OBSTETRICS

Management of women treated with buprenorphine during pregnancy

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The management of pregnancy and delivery of a woman on opiate-substitution therapy with buprenorphine requires a coordinated team approach by social services, addiction medicine, obstetrics, and pediatrics. Her obstetrical care is further complicated by the unique pharmacology of buprenorphine and the issues of pain management. Obstetrical providers should be familiar with the complex issues surrounding the optimal care of these women.

Key words: buprenorphine, opiate substitution, pregnancy

An estimated 2.25 million people in the United States are dependent on or abusing opiates.[1] Women have a higher rate than men for addiction to prescription pain relievers.[1] Substance abuse admissions for the treatment of prescription opiate addiction have increased nearly 4-fold since 1998.[2] Among women aged 15-44 years, 10.6% used illicit drugs in the past month based on 2008-2009 self-reported survey data.[1] Among women 15-25 years old, the use was higher, 7.1-15.8%. The rate was considerably lower in those who were pregnant (4.5%), but a substantial and very likely increasing number of women continue to use drugs in the peripartum period.

The general management of opiate dependency inside or outside pregnancy is grounded on psychosocial treatment including: self-help and 12 step groups, individual and group substance abuse counseling, and psychotherapy. To minimize or eliminate exposure to infectious diseases, reduce the risk of accidental overdose, and support a therapeutic environment conducive to recovery, opiate detoxification followed by abstinence or opiate-substitution maintenance is recommended. In the United States, methadone and buprenorphine are the only opiate-substitution medications approved for the treatment of opiate addiction. Both also have been used for medically supervised opiate withdrawal and detoxification, but results are disappointing because long-term abstinence is low.[3-6] For the majority of opiate-addicted women, opiate-substitution programs combined with psychosocial treatment offer the best chance of stabilization of their addiction and opportunity for a sustainable recovery.[3,7,8]

Opiate-substitution programs provide methadone through designated licensed clinics or buprenorphine through specifically trained and federally waivered physicians. Increasing demand for the treatment of opiate addiction has driven the buprenorphine/naloxone combination (Suboxone; Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA) to the 41st most prescribed drug in the United States in 2009, a year in which annual sales increased 68.1% to 5.7 million prescriptions.[9,10] Prescriptions of buprenorphine monotherapy (Subutex [Reckitt Benckiser Pharmaceuticals, Inc.] and generic), used primarily for the treatment of pregnant women, numbered approximately one-third million in 2009.[10]

During pregnancy, methadone (category B) is the recommended substitution treatment for opiate addiction and is considered the standard of care. If methadone treatment is refused or unavailable, then opiate-substitution management with buprenorphine may be considered after informed consent is obtained and the risk of inadequate experience in pregnancy is clearly documented.[3] The literature that reports buprenorphine maintenance in pregnancy is limited but growing, and buprenorphine has recently been advocated as a first-line therapy.[11-14]

There are 6 studies that report comparisons between buprenorphine and methadone-treated pregnant women and their infants.[11,13,14-17] Compared with methadone, buprenorphine-treated pregnant women had similar cesarean section rates,[11,15-17] maternal weight gain,[11] and number of prenatal visits.[11,15] Medical complications were lower in buprenorphine-treated women, and overdoses were less frequent than with methadone.[18] Retention rates until delivery were variable. Rates of neonatal abstinence syndrome were the same as or lower in the buprenorphine group[11,13,15-18] and hospitalizations shorter.[11,15,16] Birthweights were similar[17] or higher[11,13,15,16] for infants in the buprenorphine group, whereas Apgar scores were not significantly different.[11,15-17] Duration of newborn hospitalization was significantly shorter in the buprenorphine-treated group.[11,15]

The available evidence supports the use of buprenorphine in the treatment of opioid-addicted pregnant women. It appears to be a suitable alternative to methadone in the maintenance of maternal addiction, with most researchers reporting a shorter and milder abstinence syndrome in the neonate.

Barriers to treatment

There are a number of barriers to the management of opiate abuse in pregnancy. The social stigma, guilt, and shame of ongoing drug addiction during pregnancy may pressure the woman into attempting to quit using opiates on her own or denying or hiding the problem

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until delivery. One fear is that seeking treatment for her opiate addiction will result in mandatory reporting and attract the attention of government social service and health authorities. Interventions, including the monitoring of herself, her partner, and the condition of her other children, are not always welcome. Poor self-esteem, a low level of education, and legal problems are common in opiate users and interfere with self-reporting and seeking assistance.

Economic barriers include the cost of missed employment to attend rehabilitation sessions in addition to child care and transportation expenses. Housing security is often tenuous and staying with friends or being homeless may place the women back into the drug subculture they are trying to escape.

The partner's continued use of illicit drugs can be an insurmountable problem because the woman may be caught between the need for emotional and financial support with the continued temptation to relapse and the risk of social service intervention to remove a drug user from the household. Ongoing mental and physical abuse may complicate the relationship. Family dysfunction may include addicted future grandparents. There is also a higher prevalence of psychiatric disease[19,20] and chronic medical illnesses[3] in this population. Posttraumatic stress disorder because of prior sexual abuse is common among opiate users.[20,21]

In some areas access to opiate-substitution therapy is limited by distance, waiting lists, or a shortage of licensed buprenorphine prescribers. Pregnant women can expect priority acceptance into most treatment programs. Opiate-addicted maternal-infant dyads should be delivered in a medical center with physicians and nurses experienced in their assessment and management. Treatment compliance and pregnancy outcomes are improved when addiction and obstetrical care are delivered at the same location.[22]

Screening

Women are often reluctant to reveal their opiate use or addiction during the initial obstetrical intake screening visit. Providers may be unfamiliar with diagnostic and treatment options and hesitant to question the patient about drug use. An accepting open-ended interview may facilitate eliciting a history of a drug problem. Other risk factors for drug abuse are given in Table 1. After patient consent has been obtained, routine urine toxicology and opiate confirmation testing is advisable for all women. A search of a state-supported database of controlled substance prescriptions may identify women who have received multiple opiate and/or controlled substance prescriptions that may be at risk.

Cigarette smoking is very common among opiate addicted women (65-100%).[23-27] Women may be motivated to quit when they learn that neonatal abstinence syndrome may be more severe and prolonged in infants born to mothers who smoke.[23,24] Hepatitis B and C and human immunodeficiency virus (HIV) counseling and serology should be included in the routine prenatal laboratory testing and repeated in the third trimester if indicated.

Initiating treatment

Once screening is completed, women should be offered immediate and appropriate referral for substance abuse treatment. Most are already in the contemplation stage of behavior change and are readily motivated to take appropriate action.[28,29] Detoxification from opiates is not generally recommended during pregnancy.[30-34] Rather, opiate-substitution therapy using methadone or buprenorphine on a residential or outpatient basis combined with intensive group and individual counseling and social service support is recommended.

Where to refer a woman depends on community resources and individual patient preference. Methadone maintenance clinics require daily attendance to receive medication, often in a public setting, which allows contact with other drug abusers and an opportunity to engage in illicit activities.

Buprenorphine potentially offers greater privacy because it can be prescribed during a physician's office visit and may be combined with routine obstetrical care and substance-abuse counseling. Buprenorphine in usual doses (8-16 mg daily) is as effective as methadone (60 mg) in preventing relapse but not as effective as high-dose methadone (120 mg), which is customarily used in treating addiction.[3,35] Women with a long-standing addiction to high-dose intravenous opiates are at higher risk for relapse and should be considered for referral to a methadone clinic, whereas those abusing opiates orally or intranasally often are successful on buprenorphine. Release of information consent forms should be signed by the patient to authorize communication with all other medical, psychiatric, and social service providers. Mandated reporting to the state's child protective agency is best accomplished with the mother's agreement and presence during the actual contact.

TABLE 1
Risk factors for substance abuse

- Partner is a substance abuser
- Legal problems and arrests
- Multiple missed appointments
- Stigmata of drug use; perforated nasal septum; intravenous track scars, skin abscesses
- Homelessness
- Family history of drug or alcohol abuse
- History of/or ongoing psychiatric treatment
- Previous children not living with the mother
- Unexplained history of obstetrical or neonatal problems; abruption of placenta, IUGR, prematurity
- Late presentation for prenatal care
- History of/or ongoing treatment for chronic pain

IUGR, intrauterine growth retardation.

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Pharmacology of buprenorphine

Buprenorphine is a partial agonist for the mu-opioid receptor.[36] Table 2 lists the buprenorphine preparations used in the treatment of opiate addiction. In clinical practice, buprenorphine is often combined with naloxone (Narcan; Endo Pharmaceuticals, Chadds Ford, PA), a mu-opioid antagonist, which is inactive when taken as prescribed (dissolved under the tongue). The addition of naloxone prevents misuse by intravenous injection. However, the consensus is that naloxone should be avoided during pregnancy.[20]

TABLE 2
Buprenorphine preparations for treatment of opiate dependence

Drug name	Constituents	Notes
Suboxone	Buprenorphine 8 mg/naloxone 2 mg Buprenorphine 2 mg/naloxone 0.5 mg	Sublingual tablets and film in child-resistant packet
Subutex	Buprenorphine 8 mg and 2 mg	Sublingual tablets
Buprenorphine	Buprenorphine 8 mg and 2 mg generic	Sublingual tablets Elimination half-life 37 h
Probuphine	Buprenorphine 80 mg	Implant, 6 month duration Phase 3 trials completed

Suboxone and Subutex; Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA. Probuphine; Titan Pharmaceuticals, Inc., South San Francisco, CA.

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Buprenorphine has a very high affinity but low intrinsic activity for the mu receptor and can precipitate withdrawal symptoms in opiate addicts by displacing morphine, methadone, and other opiates.[3] Because of this high affinity (1000 times that of morphine), opiates cannot displace buprenorphine, and therefore, their euphoric effects are blocked.[3] Buprenorphine has a slow dissociation from the mu-opioid receptor and can be given daily or even every other day, although every-other-day therapy is not advised in pregnancy.[37] A typical daily dose of 10-16 mg occupies most mu receptors.[38] Dosage requirements may increase moderately during pregnancy.[3,33,39,40]

Buprenorphine produces typical opioid effects but is limited by a ceiling of 24-32 mg, which makes a lethal overdose from respiratory depression less likely in opiate-dependent individuals.[3] This safety margin is lost when buprenorphine is combined with alcohol or benzodiazepines.[41] In opiate-naïve subjects, 0.4 mg of buprenorphine every 6 hours is adequate for pain relief.[3] The injectable preparation of buprenorphine (Buprenex; Reckitt Benckiser Pharmaceuticals Inc.) and the transdermal (Butrans; Purdue Pharma L.P., Stamford, CT) are indicated only for pain relief in the opiate-naïve patient and not approved for the treatment of opiate addiction. A depo-buprenorphine (Probuphine; Titan Pharmaceuticals, Inc., South San Francisco, CA) subcutaneous implant is under study.[42]

Metabolism of buprenorphine is by CYP3A4-mediated N-dealkylation to norbuprenorphine, a metabolite with weak opioid potency.[43] Both then undergo glucuronidation. Drugs that inhibit CYP3A4 such as protease inhibitors for HIV treatment and azole antifungals such are fluconazole will increase buprenorphine plasma levels. CYP3A4 inducers, including many seizure medications and rifampin, may decrease buprenorphine levels.[36]

Prenatal care

Along with routine prenatal care, an expectant mother treated with buprenorphine requires additional coordination of services for optimal maternal-fetal management. Social services, community health nursing, substance abuse counseling, the obstetrical and pediatric providers, and the buprenorphine physician-prescriber must all be in regular communication. Opiate abusers are at high risk for obstetrical complications,[44-46] and although opiate-replacement therapy reduces some of these risks, multiple-drug abuse is common early in rehabilitation and may continue throughout the pregnancy. As in other high-risk pregnancies, frequent visits are indicated. One small study with 12 patients reported decreased positive urine toxicology screens and increased birthweights in 6 women who received enhanced treatment with weekly prenatal care and rewards for negative urine screens.[46] Guidelines for the prenatal care of buprenorphine-treated women are provided in Table 3.[47] Nonstress tests show increased fetal heart rate variability and more accelerations in the buprenorphine-treated fetus than in those whose mothers receive methadone.[48]

Principles of pain management in patients taking buprenorphine

Although nonsteroidal antiinflammatory agents and acetaminophen are frequently adequate for mild to moderate pain, opiates are often required during labor and delivery and for the postoperative pain following cesarean section and tubal ligation. Despite the opiate-agonist therapy of buprenorphine, additional opiates will be necessary because of the inadequate analgesia provided by the widely spaced maintenance dosing, the patient's tolerance to buprenorphine, and opioid-induced hyperalgesia (a decreased pain threshold resulting from prolonged opiate use).[49,50] A higher dosage of opiates given more frequently than usual is necessary because of the patient's cross-tolerance to all opiates. A scheduled dose, rather than as needed, reduces patient anxiety.[3] Nalbuphine (Nubain; Endo Pharmaceuticals) and butorphanol (Stadol; Bristol-Meyers Squibb, New York, NY) should never be given to opiate or buprenorphine users because these medications may precipitate acute withdrawal symptoms.[3,30] Treatment with a fixed-dose combination opiate-acetaminophen preparation runs the risk of acetaminophen toxicity as opiate requirements increase.

To prevent opiate withdrawal, buprenorphine, buprenorphine with naloxone, and methadone may be prescribed for a hospitalized patient by any licensed physician or nurse-midwife. A physician-only waiver is necessary for outpatient maintenance prescribing of all forms of buprenorphine for the treatment of addiction.

Labor management

There are several options for the management of labor pain. In many instances, no additional analgesia is necessary. The maintenance dose of buprenorphine can be divided, giving 25% of the daily dose every 6 hours. This takes advantage of the analgesic effects of the drug.[49] Nonpharmacological interventions such as showers or hot tubs and position changes should be offered as

appropriate. Additional augmentation with a short-acting injectable opioid such as morphine or fentanyl 25-50 μg every 30-60 minutes should be added as necessary. A higher dose and more frequent administration will be required than in opiate-naïve subjects. The patient's symptoms provide the guide to dosage. The fetus will be similarly habituated to opiates and should not be depressed.

When additional pain relief is necessary, epidural or spinal anesthesia may be the ideal method of analgesia in labor for opiate-addicted women. Morphine sulfate injection (Duramorph; Baxter, New Providence, NJ) is effective in buprenorphine-treated patients. Regional and local anesthesia can be safely utilized for instrumental deliveries or surgery.

Naloxone (Narcan) cannot be used during infant resuscitation because it may result in opiate withdrawal seizures in the newborn.[51] In the unlikely event of excessive opiate-induced respiratory depression, the infant should be intubated and ventilation maintained as long as necessary.

TABLE 3
Prenatal care guidelines

Intake screening: tuberculoses skin testing if appropriate	
Routine laboratory testing plus hepatitis B, C, and HIV	
Each visit:	Urine drug screening if not done elsewhere Confirm contact with buprenorphine provider (at least monthly), substance abuse counselor (at least weekly), and public health nurse Question about drug usage, dosage, and frequency Risk reduction counseling and interventions Relapse prevention counseling Smoking reduction counseling
15-20 wks:	Ultrasound for abnormalities
24-32 wks:	Ultrasound for growth Referral to pediatric provider Consider anesthesia consult if operative delivery planned Hospital social services and nursing notification of planned admission of opiate-addicted dyad

HIV, human immunodeficiency virus.
Modified from Vermont buprenorphine practice guidelines.[47]
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Postpartum pain control

Nonopioid analgesics may be adequate for routine postpartum pain after a vaginal delivery, but opioid analgesia should be made available if required.[52] An epidural catheter can be left in place postoperatively. Preloading the operative incision with a long-acting local anesthetic such as bupivacaine is useful. Injectable ketoralac can be given.[53]

When pain is more severe, patient-controlled analgesia using morphine has been advocated while maintaining the regular buprenorphine schedule.[54] Another option is to decrease the regular buprenorphine dose to 8 mg (if applicable) while offsetting the buprenorphine reduction with oxycodone (1 mg buprenorphine = 15 mg oxycodone) or morphine (1 mg = 30 mg oral) given in divided doses plus provide the regular amount of opiates routinely given for that procedure in a drug-naïve patient.[47] For example, a patient is taking 16 mg of buprenorphine as her daily maintenance dose and is having a postpartum tubal ligation the next day. Usual pain control for a tubal ligation is oxycodone-acetaminophen 5/500, 1 or 2 tablets every 4 hours. The clinician may choose to give the patient 8 mg of buprenorphine with naloxone on the morning of surgery then 120 mg (8×15) of oxycodone over the course of the postoperative day divided into 6 equal doses of 20 mg every 4 hours. This medication would be given in addition to the regular 5-10 mg dose given every 4 hours for the opiate naïve patient having a postpartum tubal ligation. When the need for opiate analgesia has decreased, then the previously withheld 8 mg of buprenorphine with naloxone should be restarted. Caution is necessary in using this formula when the baseline buprenorphine dosage exceeds 16 mg. A stool softener should be prescribed.

If more than a day or 2 of opiate pain medication will be needed, buprenorphine should be stopped. Pain should be treated with frequent administration of short-acting opiates. As buprenorphine clears the body over the next several days, the analgesic dose requirements will decrease. When the pain has decreased, buprenorphine may be restarted using an induction protocol.[3] A physician with experience in buprenorphine induction should be consulted.

The largest study of pain management during labor and delivery of 63 buprenorphine-treated women (average dose 13.7 ± 6.2 mg/d) matched with opiate-naïve untreated controls reported no increased use of intrapartum pain or analgesia medications. Following vaginal delivery, women treated with buprenorphine reported increased pain but required no increase in opioid administration. After cesarean delivery, opiate requirements were 47% higher.[55] These authors reported a 70% increase in opiate analgesic requirements for methadone-treated mothers in a previous study.[56]

Neonatal abstinence syndrome

The incidence (~50%) of neonatal abstinence syndrome (NAS) requiring treatment does not appear to be greater in infants born to mothers on buprenorphine when compared with mothers treated with methadone.[11,16,57,58] There is no relationship between maternal buprenorphine dose and severity of NAS.[59-61] The modified Finnegan scale has been utilized most frequently to monitor infant symptoms, although other scales are available.[62,63] The Finnegan neonatal abstinence score monitors 31 different NAS symptoms, evaluating each on a 1-5 scale every 4 hours. Some of the symptoms monitored include excessive crying, tremors, sleep duration, hyperthermia, tachypnea, poor feeding, irritability, and vomiting. Many of these

symptoms resemble those of infection and infants may be evaluated with a sepsis workup and started on antibiotics.

Various opiates or phenobarbital (especially with concomitant benzodiazepine abuse) are used in the management of NAS.[64,65] Maternal polydrug abuse appears to worsen NAS. Infants are usually kept in the hospital 5-7 days to monitor for the delayed appearance of NAS symptoms and longer if treatment is necessary. Treatment may be continued after discharge. Preliminary studies have found no developmental differences between low-risk infants of nonaddicted mothers and infants born to mothers who were treated with buprenorphine during pregnancy.[66-70]

Breast-feeding

According to the package insert, breast-feeding is not recommended when the mother is taking buprenorphine. However, breast-feeding appears to be safe.[71-73] Infants in their first few days of life received less than 1% dose per kilogram of the maternal buprenorphine and its metabolite, norbuprenorphine, in breast milk.[73] The risk of breast milk-induced buprenorphine addiction in the infant appears unlikely, and there is no reason to time breast-feeding to avoid peak levels of buprenorphine in maternal plasma.[73] Weaning from breast-feeding may be safely undertaken abruptly.[74] Most prescribers encourage breast-feeding in buprenorphine/naloxone-treated mothers including those infants being treated for NAS. Caution should be exercised with breast-feeding by mothers who are abusing illicit substances and/or being treated with multiple prescription drugs.

Hospital discharge

The mother can resume her regular buprenorphine dose when discharged from the hospital. The buprenorphine/naloxone combination should be used after pregnancy because naloxone is compatible with breast-feeding.[71] The buprenorphine prescriber should be notified to arrange a prescription if necessary and outpatient follow-up. Maximum family support including visiting nurse programs, lactation support, substance abuse counseling, child protective services, and psychiatric treatment (if indicated) should be arranged.

Summary

The prevalence of opiate addiction in women of child-bearing age appears to be increasing and extending into regions where medical providers may be unaccustomed to managing this complex psychosocial-medical problem. Obstetrical providers are frequently called on to treat women receiving opiate-substitution therapy with buprenorphine and should be familiar with its unique pharmacology. The management of labor and postpartum pain is controlled through reassurance based on a sound knowledge of opiate substitutes and continuous monitoring of the patient's symptoms. ■

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