The Perils of Opioid Prescribing During Pregnancy

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KEYWORDS
- Pregnancy • Opioids • Chronic pain • Teratogens • Neonatal abstinence

KEY POINTS
- Chronic opioid therapy during periconception can result in congenital anomalies.
- Neonates exposed to chronic opioid therapy in utero are at risk for neonatal abstinence symptoms.
- Opioids kept in the home should be secured from children and teens in the household to prevent accidental poisoning or experimentation.
- Chronic opioid therapy during pregnancy requires a multidisciplinary approach with obstetrics, pain specialists, and pediatricians.
- Women planning pregnancy or not using reliable contraception should be on folic acid before conception.

IS PRESCRIBING OPIOIDS FOR CHRONIC PAIN PERILOUS FOR WOMEN?

Prescribing long-term opioid therapy to women has increased dramatically over the last decade, with the incidence of use as high as 10% in reproductive aged women in some health care systems. This statistic makes it hardly surprising that prescribing of opioids during pregnancy has increased in a parallel fashion. Despite limited evidence of efficacy of chronic opioid therapy for the types of pain most commonly reported in women, clinicians will care for patients that become pregnant while taking opioids for chronic pain. The purpose of this article is to examine the perils of chronic opioid use in women in general, during pregnancy, and on the neonate.

RISK FOR MISPRESCRIPTION

Women have more pain than men. Although the cellular mechanisms underlying the sexual dimorphism of pain response remains unclear, epidemiologic studies are consistent in the finding of increased chronic pain syndromes in women.

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receive more opioid prescriptions than men, have chronic use more frequently, and are prescribed higher doses.\textsuperscript{3,6} A recent review by Darnall and colleagues\textsuperscript{3} details the evidence available for common indications for opioid treatment in women. There is no evidence to support long-term opioid use for irritable bowel symptoms, headache, or fibromyalgia, and at best, mixed evidence of efficacy for musculoskeletal pain. Once opioid use has exceeded 90 days, two-thirds of patients are still taking these drugs years later.\textsuperscript{7} Preexisting depression, anxiety, and smoking increase the risk of long-term opioid prescribing.\textsuperscript{2} Of women entering a treatment program for prescription drug abuse, 62% received the initial prescription legitimately by a physician (as opposed to illegally); over half continued opioid use through legitimate prescription, but were more than twice as likely as men to have multiple prescribers.\textsuperscript{8,9} Women who abuse prescription opioids are less likely to use opioids through a route other than orally (ie, less intravenous [IV] or intranasal use compared to men), but are more likely to use medication to modulate negative effect and psychiatric symptoms, as opposed to pain. Although some investigators suggest that opioids may play a role in the treatment of long-term multimodality pain and suffering,\textsuperscript{7} this approach has not been rigorously tested or accepted and would be beyond the scope of the general practitioner.

Overall, these findings suggest that opioids prescribed by well-intentioned providers for poorly defined pain sets the stage for chronic, higher dose opioid use for modulation of negative effect, taking a toll on the women’s life and family.\textsuperscript{8,9}

RISK FOR MISUSE, ADDICTION, OR DEPENDENCE

The blurry lines between misuse, physical dependence, and addition have been simplified in the most recent Diagnostic and Statistical Manual of the American Psychiatric Association fifth edition.\textsuperscript{10} Physical dependence has been defined as a state of adaptation that is manifested by a drug class–specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.\textsuperscript{11} Historically, the physical symptoms associated with cessation of a drug (physical withdrawal) were differentiated from substance addiction or dependence, with the latter characterized by a specific preoccupation with a desire to obtain and take the drug and persistent drug-seeking behavior. The various definitions of dependence and addiction can explain why the prevalence of addiction in individuals prescribed opioids for long periods of time ranges from 0% to 50%. In the most recent DSM-5 substance use disorder, these characteristics have been combined. Regardless of definition, there is no evidence that women are more prone to misuse, dependence, or addition than men who are prescribed long-term opioid therapy; however, it is clear that for women seeking treatment for misuse, the negative impact on family, social life, and employment is greater than men with similar medical functional impairment.\textsuperscript{8,9} Hence, another peril of prescribing chronic opioids to women: the sequelae of dependence or misuse are more severe than for men.

RISK FOR OVERDOSE

Between 1999 and 2007, the risk for unintentional opioid overdose–related death has increased by 124%.\textsuperscript{12} Although men are more likely to die following an opioid-related overdose, hospitalization following prescription drug overdose has been higher for women (2009: 16,000/100, 000) than men (2009: 13,000/100000) since 1993 and escalating more rapidly.\textsuperscript{6,13} In a predominantly male cohort,\textsuperscript{12} there is a relationship between the dose and manner in which opioids are prescribed and the risk for
opioid-related overdose death: the hazard ratio (HR) for opioid-related overdose death for individuals prescribed a maximum of 100 mg/d or more (morphine equivalents, compared to 1–20 mg/d) was increased among those with chronic pain (HR) 7.18 (95% confidence interval [CI], 4.85–10.65, absolute risk difference approximation 0.25%) and with substance use disorders (HR) 4.54 (95% CI, 2.46–8.37; absolute risk difference approximation 0.14%). There is ample evidence that prescribing for women is equally perilous. In 2010, prescription opioids were involved in 71.3% of the 9292 prescription drug–specified deaths among women, a 41.5% increase from 1999. Age and race factor into the risk of prescription opioid–related death, with the death of women in reproductive age increasing approximately 125% and American/Indian and non-Hispanic white women at highest risk. Finally, there has been a dramatic increase in heroin-related overdose since 2007, especially in the 20 to 24 year age bracket. Although a causal link cannot be made between the increase in prescription drug use and new onset heroin use, it is consistent with population dynamic models. Half of the pregnancy-associated nonnatural death that occurred in Florida between 1999 and 2005 involved prescription opioids alone or in combination with other drugs. Together, these data highlight another peril of opioid prescribing: it can be fatal.

**RISK TO CHILDREN AND ADOLESCENTS**

The presence of opioid prescriptions poses a risk to others in the home, particularly small children and adolescents. Adult medication prescriptions are significantly associated with exposures and poisonings of children of all ages. There has been an increase in childhood opioid poisoning mirroring the increase in adult opioid overdose, with a 27% risk of severe injury or 35% risk of hospitalization following opioid exposure. From 2006 to 2009, adult use of prescription opioids increased from about 3% to about 7% from 2006 to 2009; for every 1% increase in adults taking opioids there was an increase in the poisoning of 1.5/million children aged 0 to 5 years, despite recent changes in packaging. For younger children, exposure tends to be related to exploratory behavior with unintentional use. Among teens, ingestion is more likely to be intentional, with the intention for recreation or self-harm. Teen exposures are associated with substantial risk, with 40% of emergency room visits for opioid exposure among 13 to 19 year olds requiring admission to the hospital, compared with 14% of visits among 0 to 5 year olds. The number of emergency visits involving nonmedical use of opioid prescriptions more than doubled from 2004 to 2008 for patients younger than 21 years old. More than one-third of these patients using nonmedical use of opioid prescriptions obtained these medications from leftover prescriptions of their own and over half received the opioid for free from a friend or relative. Among high school seniors, there was more nonmedical use of opioids from a previous prescription among women compared with men (42% vs 31%). When young injection drug users were asked about initial exposure, a third reported first exposure with prescription opioids pilfered from a family member’s prescription. These data outline the collateral damage of opioid prescribing: medication in the home risks accidental use by children or intentional misuse by adolescents, with disastrous long-term consequences.

**RISKS OF PRESCRIBING BEFORE PREGNANCY (PERICONCEPTION)**

The risk for unintended pregnancy in the United States is almost 50%, increasing to almost 90% for women with opioid dependence. For women not using long-acting contraception, the perils of opioid use in early pregnancy should be discussed.
First trimester opioid exposure occurs in 2% to 3% of pregnancies. The largest population-based study was performed by Broussard, using the population studied in the National Birth Defects Prevention Study from 1997 to 2005. Women having a child with a birth defect and control women were interviewed about medication habits from 1 month before 3 months after conception. This study found that women who used opioids during this time frame had an increased risk for fetal cardiac defects, particularly conoventricular septal defects (odds ratio [OR] 2.7; 95% CI, 1.1–6.3); hypoplastic left heart syndrome (OR 2.4; 95% CI, 1.4–4.1), neural tube defects (OR 2.0; 95% CI, 1.3–3.2), or gastroschisis (OR 1.8, 95% CI, 1.1–2.9). A separate study based in Washington state reported the association of early pregnancy opioid exposure and open neural tube defects (OR 2.2, 95% CI, 1.2–4.2). Despite the limitations of these studies—recall bias and lack of information regarding the indication for opioid treatment—the teratogenic risk of opioids should be discussed with women considering long-term opioids to manage pain. The addition of teratogen warnings to all opioid prescriptions has been suggested but has not been initiated. Preconceptional folic acid (0.8 mg or higher) can reduce the incidence of neural tube defects, with more recent evidence suggesting reductions in cardiac defects and low birthweight. Women of reproductive age not using long-acting contraception should receive folic acid supplementation; whether this can decrease opioid-related congenital anomalies is unknown.

RISKS OF PRESCRIBING DURING PREGNANCY/POST PARTUM

The prevalence of opioid prescribing during pregnancy has increased over the last 10 years. In Tennessee, the number of opioid prescriptions increased 37% from 268 to 368/1000 pregnancies; 29% of women filled a prescription for opioids during pregnancy, with a median duration of 4 days, suggesting acute pain as the primary indication. In Minnesota, the rate of narcotic use for more than 1 month during pregnancy increased from 1/1000 to 5/1000 deliveries.

The data regarding outcomes of pregnancies in which opioids have been prescribed for chronic pain, as opposed to treatment of opioid dependence, are limited. The most serious risk to neonates exposed to opioids during pregnancy due to chronic pain is iatrogenic late preterm birth or early term birth. Kellogg reported on neonatal admission to the intensive care unit for neonates exposed to narcotics during pregnancy: 72/177 (41%) infants required admission to the neonatal intensive care unit, mostly for complications of early term delivery such as respiratory complications, hypoglycemia, jaundice, and difficulty feeding; only 10/177 infants (5.6%) were admitted for neonatal abstinence symptoms. When comparing neonatal outcome of pregnancies treated for chronic pain versus for opioid dependence, Sharpe found the median gestational age in those infants exposed to opioids for chronic pain 2 weeks shorter for those treated for opioid dependence (gestational age 37 weeks vs 39 weeks); 11/19 (58%) neonates in the pain group were preterm as opposed to 3/24 (13%) neonates exposed to opioids for maternal opioid addiction. Infants of mothers treated for chronic pain were larger (after correction for earlier gestational age) and required treatment of neonatal abstinence less frequently (chronic pain: 11%; opioid dependence 58%).

In summary, there are perils to the neonate exposed to chronic opioid therapy during pregnancy: iatrogenic early delivery for maternal pain increases the risk for neonatal morbidity. The risk for neonatal abstinence symptoms is lower than that observed for neonates exposed to opioids for the treatment of opioid addiction and is quite reassuring, although postnatal evaluation for neonatal abstinence symptoms is still required.
Breastfeeding when mothers are prescribed short-acting opioids for acute, puerperal pain has been standard practice for years. The death of a breastfed neonate attributed to maternal codeine ingestion was reported in 2006. This mother was found to have a duplication of the cytochrome p450 2d6 gene, which resulted in ultra-rapid conversion of codeine to morphine (the active metabolite) with high breast milk concentration of morphine. In 2007, the Food and Drug Administration issued a warning about the use of codeine and breastfeeding following reports of life-threatening sedation in breastfeeding infants. Although oxycodone was considered an alternative, sedation with either codeine or oxycodone was observed in almost 20% of breastfeeding infants when opioid-naive mothers are treated for postpartum pain, compared with only 0.5% of breastfed neonates of mothers taking only acetaminophen. There is concern that these adverse events are more common than reported as they are poorly captured by national reporting mechanisms.

It is not known whether infants of mothers taking short-acting opioids chronically during pregnancy are at a similar risk for sedation with breastfeeding. Because these infants are at risk for neonatal abstinence symptoms, they may be more tolerant to opioids and less susceptible to sedation from breast milk exposure, although this has not been demonstrated. This concept is supported by the finding that maternal somnolence from opioids correlates with neonatal sedation, as does maternal dose and duration of treatment. Nonetheless, there are alternatives to codeine for pain control following delivery, and avoidance would be prudent. When either codeine or oxycodone is prescribed to breastfeeding women, the mother and neonate should be monitored for sedation.

In summary, chronic opioid therapy during pregnancy poses unique risks to the pregnancy and neonate: iatrogenic prematurity and neonatal somnolence with breastfeeding, in addition to the well-described neonatal abstinence symptoms.

WHY OPIOIDS + SMOKING IS PARTICULARLY PERILOUS

Studies are remarkably consistent in the finding that smokers, in general, are more likely to require chronic opioid therapy for pain, require higher doses of opioids for pain control, have a higher risk of drug dependence, and exhibit more aberrant drug-taking behaviors compared to nonsmokers. Risks were uniformly greater in those individuals smoking more than 1 pack per day. During pregnancy, smoking poses the additional concerns of poor fetal growth, abruption, stillbirth, and preterm birth.

Risk for concurrent use of smoking and opioids is not limited to maternal opioid dependence and pregnancy complications. Infants exhibiting neonatal abstinence symptoms after in utero exposure to methadone or buprenorphine for treatment of opioid dependence had increasing neonatal abstinence symptoms and duration of treatment of abstinence symptoms with increasing maternal smoking.

Reduction of smoking volume during pregnancy can improve fetal growth, even if cessation cannot be achieved. Patients maintained on opioids for chronic pain should be aware that smoking increases risk for any pregnancy and may increase neonatal abstinence symptoms.

HOW TO APPROACH THE PREGNANT PATIENT ON CHRONIC OPIOID THERAPY FOR PAIN

Despite the increase in the prevalence of opioid use in pregnancy, the data regarding pregnancy and neonatal outcomes for women treated with opioids for chronic pain during pregnancy remain limited. An understanding of the underlying disease requiring
chronic opioid use for pain and optimization of treatment is an obvious first step (Box 1). An exploration regarding alternatives for pain control should be revisited in the context of pregnancy, as the patient may reconsider risk/benefit of continued opioid use. A good place to start would be revisiting the patient/selection and risk stratification in the Guidelines for use of chronic opioid therapy. The optimal candidate has moderate to severe pain, has failed other modalities, has improved function with opioid therapy, and does not have a history or drug or alcohol abuse. A fresh assessment of current pain and therapeutic efficacy of chronic opioids, in the context of pregnancy, is warranted. Excellent communication between the provider prescribing opioids and the obstetric provider is essential, with appropriate Health Insurance Probability and Accountability Act consents to allow free information exchange. Providers should decide who will prescribe during pregnancy, assess for therapeutic goals, and develop a plan for pain escalations during pregnancy. Random urine drug screens should be routinely performed for patients with a history of illicit use and considered for patients without such history. Although treatment of chronic pain is beyond the scope of this article, alternatives such as gabapentin, tricyclic antidepressants, and atypical antipsychotics have been used for treatment of chronic pain and can be safely prescribed during pregnancy and post partum.

A taper off of opioids can be considered during pregnancy. Although not studied in pregnancy, a dose taper of approximately 10% of the original dose every 4 to 7 days is commonly recommended and will minimize withdrawal symptoms. The major concern during discontinuation of opioids during pregnancy is precipitation of physical symptoms of opioid withdrawal, mediated by increased sympathetic nervous system activity. Symptoms experienced during a slow taper are usually mild dysphoria and

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<tr>
<th>Box 1</th>
<th>Checklist for patients on chronic opioid therapy during pregnancy</th>
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<td>Checklist: care of the pregnant patient on chronic opioid therapy:</td>
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<td></td>
<td>○ Develop the health care team: obstetrics, pediatrics, mental health/coping, pain medicine; any referral that can be used as an adjunct for the treatment of chronic pain (ie, physical therapy for back pain).</td>
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<td>○ Obtain release of information so all members of the team may share clinical information as needed.</td>
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<td>○ Establish who will prescribe, dose, and duration (limit to 30-day supply). If children in home, require lockbox (or equivalent) for safe storage and verify safe storage at each visit.</td>
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<td>○ Establish which provider will check the prescription monitoring system for duplicate prescriptions or medications that may increase the risk of opioid therapy (ie, sedative hypnotics, benzodiazepines).</td>
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<td>○ Establish which provider will perform urine drug screen monitoring, including frequency.</td>
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<td>○ Refer to pediatrics before delivery to discuss the neonatal plan for assessment and treatment of neonatal opioid abstinence symptoms.</td>
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<td>○ Encourage smoking cessation, as indicated.</td>
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<td>○ Develop the expectation of postpartum evaluation and treatment that will allow cessation or reduction of opioid therapy; emphasize not only personal benefit but reduced risk to children and teens in the home.</td>
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<td></td>
<td>○ If postpartum opioid therapy indicated, require a lockbox (or equivalent) for safe storage and verify safe storage at each visit.</td>
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anxiety. More severe symptoms of opioid withdrawal such as nausea, abdominal pain, vomiting, gooseflesh, sweating, and nasal stuffiness are uncommon with this taper. Symptoms can be managed by slowing the taper or use of ancillary medications. It would be prudent to slow or stop a taper during pregnancy if the patient experiences anything other than mild withdrawal symptoms, especially in the third trimester (24 weeks). Stewart reported on detoxification from illicit opioids during pregnancy without increasing pregnancy risks (although illicit use recurred in more than 50% of women). These data should provide reassurance for the patient who would like to taper opioids prescribed for chronic pain. Concurrent care with a specialist in chronic pain can assist the obstetrician in choosing alternative plans for pain management.

Neonatal abstinence symptoms requiring treatment has been observed in 5% to 10% of neonates exposed to opioids prescribed for chronic pain; methadone exposure may increase the risk for abstinence symptoms. Pediatric consultation before delivery is recommended; delivery should take place in a care system that can evaluate and treat or refer symptomatic infants. Neonates should be closely monitored for withdrawal symptoms for 4 to 5 days after delivery.

Breastfeeding for women on chronic opioid therapy should be encouraged. Women taking codeine- or oxycodone-containing medications should be instructed how to assess the infant for lethargy and take caution when they experience medication-associated somnolence. Maternal sedation warrants special vigilance for neonatal effects and maternal dose or frequency of opioids should be reduced. Methadone is excreted at low levels in breast milk, does not require metabolism via CYP450 2D6, and could be considered for the patient prescribed regularly scheduled opioids.

In summary, risks to chronic opioid use in pregnancy for chronic pain can be reduced as follows: stop or minimize maternal smoking; stop or minimize opioid dose; consider use of alternative medications; recommend breastfeeding but parents should be aware of the symptoms of neonatal opioid intoxication; and avoid iatrogenic prematurity or early term delivery. The obstetrician should work closely with the pain specialist throughout pregnancy to discuss ancillary and alternative therapy and with the pediatrician to plan for neonatal assessment. Women who have endured chronic pain throughout a pregnancy should be encouraged to endure until at least 39 weeks to reduce neonatal morbidity.

HOW TO MINIMIZE RISK WHEN LONG-TERM OPIOID PRESCRIBING CANNOT BE AVOIDED

Chronic noncancer pain is a complex biosocial condition; the same could be said for being a new parent. Patients on chronic opioid therapy should integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive therapies for pain. These therapies should be continued during pregnancy when feasible. There are excellent clinical guidelines regarding the use of chronic opioid therapy for noncancer pain. Any patient requiring chronic opioid therapy should be followed by a clinician with experience with chronic pain and the appropriate guidelines (Fig. 1).

Who should prescribe opioids during pregnancy? Ideally, the patient will have a long-standing relationship with the provider treating her chronic pain, with this relationship maintained during pregnancy. Issues such as frequency of prescriptions, assessment for desired therapeutic benefit (required for ongoing opioid therapy), and frequency of urine drug screening should occur should be outlined in the treatment plan. Most states have implemented (or have plans for) a prescription monitoring system. All prescribers of chronic opioid therapy should regularly check for
Prescriptions filled by a patient to avoid multiple prescriptions. This web-based system allows practitioners to see what prescriptions have been filled by a patient in that state. The obstetrician should have a release of information consent to allow communication with the provider for pain medication to allow collaborative treatment.

In summary, pregnancy is an opportunity to address important issues of chronic opioid therapy in a new context. The specific benefits of smoking cessation/reduction can be reviewed. Medication storage and safety measures to reduce access to children and teens should be emphasized. Prescribing of opioids during pregnancy can be perilous, but these perils can be reduced with thoughtful conversations and patient care.

REFERENCES


