Opioid Detoxification in Pregnancy: Systematic Review and Meta-Analysis of Perinatal Outcomes

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Abstract

Objective We sought to compare the efficacy and safety of detoxification from opioids compared with opioid replacement therapy (ORT) during pregnancy.

Study Design We searched PubMed, Embase, Cochrane Library, and ClinicalTrials.gov from inception to June 2017 for English-language randomized-controlled trials or cohort studies that compared detoxification with ORT. We sought studies with outcomes data on maternal abstinence at the time of delivery, neonatal abstinence syndrome (NAS), stillbirth, and preterm birth (PTB). We calculated pooled relative risks (RRs) with a random-effects model, assessed heterogeneity using the chi-square test for heterogeneity, and quantified heterogeneity using the I^2 test. We assessed publication bias using funnel plots and the Harbord test.

Results Three cohort studies met the inclusion criteria; eligible studies included 235 women with opioid use disorder in pregnancy. Maternal detoxification was associated with increased risk of relapse (RR = 1.91; 95% confidence interval [CI] = 1.14–3.21); however, no treatment differences were observed for the rates of NAS (RR = 0.99; 95% CI = 0.38–2.53) or PTB (RR = 0.39; 95% CI = 0.10–1.60).

Conclusion Our findings suggest an increased risk of relapse with detoxification treatment compared with ORT; however, detoxification does not alter the risk of PTB or NAS. Further studies should confirm our findings and explore mechanisms to fight the current opioid epidemic.

Keywords
► opioid use disorder
► maternal opiate use
► neonatal abstinence syndrome
► perinatal outcomes

Opioid use disorder is a fast-rising public health concern in the United States, with more than two million Americans aged 12 years or older with either pain reliever use disorder or heroin use disorder.1 Opioid abuse during pregnancy is associated with insufficient prenatal care, malnutrition, increased risks of preterm birth (PTB), fetal demise, intrauterine growth restriction, placental abruption, and neonatal abstinence syndrome (NAS).2–6 Opioid use disorder is a significant contributor to pregnancy-related deaths.7,8

Opioid replacement therapy (ORT), with either methadone or buprenorphine maintenance, is the recommended treatment for opioid use disorder during pregnancy. From a maternal perspective, when compared with continued opioid abuse during pregnancy, ORT is associated with increased adherence to prenatal care, increased birth weights, and decreased rates of PTB and perinatal death.9–11 In the general opioid-addicted population, patients undergoing ORT have fewer sexual partners, more condom use, and

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decreased rates of HIV infection, thereby decreasing potential for risky behavior that could lead to perinatal acquisition of infectious diseases and unintentional overdose.\(^{12,13}\) However, the risk of NAS, which can lead to prolonged neonatal hospitalizations, persists with ORT.\(^{14-16}\) Additionally, the long-term neurodevelopmental impact of exposure to ORT during pregnancy and NAS is unclear.\(^{5}\) Finally, although opioid withdrawal during pregnancy has long been thought to lead to an increased risk of stillbirth, this is based on case reports from the 1970s, and more recent case series of controlled opioid withdrawal do not report stillbirths.\(^{17-23}\) Thus, there has been a renewed interest in controlled opioid withdrawal during pregnancy as a possible treatment alternative. We conducted a systematic review and meta-analysis of the neonatal effects of prenatal opioid maintenance therapy versus detoxification in opioid-dependent pregnant women to assess the efficacy and safety of available treatment options.

### Methods

We searched PubMed, Embase, Cochrane Library, and ClinicalTrials.gov from inception to June 2017. We included English-language randomized controlled trials or cohort studies that compared detoxification with ORT in opioid-dependent pregnant women. We used combinations of the following medical subject headings and keywords to identify studies that compared outcomes from opioid-addicted women on maintenance therapy with those from women who underwent detoxification therapy: opioid, opiate, opiate addiction, opioid-related disorders, opioid therapy, detoxification, pregnancy complications, neonatal abstinence syndrome, premature birth, stillbirth, length of stay, maternal abstinence.

Information was abstracted by two independent reviewers (M. W. and S. K.) who assessed the titles and abstracts of all search results and full texts of potentially eligible studies. Discrepancies were reviewed by the senior author (L. M. H.).

We sought to find studies that fit the following criteria: (1) compared groups of ORT versus detoxification therapy (either as cohorts or as a randomized controlled trial) for women with opioid dependence during pregnancy and (2) reported at least one of the following outcomes: maternal abstinence at time of delivery, NAS, stillbirth, and PTB. We excluded studies for which no manuscript was available.

A random-effects model was used to calculate pooled relative risks (RRs) from the data that we gathered across all qualifying studies. We assessed heterogeneity using the chi-square test for heterogeneity and quantified heterogeneity using the \(I^2\) test. Publication bias was assessed using funnel plots and statistically using the Harbord test. All analyses were completed using STATA SE, version 13 (StataCorp, College Station, TX).

### Results

Our search within PubMed, Embase, Cochrane Library, and ClinicalTrials.gov databases yielded 671 titles. We screened those titles for potentially relevant content and selected 139 abstracts for closer review. Among those reviewed abstracts, we selected 10 full-text manuscripts. After a close review of those manuscripts, we excluded the following: descriptive studies (five), studies with no outcomes of interest (one), and studies with no manuscript available (one). This resulted in the inclusion of three observational cohort studies reporting on a total of 235 women that met our inclusion criteria. A flow diagram of our systematic review is displayed in [Fig. 1](#fig1). Characteristics of the included studies are shown in [Table 1](#table1).

A total of 235 women with opioid dependence in pregnancy were included. One-hundred thirty-nine women underwent detoxification with methadone. Of these, 22 underwent complete detoxification in the inpatient setting. One-hundred seventy-five underwent ORT during pregnancy. Of these, 97 initially had a 7-day inpatient hospitalization followed by continued detoxification in the outpatient setting. One-hundred seventy-five underwent ORT during pregnancy. Of these, 97 initially had a 7-day inpatient hospitalization followed by continued detoxification in the outpatient setting, and 78 patients were not admitted but were started and continued on ORT in the outpatient setting.

The three studies who were included were those by Haabrekke et al, Lund et al, and Jones et al; the participants in each of these different studies had a range of access to inpatient and outpatient treatment.\(^{18-20}\) Haabrekke et al included two different Norwegian cohorts: the first cohort comprised pregnant patients who were provided ORT in the outpatient setting, whereas the second cohort comprised pregnant patients from five different residential treatment centers who were provided with opioid detoxification.\(^{18}\) Haabrekke et al's study focused on neonatal outcomes and is included in the analysis of NAS; however, this study could not be included in the analysis of maternal relapse as they only report relapse outcomes for women in the detoxification group but not in the ORT group.\(^{18}\) Lund et al included patients included in the MOTHER (Maternal Opioid Treatment: Human Experimental Research) study, which included six U.S. sites and one Austrian site.\(^{19}\) This study was a retrospective review of records of pregnant women who underwent methadone-assisted withdrawal during the same time period as the MOTHER study.\(^{19}\) Records for the withdrawal group were selected from women admitted to a specialized center, the Center for Addiction and Pregnancy (CAP) located at Johns Hopkins University Bayview Medical Center (JHBM); resources at the center included ORT, individual therapy, group psychoeducation, case management, obstetrical care, psychiatric evaluation and treatment, general medical management, and on-site child care and pediatric care.\(^{19}\) Treatment began with a 7-night stay in an assisted living unit followed by intensive outpatient treatment.\(^{19}\) Jones et al used records selected from patients who underwent both methadone maintenance and methadone-assisted withdrawal who were admitted to the same center, CAP at JHBM, as those included in the withdrawal group of the study by Lunó et al.\(^{19,20}\)
Records identified through database searching (n=679)

Records after screening with Titles (n=139)

Records after screening with Abstracts (n=19)

Full-text articles assessed for eligibility (n=3)

Studies included in the meta-analysis (n=3)

Fig. 1 Flow diagram of studies included in the meta-analysis.

None of the included studies used a randomized design (intent-to-treat analysis). As such, no patients or clinicians were blinded as to treatment status. Each study described the eligibility and exclusion criteria and had comparable baseline characteristics with measures of variability. Data on specific aspects of study quality as well as outcome details are given in Table 2.

Maternal detoxification treatment was associated with an increased risk of relapse (RR = 1.91; 95% confidence interval [CI] = 1.14–3.21, $I^2$ test for heterogeneity 0%) when compared with ORT (Fig. 2). Relapse was defined as the use of non-prescribed opioids between the start of therapy and delivery.

Maternal detoxification was not associated with a decrease in the risk of NAS (RR = 0.99; 95% CI = 0.38–2.53, $I^2$ = 78%) or PTB (RR = 0.39; 95% CI = 0.10–1.60, $I^2$ = 44.9%) (Figs. 3 and 4). For the analysis of neonatal abstinence, the overall $I^2$ heterogeneity test described 71.8% of variation across studies due to heterogeneity rather than chance ($p = 0.029$). This is likely due to varied definitions of NAS, as multiple scoring systems exist and scoring can be subjective. Haabrekke et al, assessed NAS using Finnegan scores (with a cutoff score of 8) collected by trained nurses. Lund et al, included NAS assessment based on a modified Finnegan scale, which reduced the weights of some individual item scores and the addition of failure to thrive (weight loss of 10% or more of birth weight) and excessive irritability. In Jones et al's study, the assessment of NAS was based on whether the neonate was treated with medication for NAS.

In addition to those studies included in our analysis, we found three observational studies examining tapered methadone treatments (that did not qualify for our analysis as they did not have comparison groups), which had a total of 90 patients who were successfully detoxified at delivery and 66 who

Table 1 Studies of prenatal detoxification treatment versus methadone or buprenorphine maintenance treatment and neonatal outcomes

<table>
<thead>
<tr>
<th>First author, year (reference no.)</th>
<th>Study design</th>
<th>Participants</th>
<th>Method(s) of detoxification</th>
<th>Method(s) of maintenance</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haabrekke, 2014 18</td>
<td>Retrospective cohort</td>
<td>100 mother-neonate pairs</td>
<td>Inpatient methadone taper ($n = 22$)</td>
<td>Outpatient methadone ($n = 78$)</td>
<td>Sweden</td>
</tr>
<tr>
<td>Lund et al, 2012 19</td>
<td>Retrospective cohort</td>
<td>25 mother-neonate pairs</td>
<td>Outpatient methadone taper ($n = 8$)</td>
<td>Outpatient methadone or buprenorphine ($n = 17$)</td>
<td>Multinational</td>
</tr>
<tr>
<td>Jones et al, 2008 20</td>
<td>Retrospective cohort</td>
<td>175 mother-neonate pairs</td>
<td>Outpatient methadone taper ($n = 93$)</td>
<td>Outpatient methadone maintenance ($n = 80$)</td>
<td>United States</td>
</tr>
</tbody>
</table>
Table 2 Qualitative data from studies comparing detoxification treatment versus methadone or buprenorphine maintenance treatment

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Intention to treat</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blinded study</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Inpatient tapered methadone detoxification</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inpatient methadone maintenance</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Outpatient methadone maintenance</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Outpatient buprenorphine maintenance</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maternal relapse</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neonatal abstinence syndrome</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neonatal length of stay</td>
<td>–</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: Dash indicates data not reported.
<sup>a</sup>Treatment began with a 7-night stay in an assisted living unit followed by intensive outpatient treatment.

Conclusion

Though ORT is the recommended first-line treatment for pregnant women with opioid dependence, controlled detoxification during pregnancy is a potentially attractive option to decrease the incidence of NAS and assist the patient in becoming drug-free; however, our findings suggest that detoxification increases the risk of relapse without decreasing the incidence of NAS.

In the current literature, there is no evidence that detoxification is associated with decreased incidence of adverse short-term perinatal effects such as PTB or NAS. Tapered detoxification from an opioid substitute reduces neonatal exposure to opioids but does not, in fact, completely eliminate neonatal exposure during pregnancy. As such, the real-time effect of a slightly reduced neonatal opioid exposure in detoxification therapy on reducing rates of short-term neonatal morbidities may be too subtle to be detected in such short-window studies. Alternatively, the increased risk of relapse may obliterate any potential positive impact of medically assisted withdrawal on neonatal outcomes. There is no literature that directly examines longer-term outcomes of neonates exposed to detoxification therapy compared with ORT. In fact, there is very little known, in general, about the long-term effects of exposing neonates to ORT; future studies should examine the long-term neurodevelopmental outcomes of ORT-exposed neonates.<sup>5</sup>

Our analysis also found that women undergoing detoxification had higher rates of relapse than those undergoing ORT. This result, though not surprising, is significantly understudied and important. Women receiving ORT have decreased relapse attempted detoxification but relapsed before delivery.<sup>21-23</sup> In all six studies (with a total of 295 patients who underwent detoxification treatment), no stillbirths were reported.<sup>18-23</sup>

![Forest plot of outcomes (opioid relapse) of women undergoing detoxification treatment compared with opioid replacement therapy. The pooled risk ratio (RR) is 1.91 (95% confidence interval [CI] = 1.14-3.21; I<sup>2</sup> test = 0%).](image-url)
Fig. 3 Forest plot of outcomes (neonatal abstinence syndrome) of women undergoing detoxification treatment compared with opioid replacement therapy. The pooled risk ratio (RR) is 0.99 (95% confidence interval [CI] = 0.38–2.53; I² test = 71.8%).

Fig. 4 Forest plot outcomes (preterm birth) of women undergoing detoxification treatment compared with opioid replacement therapy. The pooled risk ratio (RR) is 0.99 (95% confidence interval [CI] = 0.38–2.53; I² test = 44.9%).

rates when compared with women undergoing detoxification. Jones et al, included in our analysis, found that, on average, patients undergoing any kind of ORT (continuous maintenance, maintenance after 3 days of methadone-assisted withdrawal, or maintenance after 7 days of methadone-assisted withdrawal), remained in treatment longer, attended more obstetrical visits, and more often delivered at the program hospital than patients who underwent methadone-assisted withdrawal. Lund et al concluded that a tapered methadone-assisted withdrawal could be a successful option in the treatment of opioid dependence; however, they stated that such a treatment approach is not an unequivocally suitable option for all patients. In Lund et al’s study, included in our analysis, 77% of patients switched to ORT during their pregnancy, whereas only 16% actually completed the detoxification. Similarly, in a descriptive study by Maas et al, only 17 of 58 patients attempting detoxification during pregnancy were successful.

An increased predisposition to relapse into illicit opioid or heroin use during or after the pregnancy is a valid concern in this vulnerable, high-risk population. Rates of opioid relapse are higher than relapse rates for any other drugs, with one study on opioid addiction in the general (nonobstetric) population reporting that as many as 91% of those in recovery will experience relapse; in that particular study, a staggering 80% relapsed within just 1 month of discharge from a detoxification program. Mortality is particularly
high in the immediate 2-week period after ending treatment; all-cause mortality is 24.2 to 35.2 deaths per 1,000 person-years in the first 2 weeks after leaving a methadone treatment program compared with 6.4 deaths per 1,000 person-years during a methadone treatment program.25 Among all substances of abuse, relapse with opioids is not only most common but also one of the most dangerous as many addicts may experience a precipitous reduction in their tolerance; this is hypothesized to markedly increase the risk of overdose mortality.26-29 For example, one study found that patients who “successfully” completed inpatient detoxification, thereby significantly decreasing their opioid tolerance, had a significantly increased risk of all-cause mortality within a year, with three out of five reported deaths in that cohort associated with overdose; conversely, no patients who failed to complete detoxification died within a year.29

In an obstetric setting, the potentially fatal risks of relapse in the general population compounded by lack of neonatal benefit are very concerning. Just as there is very little long-term neonatal outcome data in regard to opioid exposure, there is currently no available data that follows the long-term effects of different opioid addiction treatment modalities on maternal relapse. As the treatment for opioid addiction is a lifelong process, future studies examining the efficacy of detoxification therapy in obstetric populations should follow the risk of relapse for patients well beyond delivery.

Finally, it is important to note that all the studies included in our analyses conducted their studies in a residential inpatient setting or intensive research setting. Thus, this emphasizes that the success and compliance with a detoxification therapy in their study may be due to the controlled, monitored, supportive, and individually adapted nature of their programs.19-20 Therefore, general conclusions cannot be extrapolated from any of these studies or this meta-analysis regarding the efficacy or safety of detoxification therapy in any setting except a controlled inpatient setting. Such inpatient detoxification programs are costly and limited due to the availability of clinicians, health care teams, and hospital inpatient beds; with the literature available up to this point, it is difficult to predict whether a detoxification treatment program for opioid-addicted pregnant patients could be safe or efficacious in a step-down inpatient setting or an outpatient setting.

We acknowledge some study limitations. Despite an extensive and thorough literature search in multiple databases, this study was limited due to the few number of existing studies that directly compare detoxification treatment with ORT. As a result, we had a small sample size and were also unable to make comparisons by the type of ORT provided. The limited number of studies also prevented us from performing further analyses to assess for the impact of location of treatment methods (inpatient vs. outpatient) and type of ORT (methadone vs. buprenorphine) on the outcomes of interest.

Currently, the evidence supports that ORT should be continued as a first-line treatment for pregnant women with opioid addiction. Any consideration of detoxification needs to be done on a case-by-case basis in a controlled inpatient or research setting. Future studies should continue to examine the optimal settings for and role of opioid detoxification treatment programs during pregnancy. Although NAS is an appealing and important short-term outcome, the risk of maternal relapse through pregnancy and postpartum must be an outcome of future studies.

Conflict of Interest
None.

References
12 Lollis CM, Strothers HS, Chitwood DD, McGhee M. Sex, drugs, and HIV: does methadone maintenance reduce drug use and risky sexual behavior? J Behav Med 2000;23(3):545-557