OBSTETRICS

Use of naltrexone in treating opioid use disorder in pregnancy

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BACKGROUND: The mainstay of the management of opioid use disorder in pregnancy is with methadone or buprenorphine medication-assisted treatment. Methadone and buprenorphine are opioid agonist drugs. Naltrexone, an opioid antagonist, is also a medication-assisted treatment option; however, to date, only a few retrospective studies have reported its use in pregnancy.

OBJECTIVE: Our study objective was to evaluate prospectively obstetric and newborn outcomes and the maternal/fetal effects of the use of naltrexone as a medication-assisted treatment in pregnant patients with opioid use disorder.

STUDY DESIGN: We performed a prospective cohort study collecting data on all pregnant women who were treated with naltrexone medication-assisted treatment compared with pregnant women who were treated with methadone or buprenorphine medication-assisted treatment. Based on a sample size calculation, it was determined that for a power of 90, a minimum of 160 study participants (80 in each group) was needed with an alpha of .01 and an expected 60% rate of newborn infants who were treated for neonatal abstinence syndrome in the methadone or buprenorphine medication-assisted treatment group compared with a 30% rate in the naltrexone medication-assisted treatment group. In a random subset of 20 maternal/newborn dyads, blood levels for naltrexone and 6-beta-naltrexol (an active metabolite) were analyzed at delivery.

RESULTS: A total of 230 patients were studied: 121 patients with naltrexone medication-assisted treatment compared with 109 patients with methadone or buprenorphine medication-assisted treatment. No differences between groups were seen regarding demographics, the use of comedications/drugs, or obstetric outcomes. For newborn outcomes, the rate of neonatal abstinence syndrome in neonates >34 weeks gestation was significantly lower in the naltrexone medication-assisted treatment group (10/119 [8.4%] vs 79/105 [75.2%]; $P<.0001$). Multivariate analysis demonstrated that the only significant factor for the rate of neonatal abstinence syndrome was the form of medication-assisted treatment. Of 87 patients who received naltrexone up to delivery, no neonates experienced symptoms of neonatal abstinence syndrome. No maternal relapses occurred in the 7-day no-treatment window before the initiation of naltrexone therapy. No cases of spontaneous abortion or stillbirth occurred in either group. In 64 patients who started naltrexone therapy at ≥24 weeks gestation, no changes were seen in the fetal heart monitor tracing with drug initiation. The incidence of birth anomalies was no different between the groups. Umbilical cord blood and maternal levels for naltrexone and 6-beta-naltrexol matched; no levels were elevated, and values were undetected if naltrexone was discontinued >60 hours before delivery.

CONCLUSION: These study data demonstrate that, in pregnant women who choose to completely detoxify off opioid drugs during gestation, naltrexone, as a continued form of medication-assisted treatment, is a viable option for some pregnant patients who experience opioid use disorder. Naltrexone crosses the placenta, and maternal and fetal levels are concordant. Because naltrexone clears quickly from the maternal circulation, this rapid clearance needs to be addressed with patients. This is important because maternal relapse could occur in a short time-period if the oral drug is discontinued without the knowledge of their healthcare providers. Nonetheless, the drug is well-tolerated by both mother and fetus, and newborn infants do not experience symptoms of neonatal abstinence syndrome if naltrexone medication-assisted treatment is maintained to delivery.

Key words: buprenorphine, drug, methadone, neonatal abstinence syndrome, opioid use disorder, overdose

Opioid use disorder (OUD) is currently a major healthcare concern that results in increased hospitalizations, overdose, death, psychosocial issues, and healthcare costs.[1–3] This has also led to an increase in OUD in pregnant women.[4] The cornerstone of medical treatment for this condition is medication-assisted treatment (MAT).[5] Three primary medications (methadone, buprenorphine, and naltrexone) are recommended for MAT by the Substance Abuse and Mental Health Services Administration.[5] Methadone and buprenorphine are opioid agonist medications that continue opioid drug dependence but, if used correctly, prevent cravings for illicit opioid drugs. Naltrexone is an opioid antagonist drug that can also prevent cravings but does not produce dependence. Methadone has been the mainstay for treating OUD in pregnancy for years; however, buprenorphine recently has been added as an alternate treatment option.[6] Naltrexone, however, has not been examined extensively in the obstetric population because it requires full detoxification before it can be used.

Only a few retrospective studies that have reported the use of naltrexone in human pregnancy have been published that included >80 pregnancies; the results, at a minimum, were no different than for those women who were treated with methadone.[7–13] Through an extensive literature search using PubMed, Medline, Scopus, Google Scholar, and the Cochrane Library, we found no prospective studies on the use of

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AJOG at a Glance

Why was this study conducted?

Opioid use disorder is now a major healthcare problem in the United States and has greatly increased the rate of newborn infants who are treated for neonatal abstinence syndrome. Alternative options are needed for the treatment of pregnant women with opioid use disorder.

Key findings

The use of naltrexone as a form of medication-assisted treatment is a viable option for the treatment of some obstetrics patients with opioid use disorder.

What does this add to what is known?

This is the first prospective study to analyze the use of naltrexone in the treatment pregnant patients who experience opioid use disorder.

naltrexone in pregnancy. Furthermore, no study was found that analyzed maternal and newborn blood levels of patients who were receiving naltrexone at the time of delivery. Naltrexone is similar to naloxone (another opioid antagonist drug) but differs by the replacement of an allyl group (C_2H_3) on the naloxone molecule with a cyclopropyl-methyl group (C_3H_5) on the naltrexone molecule.[14,15] This change results in a longer duration of action for naltrexone. Naloxone and naltrexone are classified by the United States Food and Drug Administration as category C medications for use in pregnancy.[16]

In November 2016, we created a designated obstetrics OUD clinic at our institution. This clinic uses intense behavioral health management. When patients become engaged in prenatal care and are stable on traditional opioid agonist MAT, our clinic offers the option of tapering with full detoxification, if desired. If full detoxification is chosen and successful, patients are then offered naltrexone as a continued form of MAT to maintain sobriety, decrease opioid cravings, and decrease the risk for relapse. Those who choose naltrexone and those who do not are both continued in behavioral health management.

Our study objective was to perform a prospective observational cohort study that would compare those patients who chose opioid antagonist naltrexone pharmacotherapy MAT (after full detoxification) with those who opted for continued opioid agonist pharmacotherapy (traditional) MAT. Our secondary study objective was to analyze blood levels of naltrexone in paired mother/newborn infant dyads in a subset of random patients at the time of delivery.

Methods

We performed a prospective cohort study on those patients who were treated with opioid antagonist pharmacotherapy (naltrexone) MAT after full detoxification compared with those patients who were treated with continued opioid agonist pharmacotherapy (traditional) MAT of methadone or buprenorphine. The naltrexone MAT and traditional MAT populations came from the same designated obstetrics OUD clinic and delivered at University of Tennessee Medical Center, Knoxville. Pregnancies that involved fetal aneuploidy were excluded.

All patients in the designated clinic (if not already in a methadone or buprenorphine program) are placed in traditional MAT programs of buprenorphine or methadone to avoid illicit substance use. The average range of daily buprenorphine dosage was 8−16 mg and for a daily methadone dosage was 50−120 mg. For those patients who are fully engaged in traditional MAT and prenatal care, we offer 2 pregnancy management options after an informed discussion in a nondirective method. The primary concern with opioid tapering or full detoxification is the potential for maternal relapse with the inherent risk for overdose. The primary concern with continued opioid drug maintenance is the potential for newborn dependence with the inherent risk for neonatal abstinence syndrome (NAS) and other potential newborn effects.[17,18] For those patients who choose medically supervised withdrawal, there are 2 options that are either inpatient or outpatient; these have previously been described.[17] If fully detoxified, this group is then offered naltrexone MAT. Additionally, if a patient enters our program receiving naltrexone therapy, they are given the option of continuing this form of MAT after the same discussion.

The naltrexone protocol requires a patient to be opioid drug free for at least 7 days with 2 negative drug screens. Once this is accomplished, a daily 50-mg oral dose is used that is adjusted near delivery. For pregnancies at ≥24 weeks gestation, patients have continuous fetal heart rate (FHR) monitoring for 60 minutes minimum, while the initial dose is administered. For those patients at <24 weeks gestation, the FHR is evaluated by Doppler or ultrasound imaging before the initial dose, 30 minutes after dosing, and again at 60 minutes. All patients are contacted by phone 3−4 days after naltrexone initiation and are scheduled to return for follow up in 1 week. All patients in the designated obstetrics OUD clinic have biophysical profiles performed every other week from 28−32 weeks gestation and then weekly until delivery.

Maternal and neonatal outcome data were collected prospectively by the authors. Maternal data collection included demographics, medical history, social history, and delivery data. Specific information on use of tobacco, alcohol, marijuana, illicit drugs, gabapentin, and selective serotonin reuptake inhibitors (SSRIs) was recorded. Maternal drug use was confirmed by urine toxicology studies that were performed by a major laboratory. All patients had urine drug screening performed during prenatal care and at delivery in both the traditional MAT and naltrexone MAT groups. Newborn data collection included birthweight, gender, head circumference

(HC) at birth, diagnosis of NAS that led to newborn treatment, neonatal intensive care unit admission, and hospital length of stay. The criteria for making a diagnosis of NAS that resulted in newborn treatment consisted of any 2 consecutive Finnegan scores of ≥10 or a single Finnegan score of ≥12.[19]

The best obstetric estimate, as recommended by the American College of Obstetricians and Gynecologists Committee Opinion, was used for pregnancy dating in both groups.[20] More than 1 ultrasound scan was performed in every study patient before delivery. Birthweight and HC nomograms were from the American Academy of Pediatrics based on gestational age and sex.[21] HC measurements were performed by a single group of pediatric nurse practitioners and physicians on all newborn infants with a uniform approach. The HC was obtained after resolution of caput or molding if present at delivery.

One of the primary study endpoints was the rate of newborn infants who were treated for symptoms of NAS that was expected to be lower in the naltrexone MAT group. For this, we performed a sample size calculation; for a power of 90, a minimum of 160 study participants (80 in each group) was needed (with the use of an alpha of .01 and an expected 60% rate of newborns who were treated for NAS in the traditional MAT group compared with a 30% rate in the naltrexone MAT group). Based on the average number of pregnant patients who were seen in our clinic per month who choose medically supervised withdrawal and full detoxification (with the assumption that 50−60% might choose naltrexone MAT), it was calculated that this investigation would need to span a minimum of 16 months. Therefore, based on a start date of July 1, 2017, the decision was made to collect data through October 31, 2018.

For the secondary study objective, maternal and newborn blood levels were analyzed in a subset of 20 random patients for naltrexone and 6-beta-naltrexol at delivery. Statistical analysis involved chi-square, Fishers exact, and Student *t* tests, where applicable, with significance considered at a probability value of <.05. Multivariate regression analysis was also performed where indicated. All comparisons were performed against a 2-sided alternative hypothesis. This study was reviewed and approved by the institutional review board of University of Tennessee Medical Center, Knoxville. There was no commercial support or outside sponsors for this study.

Results

There were 363 patients treated in the dedicated obstetrics OUD clinic during the study period. Of these, 29 patients (8%) never engaged in a MAT program, had numerous absentee healthcare visits, and were excluded. The Figure shows that the study population consisted of 109 patients in the traditional buprenorphine/methadone MAT group compared with 121 patients in the naltrexone MAT group.

Table 1 shows the demographics between the 2 groups; no differences were seen. A median of 8 drug screens were performed for both groups; the numbers positive for other drugs during the gestation, including benzodiazepines, amphetamines, cocaine, marijuana, alcohol, gabapentin, and SSRIs were also not different. Tobacco usage during the pregnancy was based on patient report.

Table 2 provides the obstetric and newborn infant outcomes. As depicted, the obstetric outcomes were not different. The gestational age range at delivery for the naltrexone MAT group was 29.1−40.1 weeks and for the traditional MAT group was 27.6−41.2 weeks. In the naltrexone MAT group, 14 of 121 patients (11.6%) had a positive toxicology screen for an opioid drug once opioid drug free. This was not different from the 16 of 109 patients (14.7%) with a positive opioid toxicology screen that was inconsistent with the prescribed traditional MAT (P=.62).

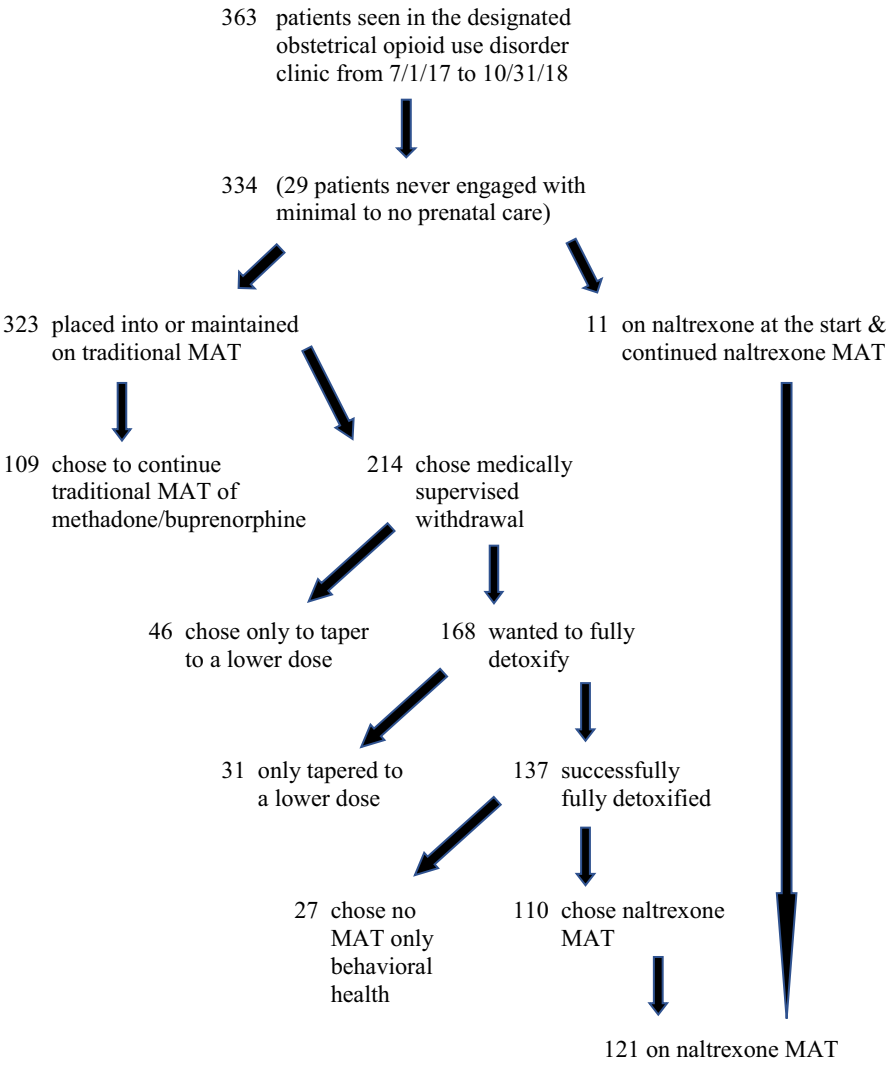
No neonates were treated for signs of NAS in the 87 (71.9%) who were receiving naltrexone to delivery. Of the 34 pregnancies that discontinued naltrexone before delivery, 10 newborn infants were treated for symptoms of NAS. The reasons that were provided for discontinuation of naltrexone were 15 "did not think I needed it," 10 "headache," and 9 "nausea." Of these 34, 20 women remained opioid drug free with intense behavioral health, and none of these newborn infants needed NAS treatment. Of the remaining 14 women, 11 went back to buprenorphine MAT; 3 were using illicit opioid drugs (1 heroin and 2 oxycodone), and 10 of these neonates were treated for signs of NAS. No cases of maternal relapse occurred in the 7-day no-treatment window before initiation of naltrexone therapy.

Sixty-four women (53%) were started on naltrexone therapy at ≥24 weeks gestation, and no changes in the FHR tracings were seen during the 60 minutes of monitoring with the first dose. Of the remaining 57 women, 11 had recently received and conceived on the naltrexone injection (Vivitrol[22]), and these 11 elected to continue with naltrexone MAT. The remaining 46 women were started at <24 weeks gestation, and no changes were seen in the FHR by auscultation or ultrasound imaging during the first naltrexone dosage administration.

There were 23 first-trimester exposures to naltrexone (19%), the 11 women who were receiving naltrexone at conception, and 12 women who were started in the first trimester; no fetal anomalies occurred. No spontaneous abortions or intrauterine fetal deaths occurred in either group. There were 2 neonates with anomalies in both groups. One infant had bilateral clubbed feet (opioid free at 33 weeks/naltrexone MAT at 36 weeks). The other infant had a small herniation of bowel into the umbilical cord stump that was repaired on day 1 of life with newborn discharge on day 6. This patient was opioid free at 14 weeks with naltrexone MAT at 18 weeks gestation. For the traditional MAT group, there was 1 cleft lip no palate (traditional MAT started at 15 weeks gestation) and a small congenital pulmonary airway malformation (traditional MAT started at 18 weeks gestation).

Of the 87 patients receiving naltrexone to delivery, 63 delivered vaginally, and 24 had cesarean deliveries. Of these, 47 women (45 vaginal and 2 cesarean) did not require an opioid drug

FIGURE
Management procedure



Breakdown of management in a designated obstetric opioid use disorder clinic.

MAT, medication-assisted treatment.

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after delivery and were administered Vivitrol injections before hospital discharge. There were 40 patients (18 vaginal deliveries with immediate subumbilical tubal ligations and 22 cesarean deliveries) who required an opioid drug postoperatively. At the 14-day scheduled follow-up appointment, 16 women went back on their previous traditional MAT; 19 women became opioid drug free again and were administered Vivitrol, and 5 women never returned. Eleven naltrexone-exposed infants have been seen 6 months after delivery, all with normal examinations and developmental scores. No pain control treatment issues occurred at delivery in the patients in the naltrexone MAT group.

For neonatal outcomes, there was no difference in mean birthweight or birthweight <10th percentile between the groups. Making a diagnosis of NAS in premature neonates at <34 weeks gestation can be difficult because many of the findings in the Finnegan Score can be demonstrated by prematurity. Therefore, gestations at <34 weeks were excluded (2 for naltrexone MAT and 4 for traditional MAT). The NAS rate was significantly lower in the naltrexone MAT group (10/119 [8.4%] vs 79/105 [75.2%]; $P<.0001$). Multivariate regression analysis was then performed. The model included maternal age, chronic maternal medical disorders, gestational age at delivery, fetal sex, birthweight, and other medications/drugs that were used during the pregnancy (including alcohol, amphetamines, benzodiazepines, cocaine, gabapentin, SSRIs, and tobacco). No factors were found to be significant in the rate of NAS, except for the form of MAT ($P>.3$). A higher neonatal intensive care unit admission rate and a longer newborn length of stay were also found to be significant ($P<.0001$), but multivariate analysis showed that these were only significant because the rate of NAS was significant.

The difference for mean HC between the naltrexone MAT group and the traditional MAT group was significant ($P=.044$). The rates for neonatal HC <10th and 3rd percentiles were not different. HC is an indirect measure of brain size. Because of the association of a smaller neonatal HC that was seen in newborn infants who were exposed to chronic maternal opioid use that led to NAS compared with no maternal opioid use[18] and because naltrexone binds to the same central nervous system receptors as opioid drugs,[14] newborn HCs were stratified by when the mother became opioid drug free and when naltrexone was initiated (Table 3). For comparisons, being drug free in the first trimester was compared with the other gestational age time periods, and none were significant. There was a strong trend, however, for those patients who were drug free in the first trimester compared with those who were drug free later in pregnancy (≥30 weeks gestation; $P=.054$). Though not significant, there was a similar downward trend in newborn HC size the further into gestation that a mother became opioid drug free and started naltrexone therapy.

Table 4 shows the paired maternal/cord blood levels for free naltrexone and free 6-beta-naltrexol. No levels were elevated,[14] and values were undetected if naltrexone was discontinued at >60

hours before delivery. Maternal and fetal levels were concordant.

Although not part of the study, 77 patients tapered their traditional MAT drug dosage before delivery (46 chose this option from the start, and 31 were not successful at complete detoxification; Figure) and 42 newborn infants (54.5%) showed symptoms of NAS that required treatment. Of 27 women who fully detoxified and declined naltrexone MAT, 5 newborn infants (18.5%) were treated for signs of NAS.

TABLE 1
Demographics of the naltrexone medication-assisted treatment group vs the traditional methadone or buprenorphine medication-assisted treatment group (230 total pregnancies)

Variable	Medication-assisted treatment group		*P* value
	Naltrexone (n=121)	Traditional (n=109)	
Demographics			
Maternal age, y[a]	28.0±5.3	28.1±5.5	.89
White, n (%)	115 (95)	104 (95.4)	.99
Multiparity, n (%)	93 (76.9)	86 (78.9)	.83
Chronic maternal medical disorders, n (%)[b]	13 (10.7)	14 (12.8)	.77
Diabetes mellitus (gestational/pregestational), n (%)	6 (5.0)	7 (6.4)	.85
Other medications/drugs used during pregnancy confirmed by urine toxicology screening, n (%)			
Benzodiazepine	12 (9.9)	14 (12.8)	.62
Amphetamine	20 (16.5)	13 (11.9)	.42
Cocaine	5 (4.1)	4 (3.7)	.99
Marijuana	31 (25.6)	32 (29.4)	.63
Gabapentin	29 (24.0)	24 (22.0)	.85
Selective serotonin reuptake inhibitor	39 (32.2)	29 (26.6)	.43
Tobacco[c]	87 (71.9)	82 (75.2)	.67
Alcohol	2 (1.7)	3 (2.8)	.67
Patients who received no comedications/drugs	10 (8.3)	13 (11.9)	.48
Patients who received >1 comedication/drug	71 (58.7)	62 (56.9)	.89

[a] Data are given as mean±standard deviation; [b] Includes hypertensive conditions, lupus, chronic renal disease, etc; [c] Based on patient report.

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Comment

Principal findings

This is the first prospective study and largest study to date on naltrexone use in pregnancy. When compared with traditional opioid agonist MAT, obstetric outcomes were similar. As expected, the rate of newborn infants who were treated for NAS was significantly lower in the naltrexone MAT group compared with the traditional MAT group ($P<.0001$). Naltrexone crosses the placenta; maternal/fetal levels are concordant; it clears quickly from the maternal blood stream; and it is well-tolerated by both mother and fetus. Because naltrexone enters the fetal circulation, a concern could be the provoking of a fetal withdrawal in utero. This could occur if the chronic effects of opioid drug exposure linger in the fetus beyond the 7-day opioid drug free period in the mother. However, no changes were seen in the FHR monitoring in the 64 patients who began naltrexone therapy at ≥24 weeks gestation.

Meaning of our observation as it relates to other studies

Our findings for obstetric outcomes were similar to the retrospective studies from Australia that reported the use of a naltrexone implant.[7−13] Regarding teratogenicity, for a drug to be implicated potentially, fetal exposure during organogenesis is of primary importance. Of 40 first-trimester naltrexone exposures (23 from our study and 17 from the Australian studies[7−10]), no newborn anomalies (0%; 95% confidence, 0−8.8%) have been identified at delivery. The more recent Australian study reported an anomaly rate of 8.8 in 100 births in 68 pregnancies that were exposed to naltrexone; however, the gestational ages of naltrexone onset and exposure were not provided.[12] In the same study, the reported rates for birth anomalies with methadone and buprenorphine were 10.6 in 100 and 4.8 in 100 cases, respectively.

Regarding newborn HC at birth with first-trimester naltrexone exposure, the mean for 16 neonates from the Australian studies[7-10] was not different from our mean (33.81±1.6 vs 34.08±2.0 cm; $P=.66$). In addition, the overall mean HC in the 68 Australian reported cases[12] was not different from our overall mean (33.9±2.5 vs 33.52±1.6 cm; $P=.21$).

We made the assumption that 50−60% of patients who fully detoxified off opioid drugs would choose naltrexone MAT. However, 80.3% chose this option (110/137 patients), which confirms the survey study results of Jones[23] regarding a strong interest in naltrexone.

Common side-effects that were reported with the use of naltrexone that were seen in ≥10% of cases included nausea, headache, nervousness, and

TABLE 2
Obstetric and newborn outcomes of the naltrexone medication-assisted treatment group vs traditional methadone or buprenorphine medication-assisted treatment group (230 total pregnancies)

Variable	Medication-assisted treatment group: Naltrexone (n=121)	Medication-assisted treatment group: Traditional (n=109)	*P* value
Obstetric outcome			
Mode of delivery: vaginal, n (%)	89 (73.6)	76 (69.7)	.62
Gestational age at delivery, wks[a]	37.9±1.8	38.0±2.1	.70
Spontaneous delivery <37 weeks gestation, n (%)	12 (9.9)	10 (9.2)	.85
Newborn outcome			
Neonatal abstinence syndrome, n (%)[b]	10 (8.4)	79 (75.2)	< .0001
Neonatal intensive care unit admission, n (%)	27 (22.3)	87 (79.8)	< .0001
Length of hospital stay, d[a]	5.5±6.1	20.8±6.0	< .0001
Male fetus, n (%)	58 (47.9)	57 (52.3)	.60
Mean birthweight, g[a]	2976±464	2901±474	.23
Birthweight ≤10%, n (%)	11 (9.1)	15 (13.8)	.36
Neonatal head circumference, cm[a]	33.52±1.6	33.06±1.8	.044
Neonatal head circumference ≤10%, n (%)	24 (19.8)	32 (29.4)	.13
Neonatal head circumference ≤3%, n (%)	4 (3.3)	8 (7.3)	.24

[a] Data are given as mean±standard deviation; [b] For this comparison, gestations of <34 weeks were excluded: 2 for the naltrexone medication-assisted treatment group and 4 for the traditional medication-assisted treatment group.

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difficulty sleeping.[14] This was similar to our 8.3% rate of headache and 7.4% rate of nausea. Overall, 84.4% of the patients had no complaints, and the drug was well-tolerated. Cost is also not an issue. In Tennessee, naltrexone is Medicaid covered; if it is not covered, the cash price is $35.00 for a month's supply. Buprenorphine is also Medicaid covered; however, most suppliers in East Tennessee do not take the Medicaid price and charge $300.00–$600.00 for a month's supply. Methadone is not covered by Medicaid, and the average price for a month's supply is $500.00.

TABLE 3
Newborn head circumferences in the naltrexone medication-assisted treatment group based on when the mother was opioid drug free and when naltrexone was initiated in gestations ≥34 weeks (n=119)

Gestational age, wks	When no longer taking opioid drugs: N	When no longer taking opioid drugs: Mean head circumference, cm[a]	When no longer taking opioid drugs: *P* value[b]	When started on naltrexone therapy: N	When started on naltrexone therapy: Mean head circumference, cm[a]	When started on naltrexone therapy: *P* value[b]
≤13	27	34.07±1.9	—	23	34.08±2.0	—
14–19	23	33.39±1.6	.18	15	33.54±1.8	.40
20–29	37	33.42±1.5	.13	44	33.43±1.5	.14
≥30	32	33.27±1.2	.054	37	33.28±1.3	.065

[a] Data are given as mean±standard deviation; [b] Comparisons made between gestations ≤13 weeks vs the other 3 gestational age categories.

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Research implications

For pregnant women who use opioid drugs illicitly, the management approach should be to place them in a traditional MAT program of methadone or buprenorphine. For those who become engaged and attend prenatal care and behavioral health visits, the option of medically supervised tapering/detoxification can be offered. A recent publication that involved the conclusions of a task force (the Society for Maternal-Fetal Medicine, American College of Obstetricians and Gynecologists, and American Society of Addiction Medicine) that met regarding substance use disorders in pregnancy reported that naltrexone should not be used as a MAT for the management of OUD in pregnancy because of insufficient data.[24] This prospective study now shows that naltrexone MAT is a viable option for some women if they are successful at complete opioid detoxification. Additionally, for those pregnant patients who already are receiving naltrexone therapy at the start of pregnancy, continuing naltrexone MAT can also be an option. However, these mothers and exposed newborn infants must be followed long term to assess their progress compared with those who are treated with traditional MAT and those who receive no opioid drugs at delivery.

This study was not designed to evaluate the differences between opioid agonist MAT and medically supervised withdrawal during pregnancy. Nevertheless, further research is needed in this area, and naltrexone can play a role in this treatment process.

Based on the findings shown in Table 3, further research is needed to evaluate neonatal HC at birth for newborn infants who are delivered of women with OUD where NAS does not

TABLE 4
Blood levels of free naltrexone and free 6-beta-naltrexol in 20 paired maternal/umbilical cord blood samples (detection level down to 0.5 ng/mL)

Patient no.	Time that naltrexone was discontinued to maternal blood draw, hrs	Free naltrexone level, ng/mL		Free 6-B-naltrexol level, ng/mL		Time from maternal blood draw to newborn blood draw, hrs
		Maternal	Fetal	Maternal	Fetal	
1	6	9.3	2.7	67	12	23
17	10	4.9	5.3	33	42	0.5
5	11	1.4	1.2	40	29	5
9	13	0.79	0.57	49	35	4
20	18	0	0	12	11	8
14	20	0.67	0.54	14	8.6	0.5
15	23	1.1	0.78	24	23	5
4	24	0	0	9.4	9.8	8
7	25	0	0	15	19	7
8	29	0	0	6.9	5.8	7
19	35	0	0	2.0	2.5	3
11	44	0	0	2.6	1.9	2
16	46	0	0	0.63	1.0	3
18	49	0	0	5.1	0.86	41
2	50	0	0	0	0	4
6	52	0	0	0.89	1.4	1.5
3	63	0	0	0	0	14
12	3 Days	0	0	0	0	10
13	4 Days	0	0	0	0	3
10	7 Days	0	0	0	0	11

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occur after delivery. This would need to be stratified by those patients with no tapering vs tapering to a lower dose vs those patients who fully detoxify (further separated by when this occurred in gestation).

Strengths and limitations

A primary strength of this study is the prospective nature. The limitation is that the study was not randomized. When dealing with addiction, the option of tapering or full detoxification should be the patient's choice. Trying to force an individual into altering her medication use based on a randomization arm would be problematic. However, because of the nature of this study, bias cannot be ruled out in that those patients who chose to taper or fully detoxify may have different motivations that are difficult to control for. In addition, the study may not be powered enough for some comparisons, leading to a type II error such as newborn birthweight and HC.

Conclusion

These data demonstrate that the use of naltrexone MAT might be a viable option for the treatment of OUD in pregnancy in some patients. The drug crosses the placenta, and maternal/fetal levels are concordant; however, it clears quickly from the maternal circulation. This rapid clearance of naltrexone needs to be addressed with these patients, who must be aware that maternal relapse can occur in a short time period if they discontinue the oral medication without notifying their healthcare providers. Nonetheless, the drug is well-tolerated by both mother and fetus, and newborn infants do not experience symptoms of NAS if naltrexone is continued to delivery. ■

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