

State of the Science on Pregnant and Parenting Women with Substance Use Disorder

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Outline

Treating substance use disorders during pregnancy and post-partum period

- 1. Historical context**
 - 2. Medication treatments for opioid use disorder**
 - 3. Behavioral treatments for opioid use disorder**
 - 4. Unanswered research questions**
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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 of Opioid Use and Women

Opioid use during pregnancy in the 1800s:

- 66–75% of opioid users were women
- Opium prescriptions to treat pain and uniquely female “issues”
- The southern United States had a larger per capita number of opioid users
- Early drug control legislation focused on immigrants and minorities and focus on white women being “lured into opium dens and corrupted”
- Media began to link and sensationalize drug use, women and sexuality in an effort to stimulate public outrage at drug use



History: 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

1975: Finnegan et al. publish a neonatal abstinence syndrome tool



Defining NAS

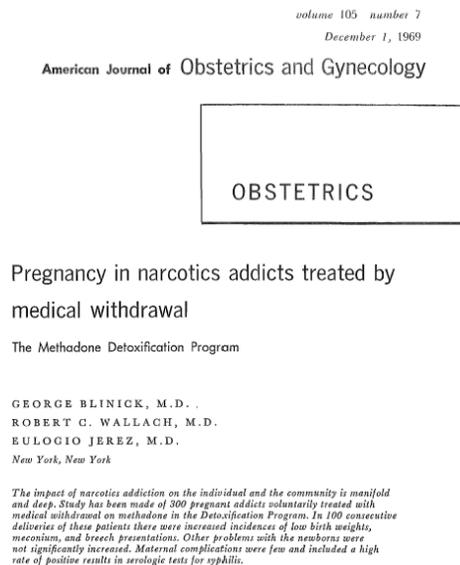
Neonatal Abstinence Syndrome (NAS) often results when a pregnant woman uses opioids (e.g., heroin, oxycodone) during pregnancy

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



Blinick G, et al., *Am J Obstet Gynecol.* 1969.

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

Zuspan. *Am J Obstet Gynecol.* 1975. et al., *Obstet Gynecol Clin North Am.* 1998.

NIDA'S Role in Supporting Research

- NIDA funded research with women in 1974
- During the 1980s sufficient evidence accumulated to suggest that the use of cocaine and other illegal drugs by pregnant women presented a major public health problem
- Research demonstration grant projects that focused on the treatment of drug-abusing pregnant and postpartum women and their drug-exposed offspring. The intent of this program was twofold: conduct treatment research and, at the same time, create many new treatment slots for the women and their children.



Perinatal-20 Treatment Research Demonstration Program projects

Current Context of Opioid Misuse in the USA for Women

Prescription Painkiller Overdoses

A growing epidemic, especially among women

July, 2013

Vital^{CDC}signs™



Nearly 48,000 women died of prescription painkiller* overdoses between 1999 and 2010.



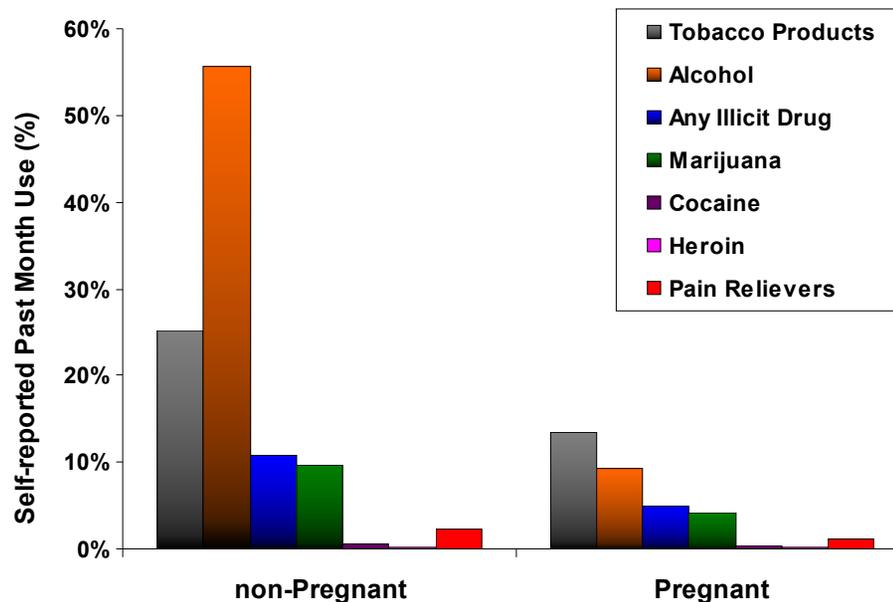
Deaths from prescription painkiller overdoses among women have increased more than 400% since 1999, compared to 265% among men.



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



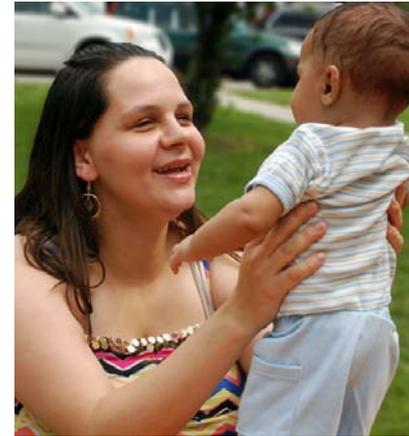
◆ The two most common drugs used by non-pregnant women have been alcohol and tobacco

◆ 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*

Pregnancy Creates A Unique Treatment Opportunity

- **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**



Screening Instruments

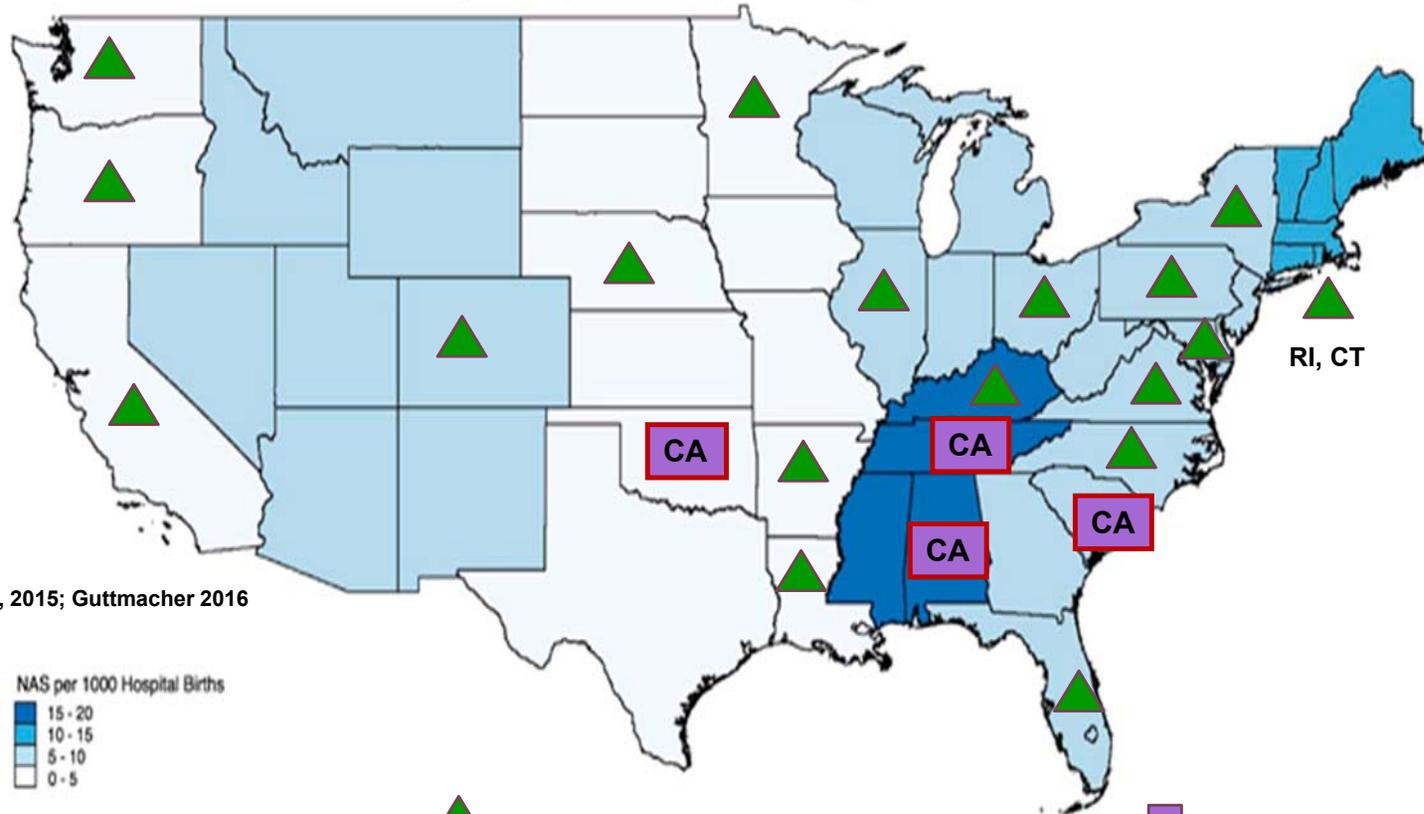
Screening Instruments for Substance Use in Prenatal or Pregnant Women							
Measure	Acronym	Substances Screened	Number of items	Method of Administration	Training in Administration Necessary	Sensitivity	Specificity
Alcohol, Smoking, and Substance Involvement Screening Test	ASSIST	Tobacco, Alcohol, and Substances	8	Interviewer	Yes	Alcohol: 67% Cannabis: 100%	Alcohol: 36% Cannabis: 20%
4P's Plus	4Ps Plus	Alcohol and General Substance Use	4	Paper-and-pencil	No	87%	76%
Substance Use Risk Profile - Pregnancy	SURP-P	Alcohol and Substances	3	Paper-and-pencil	No	†Low-risk: 80-100% High-risk: 48-100%	Low-risk: 61-64% High-risk: 84-86%
T-ACE	T-ACE	Alcohol	4	Paper-and-pencil	No	*60-91%	*37-79%
TWEAK	TWEAK	Alcohol	5	Paper-and-pencil	No	*59-92%	*64-92%

Treatment Approaches

Substance	Treatment Approaches	Comments
Tobacco	<ul style="list-style-type: none"> Nicotine Replacement Therapy (NRT): nicotine gum, transdermal nicotine patches, nicotine nasal spray, nicotine lozenge, and nicotine inhaler Bupropion Varenicline Behavioral treatments have been shown to be effective: cognitive behavioral, contingency management 5As (Ask, Advise, Assess, Assist, Arrange) as a Brief Intervention 	<ul style="list-style-type: none"> Very limited data for NRT and bupropion use in pregnancy, and no data available for varenicline, both of which are FDA pregnancy category C Voucher-based reinforcement has been proven efficacious as a behavioral treatment
Alcohol	<ul style="list-style-type: none"> Medication-assisted withdrawal from alcohol use for pregnant women frequently uses a benzodiazepine (e.g., diazepam) as pharmacotherapy Psychosocial treatment should be considered as an integral component of any withdrawal strategy 	<ul style="list-style-type: none"> Pharmacotherapy (e.g., acamprosate, naltrexone, disulfiram) should generally not be used in pregnancy due to risk to the fetus Behavioral treatments have been found to be inferior to pharmacotherapy in non-pregnant women
Cannabis	<ul style="list-style-type: none"> Behavioral treatments have been shown to be effective: cognitive behavioral, contingency management 	<ul style="list-style-type: none"> No known efficacious pharmacotherapy
Cocaine	<ul style="list-style-type: none"> Behavioral treatments have been shown to be effective: cognitive behavioral, contingency management, Motivational Interviewing 	<ul style="list-style-type: none"> No known efficacious pharmacotherapy
Amphetamines/ Methamphetamines	<ul style="list-style-type: none"> Behavioral treatments have been shown to be effective: cognitive behavioral, contingency management, Motivational Interviewing 	<ul style="list-style-type: none"> No known efficacious pharmacotherapy
Benzodiazepines	<ul style="list-style-type: none"> Gradual taper with a long-acting benzodiazepine (e.g., diazepam) with the goal of being benzodiazepine-free at birth Psychosocial treatment should be considered as an integral component of any dose reduction strategy 	<ul style="list-style-type: none"> Behavioral treatments are thought to be inferior to pharmacotherapy
Opioids	<ul style="list-style-type: none"> Opioid agonist pharmacotherapy: Methadone, Buprenorphine Opioid antagonist pharmacotherapy: naltrexone Medication-assisted withdrawal (detoxification) 	<ul style="list-style-type: none"> Medication-assisted withdrawal has a known high failure and may only be appropriate in certain cases Behavioral treatments have been found to be inferior to pharmacotherapy

As Opioid Use Increases so does NAS

Neonatal Abstinence Syndrome per 1000 Hospital Births by US Census Division, 2012



Patrick et al, J of Perinatology, 2015; Guttmacher 2016

NAS per 1000 Hospital Births
 15 - 20
 10 - 15
 5 - 10
 0 - 5

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

Specialized Care for Women Works

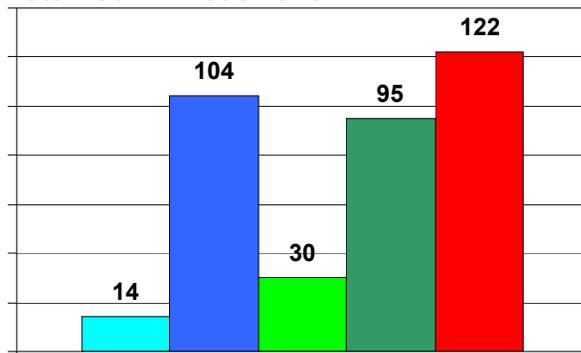
- End-of-treatment outcomes between women-only and women receiving non-gender-specific treatment are mixed
- One-year post-treatment outcomes show that women treated in women only programs have better drug outcomes and some improved criminal justice outcomes
- Ten years post-treatment, 48.4% of the women had a successful outcome. More women-only than non-gender-specific treatment women had a successful outcome (50.0% vs. 46.6%, $\chi^2 = .35$) but this difference was not statistically significant
- Of women treated in women only programs:
 - 63.6% had not used drugs
 - 91.5% had not engaged in criminal justice activity
 - 93.3% were alive
- Women only vs. mixed gender treatment increased the odds of successful outcome by 44%
- Women-only treatment was associated with fewer post-treatment arrests, which was associated with better outcomes

Medication Assisted Treatment v. Medication-Assisted Withdrawal

- **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

Days Retained in Treatment



Urine-positive Drug Screen Percentage at Delivery

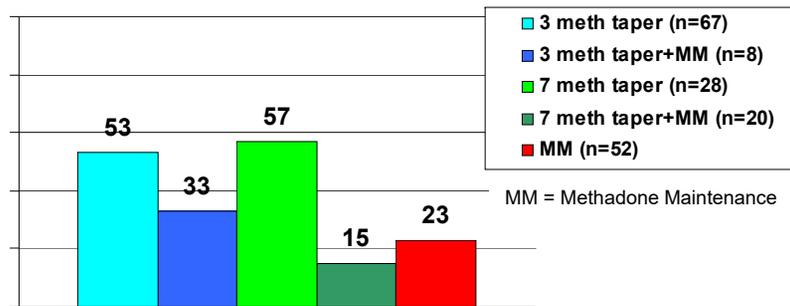


Chart review of 5 groups of patients:

- 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

	Group 1	Group 2	Group 3	Group 4	Total
Number	108	23	77	93	301
Mean maternal age, years	26.9 ± 3.7	26.4 ± 3.5	26.6 ± 3.6	27.2 ± 3.9	26.8 ± 3.7
Maternal age range, years	18–43	17–38	18–39	17–39	17–43
Maternal age <30, years	82 (76%)	18 (78%)	55 (71%)	67 (72%)	222 (74%)
Multiparity	94 (87%)	14 (61%)	54 (70%)	73 (78%)	235 (78%)
White	85 (79%) ^a	22 (96%)	74 (96%)	84 (90%) ^a	265 (88%)
African-American	22 (20%) [^]	1 (4%)	3 (4%)	8 (9%)	34 (11%)
Gestational age at detoxification and NICU admission					
Detoxification first trimester, 5–13 weeks' gestation	10 (9%)	4 (17%)	12 (15%)	2 (2%)	28 (9%)
Detoxification second trimester, 14–27 weeks' gestation	65 (60%)	10 (43%)	36 (47%)	37 (40%)	148 (49%)
Detoxification third trimester, ≥28 weeks' gestation	33 (31%)	9 (39%)	29 (38%)	54 (58%)	125 (42%)
Preterm deliveries prior to 37 weeks' gestation	21 (19%)	3 (13%)	13 (17%)	16 (17%)	53 (17.6%)
Neonatal intensive care unit admission	32 (30%)	5 (22%)	60 (78%)	22 (24%)	119 (40%)
Pregnancy outcome					
Rate of NAS	20 (18.5%)	4 (17.4%)	54 (70.1%)	16 (17.2%)	94 (31%)
Rate of relapse	25 (23.1%)	4 (17.4%)	57 (74.0%)*	57 (22.5%)	107 (36%)

^a 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

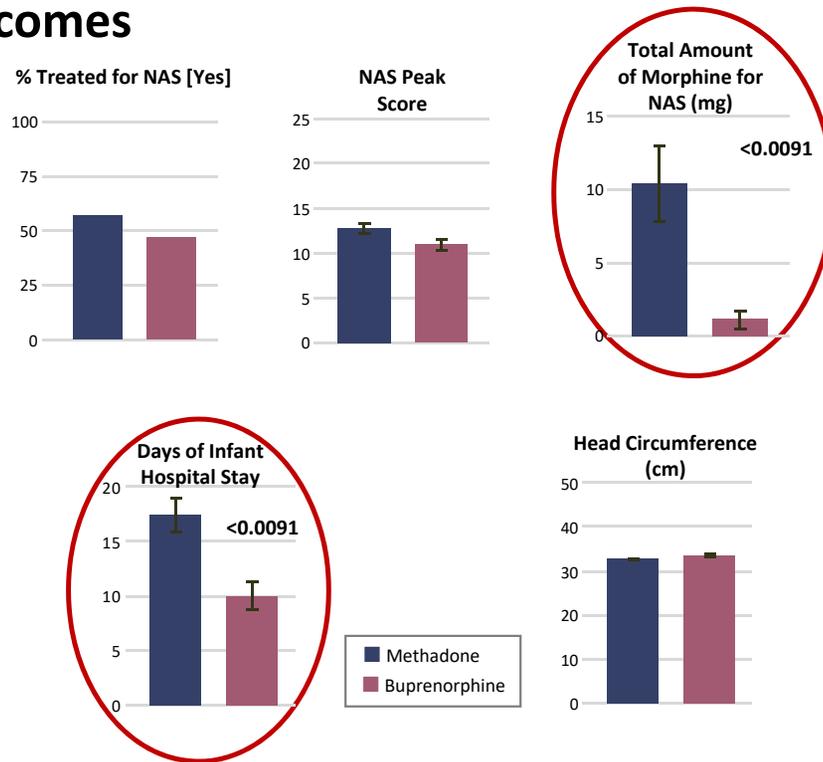
- Consistent with past literature in the ability to withdraw without obstetric complication
- Lower relapse rates than most other studies
- Lack of fetal or maternal monitoring during withdrawal
- Diagnosis of opioid dependence or use disorder was not an eligibility criterion
- Only included patients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

Medication Options

- Methadone
 - Buprenorphine alone
 - Buprenorphine + naloxone
- 

MOTHER: Buprenorphine v. Methadone

Primary Outcomes



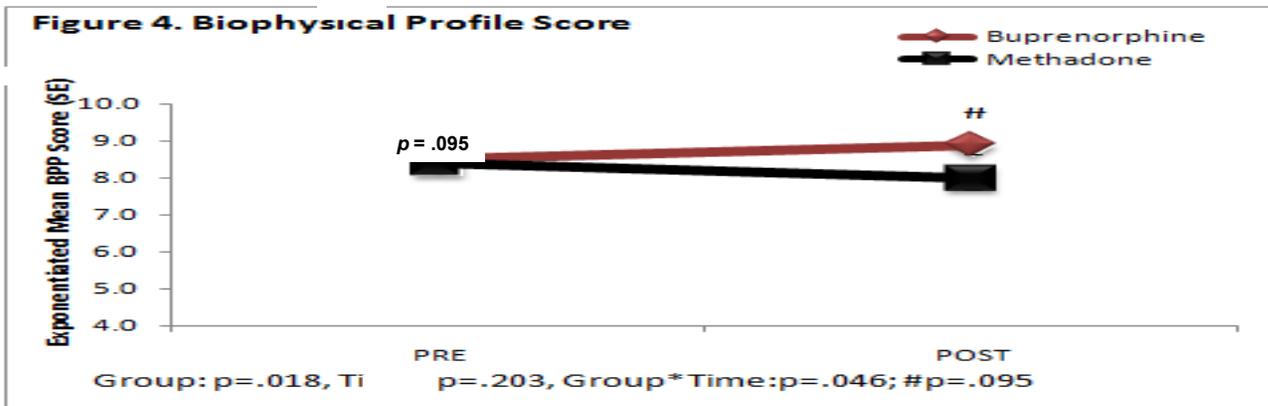
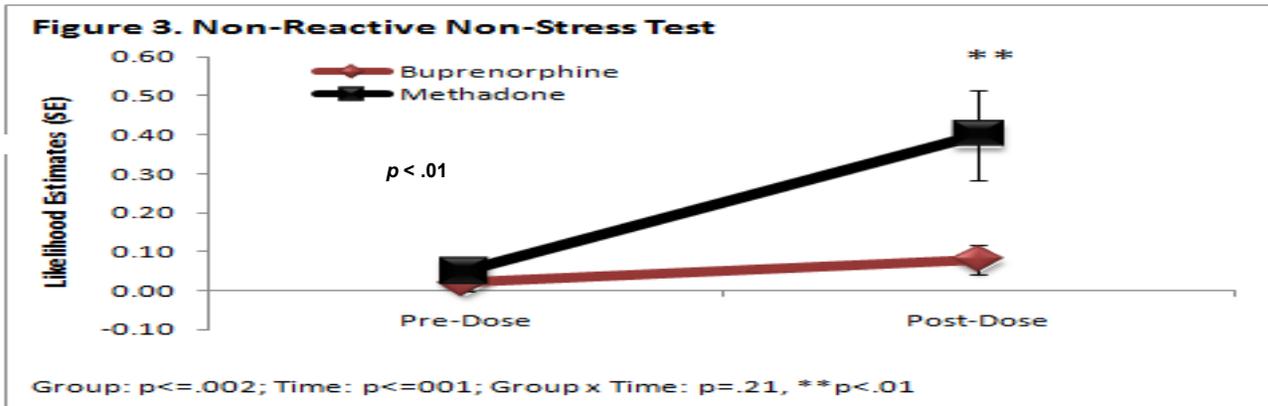
Notes: Significant results are encircled. Site was a blocking factor in all analyses. The O'Brien-Fleming α spending function resulted in $\alpha=0.0091$ for the inferential tests of the Medication Condition effect for the 5 primary outcome measures at the conclusion of the trial.

- 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

MOTHER: Secondary Analysis Studies

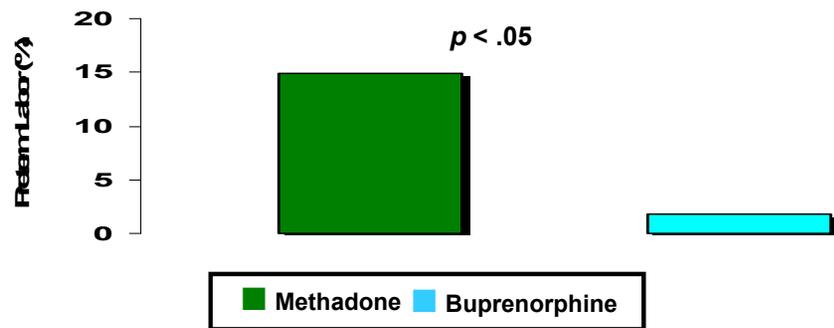
- One of the goals of the MOTHER Study was to collect comprehensive data on maternal, fetal, and neonatal behavior that could be shared with the broader research community
- An *Addiction* Supplement published collaborative MOTHER studies
- The following slides present findings from a number of these 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



MOTHER: Preterm Labor and Respiratory Distress

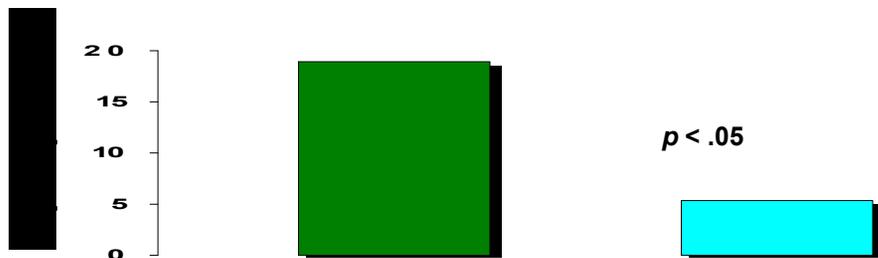
Incidence of Preterm Labor
in the Two Medication Conditions



- In comparison to maternal buprenorphine pharmacotherapy, maternal methadone pharmacotherapy was associated with:

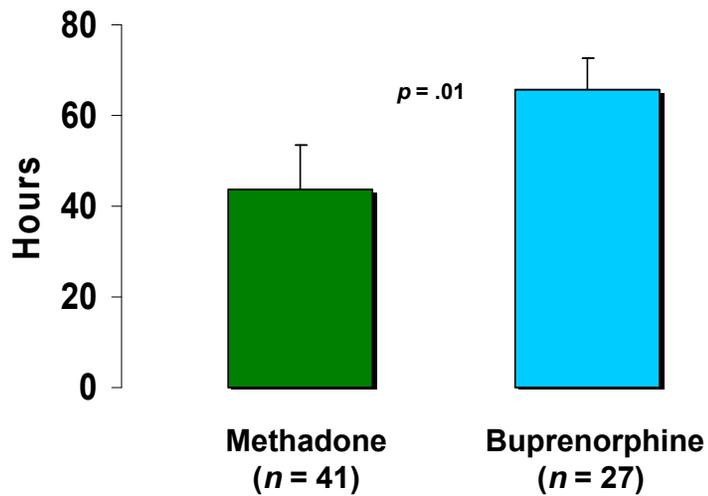
- ♦ a higher incidence of preterm labor
- ♦ a higher percentage of respiratory distress signs in neonates

Incidence of Respiratory Distress
Signs in the Two Medication
Conditions



MOTHER: Time to Start Morphine

Time to Morphine Treatment Initiation



- 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

MOTHER: Methadone v. Buprenorphine NAS

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

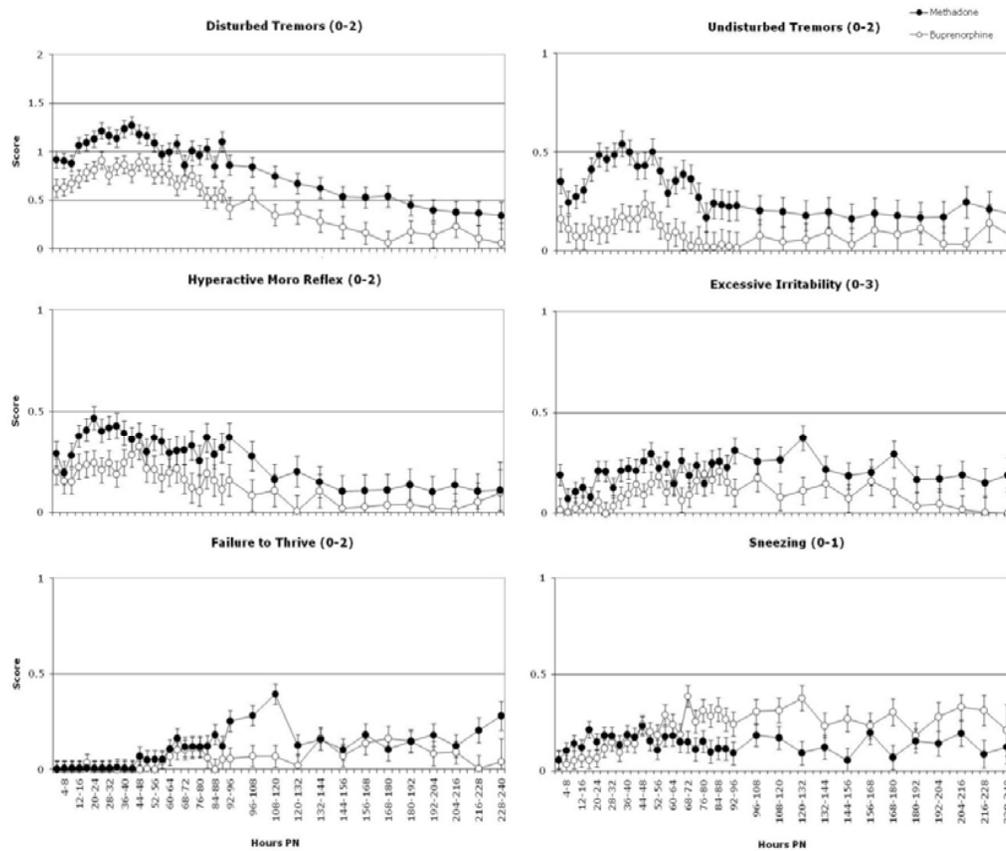
NAS sign	Methadone (n = 72)	Buprenorphine (n = 57)
NAS Total score	72 (100%)	57 (100%)
Disturbed tremors	72 (100%)	55 (97%)
Increased muscle tone	71 (99%)	57 (100%)
Sleep	65 (90%)	55 (97%)
Tachypnea	62 (86%)	51 (90%)
Fever	61 (85%)	53 (93%)
Undisturbed tremors	58 (81%)	36 (63%)
Hyperactive Moro reflex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

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

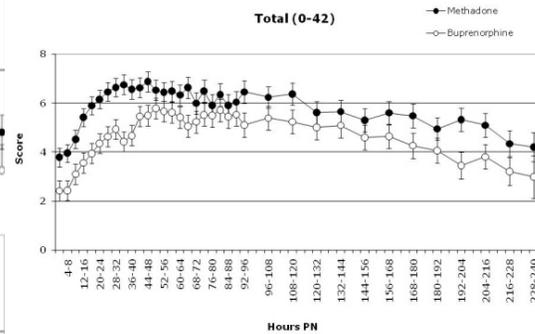
* $p \leq .02$

MOTHER: Methadone v. Buprenorphine NAS Signs



Severity of NAS Signs

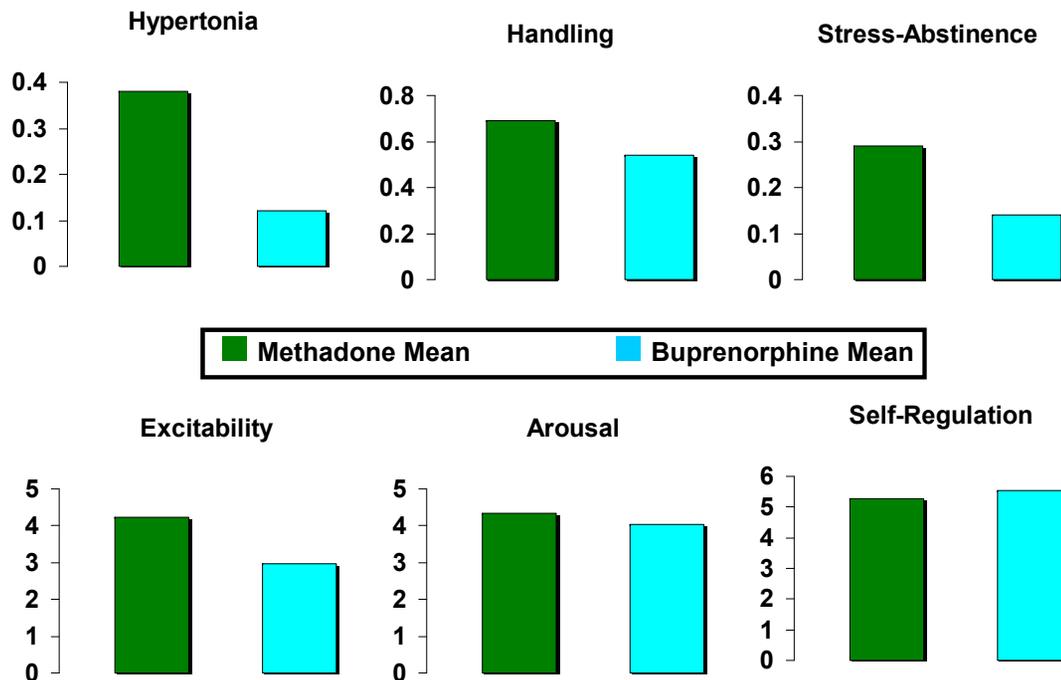
- Methadone-exposed neonates had higher mean NAS total score, and higher mean scores for: disturbed tremors, undisturbed tremors, hyperactive Moro reflex, excessive irritability and failure to thrive



- Buprenorphine-exposed neonates had higher mean scores on sneezing

All $ps \leq 0.04$

MOTHER: Neurobehavioral Functioning

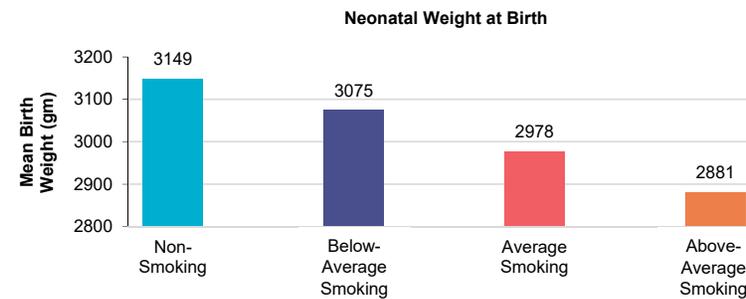
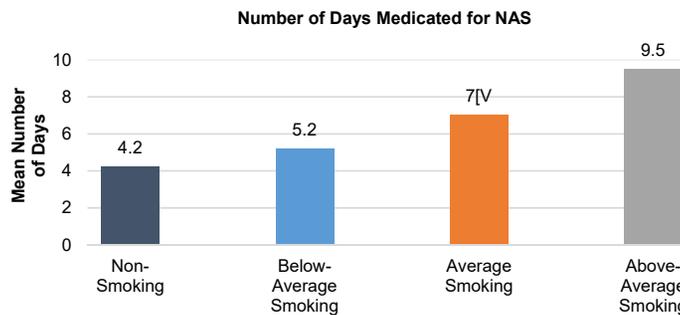
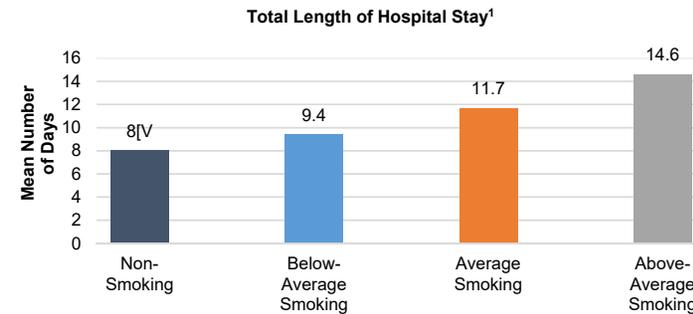
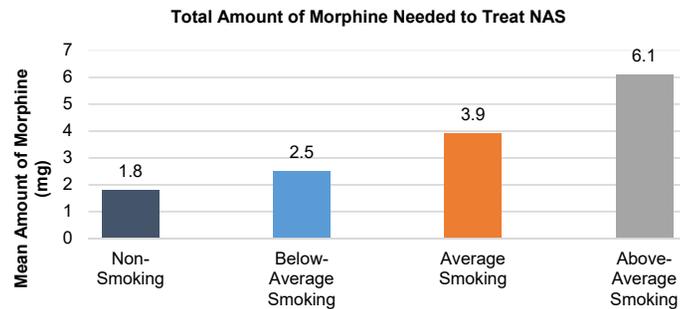


- Neurobehavioral functioning improves during the first month of life for neonates exposed to opioid-agonist medication in utero (*data not shown*)

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

All $ps < .04$

MOTHER: Smoking and NAS



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

Infant Characteristics	Methadone (n=248)		Buprenorphine (n=361)		p-Value
	n	M (SD) or n (%)	n	M (SD) or n (%)	
Male	248	111 (45%)	361	177 (49%)	0.299
EGA at delivery (weeks)	248	38.2 (2.5)	361	39.2 (2.2)	<0.001
Preterm (EGA < 37 weeks)	248	43 (17%)	361	36 (10%)	<0.001
Birth weight (grams)	248	2899.7(583.1)	361	3143.3 (578.9)	<0.001
Standardized, z score	248	-0.59 (.93)	361	-0.46 (.98)	0.089
< 5th percentile	248	32 (13%)	361	40 (11%)	0.494
Head circumference (cm)	209	33.0 (2.0)	279	33.6 (2.1)	<0.001
Standardized, z score	209	-.50 (.80)	279	-0.46 (.98)	0.669
Treated for NAS	245	106 (42%)	358	82 (23%)	<0.001
Days of NAS treatment	106	133 ± 83	79	83 ± 60	<0.001
Length of stay, days (EGA ≥ 37 weeks)	205	5.6 (2.8)	325	4.2 (12.6)	0.107
Breast milk at discharge	247	156 (63%)	358	267 (75%)	0.003
Discharged to mother/family	248	237 (96%)	360	351 (98%)	0.189

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

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

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

Buprenorphine + Naloxone v. Methadone

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

SD, standard deviation

^aMean ± SD

^b1 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

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

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

Unanswered Questions: Maternal

Substance Use and Use Disorders

- What level of substance use is harmful to the mother, fetus and child?
- What are the best methods for detecting emerging trends in substance use and prenatal exposure to substances?
- To what extent is genomics testing helpful as a component of OUD identification? If found to be 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?
- How best to prevent OUD?
- What are the unique factors and effective program elements for women?
- Which methods of contraception work best for which women with OUD (considering the likelihood of trauma history) and how can they be made most accessible ?
- Which behavioral interventions (such as contingency management) are most effective for pregnant and parenting women with OUD?
- What internal and external factors explain differences in effectiveness (e.g., type of pharmacotherapy or other maternal or community variables)?
- To what extent can contingency management be implemented in clinical settings to help women across all four trimesters improve outcomes?
- What are the most cost-effective ways to provide care for women with OUD that will lead to optimal outcomes for both mother and child?
- What are the best reimbursement structures that promote access, engagement, treatment, and optimal outcomes for women with OUD and their children?

Unanswered Questions: Maternal

For Co-occurring Health and Social Issues

- **What are the best methods to ensure universal Hepatitis C and HIV screening and treatment for pregnant women with OUD?**
- **What are the best methods to identify and address social determinants of health in pregnant and parenting women with OUD?**
- **To what extent does tobacco influence outcomes for mother, fetus and child in women receiving MAT across all four trimesters?**
- **How best to treat comorbid conditions including alcohol, benzodiazepine, stimulant, and marijuana use disorders, as well as tobacco use, depression, anxiety, PTSD, HIV, HEP C, and STIs in pregnant women with OUD?**
- **What is the relative contribution of multiple risk factors to adverse outcomes?**
- **What are the resilience factors most likely to improve these outcomes?**

Unanswered Questions: Maternal

Screenings

- **What are most optimal screening tools and procedures to identify other types of substance use disorders (SUD) in pregnant women with OUD?**
- **How best to treat women of different ages with SUD, and women who become pregnant while being treated with opioids for pain?**
- **What are the most effective tools and procedures for screening for OUD and other health and social issues in integrated care?**

Unanswered Questions: Maternal

Medication Selection, Induction and Dose Adjustments

- How should the optimal opioid agonist therapy be selected for pregnant and parenting women?
- What patient and community variables should be considered?
- Which opioid treatment regimen works best for pregnant patients using prescription opioids or heroin?
- What are the best methods for induction onto buprenorphine during pregnancy?
- What are the best methods for induction an optimal dose of methadone during pregnancy?
- To what extent does fetal stress during induction occur? What are the implications of such stress for the child?
- What are the best strategies for maintaining a safe, effective medication dose over the course of a patient's pregnancy, post-partum period, and while breastfeeding?
- To what extent is naltrexone safe and effective for OUD for the mother, fetus, and child?
- Under what circumstances would transition from one form of medication to another be beneficial to the mother, fetus, and child?
- What is the relative safety and efficacy of buprenorphine/naloxone v. buprenorphine mono-product or methadone during pregnancy?
- What is the risk/benefit of transferring a woman from buprenorphine/naloxone to another opioid agonist due to pregnancy? How should such a transition be accomplished)?

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?

Unanswered Questions: Neonatal

Screening for the presence of prenatal exposure to substances

- **What are the best biological matrices and analytical methods required to accurately determine neonatal exposure to opioids and other substances?**
- **What are the best protocols to support the mother-child dyad and ensure the safety of child and mother?**
- **What are the best strategies to help women navigate legal issues and ensure appropriate consent occurs?**
- **What is the extent and impact of poly-substance use on opioid exposure in pregnancy and NAS? In particular, what are the long-term effects of prenatal exposure to opioids, as compared to exposure to other substances or pharmaceuticals? Such research needs to be carefully controlled for social, familial, and environmental risk and protective factors encountered during childhood.**

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?**
- **What degree (amount and timing) of exposure to prescription opioids for pain should be considered a risk for NAS?**

Unanswered Questions: Neonatal

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-line therapy or, considered second-line options for the treatment of 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?**
- **What are the effects of co-occurring exposures to substances such as alcohol and other stressors on NAS severity?**
- **To what extent do maternal or infant factors alone or in combination exacerbate and mitigate NAS and its severity (such as to, tobacco use, prematurity and genetics)**
- **What are the most cost-effective ways that will produce the best outcomes and care for infants with NAS?**

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?**

Unanswered Questions: Mother-Child Dyad

- **What parenting and recovery supports are most beneficial to the maternal/child dyad? What family, maternal, child, or community variables need to be considered? What is the optimal frequency and duration of delivery for such services? What is the optimal role of peer support services?**
- **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 family, maternal, child, or community variables need to be considered? What is the optimal frequency and duration of delivery for such services?**
- **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?**



There is no such thing as
a baby, there is a baby
and someone

Donald Woods Winnicott



UNC Horizons

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