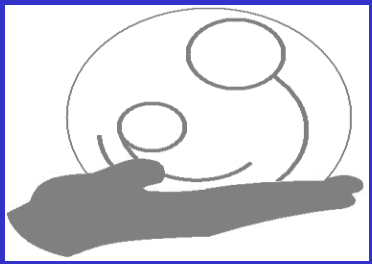
Neonatal and Maternal Outcomes from the MOTHER Study: A Randomized, Double-Blind, International Clinical Trial Comparing Methadone and Buprenorphine during Pregnancy



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Acknowledgments

- NIDA
- Site PIs, Collaborators and staff
- Reckitt Benckiser Inc. for active and placebo Subutex tablets
- Mother and child participants

Outline

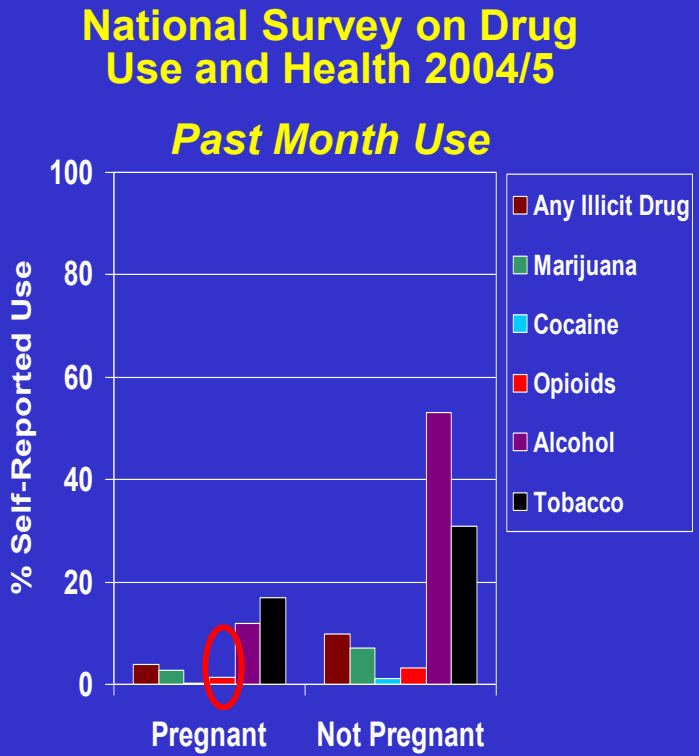
I. Background

II. Design & Procedures

III. Results

IV. Discussion & Implications

MOTHER Background



- Although fewer pregnant women use illicit drugs than licit drugs, the women who use them receive extraordinary scrutiny by society
- Drug addiction almost always begins before pregnancy and in the context of past and current exposure to factors that lead to increased vulnerability

MOTHER Background

- **Untreated maternal opioid addiction is associated with adverse medical and environmental circumstances that can negatively impact birth outcomes**
- **Stabilization on methadone is associated with better prenatal care compliance and birth outcomes**

MOTHER Background
Neonatal Abstinence Syndrome (NAS)

- **Neurologic excitability**
  hyperactivity, irritability, sleep disturbance
- **Gastrointestinal dysfunction**
  uncoordinated sucking/ swallowing, vomiting
- **Autonomic Signs**
  fever, sweating, nasal stuffiness

Finnegan et al., 1975; Finnegan & Kaltenbach, 1992

MOTHER Background

- Associated methadone withdrawal in the neonate can pose a clinical challenge
- Buprenorphine reported to produce less physical dependence in adults

Methadone

MOTHER Background

Since 1995, over 35 published reports of prenatal exposure to buprenorphine maintenance

Over 700 babies prenatally exposed to buprenorphine (number of cases per report ranged from 1 to 159; *Median*=17)

61% babies with NAS signs/symptoms
49% requiring treatment

MOTHER Background *PROMISE* Study Results

(Jones et al., 2005)

	Methadone *n*=11	Buprenorphine *n*=10 (1 set of twins)
% Treated for NAS	45.5	20.0
Morphine Drops	93.1	23.6
Birth Weight (gm)	3001.8	3530.4
Neonatal LOS	*8.1*	*6.8**
% NICU treatment	18.0	10.0
APGAR at 1minute	8.3	8.1
APGAR at 5 minutes	8.9	8.7
Length (cm)	49.6	52.8
Head Circum. (cm)	33.2	34.9

* p=.021

MOTHER Background
Current Research

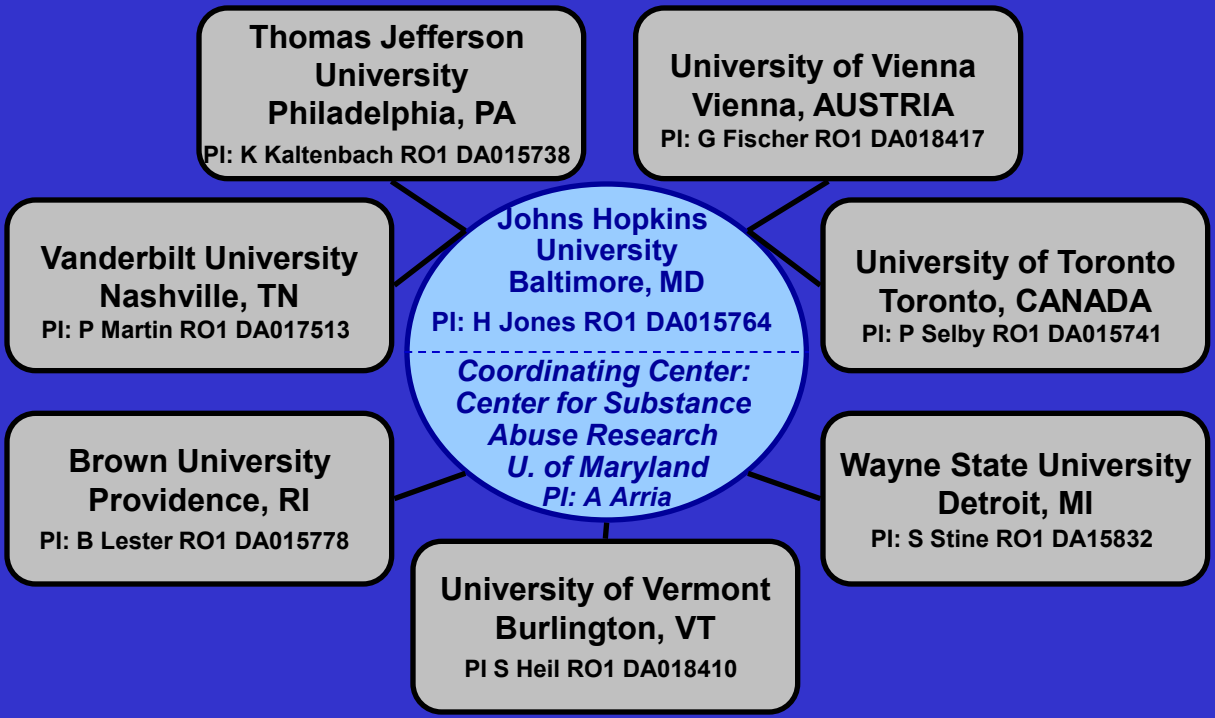
- PROMISE study combined with double-blind RCT in Vienna (Fischer et al., 2006) provided preliminary data

- The advancement of treatment research for opioid-dependent pregnant women may be best served through a multi-site international network able to conduct randomized controlled trials

MOTHER Objective

Evaluate the possible differential impact of buprenorphine and methadone, given to opioid-dependent pregnant women, on both neonatal and maternal outcomes

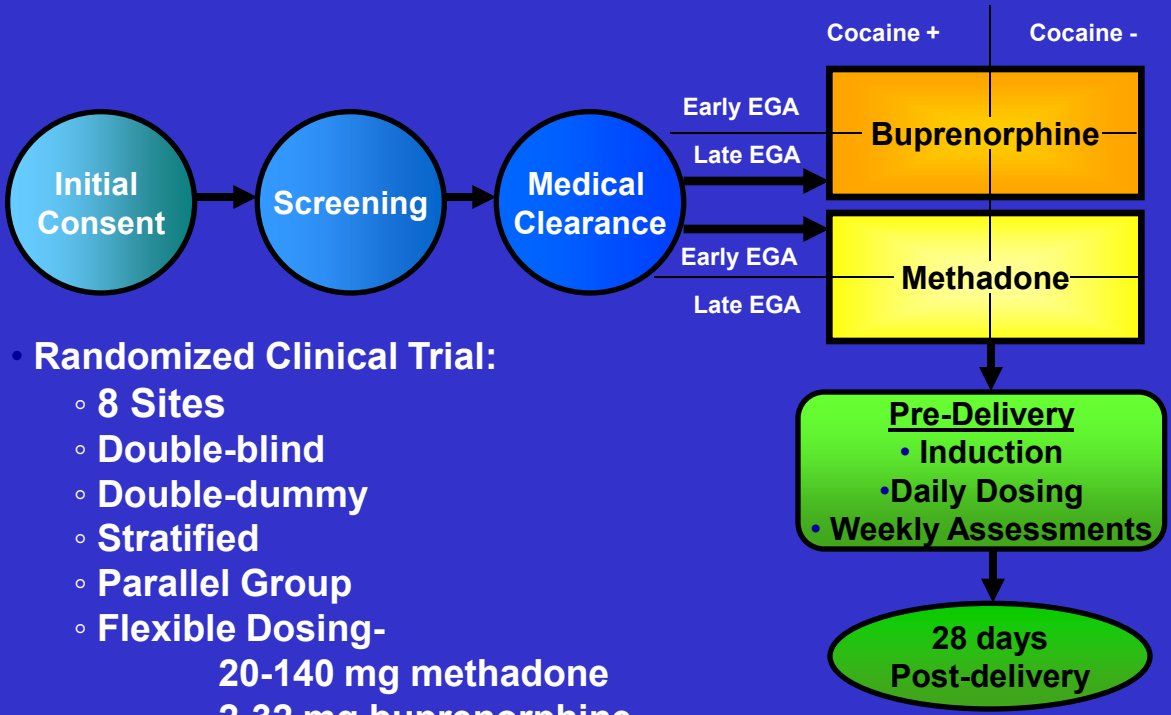
MOTHER Design
Study Clinical Sites



MOTHER Experimental Design Eligibility

- 18-40 years of age
- Gestational age 6-30 weeks
- Opioid-dependent (DSM-IV, SCID I)
- Opioid-positive urine
- Single-fetus pregnancy
- Plan to deliver at site hospital

MOTHER Experimental Design



- Randomized Clinical Trial:
  - 8 Sites
  - Double-blind
  - Double-dummy
  - Stratified
  - Parallel Group
  - Flexible Dosing-
    20-140 mg methadone
    2-32 mg buprenorphine

MOTHER Experimental Design Comprehensive Care

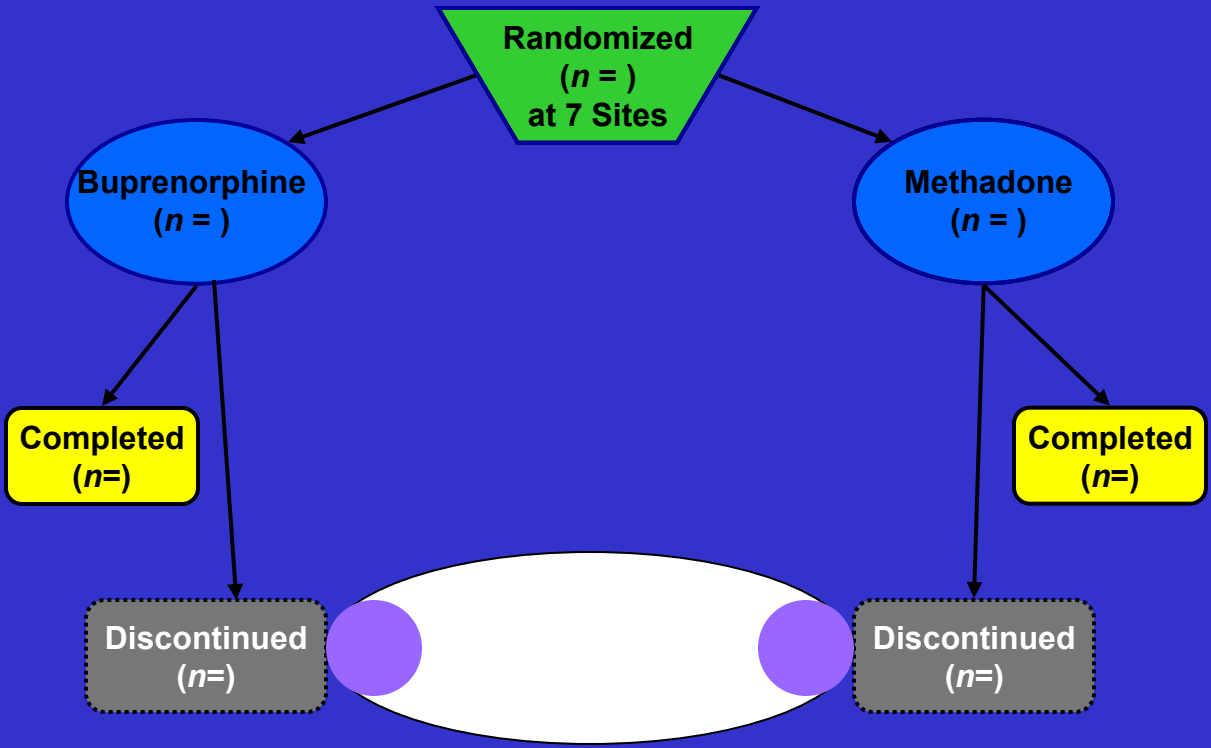
- Vouchers contingent upon drug-negative biological samples
- Vouchers contingent upon compliance with treatment
- Counseling
- Medical care
- Obstetric services

MOTHER Experimental Design Outcome Measures

Primary Outcomes

- Treated for NAS
- NAS peak score
- Total amount of morphine for NAS
- Days of infant hospital stay
- Head circumference

CONSORT Diagram



Concomitant Variables

For both primary and secondary neonatal outcomes:

- **7 variables reflecting mother's treatment compliance and drug use during the study**

For secondary maternal outcomes:

- **8 variables reflecting mother's treatment history**

► Inclusion of concomitant variables in the analyses made no difference in the Medication Condition results

Statistical Analyses Notes

- Site was a blocking factor for all analyses

- Bonferroni's principle was used to set familywise α=.0045 for the separate comparisons of baseline characteristics (nominal α=.05/11 in each case, respectively).

- An interim analysis requested by the Data Safety and Monitoring Board resulted in a recalculation of the final α based on the O'Brien-Fleming spending function, such that the end-of-trial α was .0091 for each primary outcome measure.

- Bonferroni's principle was likewise used to set familywise α=.003125 (nominal α=.05/16) for the secondary outcomes.

MOTHER Results Baseline Characteristics: Completers

Data shown at meeting

MOTHER Results

Data shown at meeting

MOTHER Results

Data shown at meeting

MOTHER Results

Data shown at meeting

Urine Results over Time

Data shown at meeting

Adverse Events

Data shown at meeting

Blind Protected

Data shown at meeting

Primary Outcome Results Summary

Data shown at meeting

Additional Results
Fetal Parameters: 24/28 weeks

	Methadone (n=8) M(SD)	Buprenorphine (n=4) M(SD)	Z
	n = 8	n = 4	
FHR (bpm)	139.11 (5.51)	136.10 (7.77)	-0.85
FHR variability	*3.69 (1.01)*	*5.05 (1.04)*	*-2.06**
Accelerations	*0.00 (0)*	*1.25 (1.89)*	*-2.09**
Motor activity	4.80 (1.45)	5.95 (.79)	-1.36
FM duration	16.07 (4.72)	27.46 (14.91)	-1.87
FHR-FM coupling(%)	*7.64 (6.49)*	*18.78 (9.26)*	*-2.04**

*p < .05. (Jansson et al., 2010)

Additional Results
Fetal Assessment: 32/36 weeks

	Methadone M(SD) n = 6	Buprenorphine M(SD) n = 5	Z
FHR (bpm)	133.42 (7.89)	134.58 (7.12)	-0.18
FHR variability	4.43 (0.78)	5.30 (2.16)	-0.37
Accelerations	1.17 (1.17)	2.80 (3.83)	0
Motor activity	*3.58 (1.18)*	*5.92 (2.95)*	*-2.01**
FM duration	*8.74 (2.71)*	*21.53 (13.22)*	*-2.01**
FHR-FM coupling(%)	27.42 (13.97)	18.88 (6.90)	-1.10

*p < .05. (Jansson et al., 2010)

Fetal Assessment Results Summary

Buprenorphine exposure relative to methadone exposure led to:

- Earlier (24/28 weeks)
  - higher levels of FHR variability
  - more accelerations in FHR
  - greater FM-FHR coupling
- Later (32/36 weeks)
  - More motor activity
  - Longer movements

Summary

- It is feasible to conduct multi-center randomized controlled trial examining medications to treat chronic illnesses like opioid dependence in pregnant women
- In terms of NAS severity, buprenorphine should be a front-line medication option for managing opioid-dependence for pregnant women
- Having more medications given in the context of comprehensive services to treat opioid-dependent pregnant women will optimize care

Discussion

- Rich array of prospective data collected
- Screening and during pregnancy course
  - Ultrasound, OB and medical data
  - Chemistry and blood tests
  - Objective drug use (licit and illicit)
  - Psychiatric and life function
  - Concomitant Medication
  - Retention in treatment
- Fetal and delivery measures
- Neonatal course and outcomes

Discussion

- Secondary outcomes answering questions:

Maternal

- Medical and obstetrical characteristics
- Co-occurring psychiatric symptoms, treatment efficacy, and retention
- Concomitant cocaine use

Neonatal

- Predicting treatment for neonatal abstinence syndrome
- Comparison of individual signs of neonatal abstinence syndrome between methadone vs. buprenorphine-exposed neonates
- Neonatal neurobehavioral effects following buprenorphine vs. methadone exposure

Discussion

- The significant clinical difference in NAS will require that buprenorphine be offered as first line medication in the management of opioid dependence during pregnancy

- The use of methadone during pregnancy will be required for those patients in which buprenorphine is not effective

Implications

- Methadone maintenance has been the recommended standard of care for pregnant opioid dependent women
- Initial research in the late 1970's suggested a relationship between maternal methadone dose and severity of withdrawal
- The concern of NAS has led to significant resistance to the use of methadone in pregnancy and/or sub-therapeutic dosing

Implications

- Research findings over the past 30 years investigating the relationship between maternal methadone dose and severity of withdrawal are contradictory
- There is no compelling evidence to reduce maternal dose to avoid NAS
- There is evidence that higher doses are associated with less illicit drug use and that reducing maternal dose may increase risk to both mother and fetus

Implications

- Despite substantial evidence to the contrary, this has been an extremely difficult obstacle to overcome

- It has only been within the last 10 years that medicating pregnant opioid dependent women appropriately in accordance with the same principles as non-pregnant patients has become the norm

Implications

- However, the concern regarding NAS is still at the forefront
- Findings from the MOTHER study will have a major impact on the field

Challenges to the Field

- Treatment programs are expected to utilize evidence based practiced
- In the USA, treatment programs may have only limited ability to provide buprenorphine to their patients
- Cost/reimbursement within the public sector
- Buprenorphine is not approved by the FDA for use in pregnancy

Challenges to the Field

- Practitioners have little experience inducting pregnant women onto buprenorphine
- Practitioners may be reluctant to continue prescribing buprenorphine during pregnancy
- No data available to inform determination of patients who should be maintained on methadone rather than buprenorphine
- Comprehensive integrated services vs. office based medication

Challenges to the Field

- Increased pressure may come from:
  - Policy and regulatory bodies
  - Criminal justice system
  - Child protective services
  - Insurance companies

Conclusion

- The MOTHER study indicates that buprenorphine and methadone are both effective in the treatment of opioid dependence during pregnancy
- Given buprenorphine's benefits for the neonate it should be considered as a front line treatment option
- Must recognize that buprenorphine is not appropriate for all patients and that a subgroup of pregnant women will require methadone
- The primary consideration must always be what is best for the mother and child

Discussion
Unanswered Questions

- What is the best induction procedure for pregnant women onto buprenorphine?
- What is maternal and infant safety and efficacy of Suboxone exposure during pregnancy?
- In what ways does the maternal and infant safety and efficacy of methadone and buprenorphine change in the presence of co-morbid alcohol and/or benzodiazepine exposure?

My Team……My Heart

The End