Treating Women for Opioid Use Disorder during Pregnancy: Methadone and Buprenorphine as a Part of a Complete Care Approach

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1. Historical context
2. Medication treatments for opioid use disorder
3. Unanswered research questions
Disclosures

- Methadone and buprenorphine have historically been labeled by the US Food and Drug Administration (FDA) as Category C for use in pregnancy for the treatment of maternal opioid dependence: “Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.”

- As of May 2016, the FDA requires methadone and buprenorphine safety labeling to include information regarding the risk of neonatal opioid withdrawal syndrome (NOWS).

- Pregnant women with opioid use disorders (OUDs) can be effectively treated with methadone or buprenorphine. However, labeling states it should be used only if the potential benefit justifies the potential risk to the fetus.

- Pregnant women with opioid use disorders can be effectively treated with methadone or buprenorphine. Both these medications should not be considered “off-label” use in the treatment of pregnant patients with opioid use disorder (Jones et al., *Am J Obstet Gynecol*, 2014).
Acknowledgements

- Study patients and infants

- National Institute on Drug Abuse
  - R01 DAs: 015764, 015738, 017513, 015778, 018410, 018417, 015741, 15832

- Maternal Opioid Treatment: Human Experimental Research (MOTHER) Site PIs and investigative teams

- Investigative teams in Chapel Hill and Michigan
Historical Context: Women

Opioid use during pregnancy in the 1800s:

• 66–75% of individuals who used opioids were women

• Opium prescriptions to treat pain and uniquely female “issues”

• Media began to link and sensationalize drug use, women and sexuality in an effort to stimulate public outrage at drug use


Historical Context: Opioids, Pregnancy, and Neonatal Withdrawal

1881: “The excessive use of this drug by one or both parents, but especially the mother, in case she is able to carry her child to full term, will modify disadvantageously the physical, mental, or moral development of the child thus born.”

1888-90s: “Congenital addiction”; delineated the syndrome of neonatal withdrawal; treat opiate-exposed infants after birth with morphine or “condition may end in death”

1903: JAMA report about “congenital morphinism” – treated infant with morphine

1965: Goodfriend et al. report neonatal withdrawal signs

1971: Zelson et al. reported frequency of signs on neonatal withdrawal in 259 of 384 infants born to drug-abusing mothers

1975: Desmond and Wilson publish Neonatal Abstinence Syndrome: Recognition and Diagnosis and Finnegan et al. publish a neonatal abstinence syndrome tool

Definition of Neonatal Abstinence Syndrome (NAS)

Neonatal Abstinence Syndrome (NAS) often results when a pregnant woman uses opioids (e.g., heroin, oxycodone) during pregnancy.

NAS defined by alterations in the:

- **Central nervous system**
  - high-pitched crying, irritability
  - exaggerated reflexes, tremors and tight muscles
  - sleep disturbances

- **Autonomic nervous system**
  - sweating, fever, yawning, and sneezing

- **Gastrointestinal distress**
  - poor feeding, vomiting and loose stools

- **Signs of respiratory distress**
  - nasal stuffiness and rapid breathing

- NAS is **not** Fetal Alcohol Syndrome (FAS)
- NAS is treatable
- NAS and treatment are not known to have long-term effects; interactions between the caregiver and child can impact resiliency/risk with potential long-term effects in some cases.

Early Methadone and Pregnancy Literature

1973 FDA said all pregnant women on methadone should undergo a 21-day detoxification

Research shows that methadone:
- Reduces maternal craving and repetitive episodes of fetal withdrawal
- When provided in the context of a comprehensive program, allows other behavior changes which decrease health risks to both mother and fetus
- Reduces the likelihood of complications with fetal development, labor, and delivery
Nearly 48,000 women died of prescription painkiller* overdoses between 1999 and 2010.

Deaths from prescription painkiller overdoses among women have increased more than 400% since 1999, compared to 265% among men.

For every woman who dies of a prescription painkiller overdose, 30 go to the emergency department for painkiller misuse or abuse.
Current Context of Substance Use during Pregnancy

National Survey on Drug Use and Health, 2015
Past Month Use

- The two most common drugs used by non-pregnant women have been alcohol and tobacco

- This same statement is true for pregnant women

Among pregnant women, approximately .2% used heroin, and 1.1% used pain relievers non-medically in the past month.
Mothers with substance use disorders have a mortality rate 8.4 times that of US women of similar age.

Pregnant women who use illicit substances may delay prenatal care and miss more healthcare visits than women who do not use substances.

Prenatal care may help to reduce the negative impact of illicit drug use on birth outcomes.

Lower prenatal care utilization may be due to a diverse set of barriers to seeking and obtaining care, including fear of child custody issues.

After childbirth, ongoing substance use disorders by caregivers and the dysfunctional home environment may create detrimental effects on children's psychological growth and development.

Maternal well-being is a key determinant of the health of the next generation.

Hser, Kagihara, Huang, Evans, & Messina, 2012; Funai et al., 2003 Staton et al., 2003 and Wagner et al., 1998; El-Mohandes et al., 2003; Roberts and Pies, 2011 and Schempf and Strobino, 2009; Chatterji and Markowitz, 2001, Clark et al., 2004, Conners et al., 2004 Hanson et al., 2006 and Linares et al., 2006
As Opioid Use Increases so does NAS

CH=substance abuse during pregnancy is considered child abuse

Targeted Program to treat SUD in pregnant women

Highest # of painkiller prescriptions/100 people

Medicaid not expanded http://familiesusa.org/sites/default/files/product_documents/MCD_Medicaid%20Expansion%2050state%20Map_infographic_02
WHO 2014 Guidelines: “Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification. Opioid maintenance treatment in this context refers to either methadone maintenance treatment or buprenorphine maintenance treatment.”

Guidance regarding maintenance versus medication-assisted withdrawal has traditionally been based largely on good clinical judgment.

Medication followed by no medication treatment has frequently been found to be unsuccessful, with relatively high attrition and a rapid return to illicit opioid use.

Maintenance medication facilitates retention of patients and reduces substance use compared to no medication.

Biggest concern with opioid agonist medication during pregnancy is the potential for occurrence of neonatal abstinence syndrome (NAS) – a treatable condition.
Maintenance v. 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 ($n=52$)

Patients in the three MM groups:
- remained in treatment longer
- had few drug 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
Most Recent Medication-Assisted Withdrawal Study

- Consistent with past literature in the ability to withdraw without obstetric complication
- Lower relapse rates than most other studies
- Lack of fetal or maternal monitoring during withdrawal
- Diagnosis of opioid dependence or use disorder was not an eligibility criterion
- Only included patients who were “fully detoxified”
- No mention of women lost to follow-up

<table>
<thead>
<tr>
<th>Number</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age, years</td>
<td>26.9 ± 3.7</td>
<td>26.4 ± 3.5</td>
<td>26.6 ± 3.6</td>
<td>27.2 ± 3.9</td>
<td>26.8 ± 3.7</td>
</tr>
<tr>
<td>Maternal age range, years</td>
<td>18–43</td>
<td>17–38</td>
<td>18–39</td>
<td>17–39</td>
<td>17–43</td>
</tr>
<tr>
<td>Maternal age &lt;30, years</td>
<td>82 (76%)</td>
<td>18 (78%)</td>
<td>55 (71%)</td>
<td>67 (72%)</td>
<td>222 (74%)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>94 (87%)</td>
<td>14 (61%)</td>
<td>54 (70%)</td>
<td>73 (78%)</td>
<td>235 (78%)</td>
</tr>
<tr>
<td>White</td>
<td>85 (79%)</td>
<td>22 (96%)</td>
<td>74 (96%)</td>
<td>84 (90%)</td>
<td>265 (88%)</td>
</tr>
<tr>
<td>African-American</td>
<td>22 (20%)</td>
<td>1 (4%)</td>
<td>3 (4%)</td>
<td>8 (9%)</td>
<td>34 (11%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational age at detoxification and NICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detoxification first trimester, 5–13 weeks’ gestation</td>
</tr>
<tr>
<td>Detoxification second trimester, 14–27 weeks’ gestation</td>
</tr>
<tr>
<td>Detoxification third trimester, ≥28 weeks’ gestation</td>
</tr>
<tr>
<td>Preterm deliveries prior to 37 weeks’ gestation</td>
</tr>
<tr>
<td>Neonatal intensive care unit admission</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Pregnancy outcome</th>
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</thead>
<tbody>
<tr>
<td>Rate of NAS</td>
</tr>
<tr>
<td>Rate of relapse</td>
</tr>
</tbody>
</table>

*One Hispanic in group 1 and one Asian in group 4

^P<.01 African American women were more likely to be Group 1 (incarcerated) than Groups 2-4

* P<.001 Group 3 had a higher rate of relapse compared to Groups 2 and 4

Medication Options

- Methadone
- Buprenorphine alone
- Buprenorphine + naloxone
MOTHER: Buprenorphine v. Methadone

Primary Outcomes

- Compared with methadone-exposed neonates, buprenorphine-exposed neonates
  - Required 89% less morphine to treat NAS
  - Spent 43% less time in the hospital
  - Spent 58% less time in the hospital being medicated for NAS

- Both medications in the context of comprehensive care produced similar maternal treatment and delivery outcomes

Notes: Significant results are encircled. Site was a blocking factor in all analyses. The O’Brien-Fleming α spending function resulted in α=0.0091 for the inferential tests of the Medication Condition effect for the 5 primary outcome measures at the conclusion of the trial.

MOTHER: Secondary Analysis Studies

- One of the goals of the MOTHER Study was to collect comprehensive data on maternal, fetal, and neonatal behavior that could be shared with the broader research community.

- An *Addiction* Supplement published collaborative MOTHER studies.

- The following slides present findings from a number of these secondary outcome studies, including:
  
  - The extent to which 32-week fetal movement and cardiac measures differ between methadone and buprenorphine before and after dosing.
  - Differences between buprenorphine- and methadone-maintained pregnant women in obstetrical and neonatal complications.
  - Liver enzymes and their relationship to buprenorphine and methadone treatment, as well as HCV status (not discussed).
  - Differences in NAS signs between medications.
  - Predicting treatment for neonatal abstinence syndrome.
  - Neonatal neurobehavioral effects following buprenorphine v. methadone exposure.
MOTHER: Fetal Outcomes

Figure 3. Non-Reactive Non-Stress Test

- Buprenorphine
- Methadone

Pre-Dose vs. Post-Dose:
- Group: p<.002
- Time: p<.001
- Group x Time: p=.21

Figure 4. Biophysical Profile Score

Pre vs. Post:
- p = .095

Salisbury et al., Addiction, 2012
MOTHER: Preterm Labor and Respiratory Distress

- In comparison to maternal buprenorphine pharmacotherapy, maternal methadone pharmacotherapy was associated with:
  - a higher incidence of preterm labor
  - a higher percentage of respiratory distress signs in neonates

Holbrook et al., Addiction, 2012
There was a significant difference between medication conditions in mean time to initiation of morphine treatment for those neonates treated for NAS, with the methadone condition requiring morphine treatment earlier than the buprenorphine condition.
Incidence of NAS signs

- All neonates in each medication condition had at least one total NAS score greater than 0 at some point during the observation period.
- Signs were observed significantly more often in the buprenorphine than in the methadone condition:
  - Sneezing
  - Loose stools
  - Nasal stuffiness
- There were no signs that were observed significantly more often in the methadone condition than in the buprenorphine condition.

### Table: N (%) of neonates who ever had a NAS score > 0

<table>
<thead>
<tr>
<th>NAS sign</th>
<th>Methadone (n = 72)</th>
<th>Buprenorphine (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbed tremors</td>
<td>72 (100%)</td>
<td>55 (97%)</td>
</tr>
<tr>
<td>Increased muscle tone</td>
<td>71 (99%)</td>
<td>57 (100%)</td>
</tr>
<tr>
<td>Sleep</td>
<td>65 (90%)</td>
<td>55 (97%)</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>62 (86%)</td>
<td>51 (90%)</td>
</tr>
<tr>
<td>Fever</td>
<td>61 (85%)</td>
<td>53 (93%)</td>
</tr>
<tr>
<td>Undisturbed tremors</td>
<td>58 (81%)</td>
<td>36 (63%)</td>
</tr>
<tr>
<td>Hyperactive Moro reflex</td>
<td>55 (76%)</td>
<td>33 (58%)</td>
</tr>
<tr>
<td>Sneezing*</td>
<td>55 (76%)</td>
<td>53 (93%)</td>
</tr>
<tr>
<td>Crying</td>
<td>40 (56%)</td>
<td>32 (56%)</td>
</tr>
<tr>
<td>Excessive irritability</td>
<td>39 (54%)</td>
<td>38 (67%)</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>39 (54%)</td>
<td>28 (49%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>38 (53%)</td>
<td>33 (58%)</td>
</tr>
<tr>
<td>Excoriation</td>
<td>34 (47%)</td>
<td>32 (56%)</td>
</tr>
<tr>
<td>Loose stools*</td>
<td>33 (46%)</td>
<td>40 (70%)</td>
</tr>
<tr>
<td>Nasal stuffiness*</td>
<td>20 (28%)</td>
<td>29 (51%)</td>
</tr>
<tr>
<td>Frequent yawning</td>
<td>15 (21%)</td>
<td>17 (30%)</td>
</tr>
<tr>
<td>Sweating</td>
<td>15 (21%)</td>
<td>12 (21%)</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>12 (17%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Generalized seizure</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

*p ≤ .02
MOTHER: Methadone v. Buprenorphine NAS Signs

Severity of NAS Signs

- Methadone-exposed neonates had higher mean NAS total score, and higher mean scores for: disturbed tremors, undisturbed tremors, hyperactive Moro reflex, excessive irritability and failure to thrive

- Buprenorphine-exposed neonates had higher mean scores on sneezing

All ps ≤ 0.04

Heil et al., Addiction, 2012
MOTHER: Neurobehavioral Functioning

- Neurobehavioral functioning improves during the first month of life for neonates exposed to opioid-agonist medication in utero (*data not shown*).

- Relative to the methadone condition, the buprenorphine condition results in superior neurobehavioral functioning on several outcomes.

All $p$s < .04

Coyle et al., *Addiction*, 2012
Ordinary least squares and Poisson regression analyses were used to test average daily number of cigarettes smoked in the past 30 days at $\alpha=0.05$, adjusting for both Medication Condition and Site. Below-average cigarette smoking was defined as 6 cigarettes/day (-1 SD), average cigarette smoking as 14 cigarettes/day (Mean), and above-average cigarette smoking as 21 cigarettes/day (+1 SD).
MOTHER Child Outcomes up to 36 months

N=96 children

• No pattern of differences in physical or behavioral development to support medication superiority

• No pattern of differences for infants treated for NAS v. infants who did not receive treatment for NAS

• Results indicate children born in the MOTHER study are following a path of normal development in terms of growth, cognitive and psychological development
# Retrospective Cohort Study of Methadone v. Buprenorphine: Newborn Outcomes

<table>
<thead>
<tr>
<th>Infant Characteristics</th>
<th>Methadone (n=248)</th>
<th>Buprenorphine (n=361)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>248</td>
<td>361</td>
<td>0.299</td>
</tr>
<tr>
<td>EGA at delivery (weeks)</td>
<td>248</td>
<td>361</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm (EGA &lt; 37 weeks)</td>
<td>248</td>
<td>361</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>248</td>
<td>361</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standardized, z score</td>
<td>248</td>
<td>361</td>
<td>0.089</td>
</tr>
<tr>
<td>&lt; 5th percentile</td>
<td>248</td>
<td>361</td>
<td>0.494</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>209</td>
<td>279</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standardized, z score</td>
<td>209</td>
<td>279</td>
<td>0.669</td>
</tr>
<tr>
<td>Treated for NAS</td>
<td>245</td>
<td>358</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days of NAS treatment</td>
<td>106</td>
<td>79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay, days (EGA ≥ 37 weeks)</td>
<td>205</td>
<td>325</td>
<td>0.107</td>
</tr>
<tr>
<td>Breast milk at discharge</td>
<td>247</td>
<td>358</td>
<td>0.003</td>
</tr>
<tr>
<td>Discharged to mother/family</td>
<td>248</td>
<td>360</td>
<td>0.189</td>
</tr>
</tbody>
</table>

EGA, estimated gestational age
Buprenorphine+Naloxone v. Buprenorphine or Methadone

Neonatal outcomes in 7 published studies: Comparing Buprenorphine+naloxone (B+N) with Buprenorphine (B), Methadone (M), and Methadone-assisted withdrawal (MAW):

• Mean head circumference was significantly higher in B+N neonates than in the MAW neonates

• Birth length for B+N neonates was shorter on average compared with B neonates, although both groups were within the normal range according to the World Health Organization (WHO) international standards of child growth

• Mean Apgar scores at 5 minutes was significantly lower in the B+N group than in the B group – with scores in the 7–10 range being considered normal

# Buprenorphine + Naloxone v. Methadone

<table>
<thead>
<tr>
<th>Neonatal Outcomes</th>
<th>Methadone (n=31)</th>
<th>Buprenorphine + Naloxone (n=31)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Treated for NAS</td>
<td>16 (51.6%)</td>
<td>8 (25.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Amount of Morphine (mg)</td>
<td>5.0 (3.3)</td>
<td>3.4 (1.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Duration of NAS treatment (days)</td>
<td>11.4 (3.4)</td>
<td>10.6 (3.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Peak NAS Score (range 1–25)</td>
<td>10.7 (3.7)</td>
<td>9.0 (4.4)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Results are given as number (%) or mean (SD)

Buprenorphine + Naloxone v. Methadone

<table>
<thead>
<tr>
<th>Neonatal Outcomes</th>
<th>Methadone</th>
<th>Buprenorphine + Naloxone</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>92</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Required NAS treatment, n (%)</td>
<td>74 (80)</td>
<td>37 (64)</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to NAS onset (days) median (range)</td>
<td>2 (1–9)</td>
<td>2 (1–6)</td>
<td>ns</td>
</tr>
<tr>
<td>Cumulative methadone dose (mg)(^a)</td>
<td>7 ± 5</td>
<td>5 ± 3</td>
<td>ns</td>
</tr>
<tr>
<td>Oral morphine equivalent (mg)(^a,b)</td>
<td>28 ± 21</td>
<td>21 ± 14</td>
<td>ns</td>
</tr>
<tr>
<td>Total NAS treatment duration (days)(^a)</td>
<td>38 ± 21</td>
<td>32 ± 21</td>
<td>ns</td>
</tr>
<tr>
<td>Required adjunctive phenobarbital, n (%)</td>
<td>5 (5)</td>
<td>4 (7)</td>
<td>ns</td>
</tr>
<tr>
<td>NAS-related hospital readmission, n (%)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>ns</td>
</tr>
</tbody>
</table>

SD, standard deviation
\(^a\)Mean ± SD
\(^b\)1 mg methadone = 4 mg morphine sulfate
NAS: Factors

Other factors that contribute to severity of NAS in neonates exposed to opioid agonists in utero:

- Genetics
- Other Substances
  - Tobacco use
  - Benzodiazepines
  - SSRIs
- Birth weight
- Hospital Protocols
  - NICU setting
  - The NAS assessment choice
  - NAS medication choice
  - Initiation and weaning protocols
  - Not breastfeeding
  - Separating mother and baby

MOTHER NAS Predictors

Receipt of NAS treatment for infants was predicted by:
- infant birthweight
- greater maternal nicotine use

Total medication dose needed to treat NAS was predicted by:
- Maternal use of SSRIs
- higher nicotine use
- fewer days of study medication received
- also predicted

Jansson and Velez, Curr Opin Pediatrics, 2012
Kaltenbach et al., Addiction, 2012
NAS: Measurement

How best to measure NAS has emerged as an important research issue:

- Secondary analysis of $N=131$ MOTHER neonatal participants
- Examined responses to the MOTHER NAS Scale (MNS)
- A five-item index proved superior to previous MNS short-form indices ($p<0.01$) and discriminated between the treated and untreated NAS groups as well as did the MNS total score ($p=0.09$)
- Secondary analysis of $N=131$ MOTHER neonatal participants
- Compared psychometric characteristics of the Finnegan Scale (FS) and the MOTHER NAS Scale (MNS)
- Both the FS and MNS demonstrated poor psychometric properties, with internal consistency (Cronbach’s alphas) failing to exceed .62 at first administration, peak NAS score, and NAS treatment initiation

Jones et al., J Opioid Manage, 2015
Jones et al., Am J Addict, 2016
Summary: MOTHER Contributions

• MOTHER provided the first large RCT to examine and confirm methadone’s efficacy for use in pregnant women with opioid use disorders
  
• Site effects were expected and controlled
  
• NAS protocol highly rigorous

• Maternal outcomes were similar between medications

• In terms of NAS severity, buprenorphine can be a front-line medication option for managing opioid-dependence for pregnant women who are new to treatment or maintained on buprenorphine pre-pregnancy

• NAS, its treatment and elucidating factors that exacerbate and minimize it, remains a significant clinical issue for prenatally opioid-exposed neonates
Specialized Care for Women is Decreasing

- Of the 13,000 facilities surveyed annually, the proportion offering women-centered services declined from 43% in 2002 to 40% in 2009 (P < .001).

- Prevalence of women with unmet need ranged from 81% to 95% across states.

- As of 2011, only 32% of all drug treatment facilities offer specialized treatment for adult women and 13% report provision of special services for pregnant and postpartum women.

- Across settings, women only programs are more likely than mixed gender programs to offer special services such as:
  - pregnancy care
  - assistance with housing
  - transportation
  - job training practical skills training
  - on-site childcare
  - child development services

Ashley et al., 2003 Brady and Ashley, 2005, Grella et al., 1999 and Hser and Niv, 2006; Terplan et al., 2015; SAMHSA, 2011 [N-SSATS report].
Examples of Unanswered Questions: Maternal

- How best to prevent OUD?
- What level of substance use is harmful to the mother, fetus and child?
- To what extent is genomics testing helpful as a component of OUD identification? If helpful, how should it be used?
- What are the best methods for supporting women with OUD who are seeking treatment?
- How can structural barriers that inhibit women from seeking, entering and/or engaging in treatment be overcome?
- How best to treat women for OUD in rural settings across all four trimesters?
- Which methods of contraception work best for which OUD women and how can they be made most accessible?
- What are the best reimbursement structures that promote access, engagement, treatment, and optimal outcomes for women with OUD and their children?

Klaman et al., under review.
Examples of Unanswered Questions: Prenatal

Medically Assisted Withdrawal

- Under what circumstances is medically assisted withdrawal appropriate for pregnant women and what medication should be used?

- What accompanying services are required to assure an optimal outcome for both mother and child?

Pain Relief

- What are the optimal pharmacological and non-pharmacological approaches to providing pain relief during pregnancy, labor and delivery, and post-partum for women receiving pharmacotherapy?
Examples of Unanswered Questions: Neonatal

Screening and Assessment of NAS

- What are the most psychometrically sound screening and assessment measures of NAS for premature, term and older infants?

- What are the best methods and tools for identifying, assessing and treating possible comorbid withdrawal from other substances such as benzodiazepines, nicotine or alcohol?

Treatment of Infants for NAS

- What is the safest, most effective protocol for using non-pharmacological NAS treatments that will also minimize the ongoing medication exposure of infants with NAS?

- Which medications should be used as first and second-line options to treat NAS and for which infants?

- What are the best protocols for dosing and weaning neonates from NAS medications?

- What are the pharmacokinetics and dynamics of NAS medications? How do they differ by medication and age of infant?
Examples of Unanswered Questions: Postnatal

Adjusting MAT AFTER delivery and feeding options

Relapses:

- What are the factors and predictors for transitioning a new mother to another medication who was stable on MAT and relapses?

Breastfeeding:

- How to best differentiate breastfeeding types and duration by OUD treatment medication?

- What are the best parameters and optimal duration for breastfeeding (expressed, supplemented with formula, standard etc.) based on OUD treatment medication?

- To what extent is breastfeeding safe while the mother is using marijuana and/or other substances?

- How best can the representation of pregnant and breastfeeding women be increased in clinical trials?
Examples of Unanswered Questions: Mother-Child Dyad

▪ What parenting and recovery supports are most beneficial to the maternal/child dyad?

▪ Which dyads will benefit from rooming in? Which dyads will benefit from outpatient treatment with medication for NAS?

▪ What in-home, early interventions or developmental assessments provide the greatest benefit to the infant?

▪ What is the safest and most effective strategy for providing ongoing NAS medication post-hospital discharge?

▪ How can SIDS and other causes of infant mortality be reduced in infants prenatally exposed to substances?

▪ To what extent does a prenatal opioid exposure environment lead to changes in fetal development and later developmental consequences?

Klaman et al., under review.
Summary

1. Historical context

2. Medication treatments for opioid use disorder

3. Unanswered research questions
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