Place of Possible Therapeutic Choice in the Treatment of Opioid-Dependent Pregnant Patients: What's Up with the International, Prospective, Double-Blind, Multi-Center Trial funded by NIDA?

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Introduction

Opioid-dependence during pregnancy often occurs in the context of complex psychosocial issues. If left untreated, this illness can have devastating consequences for the mother, child, family and larger society. Unfortunately, pregnant women have largely been left out of pharmacological advances, and those suffering from opioid-dependence are no exception, until now. While a wide range of research designs have been used to address scientific questions to improve the treatment of a medical illness such as substance dependence, the randomized, double-blind, controlled, parallel group design (RCT) provides the most rigorous data, and has the potential to provide unequivocal evidence of efficacy of treatment. Although this design is the "gold standard," when applied to a unique population of substance-dependent pregnant patients, a number of unique ethical and methodological concerns must be addressed. This document is divided into four parts. First, it highlights the ethics of conducting RCTs during pregnancy. Second, it discusses why evidence-based guidance for pharmacotherapy (e.g., opioid agonist treatment) during pregnancy is needed. Third, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study is described as an example of the RCT design in pregnant opioid-dependent women. Lastly, the implications of the results of the MOTHER study for advancing the treatment of opioid-dependent pregnant patients and future questions this network may answer are summarized.

I. Ethics of Conducting Randomized Controlled Trials Using Pregnant Participants

Without the necessary understanding, the use of any medication to treat drug addiction can be resisted by both patient and clinician. For example, methadone's ability to successfully treat opioid dependence is supported by four decades of research, yet many countries in the world and communities in the United States refuse to allow patients to receive this life-saving treatment. The stigma surrounding methadone treatment is exacerbated in pregnant women. Thus, research with pregnant patients presents numerous ethical questions for consideration. Although the U.S. Federal regulations provide guidance for research with pregnant women in subpart B sections 46.204 and 46.205 of "Protection of Human Subjects" and require ethics boards and researchers to identify and assess the risks and benefits to mother and fetus, the regulations do not provide an ethical framework to guide the assessment of such risk. Research of this type must benefit the fetus and mother. Researchers must ensure that the mother is taking only reasonable risks to her health to benefit the fetus. It is important that both the mother's health and the health of her fetus is protected and promoted. This is a critical issue in the informed consent process (McCullough, Coverdale, & Chervenak, 2005).

II. Need for evidence-based guidance for pharmacotherapy during pregnancy

Opioid-dependence during pregnancy remains a health care challenge. The largest United States study focusing on the prevalence of illicit and licit substance use during pregnancy was the National Study on Pregnancy and Health (National Institute on Drug Abuse, 1996). Results of this study suggested that approximately 53,400 babies in the U.S. were exposed in utero to heroin or the non-medical use of analgesics. Since then, both heroin and the non-medical use of opioid analgesics has increased in the general population, with the number of new non-medical users of prescription pain relievers increasing from 600,000 in 1990 to more than 2 million in 2001 (SAMHSA, 2004). This same pattern of non-medical use of opioid analgesics has also been found for pregnant women, with self-reported use increasing from 51,900 in 1993 to an average of 109,000 in 2002-2004 (SAMHSA, 2007). Thus, opioid misuse during pregnancy is a serious and growing concern in the United States.

Most women dependent on opioids prior to pregnancy are not able to stop their drug use without medication intervention. Medication treatment is critical for these patients as untreated opioid-dependence in the presence of additional complex environmental and medical factors (e.g., alcohol and nicotine use, depression, poverty) contributes to a myriad of adverse consequences, risk of infection, premature delivery, and low birth weight (Alroomi, Davidson, Evans, Cealea, & Howat, 1988; Connaughton, Reeser, & Finnegan, 1977; Glass & Evans, 1972; Hulse, Milne, English, & Holman, 1997; Kandall et al., 1977; Messinger et al., 2004; Naeye, Blanc, Leblanc, & Khataee, 1973). Given the risks both mothers and children face as a part of exposure to a drug-using lifestyle, and the previously documented effectiveness

of opioid agonist medications in reducing risk behaviors and increasing healthy behaviors (e.g., Jones, 2006a), pregnant women should not be excluded from the opportunity to receive effective opioid treatment medications.

In contrast to heroin dependence, methadone maintenance treatment during pregnancy has been associated with improved obstetrical care, increased fetal growth, reduced fetal mortality, decreased risk of HIV infection, decreased risk of preeclampsia and fetal exposure to cycles of heroin induced highs and withdrawal, and an increased likelihood of the infant being discharged to his/her parents (Finnegan, 1991; Kandall et al., 1977). Moreover, the relapse rates for women who choose detoxification during pregnancy are far greater, and the treatment retention rates far worse, than those who are maintained on methadone (Jones et al., 2006; Finnegan, 1991). Therefore, providing appropriate agonist medication during pregnancy may help mitigate the deleterious consequences of illicit drug use.

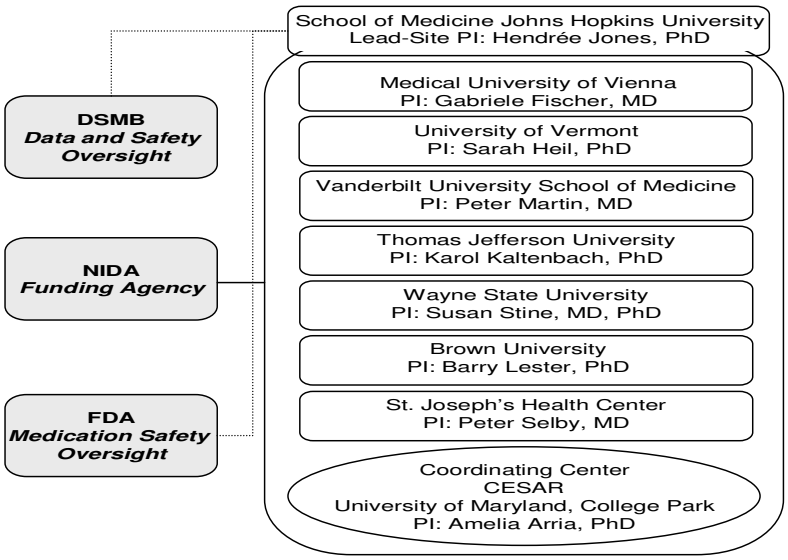
Methadone is the oldest, most widely used, and most regulated medication of any known medication prescribed during pregnancy (Jones et al., 2006b). It is available in the United States only through specialized maintenance clinics. Although clearly beneficial as a part of a comprehensive drug treatment program, methadone use during pregnancy remains controversial because of the associated Neonatal Abstinence Syndrome (NAS). NAS may appear in neonates prenatally exposed to opioid agonists after delivery. NAS is characterized as a collection of signs and symptoms indicating dysfunction of the gastrointestinal tract, and the autonomic, central nervous and respiratory systems (Finnegan & Kaltenbach, 1992). With appropriate medication and supportive interventions, NAS can be treated without adverse consequences (Berghella et al., 2003).

Buprenorphine use is approved for opioid-dependence treatment in more than 44 countries. There are two sublingual dosage forms: Subutex® (buprenorphine alone) and Suboxone® (buprenorphine/naloxone 4:1). However, like methadone, large, definitive randomized controlled trials of buprenorphine in pregnant women have not been conducted.

Although there are hundreds of published papers on methadone-exposed pregnancies, and over 32 published reports documenting perinatal buprenorphine exposure, the vast majority of the literature is open-label, retrospective, of small sample size and lack appropriate controls (e.g., prospective data collection, randomization, blind dosing and data collection, systematic collection of data, etc.) which minimize the possibility of biases entering into the purported outcome. The only two previous small sample size RCTs comparing methadone and buprenorphine (Fischer et al., 2006; Jones et al., 2005b) and a large multi-site open-label study conducted in France (LeJeune et al., 2006) provide an appropriate foundation on which to base a large multi-site clinical trial enrolling a diverse sample of pregnant opioid dependent women in order to conclusively determine the safety and efficacy of both methadone and buprenorphine. Until the study outlined below is completed, in the United States, it is expected that both methadone and buprenorphine will remain classified by the Food and Drug Administration as pregnancy category C medications due to the lack of sufficient randomized clinical trial data in pregnant women to document safety and efficacy.

III. Design of the MOTHER Study

The MOTHER study is a randomized, stratified, double-blind, double-dummy, parallel group design. Its design and procedures were based on extensive pilot research comparing the safety and feasibility of studying methadone and buprenorphine in pregnant patients and their neonates (Jones et al., 2005a; Jones et al., 2005b). The foundation for the MOTHER study is premised on the fact that advances in opioid-dependence treatment for pregnant patients is best achieved through a multi-site collaborative randomized controlled trial. The lead site, Johns Hopkins University (PI, Hendree E. Jones), brought together seven additional independently National Institute on Drug Abuse-R01 funded sites to foster collaboration and address clinical issues in opioid-dependent pregnant women (see **Figure** below). Through mutual collaboration and use of standardized research protocols and methodology, the MOTHER study is accruing a geographically and ethnically diverse sample. At the present time 125 of the 300 expected participants have been randomized. This study also establishes the infrastructure needed to conduct such trials by bringing together biomedical researchers in the field of substance dependence with clinicians having experience in treating opioid-dependent pregnant women. This highly complex project includes oversight from several entities, and interacts with a coordinating center (see **Figure**).



Following induction onto their double-blind study medication (Subutex or methadone), an individualized dosing schedule is used to minimize possible bias resulting from over- or under-medication and to potentially avoid confounding comparisons between medications due to possible differences in dose adequacy that sometimes occur in set dosing protocols. The sublingual buprenorphine and placebo tablets used in this study are supplied by Reckitt-Benckiser Inc. and given to NIDA who then ships them to each site or shipped directly to the non-US sites. Daily, all participants first receive 7 (three 8 mg size tablets and four 2 mg size tablets) to place under the tongue for 5 minutes or until the tablets dissolve. Each tablet contains 2 or 8 mg buprenorphine or placebo (no active medication). Next, all participants receive daily oral methadone (active or placebo) in a fixed volume (e.g., 40 mLs). Each site purchases methadone from their local supplier and the standardized methadone placebo is made at each site's pharmacy.

All sites provide comprehensive care to participants that include both contingency management for eliminating illicit drug use during pregnancy (Lussier, Heil, Mongeon, Badger, & Higgins, 2006), and access to individual and group substance addiction counseling, obstetric, medical and psychiatric care and a variety of other ancillary services (e.g., transportation).

The five primary outcomes of the study include (1) *Neonatal Abstinence Signs* (NAS); (2) *Number of neonates requiring treatment*; (3) *Amount of medication needed to treat NAS*; (4) *Head circumference*; and, (5) *Length of hospital stay*. Based on the pilot study (Jones et al., 2005a,b), our hypothesis is that buprenorphine will produce a superior outcome for all five variables. As such neonates are evaluated for NAS for a minimum of every 3-4 hours for 10 days. The NAS is assessed using a 28-item modified Finnegan Scale. Of these items, 19 are used for scoring and medication decisions. Definitions of each item were based on those developed by D'Apolito (1994). Medication treatment, morphine oral solution, of 0.04 mg/dose is initiated if an infant scores 9 to 12 and has a score that is similar or higher when rescored at the end of the feeding and within 1 hour. The amount of medication administered is based on the highest score. If the infant scores 13 or higher, treatment is started immediately without rescoring. The table below shows the score and respective dose of morphine for initiation.

One of the decided strengths of this study is the breath and depth of maternal and neonatal data collection. MOTHER provides the single most comprehensive biopsychosocial assessment of the impact of illicit drug use during pregnancy on both the mother and neonate ever undertaken.

IV. Implications of the Present Study

The results of the MOTHER project are expected to have numerous implications for fields of psychiatry, obstetrics, pediatrics, neonatology, and perinatology. MOTHER is one of the first large-scale projects to examine neonatal outcomes in relation to detailed prospectively collected comprehensive objective quantification of both prescribed and non-prescribed substances. The MOTHER study will provide important information about the relationship between the course of maternal obstetrical, psychiatric

and general medical conditions and psychological functioning through-out pregnancy and the neonatal outcomes at birth and over the first month of postnatal development. Conclusions from MOTHER will provide needed objective data regarding the relative safety and effectiveness of both methadone and buprenorphine in the treatment of opioid-dependent pregnant patients. Provided both medications are shown to be safe and efficacious for both mother and neonate, national and international efforts will, hopefully, be undertaken to move to a common ground regarding the provision of methadone and buprenorphine to opioid-dependent women during pregnancy. If buprenorphine should be observed to be less safe or efficacious than methadone, then MOTHER will have helped to minimize harm to future pregnant women in need of opioid treatment. Data from MOTHER, collected under rigorously controlled conditions, will allow the identification of any potential problems for both mother and child with either medication, thereby forewarning clinical service providers for the potential occurrence of such issues. This study will also provide information that will help to refine the assessment and treatment of NAS. As such there may be advances in both patient care and future research in the fields of neonatology and pediatrics. Moreover, these data may be used to provide information about better matching patients to medications, leading the advance towards individualized medicine.

In summary, the MOTHER study will move the ignored and stigmatized population of opioid-dependent pregnant women and their children into the spotlight of treatment advances. MOTHER also provides an innovative network structure from which to launch future treatment studies that could help mothers and children in the future. For example, the MOTHER network provides unprecedented opportunities for pregnant women to benefit from pharmacologic advances in opioid dependence treatments. For example, future collaborative R01 applications using this network may include: 1) smoking cessation medications; 2) comparing NAS medications or treatment protocols; 3) testing neonatal withdrawal assessment tools for opioids, other drugs, or poly-drug exposure; 4) treatment of maternal pain; and 5) trials of depression treatments (behavioral or medications).

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