

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

2019 WAPC Annual Conference

Pregnant and Parenting Women with OUD

- Often two separate 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
- This dichotomy between mother and child has become especially prevalent due to the opioid crisis
- ❖ Current focus on NAS tends to conflate appropriate maternal opioid use under the care of a physician and illicit maternal substance use, despite the fact that they have very different consequences

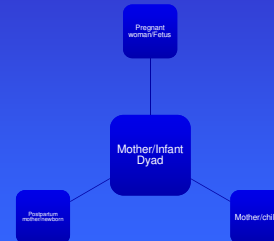
2019 WAPC Annual Conference

Pregnant and Parenting Women with OUD

- The overarching theme of this talk is that treatment for OUD needs to focus on both mother and infant in order to have optimal outcomes

2019 WAPC Annual Conference

Context



2019 WAPC Annual Conference

Outline

- Use of Medication in the Treatment of OUD
 - Methadone, buprenorphine and naltrexone
- Medication Assisted Withdrawal during Pregnancy
 - Risks and benefits
- Neonatal Abstinence Syndrome
 - Contexts and new research findings

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

Guidelines

- Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants, SAMHSA, 2018
- (*Concept of Trauma and Guidance for a Trauma Informed Approach, SAMHSA, 2014*)

All are available online

2019 WAPC Annual Conference

Medication for Addiction Treatment (MAT)

- Maternal opioid use disorder and medication for addiction treatment
- The well being of the infant is improved with the well being of the mother

2019 WAPC Annual Conference

MAT

Medication assisted 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

2019 WAPC Annual Conference

MAT

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

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

Historical Context

- The recognition of methadone as the **standard of care for pregnant women** can be traced historically in the USA through multiple federal publications:
 - Drug Dependence in Pregnancy: Clinical Management of Mother and Child, Services Research Monograph Series, NIDA, 1979
 - State Methadone Treatment Guidelines, CSAT, US DHHS, 1993
 - Effective Medical Treatment of Opiate Addiction, National Institutes of Health Consensus Development Panel, 1998

2019 WAPC Annual Conference

Historical Context

- 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 and 2018 Clinical Guidelines for Treating Pregnant and Parenting Women with OUD and Their Infants TIP 63 2018 Medications for OUD **recommend the use of methadone or buprenorphine** for pregnant women with opioid use disorder

2019 WAPC Annual Conference

Why 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

2019 WAPC Annual Conference

Methadone and Buprenorphine

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

2019 WAPC Annual Conference

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
 - ❖ Stigma

2019 WAPC Annual Conference

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 \leq 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

2019 WAPC Annual Conference

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)

2019 WAPC Annual Conference

Methadone Dose

- Dose should **NOT** be reduced during pregnancy to avoid NAS
- ❖ No clear evidence of association between that maternal dose and severity of NAS
- ❖ Non-therapeutic maternal dose may promote supplemental drug use and increase risk to fetus

2019 WAPC Annual Conference

Stigma

- Despite the overwhelming evidence of efficacy, medications for treatment of OUD are often associated with stigma
- ❖ “Substituting one drug or one addiction for another”
- ❖ “Still an addict”
- Additional stigma during pregnancy
- ❖ Think that perinatal pain meds are not needed- so patient is “drug seeking”
- ❖ Mother is “blamed” for NAS

2019 WAPC Annual Conference

Medication Assisted Treatment

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

2019 WAPC Annual Conference

Buprenorphine Induction

- Does not have 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

2019 WAPC Annual Conference

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 ≤ 30 mg 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

2019 WAPC Annual Conference

Buprenorphine During Pregnancy: Mono or Combination Product

- Initial recommendations were for mono product only (SAMHSA, 2004, 2005)
- A number of studies have recently been published that indicate it is safe to use the combination product.
- 2018 SAMHSA Clinical Guidelines
- ❖ Expert panel did not agree on whether a woman who becomes pregnant should be switched from the combination product to the mono product

2019 WAPC Annual Conference

Buprenorphine During Pregnancy: Mono or Combination Product

- 2018 SAMHSA Clinical Guidelines
- ❖ Pregnant women and their health care providers should make a decision regarding the use of the combination product based on benefit vs. risk to the dyad

2019 WAPC Annual Conference

Methadone or Buprenorphine?

- Both have benefits and disadvantages
- ↑ **Buprenorphine**: easier access to treatment, better outcomes for infant
- ↓ **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

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

Medication Assisted Withdrawal during Pregnancy

- Medication Assisted Withdrawal
- The well being of the child is improved with the well being of the mother

2019 WAPC Annual Conference

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 acute detoxification in pregnancy
- However, there were no systematic studies on whether withdrawal should only be initiated during this time period
- In 1994, study found that with monitoring, withdrawal can be conducted safely in any trimester (Jarvis and Schnoll)

2019 WAPC Annual Conference

Contemporary Data

- Several studies recently published in obstetric journals with the stated purpose to determine if withdrawal could be safely conducted
- However, end purpose is to reduce the occurrence of NAS

2019 WAPC Annual Conference

Medically Supervised Withdrawal in Pregnancy: Contemporary Data

- Dashe et al., *Obstetrics and Gynecology*, 1998
 - ❖ Small study of 34 women, safety established, **high relapse rate*** no follow up data postpartum
- Stewart et al., *American Journal of Obstetrics and Gynecology*, 2011
 - ❖ No fetal distress or demise
 - ❖ **44% relapse rate**
 - ❖ Only followed to delivery

2019 WAPC Annual Conference

Medically Supervised Withdrawal in Pregnancy: Contemporary Data

- Bell et al., *American Journal of Obstetrics and Gynecology*, 2016
 - ❖ Group 1: 108 incarcerated patients who underwent acute detoxification (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%)

2019 WAPC Annual Conference

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
 - **Places fetus at additional risk**

2019 WAPC Annual Conference

Medically Supervised Withdrawal

- Need to provide counseling and education on risk/benefits of maintenance.
- A thorough assessment is essential to determine if woman is appropriate candidate
- Should be conducted under supervision by physician accompanied by fetal monitoring

2019 WAPC Annual Conference

MAT vs. Withdrawal

- Recommendations in **support of treatment** rather than withdrawal
 - ❖ Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants, SAMHSA, 2018
 - ❖ American College of Obstetricians and Gynecologists and American Society of Addiction Medicine Joint Opinion 2017
 - ❖ WHO 2014 Guidelines
 - ❖ Treatment Improvement Protocol, US Department of Health and Human Services 2005

2019 WAPC Annual Conference

Neonatal Abstinence Syndrome

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

2019 WAPC Annual Conference

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 are directed at eliminating NAS without understanding the additional risk to the fetus
- Policies often reflect a lack of understanding of the factors that impact both the presentation and severity of NAS

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

Consequences of Illicit 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**

2019 WAPC Annual Conference

Consequences of Use of Medication for Addiction Treatment

- 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

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

Non Opioids and 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

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

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)

2019 WAPC Annual Conference

Other 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

2019 WAPC Annual Conference

Assessment

- Majority of NICUs in the USA use the Finnegan Score
- Critical issues with Finnegan score
 - ❖ Must use well defined, operational definitions for items
 - ❖ Must maintain high inter-rater reliability

2019 WAPC Annual Conference

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)

2019 WAPC Annual Conference

Treatment for NAS

- Until recently almost no research was directed at comparing the efficacy of different medications in the treatment of NAS
- Historically, used paregoric, then tincture of opium.
- 2012 AAP stated “limited evidence from controlled trials supports the use of morphine and methadone”

2019 WAPC Annual Conference

Clinical Trial Data for Treatment for NAS

- Buprenorphine vs. morphine
 - Double blind, double dummy RCT
 - Duration of treatment significantly shorter with buprenorphine (Kraft et al., *NEJM*, 2017)
- Methadone vs. morphine
 - Double blind multisite RCT
 - Length of stay shorter for methadone treated infants (Davis et al., *JAMA Pediatr*, 2018)

2019 WAPC Annual Conference

Clinical Trial Data for Treatment of NAS

- Clonidine vs. morphine
 - Small pilot trial
 - Duration of treatment significantly shorter with clonidine (Bada, et al., *Pediatrics*, 2015)
 - RCT currently being conducted (began Feb 2018, completion estimated Dec 2022)

2019 WAPC Annual Conference

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 et 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

2019 WAPC Annual Conference

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
- ❖ Academy of Breastfeeding Medicine, 2009 and 2015
- ❖ The American Society of Addiction Medicine, 2012 and 2017
- ❖ The World Health Organization 2014

2019 WAPC Annual Conference

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

2019 WAPC Annual Conference

NAS and Developmental Outcome

- NAS associated with methadone and buprenorphine treatment 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*)

2019 WAPC Annual Conference

Summary

- There are a number of factors that impact the severity of NAS including the 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 it's use as an indicator of neonatal harm should be considered cautiously

2019 WAPC Annual Conference

Keep a mother in mind in order for her to keep her child in mind

- It is essential that we focus on the mother/infant dyad if we are to **best** address the needs of mothers with opioid use disorder and her fetus, newborn and young child.

2019 WAPC Annual Conference