- We tend to think of NAS only as a direct linear effect
  
  *Prenatal opioid exposure → NAS → Consequences*

- However, although the withdrawal is an outcome of opioid exposure, the presentation and severity of NAS is related to a number of factors that must be taken into consideration in our understanding of NAS.

Confounding the Issue of NAS is Context

- Illicit vs. appropriate use of prescribed medication
- Role of non-opioid drug exposure
- Gestational age
- Genetics
- Role of the treatment environment

Illicit vs. Appropriate Use of Treatment Medications

- Illicit opioid use:
  - Heroin, prescription misuse which may include methadone, buprenorphine, oxycodone, hydrocodone
- Appropriate opioid use:
  - Methadone and buprenorphine for the treatment of women with opioid use disorders who are pregnant
  - The use of oxycodone, hydrocodone for pain management when necessary
### Consequences of Illicit Use

- Illicit opioid use
  - Fetus subjected to repeated episodes of maternal withdrawal increasing morbidity and mortality
  - Mother may receive little/no prenatal care and have untreated medical/obstetrical complications
  - Increased risk of prematurity, morbidity and mortality

### Consequences of Use of Medication for Addiction Treatment

- The use of methadone and buprenorphine for the treatment of opioid dependent pregnant women
  - Prevents erratic maternal opioid levels and protects the fetus from repeated episodes of withdrawal
  - Associated with improved obstetrical care, increased fetal growth, and reduced fetal and neonatal mortality and morbidity
  - Supports and sustains recovery
  - Maternal dose has not been found to be related to NAS

### Contexts of NAS

- Presentation and severity of NAS is also related to:
  - Other prenatal drug exposure both illicit (cocaine), licit (alcohol, nicotine) and prescription medications (SSRI's and benzodiazepines)
  - Genetics
  - Gestational age
Non-Opioid Drugs Which May Impact NAS Severity

- Cause behaviors consistent with NAS but do not require treatment
  - Alcohol
  - Benzodiazepines
  - SSRI's
- Combined with opioid exposure can exacerbate NAS
  - Alcohol
  - Benzodiazepines
  - SSRI's
  - Nicotine

Benzodiazepines and NAS

Benzodiazepine use in methadone and buprenorphine maintained pregnant women have been found to be related to prolonged length of stay for infants requiring treatment for NAS:
- Seligman et al., 2008
- Wachman et al., 2011
- Pritham et al., 2012

SSRI's and NAS

SSRI use in pregnant women maintained on methadone or buprenorphine have been found to be related to:
- Higher peak NAS scores (Kaltenbach et al., 2012)
- Higher doses of medication for infants requiring treatment (Kaltenbach, et al., 2012; Jansson et al., 2010)
- Unrelated to length of treatment (Kaltenbach et al., 2012; Wachman et al., 2011) (Dryden et al., 2009; Seligman et al., 2008 methadone only)
Tobacco and NAS

- Heavy smoking in pregnant women maintained on methadone or buprenorphine has been found to be related to:
  - Peak NAS score and amount of time to reach peak NAS score (Choo et al., 2004)
  - Increased severity of NAS (Winklbaur et al., 2009)
  - Longer duration of treatment for methadone exposed infants but not buprenorphine exposed infants (Bakstad et al., 2009)
  - Past 30-day daily average number of cigarettes smoked related to total amount of morphine needed to treat NAS, duration of treatment, and length of hospitalization (Jones, et al., 2013)

Gestational Age and NAS

- Effect of preterm delivery on the course of NAS:
  - First reported in 1991 by Doberczak et al., who found that preterm infants born to women maintained on methadone required treatment for NAS less often and displayed less CNS symptoms compared to term infants
  - Dysart et al., 2007 found differences in NAS treatment outcomes for preterm and term infants born to methadone maintained women. Preterm infants had shorter treatment courses, required less medication and had shorter length of stay
  - Ruwanpathirana et al., 2014 reported low NAS scores and less treatment among preterm infants compared to term infants.

Genetics and NAS

- Recent work by Dr. Elisha Wachman and colleagues has been progressively examining whether genetic factors play a role in the incidence and severity of NAS and have found:
  - Among infants prenatally exposed to methadone or buprenorphine, variants in the OPRM1 and COMT genes were associated with shorter length of hospital stay and less need for treatment (Wachman et al., 2013)
  - Higher methylation levels within the OPRM1 promoter were found in infants requiring ≥2 medications to treat NAS (Wachman et al., 2014)
  - SNPs in opioid receptors and PNOC genes are associated with severity of NAS (Wachman et al., 2015)
Genetics and NAS

Emerging findings require further study but suggest that genetic factors play an important role in the presentation of NAS.

Postnatal Factors that Affect NAS

Treatment of NAS impacted by:
- Assessment protocol
- Medication used for treatment, weaning protocols
- Breastfeeding
- Treatment environment

There is significant variability in hospital policies and practices that determine both the diagnosis and treatment of NAS.

Assessment of NAS

* Lipsitz PJ (1975) A proposed narcotic withdrawal score for use with newborn infants.
* Ostrea EM (1976/1993) Infants of drug-dependent mothers

* 1998 AAP, *2012 AAP
NAS Scoring Systems

- MOTHER NAS scale (2010) A modification of the Finnegan Score (some items were removed due to overlap with other items or because they do not respond to treatment with opioids and 2 items were added).

Finnegan Scoring Tool

- Majority of NICUs in the USA use the Finnegan Score
- The Lipsitz Neonatal Drug Withdrawal Scoring System is used in some institutions but is not represented in the current literature. THE MOTHER NAS Scale is the standard instrument used in a number of clinical trials
- However the majority of those that used the Finnegan 67% used “the modified version” (Sarkar and Doun, Journal of Perinatology, 2006)
- Confusion exits regarding “the” and “a” modified Finnegan

Use of Assessment Tool

- Most important elements:
  - Use of operational definitions for items
  - Maintain high inter-rater reliability
A New Approach to Assessment

- Eat, Sleep, Console (ESC) Approach
  - Focused on infants ability to function regardless of withdrawal symptoms
  - Findings suggest infants are treated less with medication using the ESC approach compared to the Finnegan Score (Grossman et al. 2018)
  - Data very preliminary

Use of Standardized Weaning Protocols

- Recent studies have found:
  - Utilizing a standard NAS treatment and weaning protocol for either morphine or methadone reduced duration of treatment and length of hospital stay (Hall et al., Pediatrics, 2014)
  - Staff education and the use of a standardized morphine protocol reduced length of stay (Asti et al., Pediatrics, 2015)
  - Use of explicit weaning guidelines resulted in shorter duration of treatment, length of stay and lower rate of adjunctive drug therapy (Hall et al., Pediatrics, 2015)

Treatment for NAS

- Pharmacological Management
  - Paregoric
  - Tincture of opium
  - Morphine
  - Methadone
  - Phenobarbital
  - Clonidine
  - Chlorpromazine
  - Diazepam

  Pediatrics, Vol. 101 No.6 June 1998

- Very few studies compare the efficacy of different medications in the treatment of NAS
Current Recommendation

- AAP 2012
  “Limited evidence from controlled trials supports the use of morphine and methadone”
- Available efficacy evidence from controlled trials is extremely limited

Clinical Trial Data for Treatment for NAS

- Buprenorphine vs. morphine
  Double blind, double dummy RCT
  Duration of treatment significantly shorter with buprenorphine (NEJM, 2017)
- Methadone vs. morphine
  Multisite RCT, expected completion date Dec, 2017
- Clonidine vs. morphine
  Small pilot trial
  Duration of treatment significantly shorter with Clonidine

Breastfeeding and NAS

- Breastfeeding has been found to decrease NAS scores, need for treatment, length of treatment, and length of hospital stay
  (Abel-Latif et al., 2006; Pritham et al., 2012; Wachman e al., 2013, Welle-Strand et al., 2013)
- The presence of drug in breast milk is minimal and the effect is thought to be due to the interactive and comforting aspects of breastfeeding
Breastfeeding in Methadone Treated Mothers in Recovery

- Methadone detected in breast milk in very low levels
- Methadone concentrations in breast milk are unrelated to maternal methadone dose
- The amount of methadone ingested by the infant is low
- Hepatitis C is not a contraindication for breastfeeding
- Contraindications: HIV+, illicit drug use, unstable recovery

AAP 2012; McQueen et al., 2011; Jansson et al., 2007; Jansson et al., 2010

Breastfeeding in Buprenorphine Treated Mothers in Recovery

- Buprenorphine is found in breast milk 2 hours post-maternal dosing
- Concentration of buprenorphine in breast milk is low
- Amount of buprenorphine or norbuprenorphine the infant receives via breast milk is only 1%
- Most recent guidelines: “the amounts of buprenorphine in human milk are small and unlikely to have negative effects on the developing infant”

Atkinson et al., 1990; Marquet et al., 1997; Johnson, et al., 2001; Grimm et al., 2005; Lindemalm et al., 2009; Jansson et al., 2009; Müller et al., 2011

Breastfeeding and MAT

- Mothers receiving methadone or buprenorphine for the treatment of OUD who are engaged in treatment and do not have any contraindications should be encouraged and supported in breastfeeding
  - The American Society of Addiction Medicine, 2012 and 2017
  - Academy of Breastfeeding Medicine, 2009 and 2015
  - The World Health Organization 2014
Treatment Environment

- Until very recently the standard of care has been to transfer infants who require treatment for NAS to the NICU
- Recent studies suggest the need for NAS treatment is reduced when babies room-in with mothers (Abrahams et al., 2010)
- Supported by VON INICQ 2013-2015
  - Integrating mothers as partners in the care of their infants has decreased the need to treat NAS and length of hospital stay

Impact on Infant

- The well being of the infant is improved with the well being of the mother

Summary

- There are a number of factors that impact the severity of NAS including the in-utero interaction of opioids and non-opioids
- Genetic and epigenetic factors appear to play a role in the variability of NAS
- There are a number of postnatal caretaking and environmental factors that may minimize NAS
- NAS is a complex phenomenon and its use as an indicator of neonatal harm should be considered prudently
Keep a mother in mind in order for her to keep her child in mind

Meeting the needs of pregnant and parenting women with opioid use disorder includes not only medication treatment and care of the opioid exposed newborn but requires a comprehensive model of care that focuses on how we can obtain optimal outcomes for both mother and child.