PHARMACOTHERAPY

Methadone, Buprenorphine, and Naltrexone for the Treatment of Opioid Use Disorder in Pregnant Women

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Pregnant women with opioid use disorder can be treated with methadone, buprenorphine, or naltrexone to reduce opioid use and improve retention to treatment. In this review, we compare the pregnancy outcomes of methadone, buprenorphine, and naltrexone in clinical trials and discuss the potential behavioral and developmental effects of these agents seen in offspring in animal studies. Important clinical considerations in the management of opioid use disorder in pregnant women and their infants are also discussed. Outside of pregnancy, buprenorphine is used in combination with naloxone to reduce opioid abuse and diversion. During pregnancy, however, the use of buprenorphine as a single agent is preferred to prevent prenatal naloxone exposure. Both methadone and buprenorphine are widely used to treat opioid use disorder; however, compared with methadone, buprenorphine is associated with shorter treatment duration, less medication needed to treat neonatal abstinence syndrome (NAS) symptoms, and shorter hospitalizations for neonates. Despite being the standard of care, medication-assisted treatment with methadone or buprenorphine is still underused, making it apparent that more options are necessary. Naltrexone is not a first-line treatment primarily because both detoxification and an opioid-free period are required. More research is needed to determine naltrexone safety and benefits in pregnant women. Animal studies suggest that changes in pain sensitivity, developmental processes, and behavioral responses may occur in children born to mothers receiving methadone, buprenorphine, or naltrexone and is an area that warrants future studies.
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Every day, nearly 18 women in the United States die of an opioid overdose.[1] Furthermore, women are more likely than men to be prescribed opioids, receive higher doses, and be taking them for longer durations.[1] Emergency department visits for opioid misuse and abuse are more likely in women of childbearing age than in any other age group.[1] Claims data listing pregnancy drug dependence diagnoses rose over 500% from 2007 to 2014.[2] Similarly, over a 7-year duration since 2002, the number of births to mothers using opioids has increased by nearly 5 times.[3] The Treatment Episodes Data Set, maintained by the Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration (SAMHSA), shows that in 2012, the percentage of pregnant women entering treatment reporting prescription opioid misuse was 28%, and a prescription opioid as the primary substance of abuse was 19%, a staggering increase from 2% and 1%, respectively, in 1992.[4]

Maternal opioid use results in harmful medical and social consequences for both mother and infant. Both opioid intoxication and acute withdrawal can cause harm. Opioid use can increase the risk of spontaneous abortion, stillbirth,

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prematurity, and neonates born with low birth weight, undesired neural effects, or birth defects.[5] Abrupt withdrawal from opioids can lead to preterm labor, fetal distress, and fetal withdrawal symptoms.[5] Given that opioid abuse is associated with high rates of relapse, this vicious cycle of opioid use and withdrawal can occur numerous times throughout a pregnancy, increasing the potential for dangerous consequences. Environmental factors associated with opioid abuse such as erratic lifestyle, inadequate or absent obstetric and medical care, and human immunodeficiency virus and hepatitis C virus transmission from intravenous drug use can also contribute to poor pregnancy outcomes. Therefore, it is imperative for pregnant women with substance abuse to seek specialist care and counseling. Clinicians also must be familiar with all the acceptable treatments to inform and support these women in their decision to minimize harm to themselves and their infants.

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) states that "opiate use disorder is a problematic pattern of opioid use leading to clinically significant impairment or distress," and the diagnosis is based on criteria specified in the DSM-V.[6] Opioid use disorder can be treated with either medication-assisted treatment (MAT) or medically assisted withdrawal (MAW), also known as medically supervised withdrawal or detoxification. MAT combines medications and behavioral therapy using long-acting opioid agonists, such as methadone and buprenorphine, to minimize the maternal opioid levels and reduce the fetal opioid exposure seen with illicit opioid use. Maximum benefit occurs when medications are used in conjunction with psychosocial therapy; thus, treatment with medications alone is never appropriate. Methadone, buprenorphine, and naltrexone are all approved by the U.S. Food and Drug Administration (FDA) for the treatment of opioid dependence but have only been studied in varying degrees during pregnancy. Although none of the medications include treatment of opioid dependence in pregnancy as an approved indication, it has been reported that use in opioid-dependent pregnant women should not be considered "off-label."[7] Outside of pregnancy, buprenorphine is used in combination with naloxone to reduce abuse and diversion. However, during pregnancy, the use of buprenorphine as a single agent is preferred to prevent prenatal naloxone exposure, which may precipitate withdrawal.[8] MAT works by maintaining a lower level of opioid in the body than that seen with illicit opioid use to minimize cravings and withdrawal symptoms that occur when opioids are discontinued. Alternatively, MAW involves tapering a medication, such as methadone or buprenorphine or symptomatic treatment with clonidine, to provide a tolerable transition from illicit opioid use to being opioid free.[9] Thereafter, an opioid antagonist such as naltrexone can be initiated during the opioid-free period to promote continued opioid abstinence. Abrupt discontinuation of opioids is rarely successful and frequently results in rapid return to opioid use, whereas assistance with medications to treat opioid use disorders can reduce substance abuse and facilitate retention to treatment.

Two new reports issued in 2016 by SAMHSA provide some consensus and guidance on caring for pregnant women with opioid use disorders and their infants. The first report, "A Collaborative Approach to the Treatment of Pregnant Women with Opioid Use Disorders," was created to address the needs of pregnant women with opioid use disorders through state and local efforts.[5] The second report, "Advancing the Care of Pregnant and Parenting Women with Opioid Use Disorder and Their Infants: A Foundation for Clinical Guidance," assists in clinical decision-making regarding the comprehensive care of pregnant and parenting women with opioid use disorder and their opioid-exposed infants.[10] The latter report identifies specific points in clinical decision-making, with a high level of agreement among experts on counseling, medication changes, treatment of relapse, and pain relief during the pregnancy and postnatal periods. Both reports recommend MAT over either MAW or abstinence as the standard of care for pregnant woman with opioid use disorder. These recommendations are unchanged from historical guidance by the American College of Obstetricians and Gynecologists Committee (ACOG), which also favored MAT accompanied by adjunctive psychosocial and cognitive behavioral therapy as the preferable strategy for treatment success in maternal opioid use.[8]

At this time, risks of birth defects have not been shown with methadone, buprenorphine, or naltrexone. However, as with any drug, risks and benefits to both mother and fetus during pregnancy with all three drugs require careful consideration by the mother receiving treatment as well as the clinicians advising her in these decisions. One of the risks distinguishing opioid agonists from opioid antagonists is the concern

for neonatal abstinence syndrome (NAS). NAS, also referred to as neonatal opioid withdrawal syndrome, describes the constellation of symptoms typically associated with opioid withdrawal in newborns.[11] Symptoms of NAS include high-pitched crying, irritability, tremors, vomiting, diarrhea, rapid breathing, poor sleep, and low-grade fevers. During gestation, mothers using illicit opioids or on MAT with opioid agonists expose the fetus to opioids through the placenta, which can cause fetal opioid dependence. Following delivery, the newborn is no longer exposed to opioids from the mother and may experience withdrawal. Newborns with NAS often require hospitalization and pharmacologic or nonpharmacologic treatment to bridge them through the withdrawal period.

Although NAS is treatable and has not been associated with long-term adverse consequences, some mothers may opt for MAW to eliminate any risk of NAS.[10, 12] Withdrawal from opioids can cause premature labor, fetal distress, and miscarriages as well as increase the risk for overdose death from the high likelihood of subsequent relapse. Thus, MAW should always be conducted under the supervision of physicians experienced in perinatal addiction. Under these circumstances, drugs such as naltrexone may have a role in maintaining abstinence. The World Health Organization (WHO) guidelines for the identification and management of substance use and substance use disorders in pregnancy highlights the importance of respecting the pregnant women's autonomy to be fully informed of all her treatment options.[13] This reinforces a mother's right to make decisions about her health care and the care of her infant even if she decides against the standard of care.

This review compares the treatment options for opioid use disorder including methadone, buprenorphine, and naltrexone during pregnancy to describe their efficacy in reducing opioid use. The effect of these medications on pregnancy outcomes such as gestational age and birth weight in human studies, and behavioral and developmental effects in animal studies, are reviewed. Last, clinical considerations relevant to these medications are also discussed to aid clinicians in their management of opioid use disorders in pregnant women.

Literature Review

A search of English-language randomized controlled trials (RCTs) and observational cohort studies of these agents in treating opioid-dependent pregnant women was performed through the PubMed, EMBASE, and Cochrane Library databases (inception through September 2016). Priority was given to RCTs and trials in pregnant women; however, due to the limited number of obstetric studies with naltrexone or long-term human studies describing behavioral or developmental outcomes with these agents, we included case studies and animal data describing pertinent effects. The bibliographies of these trials as well as guidance reports were reviewed for other relevant articles.

Efficacy of Opioid Agonists and Antagonists in Opioid Use Disorder

In nonpregnant individuals, methadone, buprenorphine alone and in combination with naloxone, and naltrexone are the primary options for MAT and/or MAW.[14] Methadone is a full opioid agonist with high affinity at the μ receptor and a long half-life, allowing it to act as an easily managed substitute for both illegal and pharmaceutical opioids while limiting the potential euphoric effects of these agents and preventing withdrawal symptoms.[14, 15] Buprenorphine is a partial opioid agonist at the μ receptor and an antagonist at the κ receptor, which makes it an advantageous alternative to methadone due to its ceiling effect for respiratory depression and improved adverse effect profile when compared with full agonists.[14, 16] Buprenorphine combined with the opioid antagonist naloxone is preferred in the nonpregnant population to prevent abuse and diversion. Similar to naloxone, naltrexone is a competitive antagonist at opioid receptors that may be orally dosed daily and functions by blocking the effects of the opioid agent on which the patient is dependent.[14, 17]

Of the three primary treatment options, methadone is the most studied and has over a 50-year history of use for MAT and MAW. In traditional opioid treatment programs, daily methadone administration is completed in a supervised fashion at a treatment center and not in the home of the patient or in a physician office setting to limit misuse or diversion of the agent, but alternate modalities may be available to patients who still meet federal prescribing and dispensing requirements.[18] In a large-scale meta-analysis published by the Cochrane Collaboration, methadone was shown to be more effective than no opioid replacement therapy for patients with heroin dependence.[19] In this

analysis, the results of six randomized clinical trials showed statistical significance in relation to both retention in treatment and suppression of heroin use (relative risk [RR] 0.66, 95% confidence interval [CI] 0.56–0.78).[19] Although efficacy has been clearly demonstrated, there are some concerns associated with methadone management. Requiring most patients to return to a treatment center daily may limit its long-term attractiveness to patients due to interference with daily activities such as work or education. In addition, as an opioid agonist itself, methadone can be addicting; however, this can be an acceptable alternative for patients abusing heroin.

The concerns regarding methadone triggered interest in buprenorphine as a treatment option in MAT and MAW, with the earliest study published in 1998.[16] As previously noted, buprenorphine is theorized to be safer than methadone in the management of dependence due to its partial agonist design. It allows for a lower level of euphoria for the patient, which may lessen cravings due to decreased perceived rewards of abuse.[14, 17] In addition, it may be preferred by patients due to its alternative 3-times/week dosing versus the daily dosing of methadone.[20] Buprenorphine is available in a number of dosage forms, and those specifically used in pregnanct patients will be discussed later in this review. Buprenorphine may be administered in opioid treatment programs, but it is also a candidate for office-based treatment pathways where prescriptions are given for weekly or monthly filling.[18] When compared to placebo, buprenorphine demonstrated statistical significance when used at doses of 16 mg or higher for both retention in treatment (RR 1.82, 95% CI 1.15–2.90) and suppression of illicit drug use (standardized mean difference −1.17, 95% CI −1.85 to −0.49).[21] However, the optimal dosing regimen of buprenorphine has not been elucidated yet, with flexible dosing plans showing less effectiveness than methadone (RR 0.83, 95% CI 0.72–0.95) and fixed dosing plans at low doses showing similar results (RR 0.67, 95% CI 0.52–0.87), but moderate-to-high fixed doses showing no statistically significant difference in effectiveness when compared to methadone (RR 0.87, 95% CI 0.69–1.10).[21] In addition to its availability as a single agent, buprenorphine is available as a combination product paired with the opioid antagonist naloxone in buccal film strips or sublingual oral tablet dosage forms. When the combination product is taken sublingually, the impact of naloxone is negligible; however, if taken by other routes that are often used for abuse of the product (e.g., intravenous, intranasal), the effect of naloxone will surpass the buprenorphine effect and result in significantly decreased euphoria and/or initiation of withdrawal symptoms.[14] The combination product should not be used during the induction phase of treatment for long-acting opioids or methadone but can be used in later stages of treatment, whereas the combination product is the preferred therapy for induction and maintenance for short-acting opioids.[15, 17, 18]

Naltrexone's antagonist properties move away from the concept of replacing the opioid and providing support during withdrawal and, instead, block the perceived gains of abuse.[14] Although conceptually a strong deterrent for continued abuse, naltrexone has not demonstrated efficacy in treatment retention or in preventing use of the abuse agent when compared to placebo or no pharmacologic agents in trials outside of directly monitored treatment centers (RR 1.43, 95% CI 0.72–2.82).[22] It has been theorized that this may be due to high need for adherence with this agent and low implied "reward."[14, 17] Two small studies with forced adherence demonstrated positive trends for both retention and maintained abstinence.[22] It should be noted that there have been considerably fewer trials evaluating naltrexone for MAT or MAW than either methadone or buprenorphine, and additional trials may yield different results. An alternative approach to lessen the impact of daily adherence is the use of the long-acting injectable dosage form of naltrexone which can be given once every 4 weeks. In a study comparing the long-acting version to placebo, the proportion of weeks with urine screening–confirmed abstinence was significantly greater in the naltrexone group (90% vs 35%, p=0.0002).[23] The statistical analysis of this trial was completed on an intention-to-treat protocol; however, 53.2% of the patients in the active arm did not complete the full 24-week trial.

To our knowledge, a trial directly comparing all three agents has not been completed. Initial review of the literature indicates success with methadone and buprenorphine but questionable results with naltrexone. While acknowledging the varied results in the available literature, the American Society of Addiction Medicine (ASAM) chose to not select one specific agent as the preferred choice in their 2015 national practice guideline.[18] ASAM instead noted that selection

of each agent may have a viable role in patients with select criteria and that product selection should be handled individually.[18]

Clinical Trials in Pregnant Women

Treatment selection in pregnant women is even more complicated because the impact of the medication on pregnancy outcomes must be considered. The human data evaluated in this article include head-to-head trials evaluating buprenorphine or buprenorphine and naloxone combination compared with methadone in the treatment of opioid-dependent pregnant women. Three prospective RCTs[24–26] and eight prospective, observational, cohort, controlled studies[27–34] comparing buprenorphine and methadone were included. In addition, four recent retrospective studies published in the past 2 years evaluating methadone versus buprenorphine or buprenorphine and naloxone combination in opioid-addicted women were also included.[35–38] There are very limited human data evaluating naltrexone use for treatment of opioid-dependent pregnant women, with only two case studies identified and included in this article.[39, 40]

One study was a single-site, randomized, double-dummy, double-blind, flexible dosing comparison study evaluating 18 women who were assigned either methadone or buprenorphine during weeks 24–29 of gestation.[24] Fourteen women completed the trial; six neonates were exposed to methadone, of whom three (50%) required treatment for NAS, and eight received buprenorphine, of whom five (63%) required treatment for NAS. This study identified an earlier onset of NAS in the methadone group after the last maternal medication dose (mean 60 hrs [range 52–68; SD 11.3 hrs] versus mean 72 hrs [range 35–109; SD 11.3 hrs] in the buprenorphine group) (p=0.537). The mean duration of treatment for NAS was 5.3 vs 4.8 days (p=0.766) in the methadone versus buprenorphine groups. No statistically significant differences were found between the two neonate groups.

The Buprenorphine versus Methadone in the Treatment of Pregnant Opioid Dependent Patient: Effects on the Neonatal Abstinence Syndrome, or PROMISE, trial was a single-site, randomized, double-blind, double-dummy, flexible-dosing, parallel-group controlled trial.[25] This trial compared rates of NAS in neonates of pregnant, opioid-dependent mothers who were enrolled between 16–30 weeks of gestation, and was designed to provide safety and efficacy data for a future larger trial. Thirty women were randomized into the study, and 21 neonates were evaluated. Ten neonates were exposed to buprenorphine, of whom two (20%) required treatment for NAS; 11 neonates were exposed to methadone, of whom five (46%) required treatment for NAS (p=0.23). Peak NAS scores did not significantly differ between treatment groups, but length of hospitalization was longer for neonates exposed to methadone compared to buprenorphine (8.1 vs 6.8 days, p=0.021).

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial was a multisite, double-blind, double-dummy, flexible-dosing RCT that evaluated buprenorphine and methadone for treatment of opioid dependence in pregnant mothers enrolled between 6 and 30 weeks of gestation.[26] One hundred thirty-one maternal–neonate pairs completed the trial, of which 73 were exposed to methadone and 58 were exposed to buprenorphine. Of the neonates exposed to methadone, 41 (57%) of 73 required treatment for NAS, and of those exposed to buprenorphine, 27 (47%) of 58 required treatment for NAS (p=0.26). Although no statistically significant difference was noted in the proportion of neonates requiring treatment for NAS, the neonates exposed to buprenorphine required significantly less morphine (mean ± SD 1.1 ± 0.7 mg vs 10.4 ± 2.6 mg, $p<0.0091$), had a significantly shorter duration of NAS treatment (mean ± SD 4.1 ± 1.0 days vs 9.9 ± 1.6 days, $p<0.003$), and had a significantly shorter hospital stay (mean ± SD 10.0 ± 1.2 days vs 17.5 ± 1.5 days, $p<0.009$). These are the significant outcomes that are frequently cited in favor of buprenorphine and would eventually propel its use in MAT.

The attrition rate for these RCTs ranged from 22% to 33% overall.[24–26, 41] However, a Cochrane Review found that the dropout rate for treatment in the methadone group was lower than that in the buprenorphine group (RR 0.64, 95% CI 0.41–1.01 [three studies, 223 participants]),[42] a finding similar to results of trials in nonpregnant patients.[26, 43] Maternal opioid use did not significantly differ between the methadone and buprenorphine groups (RR 1.81, 95% CI, 0.70–4.69, two studies, 151 participants).[42]In this meta-analysis (166 patients combined), the proportion of newborns requiring treatment for NAS was not significantly different between the buprenorphine and methadone groups.[42] As noted here earlier, however, results from the larger RCT (131 patients)[26] differed from the two

smaller trials (35 patients combined)[24, 25] because the results demonstrated significantly less neonatal morphine use and shorter duration of NAS treatment with buprenorphine. Pooled data from two of the trials demonstrated that birth weight was higher in the buprenorphine group (mean difference −365.45 g, 95% CI −673.84 to 57.07 [two studies, 150 participants]). The third trial was unable to be pooled and found no significant difference.[42] However, birth weight is influenced by sex, gestational age, multifetal pregnancy, maternal cigarette smoking, and use of other substances, which were not controlled for in these studies. Two studies evaluated the Apgar score, which is a measure of the physical condition of the newborn infant and includes heart rate, respiratory effort, muscle tone, response to stimulation, and skin coloration; however, these studies did not find a significant difference between treatment groups.[42] There were no significant differences in the frequency of maternal adverse effects between treatment groups; however, newborns experienced fewer serious adverse effects in the buprenorphine group (Table 1).[42]

Eight prospective observational studies evaluating buprenorphine versus methadone were published in English, identified, and included in this review (Table 2).[27–34] Seven studies included evaluation of the frequency of NAS treatment.[28–34] Results of two studies demonstrated that a significantly lower proportion of buprenorphine-exposed neonates required NAS treatment,[29, 31] and results of five studies demonstrated no significant difference or did not report this data.[28, 30, 32–34] Five studies reported data regarding gestational age at delivery: one study found that women receiving methadone delivered significantly earlier,[28] and the other four studies did not detect a significant difference.[31–33] There was no significant difference in frequency of preterm births between women receiving methadone or buprenorphine in the seven studies reporting these data.[27–31, 33, 34] A meta-analysis, which included six of the observational trials listed here in addition to one retrospective study found that the RR of preterm birth was higher with methadone treatment (RR 0.67, 95% CI 0.50–0.90).[41] Spontaneous fetal death and congenital anomalies were infrequently reported and are lower frequency events; three studies found no significant difference between groups for both of these measures.[27, 29, 31] Head circumference was reported in three studies, all without significant differences.[28, 30, 31] Seven

Table 1. Randomized Controlled Trials Evaluating the Effects of Methadone and Buprenorphine on Pregnancy Outcomes

Year of publication/study	Treatment groups	Treated for neonatal abstinence syndrome	Gestational age at delivery (wks)	Preterm birth (< 37 wks gestational age)	Spontaneous fetal death	Fetal and congenital anomalies	Head circumference (cm)	Low birth weight (< 2500 g)	Birth weight (g)
2006[24]	Methadone (n=6)	3 (50)	–	3 (50)	–	0 (0)	–	–	–
	Buprenorphine (n=8)	5 (63)	–	2 (25)	–	0 (0)	–	–	–
	p value	–	–	–	–	–	–	–	–
2005 (PROMISE)[25]	Methadone (n=11)	5 (46)	38.8	1 (9)	–	0 (0)	33.2	–	3001.8
	Buprenorphine (n=9)*	2/10* (20)	38.8	0 (0)	–	0 (0)	34.9	–	3530.4
	p value	0.23	0.911	–	–	–	0.106	–	0.091
2010 (MOTHER)[26]	Methadone (n=73)	41 (57)	37.9	14 (19)	–	–	33	–	2878.5
	Buprenorphine (n=58)	27 (47)	39.1	4 (7)	–	–	33.8	–	3093.7
	p value	0.26	0.007	0.07	–	–	0.03	–	0.03

Data are no. (%) of patients.
– = no data available.
*Nine mothers were treated with buprenorphine; twin pregnancy resulted in ten infants exposed to buprenorphine.

Table 2. Prospective Observational Trials Evaluating the Effects of Methadone and Buprenorphine on Pregnancy Outcomes

Year of publication/study	Treatment groups	Treated for neonatal abstinence syndrome	Gestational age at delivery (wks)	Preterm birth (< 37 wks gestational age)	Spontaneous fetal death	Fetal and congenital anomalies	Head circumference (cm)	Low birth weight (< 2500 g)	Birth weight (g)
2012[27, 41]	Methadone (n=25)	–	–	3 (12)	0 (0)	0 (0)	–	–	–
	Buprenorphine (n=25)	–	–	2 (8)	3 (12)	1 (4)	–	–	–
	p value	–	–	NS	NS	NS	–	–	–
2011[28]	Methadone (n=51)	31 (61)	38.6	6 (12)	–	–	32.9	–	2729.1
	Buprenorphine (n=26)	15 (58)	39.7	1 (4)	–	–	33.56	–	3151.1
	p value	NS	0.003	NS	–	–	0.59	–	0.011
2011[29]	Methadone (n=45)	20 (44)	–	4 (9)	3	2 (4)	–	–	2892
	Buprenorphine (n=90)	20 (22)	–	16 (18)	3	4 (4)	–	–	2731
	p value	0.03	–	NS	–	–	–	–	NS
2009[30]	Methadone (n=26)	15 (58)	–	1 (4)	–	–	33.9	–	3150
	Buprenorphine (n=12)	8 (67)	–	1 (8)	–	–	34.3	–	3130
	p value	0.73	–	NS	–	–	NS	–	NS
2008[31]	Methadone (n=36)	19 (53)	38.6	3 (8)	0	0	33.8	9 (25)	2941
	Buprenorphine (n=47)	7 (15)	39.5	4 (9)	2 (4)	0	34	3 (6)	3250
	p value	0.0004	0.06	NS	–	–	NS	0.03	0.008
2008[32]	Methadone (n=9)	9 (100)	39.1	–	–	–	–	–	2826
	Buprenorphine (n=13)	13 (100)	39.9	–	–	–	–	–	3093
	p value	–	–	–	–	–	–	–	0.193
2008[33]	Methadone (n=32)	32 (100)	37.3	7 (22)	–	–	–	–	2900
	Buprenorphine (n=38)	(86)	38.6	10 (26)	–	–	–	–	3050
	p value	–	0.073	NS	–	–	–	–	0.128
2006[34]	Methadone (n=101)	49 (49)	38.4	16 (16)	–	–	–	–	2790
	Buprenorphine (n=159)	83 (52)	38.8	10 (6)	–	–	–	–	2843
	p value	NS	NS	NS	–	–	–	–	NS

– = no data available; NS = not statistically significant.

studies reported birth weight: two studies found neonates prenatally exposed to methadone had a lower mean birth weight,[28, 31] and five studies found no significant differences.[29–33] The aforementioned meta-analysis also reported a weighted mean difference of 265 g (range 196–335 g) lower in birth weight for neonates exposed to methadone.[41]

During the past 2 years, four retrospective studies have been published evaluating methadone versus buprenorphine or buprenorphine and naloxone in opioid-addicted pregnant women.[35–37] The largest cohort included 609 pregnant, opioid-dependent women, of whom 248 received methadone and 361 received buprenorphine.[35] This study found that mothers exposed to buprenorphine were less likely to have a preterm delivery (10% vs 17%, p<0.001), and infants were less likely to be treated for NAS (23% vs 42%, p<0.001) and had a shorter duration of NAS treatment (83 vs 133 days, p<0.001) than mothers exposed to methadone.[35] However, infants exposed to buprenorphine had a lower mean birth weight than those exposed to methadone (3143.3 vs 2899.7 g, p<0.001).[35] Researchers[36] identified 950,172 pregnancies in a Danish population-based study, of whom 167 women were exposed to buprenorphine and 197 were exposed to methadone. This study reported the prevalence ratio (PR) of outcomes for opioid-exposed women compared with women without opioid exposure. This study identified that women exposed to buprenorphine had a lower likelihood of preterm birth (PR 2.4 [95% CI 1.6–3.5] vs 3.5 [95% CI 2.6–4.7]), low birth weight (PR 0.9 [95% CI 0.2–3.6] vs 6.3 [95% CI 3.8–10.5]), and congenital malformation (PR 2.0 [95% CI 1.2–3.2] vs 2.4 [95% CI 1.6–3.7]) compared to methadone.[36] Infants exhibited NAS in 6.6% of women exposed to buprenorphine vs 55% of those exposed to methadone.[36] Another population-based study in Sweden found similar results when they evaluated 746,257 pregnancies and identified 176 women exposed to buprenorphine or buprenorphine and naloxone combination, and 52 exposed to methadone.[38] This study calculated a PR compared to the general population and also found that women exposed to buprenorphine versus methadone had a lower likelihood of preterm birth (PR 1.31 [95% CI 0.79–2.16] vs 2.21 [95% CI 1.11–4.41]), any congenital malformation (PR 0.76 [95% CI 0.41–1.38] vs 2.05 [95% CI 1.08–3.87]), and a nonsignificant trend toward low birth weight (PR 1.42 [95% CI 0.80–2.51] vs 1.74 [95% CI 0.68–4.47]).[38] This study also found a lower rate of infant NAS with buprenorphine compared to methadone (PR 1358 [95% CI 987–1868] vs 2242 [95% CI 1525–3295]).[38] Last, a smaller retrospective study in North Carolina identified 31 women exposed to buprenorphine and naloxone combination and 31 exposed to methadone.[37] This study also identified that buprenorphine and naloxone combination exposure correlated with a lower incidence of NAS treatment (25.1% vs 51.6%, odds ratio [OR] 2.55, 95% CI 1.31–4.98, p=0.01) and shorter overall hospitalization (mean ± SD 5.6 ± 5.0 vs 9.8 ± 7.4 days, p=0.02). However, there was no significant difference in incidence of preterm birth (3.2% vs 16.1%, p=0.20), birth weight (mean ± SD 3174 ± 532 vs 2885 ± 691 g, p=0.92), or duration of NAS treatment (mean ± SD 10.6 ± 3.1 vs 11.4 ± 3.4 days, p=0.88).[37] Taken as a whole, these retrospective studies indicate that buprenorphine may be associated with a lower incidence of preterm birth and congenital anomalies, lower frequency of NAS treatment, and shorter duration of NAS treatment compared with methadone.

Human data evaluating naltrexone for treatment of the opioid-addicted woman are limited. Initial data introduced into the literature includes a series of nine case reports using a naltrexone implant in pregnant heroin users.[39] This case series reported that neonatal outcomes, including weeks at delivery, birth weight, head circumference, body length, and APGAR scores, were unremarkable. A second publication reported obstetric and neonatal outcomes for 17 women who were exposed to a naltrexone implant and are compared with 90 women who were managed with methadone.[40] This study found that the mean 1-minute Apgar score was significantly better for neonates exposed to naltrexone (9 ± 0 vs 7.9 ± 1.54, p=0.005). No significant differences in the percentage of deliveries occurring at less than 37 weeks' gestational age or percentage of infants with birth weight less than 2500 g were noted between the two groups. Human data evaluating this treatment option are sparse and should be evaluated with caution.

The medical, psychosocial, and legal complexities of opioid use in pregnancy make studying treatment challenging. Without placebo-controlled trials or consensus on valid outcome measures, our guidance is limited by the weaknesses and biases inherent of the small

comparative outcome trials, prospective observational studies, and case studies presented in this article.

Behavioral, Developmental, and Biological Effects in Animal Studies

Opioid receptor involvement in long-term behavioral and developmental effects is still largely unknown. Methadone, unlike buprenorphine and naltrexone, has been around for nearly 5 decades, with more conflicting data than clarity on long-term outcomes in children exposed to methadone in utero. The evidence is, furthermore, muddied by confounding factors such as socioeconomic, family, parenting, and nutritional differences.[44–46]

Studies of methadone in animals are devoid of these confounders and address a potential biological mechanism for long-term effects. Methadone is associated with differential effects on dopaminergic and cholinergic development.[47, 48] In rat pups exposed to methadone prenatally, evidence of alternations in early myelination[49] and increased expression of myelin basic proteins[49, 50] may disrupt normal connectivity in the developing brain.[8] Human adolescence is marked with substantial myelin formation; therefore, long-term effects of prenatal methadone exposure are unknown.[49]

Likewise, opioid agonists given to male rats prior to conception adversely affected behavioral and survival outcomes of future pups.[51] Behavioral effects, such as decreased levels of serotonin and brain-derived neurotrophic factor (BDNF), resulted in depression-like behavior in pups.[52, 53] In addition to lower levels, the pups in both studies exhibited a longer immobility time for a swimming test and tail suspension test, which are commonly used for a depressive measurement in rats. The authors concluded that although the cause of depression in humans is not clear, decreased BDNF and serotonin levels may play a role.

Anxiety-like behaviors have also been demonstrated with opioid agonists in animal studies. Prenatal exposure to opioids may alter learning and/or memory via the opioid receptor system.[54] Reduced social behaviors may be associated with changes in μ-opioid receptor function.[54] Pups that were prenatally exposed to buprenorphine or methadone exhibited impairment in an object recognition test and reduced social interactions.[54] Light-dark transitions and maze ambulation were altered in both groups, with female pups spending significantly more time in open air than did male pups.[54]

Interestingly, some researchers have coadministered dextromethorphan (2–7 mg/kg subcutaneously twice/day) with methadone in an attempt to prevent negative outcomes associated with prenatal methadone[55] and morphine[56] exposure. Coadministration of dextromethorphan with methadone prevented an increase in withdrawal symptoms that was observed in the methadone-only group.[55] Compared to pregnant rats that only received morphine, those that received morphine and dextromethorphan demonstrated prevention in mortality, pup weight gain, and withdrawal symptoms.[56] The authors theorized that chronic exogenous opioid use may lead to excess activity of *N*-methyl-D-aspartate receptors that are antagonized by dextromethorphan and methadone.[55, 56]

Long-term neonatal consequences of prenatal exposure to buprenorphine are largely unknown. Compared to methadone, buprenorphine has been available only a quarter of the time, and not enough births to mothers exposed to buprenorphine in utero have been followed for an extended period to demonstrate significant effects on cognitive, behavioral, and social development.

Pups exposed to either morphine, methadone, or buprenorphine during gestation all developed faster tolerance to morphine later in life compared to controls.[57] Pups exposed to buprenorphine demonstrated a significantly higher cross-tolerance to morphine than did pups prenatally exposed to morphine or methadone.[57] Locomotor activities were not altered in offspring exposed to either buprenorphine or methadone during gestation, suggesting that neuroadaptation may occur after chronic prenatal exposure.[55]

It is unknown whether naltrexone administered prenatally has an impact on developmental opioid receptors. Endogenous opioids may play a role in brain development,[57] and it has been suggested that blockade of opioid receptors alters developmental effects.[58] Animal studies examining naltrexone effects on development have produced inconsistent results (e.g., no effects, stimulatory or inhibitory effects on growth shown).[58–61] In one study of sustained-release naltrexone in pregnant rats, the pups exposed to naltrexone had significant developmental effects that also appeared into adulthood.[59] In addition, behavioral effects such as significantly enhanced morphine self-administration were observed compared to pups not

exposed to naltrexone prenatally. It was hypothesized that naltrexone may negatively impact brain circuitry, encephalin signaling, or proteins needed for signaling pathways.

Another study demonstrated higher DNA content in the naltrexone-exposed pups compared to controls, suggesting that endogenous opioid blockade may alter DNA synthesis regulatory control.[60] In pregnant rats, one intraperitoneal injection of naltrexone up to 50 times the human therapeutic dose passed through the placenta and was detected in the fetal brain, heart, and liver tissue but did not adversely impact maternal rat health measures.[61] With doses up to 200 times the human therapeutic dose administered to rats and rabbits, there was no evidence of teratogenicity; however, fetal loss occurred in rats that received 30 times the human therapeutic dose and occurred in rabbits at oral doses of up to 60 times the human therapeutic dose.[62] Although the half-life of naltrexone is longer in rats compared to humans, the timetable of brain development is similar in both groups.[59] Compared to pregnant controls, pregnant rats receiving naltrexone at 50 times the human therapeutic dose (by sustained-release implant or intraperitoneal injections) experienced similar durations of gestation, litter sizes, and pup mortality.[58–60] Pups exposed to naltrexone prenatally had significantly higher birth weights,[58–60] longer body lengths, and higher organ weights.[58, 60]

Data from animal methods prompt discussion on whether pain sensitivity and response to stress and/or emotional responses such as fear and pleasure can be altered in children of mothers treated with methadone, buprenorphine, or naltrexone. In addition, it is unknown whether these medications change sensitivity to opioid-induced pain relief or modify risk of addiction in children. Until further research focuses on these topics, several questions remain unanswered regarding the long-term outcomes in children of pregnant women taking these medications.

Additional Clinical Considerations

Treatment with methadone, buprenorphine, or naltrexone should involve a comprehensive plan that incorporates counseling on chemical dependency, family counseling, nutritional education, and social support (Table 3). Methadone can only be dispensed through a registered opioid treatment program certified by SAMHSA. Doses often need to be increased throughout the pregnancy as drug metabolism increases, especially during the third trimester, to ensure the patient remains asymptomatic. The length of methadone treatment should be for 12 months. After demonstrating stability, the patient may be allowed to take doses at home, between appointments, based on the discretion of the provider as to whether the patient has demonstrated adherence and documented progress with treatment.[8, 10] Criteria used to make that determination include lack of recent drug use, regular attendance to the clinic, lack of serious behavioral problems, lack of criminal activity, a stable home environment, good social relationships, length of time in treatment, assurance that take-home medication will be safely stored, and judgment that the rehabilitative benefit to the patient outweighs the potential risk of diversion.[63]

Although methadone has a long history of use, it has limitations including many drug interactions, QTc-interval prolongation, and a long unpredictable half-life. Toxicity with methadone may take days to manifest because of the length of time required for the drug to reach steady-state concentrations. Thus, dose titrations should be performed slowly and cautiously based on symptoms and individual response. Treatment with methadone also requires frequent appointments and may require being on waiting lists to enter the treatment clinics.[7]

Fortunately, pregnant women facing long waiting lists for methadone now have expanded pharmacotherapy options.[64] Buprenorphine offers the benefit of treating opioid dependency in various settings such as a medical office, community hospital, or correctional facility, which makes access to treatment easier for a patient. There may be a lower risk of overdose and fewer drug interactions compared to methadone. However, limitations to its use include hepatic dysfunction, lack of long-term data, and diminished efficacy in some cases as evidenced by higher patient dropout rates from patient dissatisfaction.

No special training is required for a licensed health care provider to prescribe oral naltrexone.[7] This allows for better access to treatment for many patients. However, the naltrexone extended-release implant, approved by the FDA in 2016, does require the prescriber to be certified through a risk evaluation and mitigation strategy (REMS) program. The REMS requirement is in response to the risks of surgical

Table 3. Clinical Considerations for Opioid Use Disorder in Pregnant Women[5, 8, 18, 20, 51, 65–71]

Consideration	Methadone	Buprenorphine	Naltrexone
Controlled substance category	Schedule II	Schedule III	NA
Mechanism of action	Synthetic μ-opioid receptor agonist, also uniquely a δ-opioid receptor agonist, and NMDA receptor antagonist	Semisynthetic derivative of the opioid alkaloid thebaine μ-opioid receptor partial agonist primarily antagonistic actions on κ-opioid and δ-opioid receptors	Synthetic μ-opioid antagonist and, to a lesser extent, κ-opioid antagonist
Estimated half-life	8–59 hrs, undergoes extensive CYP3A4, CYP2B6, and CYP2C19 metabolism in the liver primarily to 2 inactive metabolites Females may metabolize methadone more rapidly than males	24–60 hrs, undergoes CYP3A4 metabolism in liver to active metabolite norbuprenorphine	5–10 days when given i.m., depending on erosion of polymer delivery system; non-CYP metabolism to active metabolite 6-β-naltrexol with half-life of 13 hrs
Dosing	Initiate at 10–30 mg/day; do not exceed total daily dose of 40 mg on day 1. To treat withdrawal symptoms, incremental dose increases of 5–10 mg every 2–4 hrs as needed can be used. Dosing is the same for pregnant patients; may need to increase dose or shorten dosing interval during 2nd or 3rd trimesters due to increased elimination during pregnancy. Optimal dose varies greatly; concentrations with equivalent doses can vary between 17- and 41-fold even after adjustment for body weight. Duration of analgesic is much shorter than elimination half-life. Do not increase dose without waiting for steady-state to be achieved. Reassure patient that duration of effect will increase as methadone accumulates.	Induction typically occurs over a 3–4-day period, beginning with either 2 or 4 mg, with a maximum dose of 8 mg on day 1 and 12–16 mg/day on days 2–4. Initiate at least 4 hrs after the last short-acting opioid dose, ideally after first signs of withdrawal. Alternate dosing[18]: Induction: 2–4 mg; if no signs of precipitated withdrawal after 60–90 minutes, may increase in increments of 2–4 mg. Once initial dose is tolerated, may increase to a dose that is clinically effective and provides 24 hrs of stabilization. After induction and titration, daily dose is usually ≥ 8 mg/day. In continued opioid use, consider increasing the dose by 4–8 mg to a daily dose of ≥ 12–16 mg/day. Initiation should begin after mild to moderate opioid withdrawal signs appear (to avoid precipitated withdrawal), which is generally at least 6–12 hrs after last use of short-acting opioids (e.g., heroin, most prescription narcotics) and 24–72 hrs after last use of long-acting opioids (i.e., methadone). Alternate dosing[20]: 112 mg/70 kg/week, given as thrice-weekly dosing (34 mg/70 kg on Fridays and Sundays and 44/mg/70 kg on Tuesdays) Subdermal implant: Insert 4 implants subdermally in the inner side of the upper arm. Remove no later than 6 months after the date of insertion; if continued treatment is desired, insert 4 new implants subdermally in the inner side of the contralateral arm. After one insertion in each arm, discontinue treatment with subdermal implants. Converting back to sublingual oral tablet: On day of implant removal, resume buprenorphine treatment at previous sublingual dose. Because dose adjustments cannot be made, implants may not be appropriate in pregnant women.	Administered as an injectable long-acting formulation sometimes called "depot naltrexone." Patients must be detoxified from opioids and opioid free for 7–10 days. Risk of narcotic overdose if a patient who is being treated with naltrexone misses a dose and takes an opioid, or if the patient takes large quantities of opioids in an attempt to break the blockade. Compliance measures to closely monitor patients during the treatment period may be beneficial.
Cost	Less expensive based on drug costs alone, but clinic visits are more frequent 5-mg oral tablets: $32/100 tablets	Buccal film strips: $300–$700/60 strips (price increases with higher doses) 2-mg sublingual oral tablets: $135/30 tablets; 8-mg tablets: $250/30 tablets 74.2-mg subdermal implant: $5940/4 implants	50-mg oral tablets: $130/30 tablets i.m. injection: $1570/380-mg injection

(continued)

Table 3 (continued)

Consideration	Methadone	Buprenorphine	Naltrexone
FDA pregnancy considerations	Crosses placenta; weigh potential benefits versus risks	Crosses placenta; weigh potential benefits versus risks	Unknown if crosses placenta, but lower molecular weight, low protein binding, and long half-life suggest it may cross placenta
Dosage forms	Oral: liquid concentrate, tablet, oral solution of diskette or powder	Buprenorphine as a single agent: sublingual oral tablets, buccal film strips, transdermal patch, and subdermalimplant For subdermal implant, supplemental doses of buprenorphine may be necessary; do not give prescriptions for as-needed transmucosal buprenorphine; if use of supplemental doses is ongoing, consider alternative buprenorphine products for maintenance treatment	Extended-release i.m. injection every 4 wks Naltrexone 50-mg oral tablets (daily dosing)
Regulations	Can only be dispensed in a SAMHSA-certified opioid treatment program Daily administration on site or at home for clinically stable patients	Can be prescribed by physician with board certification in addiction medicine or addiction psychiatry and/or completion of training to qualify for a federal waiver to prescribe buprenorphine Any pharmacy can dispense a prescription for buprenorphine except for implants, which are not supplied in pharmacies and can only be prescribed by certified providers through a restricted distribution program.	Can be prescribed by any individual licensed to prescribe medications
Advantages	Long history of use and supporting literature More effective for severe dependence	Less abuse potential Less severe NAS	Monthly depot injection Limited potential for drug diversion
Disadvantages	Requires multiple dosage adjustments during pregnancy due to pharmacokinetics Accumulation of drug Daily clinic visits	Less drug-drug interactions compared with methadone Potentially lower patient satisfaction Patient needs to be in mild-moderate withdrawal on initiation of agent	Less efficacy data Precipitates withdrawal in a patient currently using opioids Possible hepatic impairment Injection-site reactions
Breastfeeding	Detected in breast milk in very low levels and may be inadequate to prevent NAS Concentrations in breast milk are unrelated to maternal methadone dose Amount ingested by infant is low and remains low even 6 months later Advantages of breastfeeding in reduced NAS severity and duration prevail despite risks of infant opiate intoxication Counsel mothers on identifying signs of sedation and respiratory depression in breast-fed infants Milk to maternal plasma ratio: 0.05 to 1.2 Contraindications: HIV positive, unstable recovery	Found in breast milk 2 hrs after maternal dosing Concentration of buprenorphine in breast milk is low; amount infant receives through breast milk is only 1% Most recent guidelines indicate that the amount in human milk is small and is unlikely to have negative effects on the developing Infant. Advantages of breastfeeding in infants with reduced NAS severity and duration prevail despite risks of infant opiate intoxication Counsel mothers on identifying signs of sedation and respiratory depression in breast-fed infants Contraindications: HIV positive, unstable recovery	Extent to which breast milk production might be altered is currently unknown Amount that may be transferred to the infant through breast milk is currently unknown Effects on the nursing infant are unknown

(continued)

Table 3 (continued)

Consideration	Methadone	Buprenorphine	Naltrexone
Pain management	Uninterrupted methadone maintenance treatment is critical Aggressive pain management with behavioral interventions (e.g., breathing exercises) and use of nonopioid pain-relief medications (e.g., acetaminophen) No good correlation between plasma levels and pain relief. Methadone is not appropriate for short-term analgesia during labor and delivery; additional pain management options should be considered. Reduce anxiety of patient with clear, open communication	Maintenance dose of buprenorphine will not provide adequate pain relief during labor. Medications that are full agonist opioids can effectively treat pain in stabilized patients The importance of uninterrupted treatment in these patients is critical Each patient needs a pain management plan before delivery. Dosage adjustments are not needed as often as with methadone.	Precludes use of opioids for pain relief Maternal exposure during pregnancy may decrease pain threshold and require tailored pain management using nonopioid medications such as high-dose nonsteroidal antiinflammatory medications and/or local anesthesia.

NA = not applicable; NMDA = *N*-methyl-D-aspartate; CYP = cytochrome P450; HIV = human immunodeficiency virus; FDA = U.S. Food and Drug Administration; SAMHSA = Substance Abuse and Mental Health Services Administration; NAS = neonatal abstinence syndrome; HIV = human immunodeficiency virus.

complications and because of the potential for accidental overdose, misuse, and abuse if the implant is expelled or protrudes from the skin. Children exposed to a protruding or migrated implant are also at risk for overdose. Visits to the physician should be made within 1 week of implant insertion and at least monthly thereafter for counseling and psychosocial support.

Preliminary evidence from a case series demonstrated that implantable naltrexone may be useful in pregnant women who are at risk for relapse from nonadherence to daily naltrexone,[40] although more support from a large controlled study is warranted. In 2012, a survey conducted in pregnant patients indicated a high interest in naltrexone as a treatment option.[64] This survey was completed by 112 pregnant patients undergoing comprehensive treatment for substance abuse while enrolled at a naltrexone treatment program at the Center for Addiction and Pregnancy in Baltimore, Maryland.

The intensity of NAS with methadone or buprenorphine is not dose dependent; thus, lowering the doses of these drugs does not have any advantage over other evidence-based strategies for minimizing NAS such as smoking cessation and breastfeeding. Women hoping to reduce NAS should be advised against switching to buprenorphine if they are currently on stable doses of methadone.[10]

For pregnant women who are stable on buprenorphine or methadone for opioid use disorder and wish to discontinue MAT, they should be advised of the risks of MAW including the high potential for relapse and subsequent stress to the fetus.[7] If methadone or buprenorphine is refused, or if methadone maintenance is unavailable, MAW can be started during the second trimester, if possible, under the supervision of a physician with experience in perinatal addiction treatment. Starting MAW in the first trimester is advised if the only alternative is continuation of the illicit drug.[8] Previous SAMHSA guidelines state that appropriate patients for MAW in pregnancy include those who live where methadone maintenance is unavailable, have been stable on MAT and request MAW prior to delivery, refuse to be maintained on methadone, or plan to undergo MAW through a structured treatment program.[65]

The Guttmacher Institute released a report, updated in November 2016, that indicates some points regarding the legislation surrounding substance abuse in pregnancy in each state.[66] Tennessee became the only state in which criminal

charges can be filed against drug users during pregnancy, whereas 18 states consider drug abuse during pregnancy to be child abuse. Eighteen states require health care providers to report prenatal drug abuse if suspected, whereas four states require drug exposure testing in patients in whom abuse is suspected. Funded drug treatment programs for pregnant women exist in 19 states, with 13 states providing priority access to pregnant women for drug treatment programs. Four states prohibit the discrimination of pregnant women by publically funded drug treatment programs. This variability in legislation from state to state can lead to a patient who is fearful of reporting drug addiction and seeking treatment during pregnancy.

Discussion

Whether MAT or MAW is selected, psychosocial support and comprehensive obstetric care should always accompany medication to minimize the risks of potential maternal and fetal complications. Currently, methadone and buprenorphine are both widely used as the backbone of MAT. The distinguishing outcomes in studies among these two opioid agonists are that infants exposed to buprenorphine in clinical trials required shorter treatment duration, less medication to treat the NAS symptoms and experienced shorter hospitalizations compared to infants exposed to methadone. A caveat to these findings is that some of the supporting data were based on using buprenorphine in combination with naloxone instead of buprenorphine as a single agent. Despite being the standard of care, two-thirds of pregnant women admitted to treatment centers did not receive MAT, making it apparent that more options are necessary.[4]

More research with naltrexone in pregnant women is needed to determine its safety and benefits. Currently, naltrexone is not advised because it requires detoxification and an opioid-free period, which exposes individuals to a vulnerable period for relapse, reestablishment of physical dependence, increased risky behaviors, treatment dropout, and the possibility of opioid overdose and death.

Although recommendations made by national and international organizations, such as the ACOG, WHO, U.S. Department of Health and Human Services, SAMHSA, ASAM, Legal Action Center, and American Academy of Pediatrics, exist, collectively, they are limited by the lack of robust placebo-controlled RCTs in maternal opioid use disorder. Currently, published literature only consists of three prospective RCTs, a handful of smaller prospective observational studies, and five retrospective studies to support recent recommendations.

Moreover, challenging medical, psychosocial, and legal variables make studying this population difficult, especially in the presence of stigma and misconceptions from the public and health care professionals about opioid use disorder.[10] Overcoming these obstacles will continue to be a challenge for investigators seeking to optimize care for the growing population of mothers and infants affected by this disorder.

Animal studies, particularly in rats, allow prospective research on the effects of opioid blockade during gestation. Available data in animals propose that methadone, buprenorphine, and naltrexone may have broader effects on behavioral and brain development, which have not been fully explored in current literature in humans. Depression, anxiety, learning, and social behaviors seen in animal studies with opioid agonists are worth exploring to rule out consequential long-term outcomes that may alter therapeutic recommendations or preferences of pregnant women abusing opioids. Additional long-term follow-up studies in humans, assessing both maternal and offspring outcomes, is crucial to capture the full spectrum of effects resulting from exposure to these medications during pregnancy.

Conclusion

Because of the high rate of opioid use and misuse among pregnant women and women in general, communities are more often having to confront this concern. As we seek to learn more about how to respond successfully to the complex needs of pregnant women with opioid use disorders, it becomes important to leverage opportunities to collect valuable data for thoughtful and efficacious treatment selection. The prevalence of substance use during pregnancy is underreported, partly due to punitive legal implications and the lack of universal screening for substance use during pregnancy. More information regarding the postnatal effects of these treatments will be gained by earlier identification and initiation of treatment in these women. With an increasing number of newborns delivered to women receiving MAT or MAW, more data can be collected to measure the

success and effectiveness of different interventions and approaches. Methods to collect these data should be identified.

Conflicts of Interest

The authors declare they have no financial conflicts of interest.

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