The opioid epidemic and pregnancy: implications for anesthetic care

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Purpose of review
This review summarizes evolving knowledge regarding adverse maternal, fetal, and neonatal effects of opioid exposure during pregnancy, and current treatment options for opioid use disorder (OUD). Maternal and fetal implications of maternal opioid maintenance with methadone and buprenorphine are described. Finally, acute and chronic pain management strategies in opioid-tolerant parturients are reviewed.

Recent findings
Opioid use among parturients has risen dramatically, with opioid use during pregnancy as high as 20%. Of women with chronic pain, most continue to take opioids during pregnancy. Medication-assisted therapy with methadone or buprenorphine is currently the standard for treatment of opiate use disorder. Buprenorphine has unique pharmacologic properties that account for its preference over methadone. It has also been shown to produce more favorable neonatal outcomes compared with methadone. Increased clearance and volume of distribution associated with pregnancy require adjustment of dosing regimens of both medications. Multimodal adjuncts can be important alternatives for treatment of pain in opioid-tolerant parturients.

Summary
The dramatic rise in OUD in pregnancy has had staggering socioeconomic consequences, carrying with it profound maternal and fetal health problems. Medication-assisted treatment utilizing either methadone, or more commonly buprenorphine, is considered the standard of care for OUD during pregnancy. Peripartum pain management for opioid-tolerant patients is challenging and requires consideration for regional anesthesia along with multimodal pharmacotherapy.

Keywords
buprenorphine, medication-assisted therapy, neonatal abstinence disorder, opiate use disorder, pregnancy

INTRODUCTION: COPE OF THE PROBLEM

More than 6600 women died from opioid overdose in 2010, a four-fold increase over a decade [1]. Prevalence of prescription opioid use among reproductive-aged American women was estimated to be 39% for Medicaid recipients and 28% for the privately insured from 2008 to 2012 [2]. A concomitant rise in opioid use among pregnant women has also been observed. A Medicaid database cohort study of 1.1 million pregnant women revealed a 23% increase in opioids prescribed from 2000 to 2007, with one in five filling an opioid prescription during pregnancy [3]. In a similar private insurer database analysis of over 0.5 million parturients (from 2005 to 2011), 14% were dispensed an opioid during pregnancy [4], thus mirroring the observed discrepancy in prevalance of prescription opioid use among Medicaid versus privately insured reproductive-aged women [2]. Considerable geographic variation exists, with statewide opioid usage rates during pregnancy ranging from 6.5 to 26.3%, lowest in the Northeast and highest in the Southeast [4].

According to the National Survey on Drug Use and Health (2005–2014), 5.1% of pregnant women reported nonmedical use of prescription opioids within the last year, a two-fold increase over a decade [5–7]. Most were under the age of 26 (63%), Caucasian (67%), and reported concomitant tobacco use (65%) [8▪]. Additionally, pregnant women living below the poverty level were twice as likely to report misusing opioids within the past

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KEY POINTS

- The opioid epidemic also influences the parturient population, with nearly one in five women filling opioid prescriptions during pregnancy.
- Most women with chronic pain continue to use opioids through pregnancy.
- Medication-assisted therapy is the standard for treatment of OUD during pregnancy. Compared with methadone, buprenorphine offers unique pharmacologic and economic advantages, as well as emerging evidence of its benefit with milder neonatal abstinence syndrome.
- Treatment of acute and chronic pain for opioid-tolerant women can be challenging. Pharmacokinetic changes during pregnancy requires increased dosage and frequency of administration of opioids, and multimodal adjuncts or regional blockade may be helpful components to treatment of pain.

month compared with those living at or above [9]. Concurrent use of alcohol, tobacco, or marijuana is strongly associated with opioid use disorder (OUD) [5]. OUD has replaced the terms 'opioid abuse' and 'opioid dependence,' and describes the pattern of use characterized by tolerance, craving, inability to control use, and continued use despite adverse consequences, including the spectrum of addictive disease from mild to severe [10]. Of pregnant women reporting prescription nonmedical misuse within the past month, nearly half identified their own doctor as their source for opioids, compared with only 27.6% of nonpregnant women [11]. Increasingly restrictive regulations on prescription opioids has given rise to increased use of injectable opioids [12]. Heroin use was reported in nearly a quarter of pregnant women admitted for substance misuse treatment in 2012 [9]. Actual prevalence of opioid use by parturients is likely underestimated, as data are limited to opioids dispensed by outpatient pharmacies [3,4], or exclude nonprescription use and prescriptions paid out-of-pocket [2]. Stigma and fear of loss of child custody may also contribute to underreporting [13].

Opioid use among pregnant women is either prescribed or illicit, and can be divided into three distinct categories – untreated OUD, OUD treated with medication-assisted pharmacotherapy (MAT), and medical treatment of chronic pain [14▪▪,15▪]. Each involves unique maternal and fetal drug exposures, context-specific factors (socioeconomic, psychological, stigmatization), and maternal and fetal implications [15▪]. Although this review focuses primarily on OUD, the proportion of pregnant women who take opioids for chronic pain is growing. In the US private insurer database study cited above, 5838 of 534 500 (1%) women took prescribed opioids chronically before pregnancy, and most continued these during the first two trimesters [4]. Leading indications for use were back pain (68%), abdominal pain (41%), joint pain (28%), migraines (22%), and fibromyalgia (18%) [4]. A Canadian database study analyzed fee-for-service medical claims for all parturients in Manitoba from 2001 to 2013, and reported a modest decline in the proportion of prescription opioid users throughout each trimester, from 6.7% in the prepregnancy period to 2.9% in the third trimester [16]. However, among parturients who continued using opioids, the dose used (oral morphine equivalent) remained constant relative to prepregnancy use.

Maternal effects of opioid exposure during pregnancy

Opioid use imposes complexity on pregnancy, including psychosocial and physical health problems, reduced frequency of prenatal care, and not uncommonly, co-associated factors (mental illness, malnutrition, inadequate support or funds, and polysubstance use for some mothers) [13]. Unique postpartum challenges and stresses further render the opioid-dependent mother vulnerable to a host of problems, including depression, relapse, risks to infant well being, and threats to maternal safety [14▪▪,17▪▪,18]. Relapse risk is much greater during the postpartum period than antenatally [14▪▪], and carries with it risks of repeated cycles of withdrawal, contraction of infectious diseases, and even overdose and death [18,19▪]. Additionally, women with OUD are at considerable risk for unintended pregnancy [20], highlighting the importance of contraceptive planning and of actualizing intended postpartum interventions [14▪▪,21,22]. Finally, of 211 maternal deaths in Colorado during the 9 years, 2004–2013, 30% were by self-harm (accidental overdose or suicide) [18]. Most of these deaths occurred during the postpartum period and involved OUD and/or psychiatric disorders.

Fetal implications: teratogenicity/birth defects

Maternal opioid use results in fetal opioid exposure (see Malek and Mattison for a review of placental functional effects [23]). The 2017 ACOG Committee Opinion on OUD cites nine studies examining links between prenatal opioid exposure and congenital birth defects [14▪▪]. Most have failed to establish an association, whereas a minority have. Of the latter,

methodological problems limit meaningful conclusions. As for long-acting opioids, Zedler *et al.* [24▪▪] conducted a systematic review and meta-analysis of studies comparing maternal and fetal safety of buprenorphine versus methadone pharmacotherapy during pregnancy. Three randomized controlled trials (RCTs) and 15 cohort studies met inclusion criteria and constituted 2146 patients. No differences were observed for congenital anomalies, but the power to detect differences was insufficient. Incidence of anomalies was similar to that expected in the general population.

Neonatal abstinence syndrome

Neonatal abstinence syndrome (NAS) occurs at birth with the abrupt cessation of long-term in utero opioid exposure. Withdrawal causes hyperactivity of the central and autonomic nervous systems and gastrointestinal system [25,26], with signs that include tremors, poor feeding, irritability, gastrointestinal dysfunction, and temperature or autonomic nervous system instability [8▪,25,26,27▪]. Mirroring opioid use in pregnancy, the incidence of NAS in the United States increased fivefold from 2000 to 2012, to 5.8 per 1000 hospital births (one neonate born with NAS every 25 min) [7]. Co-exposure to other psychotropic drugs further increases risk of NAS [28]. Patrick *et al.* analyzed United States hospital discharge data from 2009 to 2012. For infants with NAS, mean hospital length of stay was 17 days with average hospital charges $66 700 (23 days, $93 400 for those requiring pharmacologic treatment). This compares with only 2.1 days, $3500, for uncomplicated term infants [7]. NAS aggregate hospital charges increased over 3 years, from $732 million in 2009 to a staggering $1.45 billion in 2012, with 80% financed by Medicaid [7,8▪]. Hospital stay and costs derive from recommended NAS surveillance for at-risk neonates [29] and high rates of pharmacologic treatment for babies who develop NAS [25]. Morphine and methadone are used most commonly for the latter [26,27▪,29,30], but buprenorphine has shown promise in reducing treatment duration and costs [27▪,31,32▪].

Implications for childhood and beyond

Uebel *et al.* reviewed population-based hospitalization and death records data in Australia from 2000 to 2011 on long-term consequences for children of mothers with OUD. They reported higher rates of hospitalization throughout childhood and adolescence for maltreatment, trauma, and mental and behavioral disorders in infants diagnosed with NAS [33]. Contributory cause is difficult to establish because of confounding by numerous difficult-to-measure social, environmental, and medical issues that co-associate with opioid-using mothers [34]. Nonetheless, long-term outcomes highlight the high-risk status associated with a diagnosis of NAS [26].

BENEFITS OF OPIOID SUBSTITUTION MEDICATION-ASSISTED TREATMENT

Medically supervised withdrawal (detoxification) and abstinence during pregnancy are possible, and may be well tolerated for the fetus [19▪,35], but relapse rates may exceed 50% even among motivated parturients [17▪▪]. Medication-assisted treatment (MAT) is considered the standard of care for OUD during pregnancy. Scheduled administration of long-acting methadone or buprenorphine effectively prevents the frequent cycles of withdrawal experienced by women with OUD [17▪▪]. Consequently, MAT is associated with improved fetal and obstetric outcomes, including compliance with prenatal care, lower rates of preterm birth, reduced fetal and neonatal morbidity and mortality, and a higher likelihood of newborn being discharged to his/her parents [17▪▪]. Despite this, many pregnant women with OUD remain untreated. Data analyzed from the 1992 to 2012 Treatment Episode Data Set (TEDS) revealed that only one in three parturients admitted to a treatment facility for OUD received MAT [36]. Thus, ACOG is currently emphasizing the importance of early universal screening for OUD during pregnancy, referral for specialized care, and advocacy for improved access [14▪▪].

Methadone versus buprenorphine for medication-assisted treatment

Methadone, first introduced for MAT in the 1970s, has long been the standard treatment for OUD in pregnancy. Its full opioid agonist properties and long half-life carry risk of life-threatening respiratory depression. However, outcomes after maternal methadone maintenance are favorable, with 92% of treated patients remaining relapse-free at delivery and only 29% of newborns requiring treatment for NAS [37]. Pharmacokinetics of methadone are altered by pregnancy. A systematic review of pharmacokinetics and dosing studies in pregnant patients published through mid-2012 yielded three pharmacokinetic trials and four reports examining split-dosing [38]. Total and renal clearances are significantly higher, and trough drug concentrations are lower (corresponding to maternal withdrawal effects) in pregnancy compared with postpartum.

These changes progress through the course of pregnancy and necessitate higher doses, ideally in divided doses [15▪].

Buprenorphine has unique pharmacologic properties that make it an attractive alternative to methadone. It differs from methadone in having an extremely high affinity for μ-opioid receptors, a longer half-life, and incomplete intrinsic agonist activity [39,40]. Buprenorphine exhibits unique ceiling effects for respiratory depression, sedation, and euphoria [39,40]. Analgesic ceiling effects described in early rat studies [41] have not been observed in other animal studies or in humans, making the drug an attractive choice for treating addiction and for postcesarean analgesia [42,43]. Whether buprenorphine suppresses or precipitates withdrawal in the presence of chronic opioid use depends on the particular opioid, dose, and plasma levels [40]. A meta-analysis by Zedler *et al.* [24▪▪] yielded moderately strong evidence in favor of buprenorphine over methadone for lower risk of preterm birth, greater birth weight, larger head circumference, and no increased risk of harm. Decreased rates of NAS and need for pharmacologic treatment, as well as shorter duration of treatment and length of hospital stay have been reported for infants of mothers maintained on buprenorphine compared with methadone during pregnancy [44,45▪,46▪]. The greater convenience and lower costs associated with buprenorphine (unsupervised off-site, take-home maintenance), along with its ceiling effect for respiratory depression, sedation, and subjective measures, have likely further contributed to its increasing use for MAT in pregnant women [15▪], although there is potential risk for diversion and unsanctioned use [47]. Of note, recent pharmacokinetic studies suggest need for increasing daily buprenorphine dose and dosing frequency (three to four times daily) during pregnancy [48,49▪▪]. Volume of distribution and clearance increases during pregnancy yield 50% reductions in dose-normalized drug levels (often subtherapeutic), compared with postpartum [48,49▪▪].

Despite long-standing clinical treatment of chronic opioid use with methadone, and more recently buprenorphine, there is a paucity of decisive evidence regarding best practices for pregnant women, as is also true for nonpregnant patients [47,50]. Although MAT using long-acting opioids is the standard for OUD in pregnancy, a 2013 Cochrane review identified only four relevant RCTs, which were deemed insufficient to determine superiority of a particular drug with regard to any maternal, fetal, or neonatal outcome [51]. Table 1, from Reddy *et al.* [17▪▪], contrasts clinically relevant characteristics of methadone and buprenorphine.

PERIPARTUM PAIN MANAGEMENT IN OPIOID-TOLERANT MOTHERS

Chronic opioid exposure induces tolerance to the analgesic effects of opioids, which renders traditional postpartum analgesic strategies that include systemic or neuraxial opioids less effective in opioid-tolerant parturients following cesarean delivery, repair of severe perineal tears, or postpartum tubal sterilization [52,53]. Despite cross-tolerance to long-acting opioid maintenance drugs, effective postcesarean analgesia is reported with administration of higher opioid doses along with nonopioid analgesic modalities, particularly NSAIDs, in addition to continued opioid maintenance [52–57]. Meyer *et al.* [55] reported higher postoperative pain scores after cesarean and 70% greater opioid analgesic use in 33 parturients maintained on methadone compared with opioid-naive matched controls. These findings were unaffected by inclusion of intrathecal morphine in a subset (9 of 33) of methadone patients. The same group reported similar findings among 19 postcesarean patients maintained on buprenorphine, suggesting that both methadone and buprenorphine interfere with postcesarean opioid analgesia to a similar degree [57]. It is important that clinicians consider the higher than average postcesarean analgesia requirements of this population, utilize nonopioid modalities, and not underdose opioid analgesics [53]. Consistent with ACOG guidelines, women on methadone or buprenorphine should, at a minimum, continue their maintenance dose through the peripartum period [14▪▪]. Although definitive trials of peripartum MAT adjustment have yet to be performed, current recommendations are based upon successful case series and expert opinion. To take advantage of the analgesic benefits of buprenorphine, a maintenance dose divided into three to four administrations over 24 h yields more consistent plasma concentrations during pregnancy [49▪▪]. However, additional full opioid agonists willl still likely be required to supplement analgesia following cesarean delivery, and present data endorses that buprenorphine-maintained patients are able to mount an analgesic response to that additional opioid therapy [56].

Non-opioid strategies

In a recent meta-analysis of 22 RCTs evaluating the effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) for postcesarean analgesia in opioid-naive parturients, Zeng *et al.* [58] reported that those who received perioperative NSAIDs reported lower static and dynamic postoperative pain scores, used less systemic opioid analgesia, and experienced less drowsiness compared with

Table 1. Characteristics of methadone and buprenorphine use during pregnancy

Characteristics	Methadone	Buprenorphine
Dosing	Directly observed therapy	Outpatient prescription Risk of diversion greater
First dose	20 mg (oral; range 15–30 mg)	2–4 mg (sublingual)
During withdrawal symptoms	5–10 mg every 3–6 h. Day 2: combined total of doses given in first 24 h	2 mg within 1–2 h
Dose increase interval	3 days	1 day
Dose initial maintenance	69 mg (range 8–160 mg)	Maintenance dose range: 8–24 mg
	At delivery: 93 mg (range 12–185 mg)	(beyond 32 mg, little increase in effect)
Half-life[a]	8–20 h	30 h
Polysubstance abuse	Preferred treatment for long-standing polysubstance abuse	May be more effective for prescription opioid users or new heroin users
Patient convenience	Less convenient – requires daily visits to federally licensed clinic. Take-home doses are allowed for Sundays or holidays unless random monthly urine drug screen is positive	More convenient – dispensed from office weekly or biweekly
Retention rates	Higher in treatment settings (78.1%)	Lower in treatment settings (57.7%)
Risk of overdose mortality in treatment	Higher, 4.18 /1000 person-years in treatment	Lower, 0.98 deaths/1000 person-years
NAS incidence[b]	Equal (57%)	Equal (47%)
NAS treatment duration	Longer (9.9 days)	Shorter (4.1 days)
Breastfeeding	Safe	Safe
Neurodevelopmental outcome of exposed children	No different from controls matched for age, race, and socioeconomic status	Limited evidence

Reproduced with permission from [17▪▪]. NAS, neonatal abstinence syndrome.
[a]Reduced half-life as pregnancy advances.
[b]Not statistically different.

postcesarean patients randomized to placebo. These findings highlight the importance ascribed to scheduled NSAID administration in opioid-tolerant parturients [52–57].

Substituting postcesarean low-dose epidural bupivacaine analgesia (thoracic or lumbar) in lieu of opioid analgesia has been described in buprenorphine-maintained parturients [52]. Given the demonstrated analgesic effectiveness following other low abdominal and pelvic surgeries, epidural analgesia or other regional modalities should be considered in addition to continued maintenance opioid therapy. A four-case series by Leighton and Crock [52] reported excellent analgesia in buprenorphine-maintained parturients utilizing thoracic epidural analgesia following cesarean delivery. Potential side effects and increased resource allocation are considerations, and a prospective trial would be very helpful in determining the role of neuraxial analgesia in this population. The most recent meta-analysis of effects of transversus abdominus plane (TAP) blocks on postcesarean analgesia identified 20 high-quality RCTs published through mid-2016, 14 including ultrasound guidance [59]. TAP blocks reduce opioid analgesic consumption and improve analgesia compared with placebo or no block, but only in patients who do not receive intrathecal morphine. This may have clinical relevance in the opioid-tolerant parturient after cesarean delivery, in whom intrathecal morphine may be ineffective, but studies of TAP blocks in these patients are lacking. In a more recent RCT demonstrating similar results, Fusco *et al.* emphasized the importance of ensuring correct performance of the block with ultrasound guidance in effecting benefit [60]. Rapid local anesthetic uptake [61] and local anesthetic systemic toxicity [62] have been reported with TAP blocks after cesarean delivery, and warrant caution.

Opioid-naive postcesarean women were reported to use 40% less as-needed oral opioid analgesics following a departmental protocol change from as-needed to scheduled acetaminophen dosing [63]. These findings are limited by very low pain scores that were not different between groups (all patients received spinal morphine), and by potential confounding associated with retrospective cohort impact studies. In a double-blind placebo-controlled study of patients undergoing elective cesarean under general anesthesia (no neuraxial morphine), preoperative administration of

intravenous acetaminophen improved pain scores during the first 12 postoperative hours, and halved opioid consumption during the first 24 h [64]. A retrospective analysis of a national healthcare database reported an association between adding intravenous acetaminophen to the postcesarean analgesia regimen and reduced opioid use [65]. However, the investigators reported conflicts of interest, and findings are limited by potential bias and confounding inherent in the study design. Acetaminophen appears to have a modest opioid-sparing effect in perioperative patients, without altering rates of opioid adverse effects [66]. Despite insufficient evidence regarding its routine use, acetaminophen's low risk, low cost, and potential benefit may make its use in opioid-tolerant postpartum women reasonable.

In a 2010 RCT of 46 women, a single preoperative dose of gabapentin 600 mg improved visual analogue scale (VAS) pain on movement 24 h after cesarean delivery compared with placebo, but caused a greater incidence of severe sedation (19 versus 0%) [67]. In a subsequent trial from the same institution, parturients randomized to receive a perioperative course (600 mg before cesarean delivery and 200 mg every 8 h for 2 days) reported marginally lower VAS pain scores with movement in the first 24 h, but greater sedation (55 versus 39%) at 24 h, compared with the placebo control group [68]. Given the lack of evidence of clinically significant benefit in the opioid-tolerant postcesarean patient, and its known unwanted side effects, evidence does not support routine use of gabapentin in this population.

CONCLUSION

Increasing opioid use among pregnant women is keeping pace with the opioid epidemic more generally, and the consequences for expectant mothers, their babies, and society at large, are profound. In response, ACOG, along with numerous specialties that collaborate in the care of expectant mothers, have issued strong position statements on best practices and knowledge gaps [14▪▪,17▪▪]. Emerging research has focused on better identification of opioid dependence in mothers, and treatment that reduces maternal, fetal, obstetric, and neonatal complications. Postcesarean analgesia is challenging because of tolerance and the unique pharmacology of the two long-acting opioids commonly used in medically assisted maintenance pharmacotherapy. Increased opioid doses and use of nonopioid modalities are reported to be helpful, although the most effective analgesic strategy in these patients is yet to be determined.

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Conflicts of interest

There are no conflicts of interest.

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