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Opioid Detoxification During Pregnancy:

A Systematic Review

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Abstract

OBJECTIVE—To systematically review maternal and neonatal outcomes associated with opioid detoxification during pregnancy.

DATA SOURCES—PubMed, PsycINFO, EMBASE, Cochrane, and ClinicalTrials.gov databases were searched from January 1, 1966, to September 1, 2016.

METHODS OF STUDY SELECTION—English-language studies that reported outcomes associated with opioid detoxification among pregnant women with opioid use disorder were included. Nonoriginal research articles (case reports, editorials, reviews) and studies that failed to report outcomes for detoxification participants were excluded. Bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias and quality was assessed using the U.S. Preventive Service Task Force Quality of Evidence scale.

TABULATION, INTEGRATION, AND RESULTS—Of 1,315 unique abstracts identified, 15 met criteria for inclusion and included 1,997 participants, of whom 1,126 underwent detoxification. Study quality ranged from fair to poor as a result of the lack of a randomized control or comparison arm and high risk of bias across all studies. Only nine studies had a comparison arm. Detoxification completion (9–100%) and illicit drug relapse (0–100%) rates varied widely across studies depending on whether data from participants who did not complete detoxification or who were lost to follow-up were included in analyses. The reported rate of fetal

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loss was similar among women who did (14 [1.2%]) and did not undergo detoxification (17 [2.0%]).

CONCLUSIONS—Evidence does not support detoxification as a recommended treatment intervention as a result of low detoxification completion rates, high rates of relapse, and limited data regarding the effect of detoxification on maternal and neonatal outcomes beyond delivery.

Opioid agonist pharmacotherapy (with either methadone or buprenorphine) is endorsed by the American College of Obstetricians and Gynecologists and other professional societies as the optimal treatment for opioid use disorder during pregnancy.^{1–3} Initial recommendations for the use of pharmacotherapy during pregnancy were largely based on a case report of stillbirth after detoxification coupled with evidence of increased catecholamine release (measured by serial amniocentesis) indicating fetal stress during maternal withdrawal.^{4,5} Additional support for the effectiveness of opioid pharmacotherapy emerged from data in the 1970s, which demonstrated that women treated with methadone as part of a comprehensive addiction and prenatal care program had similar birth outcomes compared with women without a substance use disorder.^{6,7}

Over the past 15 years, the escalating use of opioids has led to a crisis of epidemic proportions in the United States. As a result, drug treatment admissions for opioid use disorder during pregnancy have risen markedly as have rates of newborns with neonatal abstinence syndrome and the costs necessary to treat them.^{8–10} Efforts to respond to the opioid epidemic among pregnant women have led to a reappraisal of detoxification during pregnancy, but its efficacy and role as an effective treatment option during pregnancy is unclear.¹¹ Thus, we systematically reviewed the published literature to evaluate the evidence regarding opioid detoxification during pregnancy with a focus on 1) describing the detoxification process; 2) summarizing adverse maternal and neonatal outcomes associated with detoxification including fetal demise, maternal relapse, and neonatal abstinence syndrome; and 3) identifying gaps in the existing literature to guide future research.

SOURCES

The study protocol was developed and the review performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and Meta-analysis Of Observational Studies in Epidemiology guidelines.^{12,13} PubMed, PsycINFO, EMBASE, Cochrane, and clinicaltrials.gov electronic databases were searched between January 1, 1966 (when records became indexed on Medline) and September 1, 2016. A reference librarian performed the database search and removed any duplicate records. The references of review articles were also reviewed to ensure capture of all publications related to opioids, pregnancy, and detoxification (Appendix 1, available online at <http://links.lww.com/AOG/B79>).

STUDY SELECTION

Six authors (M.T., E.E.K., T.E.W., A.P., D.J.H., C.E.M.) were organized into three author pairs and each author independently screened all titles and abstracts for inclusion. To be included, studies had to focus on pregnant women with opioid use disorder who received

opioid detoxification as the primary intervention. Studies that were not original research studies, were not in English, and that did not identify detoxification as the intervention were excluded. Titles and abstracts were included in the full-text review if there was any discrepancy in the decisions of author pairs. For full-text review, author pairs independently reviewed each article to identify studies that met inclusion criteria with any disagreements resolved by another author pair. For data extraction, eight authors (M.T., E.E.K., T.E.W., A.P., D.J.H., C.E.M., M.C.M., H.E.J.) were organized into four author pairs and relevant data from included articles were entered into a data extraction tool developed by the authors. The accuracy of extracted data was reviewed by two authors (M.T., E.E.K.). Each study's design and findings were qualitatively described. Meta-analysis was not performed as a result of heterogeneity in study designs, detoxification processes, and in how and what adverse maternal and neonatal outcomes were assessed. Authors were not contacted and additional data from included studies were not obtained beyond what was available in the published manuscripts.

Each author pair evaluated risk of bias in individual studies using the Cochrane Collaboration's tool for assessing risk of bias (Appendix 2, available online at <http://links.lww.com/AOG/B79>)¹⁴ and included six domains: selection, performance, detection, attrition, reporting, and other bias. Summary assessments of risk of bias (high risk, unclear risk, and low risk) were made independently by two authors (M.T., E.E.K.) per Cochrane Collaboration's guidelines. Study quality was assessed independently by two authors (M.T., E.E.K.) according to the risk of bias and the overall evidence provided for adverse maternal and neonatal outcomes using the 3-point U.S. Preventative Services Task Force grading scale (good, fair, poor).¹⁵ A "good"-quality study was well designed with no important limitations, a "fair" study was adequate to determine effects on outcomes, but had limitations as a result of the indirect nature of the evidence, and a "poor" study was insufficient to assess effects on outcomes as a result of limited power, important flaws, or a lack of information regarding outcomes.¹⁵

RESULTS

Our systematic review captured 1,315 unique citations, of which 110 were assessed for full-text review. Three of these studies were secondary analyses of data from larger studies that met inclusion criteria and were thus excluded to avoid duplicating data.^{16–18} Fifteen studies were included in the qualitative synthesis (Fig. 1). The publication periods for the included studies ranged from 1975 to 2016. Among these, 10 studies were published after 2000 during the current opioid crisis. Study location varied with eight studies conducted in the United States, one in Canada, and six conducted in Europe and Australia.

No randomized clinical trials were identified (Table 1). All included studies were observational and only five studies had prospectively collected data.^{19–23} Before detoxification, most participants had documented opioid use (primarily through urine drug testing), although the distinction between heroin and prescription opioids was not always clear. Other non-opioid illicit substance use was reported in six studies^{20,23–27} and tobacco use was reported in five.^{23,25–28} Significant heterogeneity related to the presence of a comparison group and the types of comparison groups used to evaluate differences in

maternal and neonatal outcomes existed across the studies. Only nine of the included studies had a comparison group, which ranged from women without opioid use disorder (n=4)^{20,21,25,29} to women with opioid use disorder on opioid agonist pharmacotherapy (n=4)^{22,26,28,30} to women with illicit opioid (n=2)^{20,31} and drug (n=2)^{22,25} use. The majority of studies also conducted within-group comparisons (eg, successful detoxification compared with in process of methadone taper compared with illicit opioid use after detoxification) rather than prospectively based on their planned treatment regimen.

A total of 1,997 participants, of whom 1,126 underwent detoxification as the primary treatment for opioid use disorder were included (Table 2). Detoxification primarily took place in inpatient settings (n=9) and in two studies, detoxification took place as part of a residential treatment program.^{22,25} Three studies included patients who were incarcerated at the time of the detoxification.^{19,25,32} In Bell et al, 108 women with opioid use disorder underwent “involuntary withdrawal” as a result of the absence of opioid pharmacotherapy availability in the penal system.¹⁹ In Haabrekke et al, eight women were involuntarily institutionalized and forced into detoxification²⁵; in Sinha et al, of the 10 women who completed detoxification, nine did so without medical supervision (“quit cold turkey”) and one underwent supervised withdrawal in prison.³² Gestational age at the time of withdrawal was reported in all but the oldest study³⁰ and predominantly occurred in the second or third trimester.

Pharmacotherapy was specified in all but one study.²² In most studies either methadone or buprenorphine was used, with the exception of LePreau et al, in which clonidine was used followed by phenobarbital,²³ Hulse et al, in which sedation was used,³³ and Haabrekke et al, in which the type of opioid agonist used was not specified.²⁵ In Bell et al, women who were involuntarily detoxified while incarcerated received clonidine and supportive medications.¹⁹ The reported duration of withdrawal ranged from 3 days to 16 weeks and was not reported in five studies. Only seven studies reported fetal monitoring, and only one described fetal monitoring as part of a formal detoxification protocol.²³ Behavioral counseling that occurred either concurrently or after withdrawal was mentioned in 11 studies, although descriptions of the type and content of the counseling were vague and adherence was not reported. Prenatal care engagement was reported by most studies, although timing and frequency of visits were not reported. The majority of studies limited maternal follow-up to delivery with only two studies following participants postpartum.^{20,30}

Table 1 summarizes select maternal, birth, and neonatal outcomes for women who underwent detoxification. Detoxification completion rates varied widely (9–100%) among included studies, which was largely secondary to whether data included in analyses were from participants who did not complete detoxification or who were lost to follow-up. In Hulse et al, one participant underwent detoxification twice.³³ Importantly, the two studies with detoxification completion rates of 100% were inpatient residential treatment programs, one of which included women who were involuntarily institutionalized.²⁵ Similarly, relapse, captured primarily by positive urine toxicology, ranged from 0 to 100%; this variability was also dependent on which groups of participants were included in the analysis. For example, in Luty et al, 101 women entered the detoxification program, but only 42 women completed the process.²⁹ Among these women, obstetric records were available for only 28 women and

of these, four records were incomplete. Among the 24 women with adequate obstetric records, 23 (96%) had a positive urine toxicology at delivery. Importantly, maternal death resulting from opioid overdose was reported by one study. In Wallach et al, two maternal deaths resulting from overdose at 2 and 6 weeks postpartum were reported among women who underwent detoxification during pregnancy.³⁰

Fetal demise including miscarriage was reported in most studies. In detoxification groups (n=1,126), there were 14 total demises: three first trimester (less than 14 weeks of gestation), five second trimester (14 weeks or greater but less than 28 weeks of gestation), one third trimester (28 weeks of gestation or greater), and five with gestational ages not reported. In comparison groups (n=871), there were 17 total demises: five first trimester (one at 13 weeks of gestation and four reported as spontaneous abortions without exact gestational ages), two second trimester, five with birth weight reported (970, 531, 2,200, 1,800, 1,200 g) instead of gestational age, and five with gestational ages not reported. Therefore, the rate of loss among the women undergoing detoxification (1.24%; 95% CI 0.70–2.21) and the rate of loss within the comparison groups (1.95%; 95% CI 1.10–3.10) were similar and both rates were less than the reported rate of fetal loss in the general population.³⁴ The majority of the fetal losses were not attributed to the withdrawal process by the authors because most occurred after detoxification.

Birth weight was reported in 14 studies and intrauterine growth restriction was reported in one. The birth weight of neonates for women who were detoxified was found to be greater than those of women with ongoing illicit drug use in two studies^{22,27} and significantly less than neonates of women without opioid use disorder in two studies.^{20,21} Rates of preterm birth varied from 0 to 38% and there were no statistically significant differences reported in the rates of preterm birth between women who underwent detoxification and comparison groups. There was a minimal difference in the rates of preterm birth in the two studies that had a comparison group of women without opioid use disorder (5.5% vs 5.8%²⁰ and 0% vs 0%²⁵).

Neonatal abstinence syndrome was reported in 11 studies and was defined by pharmacotherapy treatment. Across studies, neonatal abstinence syndrome treatment rates ranged from 0 to 100%. Only two studies reported no newborn withdrawal among women who underwent detoxification.^{25,32} Variability in neonatal abstinence syndrome rates may in part be attributable to variability in treatment thresholds within the studies. Except for Sinha et al,³² which used a scoring system described by Rivers (Rivers score greater than 2),³⁵ all of the studies used the Finnegan scoring system to determine treatment for neonatal abstinence syndrome.³⁶ A Finnegan score greater than 7 was used by one study,²⁰ a score 8 or greater was used by four studies,^{21,24,25,31} a score 9 or greater was used by two studies,^{26,28} a score 10 or greater was used by one study,¹⁹ and the scores used to treat neonates were not recorded in two studies.^{27,30} In addition to variability in scoring thresholds, many studies required more than two threshold scores to initiate treatment.^{19,21,24} Among the neonates whose mothers underwent detoxification, neonatal abstinence syndrome rates were significantly higher in Dooley et al (12.8% vs 6.2%; $P<.001$)²⁰ and significantly lower in Haabrekke et al (0% vs 76.9%; $P<.001$)²⁵ compared with pregnant women with illicit opioid use. Higher rates in Dooley et al may be in part the result of only “occasional” opioid use

and a high spontaneous “quit” rate among pregnant women in the opioid comparison group. Significantly lower within-group differences were also found in neonatal abstinence syndrome rates among women who successfully completed detoxification compared with women who either resumed illicit opioid use^{27,32} or who resumed opioid pharmacotherapy during the detoxification process.^{21,32} Neonatal length of stay was reported in only nine of the studies. Pediatric outcomes beyond the neonatal period were reported for a small percentage of children in two studies. In Wallach et al, normal physical development and psychometric testing (“normal” [n=12], “high normal” [n=1], and “low normal results” [n=1]) for 14 children was provided at 4 years of age.³⁰ Neuroanatomic, neurocognitive, and visual acuity outcomes from Haabrekke were reported for 12 children at 4.5 years of age in Walhovd.¹⁸ A detailed summary of maternal and neonatal outcomes reported by included studies is described in Appendices 3 and 4, available online at <http://links.lww.com/AOG/B79>.

The overall quality of the evidence ranged from “fair” to “poor” primarily as a result of study design, the lack of randomized controls, and a high risk of bias. Bias and quality judgments by the authors were informed by the largely retrospective approaches to data collection, minimal information about the detoxification and comparison group populations, insufficient detail about inclusion and exclusion criteria, self-selection of patients into detoxification groups, and failure to account for lost to follow-up and missing data. Together, these limitations prevent the interpretation of pregnancy outcomes after detoxification. A detailed description of bias and quality assessments for each included study are described in Appendix 2 (<http://links.lww.com/AOG/B79>).

DISCUSSION

Our review supports the recommendations of the American Society of Addiction Medicine, the American College of Obstetricians and Gynecologists, and the World Health Organization, which promote pharmacotherapy over detoxification for opioid use disorder in pregnancy as a result of low detoxification completion rates, high rates of relapse, and limited data regarding the effect of detoxification on maternal and neonatal outcomes beyond delivery.^{1–3} Although the current opioid crisis has prompted a reappraisal of detoxification, our review demonstrates that interest in detoxification during pregnancy has been present since the introduction of opioid pharmacotherapy. Although the evidence suggests that fetal demise is not increased with detoxification, loss to follow-up was an important limitation of all studies. As such, the strength of this finding should not be taken as support for abandoning opioid pharmacotherapy as the optimal treatment for opioid use disorder in pregnancy.

Interest in detoxification is driven in part from a desire to decrease the number of neonates with neonatal abstinence syndrome and their associated health care costs. However, our review does not support detoxification for the prevention of neonatal abstinence syndrome as a result of the high rate of relapse and, therefore, continued fetal opioid exposure. Furthermore, relapse as reported in the included studies was likely underreported as a result of lack of follow-up beyond the immediate postpartum period as well as high lost-to-follow-up rates across all studies. Relapse also increases the risk of human immunodeficiency virus,

hepatitis, and overdose as exemplified by the two overdose deaths reported by Wallach et al.³⁰

Addiction is a chronic neurochemical disease of brain reward, motivation, memory, and related circuitry whose symptoms manifest in behaviors.³⁷ Detoxification is an acute intervention, which can manage the physical symptoms associated with withdrawal but does not address the chronic cycles of relapse and remission that characterize the illness. To wit, neither the Substance Abuse Mental Health Association nor the American Society of Addiction Medicine considers detoxification as standalone treatment and patients should be advised about risk of relapse from detoxification.^{1,38} The general addiction literature is illustrative here. Since the 1970s, detoxification has been associated with high rates of relapse³⁹ and low treatment retention in contrast to methadone maintenance.⁴⁰ A recent Cochrane review contrasting detoxification with buprenorphine maintenance similarly demonstrated increased rates of relapse and poor treatment adherence among individuals receiving detoxification alone.⁴¹ Although detoxification can be conceptualized as a door to treatment, the failure to provide ongoing behavioral and psychosocial interventions may contribute to the high rates of relapse associated with this process.³⁸ Among the studies included in this review, few described any ongoing behavioral care after detoxification and none reported any supportive services after delivery.

Although some women may benefit from detoxification, future investigations should be aimed at characterizing the subpopulation of pregnant women for whom withdrawal is most beneficial. Guidelines regarding the optimal treatment regimen (ie, pharmacotherapeutic agent, setting, intensity, and duration of supporting psychosocial services) without increasing maternal and neonatal morbidity and mortality are warranted. Furthermore, as a result of the poor quality of the existing literature, rigorous, multicenter, randomized clinical trials with appropriate control groups are necessary to fully understand the short- and long-term consequences of opioid detoxification compared with pharmacotherapy during pregnancy. An intention-to-treat analytic approach including close attention to participants who are lost to follow-up should be used. To properly assess the risk of relapse, overdose, and overdose death, participants should be followed for at least 1 year after delivery with the effects of postpartum substance use on both maternal and pediatric outcomes evaluated.^{42–44} Finally, all participants should receive robust behavioral health counseling.

Clinical care considerations for pregnant women with opioid use disorder should be focused on the mother–infant dyad.⁴⁵ Most participants in the included studies voluntarily participated in the detoxification process, which emphasizes the importance of pregnancy as a time of enhanced maternal investment in behavior change. However, taking advantage of the “pregnancy opportunity” to reinforce patient fears related to fetal opioid exposure and withdrawal by ceasing or not initiating pharmacotherapy should not be the primary driving force behind prevention and treatment efforts. Instead, gender-specific public health and treatment approaches highlighting the chronic nature of addiction and targeting women across the life course should be emphasized. Overall, the dialogue regarding opioid use disorder among women should be modified to emphasize that effective treatments are available before, during, and after pregnancy and efforts to expand comprehensive, women-

centered treatment availability and accessibility are a more efficient and effective way to improve maternal and neonatal outcomes within and well beyond the perinatal period.

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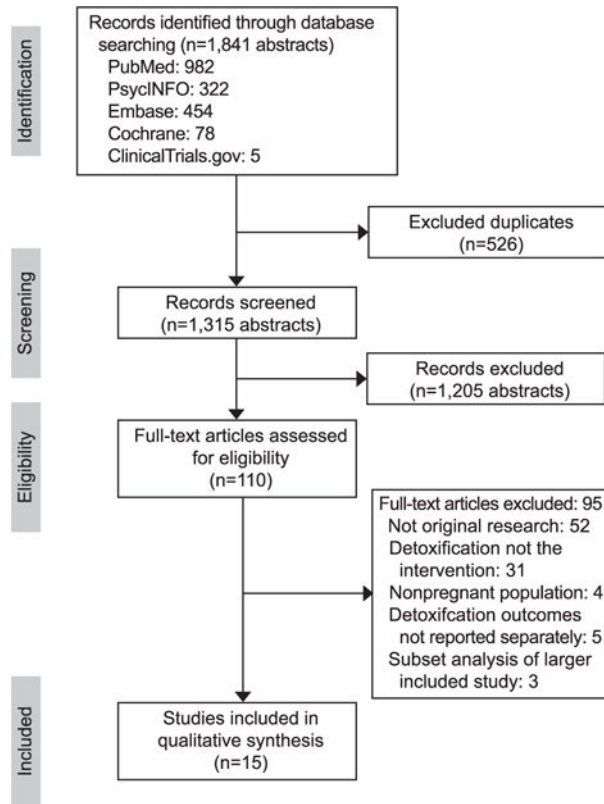


Fig. 1. Flow diagram
Terplan. Opioid Detoxification During Pregnancy. *Obstet Gynecol* 2018.

Table 1

Summary of Evidence Regarding Detoxification During Pregnancy*

Author (year; country)	Study Design	Total n	Detox Group(s), n	Comparison Group(s)	Summary Outcomes Among Women Undergoing Detoxification			
					Maternal	Birth	Neonatal	Quality
Bell et al (2016; United States) ¹⁹	Retrospective analysis of prospectively collected data	301	Detoxification by 4 methods, total n=301 1 Acute detoxification in jail, n=108 2 Inpt bup detoxification + outpt follow-up, n=23 3 Inpt bup detoxification only, n=77 4 Slow outpt bup detoxification, n=93	None, within-group comparisons made among 4 detoxification groups	Detoxification comp: NR Drug use: 17.4–74% [†]	Demise: n=2 Growth: IUGR 5% PTB: 13–19% [†]	NAS: 17.2–70.1% [†] # LOS: NR	Poor
Dooley et al (2015; Canada) ²⁰	Prospective cohort comparison	600	Morphine and bup detoxification in remote First Nations communities, n=86	Pregnant with occasional opioid use, n=80	Detoxification comp: 9.3%	Demise: n=2	NAS: 12.8% [†]	Fair
Haabrekke et al (2014; Norway) ²⁵	Retrospective cohort comparison	187	Residential detoxification (2004–2008), n=21	Non-OUID pregnant, n=434 Pregnant with SUD (1991–1996), n=78	Drug use: 34.8% Detoxification comp: 100%	Growth: 3.301 g [↓] PTB: 5.8%	LOS: 2.4 d [†]	Poor
Stewart et al (2013, United States) ²⁷	Retrospective cohort	95	Methadone detoxification, n=95	Non-OUID pregnant (1991–1996), n=58 Non-OUID pregnant (2004–2008), n=30 None, within-group comparisons between detoxification participants who did (n=42) and did not (n=53) use opioids	Drug use: 0% Detoxification comp: 80%	Growth: 3.293 g PTB: 0% Demise: n=3	LOS: NR NAS: 10–80% [†] #	Poor
Lund et al (2012, United States) ²⁸	Retrospective cohort comparison	25	Methadone detoxification, n=8	Pregnant with OUD on MM, n=12 Pregnant with OUD on BM, n=5	Drug use: 44.2% Detoxification comp: 15.7%	Growth: 2.788–3.065 g [†] # PTB: 10–18% [†]	LOS: 3–22 d [†]	Poor
Jones et al (2008, United States) ²⁶	Retrospective comparison	175	Detoxification by 2 methods, total n=123	Pregnant with OUD on MM, n=52; within-group comparisons between participants who received MM in both detoxification groups (1. n=8; 2. n=20)	Drug use: 14.3% Detoxification comp: 58.3–89.3%	Growth: 3.023 g PTB: 37.5% Demise: n=3	LOS: 7.0 d NAS: 25–36% [†]	Poor

Author (year; country)	Study Design	Total n	Detox Group(s), n	Comparison Group(s)	Summary Outcomes Among Women Undergoing Detoxification			Quality
					Maternal	Birth	Neonatal	
Kahila et al (2007, Finland) ²¹	Prospective cohort	67	1 3-d methadone detoxification, n=75	Finland population data, n=57,759; within-group comparisons between detoxification participants who received BM and were (n=21) and were not compliant (n=37) with treatment visits	Drug use: 15.0–57.1% † #	Growth: 2,824–3,054 g † PTB: 27–36% †	LOS: 6.0–9.6 d †	Fair
			2 7-d methadone detoxification, n=48					
Luty et al (2003, United Kingdom) ²⁹	Retrospective case series	101	Methadone detoxification, n=101	Published rates of SAB and premature delivery in the general population	Drug use: 33.3–45.9% †	Growth: 3,180 g † PTB: 0–5.4% †	LOS: 11.6–28.1 d † #	Poor
Hulse et al (2001; Australia, Portugal, United Kingdom) ³³	Retrospective case series	18	Rapid detoxification with sedation, n=18**	None	Detoxification comp: 41.6%	Demise: n=1	NAS: NR	Poor
					Drug use: 95.8%	Growth: 2,564 g PTB: NR	LOS: NR	
Sinha et al (2001, United Kingdom) ³²	Retrospective case study	51	Methadone detoxification, n=51	None, within-group comparisons between detoxification participants who received MM (n=22) and used opioids (n=19)	Drug use: 16.7%	Growth: 3,008 g PTB: 0%	LOS: NR	Poor
					Detoxification comp: 19.6%	Demise: n=1	NAS: 0–81% † #	
Dashe et al (1998; United States) ²⁴	Retrospective case series	34	Detoxification by 2 methods, total n=34	None, within-group comparisons among detoxification participants after methadone (n=21) and clonidine (n=13) detoxification and among those who received MM (n=4) and used opioids (n=10)	Drug use: 37.3%	Growth: 2,754–3,800 g † PTB: NR	LOS: 7.8–33.2 d † #	Poor
					Detoxification comp: 73.5% †	Demise: n=0	NAS: 15%	
Kyei-Aboagye et al (1998, United States) ²²	Prospective case series	74	1 Methadone, n=21	Pregnant with SUD, n=44 (OUD on MM n=15), cocaine use [n=29]	Drug use: 29.4%	Growth: 3,075 g PTB: 18%	LOS: 8 d †	Poor
			2 Drug-free residential detoxification, n=30					
					Drug use: 0%	Growth: 3,218 g † PTB: NR	LOS: 3 d †	

Author (year; country)	Study Design	Total n	Detox Group(s), n	Comparison Group(s)	Summary Outcomes Among Women Undergoing Detoxification			Quality
					Maternal	Birth	Neonatal	
LePreau et al (1995, United States) ²³	Prospective cohort	33	Clonidine detoxification, n=33	None	Detoxification comp: 69.7%	Demise: n=1	NAS: NR	Poor
Maas et al (1990, Germany) ³¹	Retrospective case series	75	Methadone detoxification, n=58	Pregnant with OUD, n=17; within-group comparisons among detoxification participants who received MM (n=8) and used opioids (n=32)	Drug use: NR Detoxification comp: 29.8%	Growth: 3,008 g PTB: NR Demise: n=0	LOS: NR NAS: 11.8–75% [†] ↓	Poor
Wallach et al (1975, United States) ³⁰	Retrospective cohort	161	Methadone detoxification, n=100	Pregnant with OUD on MM, n=61	Drug use: 56.1% Detoxification comp: NR	Growth: 2,625–3,070 g [‡] PTB: 11.8–50% [‡]	LOS: NR NAS: NR	Poor

NR, not reported; NAS, neonatal abstinence syndrome; LOS, neonatal length of stay; Demise, number of fetal demises; Growth, mean fetal growth; PTB, rate of preterm birth; IUGR, rate of intrauterine growth restriction; SUD, substance use disorder; OUD, opioid use disorder; MM, methadone maintenance; BM, buprenorphine maintenance; SAB, spontaneous abortion; inpt, inpatient; outpt, outpatient; Drug use, rate of illicit drug use or relapse; Detoxification comp, rate of participants completing detoxification process; bup, buprenorphine.

[†] Detoxification outcome significantly greater than nondetoxification comparison outcome; [‡] detoxification outcome significantly less than nondetoxification comparison outcome.

^{*} Detailed outcome data between detoxification and control and within detoxification comparison groups is reported in Appendix 3 (available online at <http://links.lww.com/AOG/B79>).

[‡] Range across all detoxification groups; 1 participant underwent detoxification twice.

[‡] Four patients delivered during their detoxification hospitalization.

[§] NAS treatment duration.

^{||} Length of stay does not include 7- to 10-d stay in outpatient facility for follow-up and NAS surveillance.

[¶] Two participants on naltrexone maintenance.

[#] Significant within-group differences among detoxification groups.

Table 2

Summary of Detoxification Process in Included Studies

Author	Detoxification, n	Setting	Trimester or Gestational Age at Detoxification, n (%) [*]	Duration	Pharmacotherapy	Fetal Monitoring	Behavioral Health	Follow-up
Bell et al ¹⁹	301	Detoxification 1: jail	1: 1st: 10 (9), 2nd: 65 (60), 3rd: 33 (31)	1: NR	1: Clonidine, antiemetic, antidiarrheal	FHT	1: None	Delivery
		Detoxification 2: inpatient	2: 1st: 4 (17), 2nd: 10 (43), 3rd: 9 (39)	2: 5–8 d	2: Buprenorphine		2: Residential or 8 h daily	
		Detoxification 3: inpatient	3: 1st: 12 (15), 2nd: 36 (47), 3rd: 29 (38)	3: 5–8 d	3: Buprenorphine		3: None	
		Detoxification 4: outpatient	4: 1st: 2 (2), 2nd: 37 (40), 3rd: 54 (58)	4: 8–16 wk	4: Buprenorphine		4: Ongoing outpatient	
Dooley et al ²⁰	86	Outpatient	1st: 14 (16), 2nd: 32 (37), 3rd: 32 (37)	101 (SD±67) d [†]	Morphine (n=72); buprenorphine (n=8)	NR	Case-by-case basis	7–10 d pp
Haabrekke et al ²⁵	21	Residential [‡]	1st: 4 (19), 2nd: 7 (33), 3rd: 10 (48)	NR	Opioid agonists and pain medications for severe withdrawal	NR	During residential stay for up to 1 y after delivery	Delivery
Stewart et al ²⁷	95	Inpatient	20 [§]	15–25 d				Neonatal: n=12 for 4.5 y ^{§§}
Lund et al ²⁸	8 [#]	Inpatient	22.8 (SD±8.3) [‡]	7 d	Methadone	>24 wk	Offered admission to outpatient drug rehabilitation facility [¶]	Delivery
Jones et al ²⁶	123	Inpatient	20.3 (range 5–39) [‡]	Detoxification 1: 3 d 2: 7 d	Methadone	NR	Outpatient	Delivery
Kahila et al ²¹	67	Outpatient	1st: 38 (57), 2nd–3rd: 13 (21)	NR	Buprenorphine	BPP/growth >24 wk, NST >26 wk	NR	Delivery
Luty et al ²⁹	101	Inpatient	1st: 5 (5), 2nd: 54 (53), 3rd: 57 (56)	19.5 (SE=1.1) d	Methadone	NR	NR	Delivery
Hulse et al ³³	18 ^{**}	NR	1st: 2 (11), 2nd: 11 (61), 3rd: 6 (33)	NR	Oral or IV sedation	US, n=4	NR	Delivery
Sinha et al ³²	51	NR ^{††}	2nd: 51 (100)	NR	Methadone ^{‡‡}	NR	Outpatient during prenatal care	Delivery

Author	Detoxification, n	Setting	Trimester or Gestational Age at Detoxification, n (%) [*]	Duration	Pharmacotherapy	Fetal Monitoring	Behavioral Health	Follow-up
Dashe et al ²⁴	34	Inpatient	24.2 (SD±8.1) [‡]	12 (range 3–39) ^d	Methadone for severe withdrawal, n=21; clonidine for mild withdrawal, n=13	FHT	Outpatient during prenatal care	Delivery
Kyei-Aboagye et al ²²	30	Residential	Up to the 2nd	NR	NR	NR	Part of residential program	Delivery
LePreau et al ²³	33	Inpatient	15.2 (range 4–36) [‡]	5 d	Clonidine, antiemetic and antidiarrheal medications	NST >32 wk	Daily group and individual counseling during detoxification, referred to outpatient counseling after detoxification [¶]	Delivery
Maas et al ³¹	58	Initially inpatient then outpatient	28 (range 9–40) [§]	9 (range 0–28) [§]	Methadone	FHT	NR	Delivery
Wallach et al ³⁰	100	Inpatient	NR	10 d	Methadone	NR	2–4 wk of inpatient counseling after detoxification	6 wk pp
								Neonatal: N=14 for 4 y

NR, not reported; IV, intravenous; FHT, fetal heart tone auscultation, US, ultrasonography; NST, nonstress test; pp, postpartum; BPP, biophysical profile; SE, standard error.

^{*} n (%) unless otherwise specified.

[‡]Mean.

[‡]n=8 pregnant women were involuntarily institutionalized.

[§]Median.

[¶]Median duration of detoxification for women with and without illicit drug use at delivery.

[¶]Program attendance was not reported.

[#] n=51 initiated detoxification, but data for women who did not complete detoxification were not reported.

^{**} One participant underwent detoxification twice.

^{††} n=1 patient had supervised withdrawal in prison.

^{†††} n=9 women underwent self-directed “cold turkey” withdrawal.

Reported in Walhovd et al. 18
§§§

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