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# Characteristics of Opioid-Using Pregnant Women Who Accept or Refuse Participation in a Clinical Trial: Screening Results from the MOTHER Study

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## Abstract

**Background—**Although concerns arise about the generalizability of results from Randomized Controlled Trials (RCTs), few studies systematically examine this issue.

**Objectives—**This study compared the characteristics of 427 opioid-using pregnant women who did (*n* =208) and did not consent (*n*=219) to enrollment in a multi-center clinical trial of agonist medications (i.e., the MOTHER study).

**Methods—**Logistic regression models were used to compare consenters and non-consenters to examine the effect of screening variables on the likelihood of consenting.

**Results—**Of nine characteristics examined, most differences did not reach statistical significance. Consenting participants were less likely than non-consenting women to be currently enrolled in a methadone maintenance program (74.5% vs. 84.5%, *p*=.01).

**Conclusion and Scientific Significance—**These data show that the recruited sample of drug-dependent pregnant women enrolled in an intensive RCT is representative of the larger population of treated opioid-dependent patients and supports the generalizability of randomized controlled trials in this population.

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**Keywords**

Substance use; opiates; opioids; substance abuse; pregnant women; treatment acceptance; methadone; buprenorphine

## BACKGROUND

Although randomized controlled clinical trials are considered the "gold standard" for evaluating the efficacy of pharmacological interventions, as well as guiding clinical care, their external validity or generalizability is often questioned (1). These questions arise in large part because of the stringent inclusion and exclusion criteria utilized by many randomized controlled trials (RCTs). On one hand, strict criteria are necessary to answer efficacy questions about medications (2,3). On the other hand, greater generalizability which may require relaxing of the inclusion/exclusion criteria, increases applicability of RCT results to clinical practice (1). The generalizability of the RCT for special populations is especially problematic (4–6). One study examining treatment outcomes, reported that special populations, including women, pregnant women, children, the elderly, or those with common medical conditions were most often excluded from these trials, thus limiting the value of the conclusions for the aforementioned populations. They also noted that multicenter RCTs and those that examined medications were the most likely to have extensive exclusions (7) which may improve reliability of findings from one site to the other but reduce real world applicability. As a result, when the differences between the populations studied and clinical practice have been carefully examined, it has been concluded that the generalizability of most individual trials is poor (8).

Although concerns are repeatedly raised about the generalizability of RCT results, there are few studies that systematically examine or address this issue (5), particularly among RCTs for opioid dependence. Ideally, generalizability would be empirically established by replicating studies using more relaxed inclusion/exclusion criteria (5,6). However, given the resources required for RCTs, this is unfeasible. Another approach is to synthesize data from multiple trials whose inclusion/exclusion criteria vary somewhat (5,6). The results of a recent Cochrane Review (9) comparing methadone and buprenorphine in non-pregnant patients concluded that for larger trials using adequate maintenance doses, although each trial included only selected patients, either the inclusion/exclusion criteria appeared to allow for heterogeneity and good external validity or the characteristics of the opioid-dependent samples appeared to be reasonably heterogeneous and had good external validity (9). For pregnant opioid dependent patients, there have been only two small RCTs comparing methadone and buprenorphine for the treatment of opioid dependence during pregnancy (10,11). A recent Cochrane Review synthesized the results of these studies, but did not address the potential external generalizability of the results given the small number of studies available (12).

Another method for examining generalizability is to compare a specific set of characteristics in participants who agreed (consenters) to those who declined (non-consenters) research participation (13). This approach has an added benefit in that where differences are observed, these differences could be used to help identify limitations of the study generalizability as well as to inform targeted application of the study in subpopulations or develop educational strategies to engage and enhance participation by less represented groups 13). The Maternal Opioid Treatment: Human Experimental Research (MOTHER) study, a recently completed double-blind, double-dummy, randomized controlled clinical trial comparing the efficacy of methadone and buprenorphine, collected screening data from pregnant women at multiple sites (14). This dataset provides a unique opportunity to

compare consenters to non-consenters in the larger intent-to treat population screened by the MOTHER study before final selection and randomization. It also provides a first step towards establishing the representativeness of this sample relative to the larger population of opioid-dependent pregnant patients seeking opioid agonist treatment.

### Purpose of the Current Study

The purpose of this current study was to evaluate the association between sociodemographic factors (e.g., age, education level, employment, minority and marital status), substance use history, gestational age and treatment history variables and consent for participation in this RCT.

## METHODS

### Study Design

The current study analyzed data gathered as part of the MOTHER study, an eight-site*, double-blind, double-dummy, randomized controlled clinical trial that completed enrollment as of October 31st, 2008. It should be noted that seven* of the eight sites successfully randomized participants to the study medications. All sites received local Institutional Review Board approval, and independent data and safety oversight was conducted by a Data and Safety Monitoring Board. For a more detailed description of site selection, study coordination, subject selection, and protocol details, see Jones et al. (14).

### Screening Assessment

At each site, study staff obtained written informed consent and conducted a brief (15 min.) interview or chart review to complete the initial screening assessment. The screening assessment was developed specifically for the trial and assessed basic demographics, information about the current pregnancy, and information about current and past drug use that allowed study staff to assess each woman's status with regard to major trial inclusion and exclusion criteria. Demographic information was collected, including age, race, education level, marital and employment status. Clinical information was collected including estimated gestational age of current pregnancy, cocaine use and treatment, and history variables (current methadone treatment and number of prior treatment episodes). Women who met all major initial inclusion criteria and no exclusion criteria† were then invited to consent to further participation in medical screening and possible study participation involving randomization to treatment in the MOTHER study (14). Thus the populations compared in this study of consenters and non-consenters were an intent-to-treat population of opioid users in initial screening without DSM IV dependence diagnosis having been confirmed.

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*The MOTHER clinical sites are: Johns Hopkins University School of Medicine, Baltimore, MD (lead site); Thomas Jefferson University, Philadelphia, PA; Vanderbilt University School of Medicine, Nashville, TN; Wayne State University, Detroit, MI; University of Vermont, Burlington, VT; Alpert School of Medicine at Brown University, Providence, RI; University of Vienna, Vienna, AUSTRIA; University of Toronto, Toronto, CANADA (did not randomize participants).

†Final determination of inclusion into the MOTHER study required meeting DSM-IV criteria for current opioid dependence, providing an opioid-positive urine sample indicating current opioid use or being currently on agonist treatment for opioid dependence. In addition, randomized participants were required to have a single fetus pregnancy, with an estimated gestational age (EGA) of 6 to 30 weeks and a normal fetal heartbeat identified by ultrasound. Exclusionary criteria for the study were: (1) a medical condition making participation medically hazardous (eg, HIV, preterm labor, evidence of congenital fetal malformation, abnormal fetal heartbeat); (2) an acute severe psychiatric condition in need of immediate treatment or which represented an imminent risk to the woman herself or others; (3) a current diagnosis of benzodiazepine or alcohol abuse or dependence according to the E module of the SCID I; (4) regular use of alcohol or benzodiazepines in the past 30 days (as determined by Addiction Severity Index); (5) a positive alcohol breath test or benzodiazepine positive urine during screening; or (6) pending legal action that could prohibit or interfere with participation. For a more detailed description of site selection, study coordination, subject selection and protocol details, also see Jones et al.(14)

### Subjects

In total, 1074 women were initially screened for inclusion. Of those women, 502 were eligible for further screening based on inclusionary/exclusionary criteria[‡], and 428 were approached to participate in further screening. Among those approached for participation, 1 never responded, 208 consented to further screening, and 219 did not consent.

### Data Analysis

Of the 437 potentially eligible women who were approached, 435 responded to initial screening. Of these 435 women, 48% consented to be enrolled in the clinical trial. Consenting and non-consenting women were compared with respect to demographic characteristics, estimated gestational age (EGA), treatment history, methadone treatment status and concomitant cocaine use. Logistic regression models were used to estimate the association between patient characteristics and consent to participate. A series of bivariate logistic regressions were developed using Stata 10.0 to examine the effect of each variable independently on the likelihood of consenting versus not consenting. Finally, all demographic, treatment, and drug use variables were entered into a single logistic regression model predicting consent to adjust for any potential confounding. For ease of interpretation, odds ratios and confidence intervals are reported.

## RESULTS

Table 1 summarizes the results of the bivariate and multivariate comparisons between consenting vs. non-consenting women. As a whole, the sample was in their late 20's, White, unmarried, unemployed, and had less than a high school education. On average, they were in the second trimester of pregnancy. The majority was currently enrolled in methadone maintenance treatment and on average, had been in drug treatment more than three times before. A little more than one-third were currently using cocaine.

The only statistically significant difference observed between consenting and non-consenting women in the bivariate analyses was that women currently enrolled in a methadone maintenance program were less likely to consent to participation(74.5% vs. 84.5%, $p$=.01). Results of multivariate analyses were largely the same, with enrollment in a methadone maintenance program remaining significantly different between the groups ($p$=.01).

## DISCUSSION

There are three aspects of the present study that merit comment. First, the extent to which subjects who consent to participation in the clinical trial can be distinguished from those who refuse based on major demographic and basic clinical characteristics; second, how the results fit into the larger literature on characteristics of opioid-dependent patients, (i.e., the extent to which the current sample is representative of the larger opioid-dependent pregnant population); and third, the strengths, limitations and implications of the present study.

First, we observed only one statistically significant difference between opioid-using pregnant women who did and did not consent to enrollment in a clinical trial of agonist

[‡]The 572 participants who were disqualified from further screening were disqualified for the following reasons (multiple reasons could apply): Outside the 18–41 years age range: 14 (2.4%); Concurrent benzodiazepine use/abuse: 145 (25.3%); Impending legal issues: 78 (13.6%); EGA less than 6 or greater than 30 weeks: 151 (26.4%); Currently in detoxification: 14 (2.4%); Psychiatric issues: 37 (6.4%); Multiple fetus pregnancy: 12 (2.1%); Concurrent alcohol use/abuse: 70 (12.2%); Medical issues: 128 (22.4%); Non-English (in North America) or non-German (in Austria) speaking: 2 (0.3%); Failed to attend the appointment where they would be approached to consent 39 (6.8%); Not dependent on opioids and did not qualify for maintenance at the time of screening: 10 (1.7%); Other reasons that the site deemed appropriate for exclusion 17 (3.0%).

medications, namely, the percentage of each group who were currently enrolled in a methadone maintenance program (74.5% vs. 84. 5%, $p$=.01). These results suggest that the study was more successful in attracting pregnant women who were not already established in a methadone-maintenance program. Understanding the reasons for this are not within the scope of the current study but it may be that women stable in treatment on methadone prefer to remain on this medication or were unwilling to be hospitalized for induction onto a potentially different medication while they were pregnant.. A small number of studies (15–20) have examined predictors of treatment acceptance among pregnant opioid-dependent women. While treatment acceptance is not precisely identical to consent to RCT participation these studies are nevertheless informative for comparison. Overall, the results of this study suggest that both the consenting and the non-consenting samples are similar in the descriptive variables examined.

The extent to which our study population is representative of the larger population of pregnant women using opioids can be examined by comparing the results of the present study with those of the two smaller RCTS in opioid-dependent pregnant women (10,11). Because the inclusion/exclusion criteria associated with RCTs may systematically alter the characteristics of the recruited sample, we also compared the results of the present study with the results of other reports of treatment acceptance in opioid-dependent pregnant women. There are several previous studies reporting characteristics associated with treatment outcomes in this population (15–20). These studies used varied outcomes as indicators of treatment acceptance or non-acceptance, (e.g, , leaving treatment early (17,18), treatment acceptance defined as agreeing to referral (19), compliance with outpatient treatment (15) or retention (16,,20) that were not precisely similar to acceptance of participation (consent) in a clinical trial as was used in this study. These studies also used varied designs being generally either retrospective chart reviews (15,18,20) or prospective descriptive studies (16,17,19). None of the studies considered baseline methadone treatment as a possible factor in treatment acceptance. Although the studies differed from each other in method and in specific demographic characteristics associated with treatment acceptance or participation, the studies taken as a whole were all strikingly similar in their general population description; women were generally White, young (in their 20s), single, and unemployed. The most similar previous study in outcome measure to this study, the Messer et al. study (19) which used treatment acceptance, reported that acceptors were more likely to be married and less likely to be African American (characteristics that showed a slight trend toward a difference between groups in this study). Overall, there also appears to be good agreement on major characteristics between samples from RCTs (present study, 9, 10) and convenience samples gathered in both the U.S. (21,22) and internationally (23,24,25), suggesting that the MOTHER sample is representative of the larger population of opioid-dependent pregnant women. Specifically, as in previous investigations, this study supports the descriptive profile of the pregnant opioid-dependent female as having a mean age in the late 20’s, being unmarried, unemployed, and having less than a high school education.

While the results of the present study are consistent with those in the broader population of opioid-dependent pregnant women, there appear to be some differences between opioid-dependent pregnant women and the larger population of non-pregnant opioid-dependent women. For example, two reports suggest that opioid-dependent pregnant women are younger at treatment entry (21,25). Although the present study does not represent the first treatment (or “treatment entry”) for all subjects, our observations support the younger age of the pregnant opioid-using patient. In addition, Crandall et al. (21) report that fewer pregnant opioid-dependent women were married and fewer were diagnosed with a psychiatric disorder compared to non-pregnant opioid-dependent women. Interestingly, Peles & Adelson (25) report that twice as many pregnant methadone-maintained women were drug-abstinent after one year in treatment compared to non-pregnant methadone-maintained

women (66 % vs. 28%, respectively), suggesting that the differences noted may not impede overall treatment success of opioid-dependent pregnant women. It may therefore be that pregnancy and the expected newborn baby provide significant incentive to stay drug abstinent.

The present study has a number of notable strengths, including systematic data collection from a large sample across seven diverse clinical sites and settings. An important limitation is the restriction in the number of characteristics examined, since this population was assessed at an early stage in screening (women consenting to further screening were compared to non-consenting women). While a strength of this study is that it reports on the intent-to-treat sample before final inclusion and exclusion criteria are applied, it is unable to compare this sample to patients that were not approached for the study. This study also does not address the differences between randomized and excluded subjects in the overall study. Still, the similarities observed in informal comparisons to other RCTs (9,10) and U.S and international convenience samples (21–25) of opioid-dependent pregnant women suggest that such a comparison would likely indicate significant commonalities between these groups as well.

In conclusion, only one difference, current enrollment in a methadone maintenance program, was found between consenting and non-consenting women in this study. Therefore, the data suggest that results from this clinical trial have a high likelihood of generalizing to the broader population of opioid-dependent pregnant women, an important finding that should facilitate future investigations involving the treatment of this high-risk population of women. Continued research on the generalizability of randomized controlled trial results will be important to ensure applicability to clinical practice with this and other populations.

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**Table 1**

Comparison of consenting and non-consenting opioid-using pregnant women on sociodemographic and clinical characteristics

| | Total (*N*=427) | Consenting (*n*=208) | Non- consenting (*n* =219) | Bivariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | OR | 95% *CI* | *p* | AOR | 95% *CI* | *p* |
| **Sociodemographic Characteristics** | | | | | | | | | |
| Years of age, M(SD) | 27.6 (5.9) | 27.6 (5.9) | 27.6 (5.9) | 1.00 | 0.97–1.03 | 0.91 | 1.01 | 0.97–1.06 | 0.51 |
| Race, % white | 78.5% | 81.7% | 75.3% | 1.41 | 0.88–2.24 | 0.15 | 1.63 | 0.90–2.94 | 0.11 |
| Marital status, % married | 11.0% | 12.5% | 9.6% | 1.28 | 0.71–2.32 | 0.42 | 1.69 | 0.86–3.32 | 0.13 |
| Weeks estimated gestational age, M(SD) | 17.5 (6.7) | 17.4 (6.7) | 17.5 (6.7) | 1.00 | 0.97–1.03 | 0.83 | 1.00 | 0.97–1.03 | 0.83 |
| Years of education, M(SD) | 11.3 (1.8) | 11.4 (1.9) | 11.1 (1.7) | 1.11 | 0.99–1.24 | 0.07 | 1.10 | 0.98–1.24 | 0.10 |
| Employment status, % employed | 14.8% | 13.5% | 16.0% | 0.79 | 0.46–1.35 | 0.39 | 0.65 | 0.34–1.22 | 0.18 |
| **Drug Treatment History and Cocaine Use** | | | | | | | | | |
| Currently enrolled in maintenance, % enrolled | 79.6% | 74.5% | 84.5% | **0.54** | **0.32–0.87** | **0.01** | **0.46** | **0.26–0.79** | **0.01** |
| Number of prior drug treatments, M(SD) | 3.2 (3.8) | 3.2 (4.2) | 3.1 (3.3) | 1.00 | 0.95–1.06 | 0.89 | 1.00 | 0.95–1.06 | 0.98 |
| Reported cocaine use in past 30 days, % used | 36.8% | 38.9% | 34.7% | 1.23 | 0.83–1.81 | 0.31 | 1.14 | 0.73–1.80 | 0.56 |

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