Use of buprenorphine in pregnancy: patient management and effects on the neonate

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Abstract

It is estimated that 55–94% of infants born to opioid-dependent mothers in US will show signs of opioid withdrawal. Buprenorphine has been reported to produce little or no autonomic signs or symptoms of opioid withdrawal following abrupt termination in adults. To date, there have been 21 published reports representing approximately 15 evaluable cohorts of infants exposed to buprenorphine in utero. Of approximately 309 infants exposed, a neonatal abstinence syndrome (NAS) has been reported in 62% infants with 48% requiring treatment; apparently greater than 40% of these cases are confounded by illicit drug use. The NAS associated with buprenorphine generally appears within 12–48 h, peaks at approximately 72–96 h, and lasts for 120–168 h. These results appear similar to or less than that observed following in utero exposure to methadone. From a review of the literature, buprenorphine appears to be safe and effective in both mother and infant with an NAS that may differ from methadone both qualitatively and quantitatively.

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1. Introduction

In both the United States and Europe, one-third of the population entering treatment for opioid abuse and dependence are women in their childbearing years. As the availability of buprenorphine increases, the number of women who become pregnant while being treated with buprenorphine will increase. The treating physician will have three options: dose taper, opioid maintenance on a recommended pharmacotherapy, or continued buprenorphine administration. Dose taper is not recommended (FDA/NIDA Guidance, 1992; Finnegan, 1991a; Finnegan and Wapner, 1988) since it has been reported in one subject to induce fetal stress (Zuspan et al., 1975), and currently the only recommended maintenance therapy in the United States and Europe for opioid-dependent pregnant women is methadone.

Data from a 1992 survey reported that an estimated 7000 heroin- and methadone-exposed infants are born (National Pregnancy and Health Survey, 1996) annually in US and approximately 55–94% of these infants will show signs of an opioid withdrawal syndrome (American Academy of Pediatrics Committee on Drugs, 1998). The neonatal abstinence syndrome (NAS) is a generalized disorder characterized by signs and symptoms indicating dysfunction of the autonomic nervous system, gastrointestinal tract, and respiratory system (e.g., Kaltenbach and Finnegan, 1990; Connaughton et al., 1975; Blinick et al., 1969). In general, neonates of heroin-dependent and methadone-maintained mothers exhibit an opioid withdrawal syndrome following birth (e.g., Zelson et al., 1971; Glass, 1975; Harper et al., 1977), which requires intensive and extended treatment.
Infants born to methadone-maintained mothers tend to be in a neurologically distressed condition; they cry incessantly, are more labile, tremulous, irritable, excited, hypertonic, aroused, respond poorly to visual stimuli, and have less motor maturity (e.g., Kaltenbach and Finnegan, 1990). One study has suggested that the duration of tremulousness and irritability is longer in babies born to methadone-maintained mothers when compared with mothers using heroin (Rajeqowda et al., 1972). Of the neonates born to methadone-maintained mothers, 60–87% require treatment for an opioid NAS (Rosen and Johnson, 1982; Wilson et al., 1981; Connaughton et al., 1975; Stimmel et al., 1982–1983; Finnegan, 1988; Finnegan and Ehrlich, 1990) and 10–30% of these are admitted to the Neonatal Intensive Care Unit (NICU; Svikis et al., 1997; Kissin et al., 1997). The NAS and prematurity are the primary reasons for extended hospitalization in these infants. In one study, mean duration of hospitalization varied in infants between 17 (methadone-treated plus prenatal care) and 20 days (heroin-exposed with no prenatal care) (Connaughton et al., 1977), while in another study (Fischer et al., 1999) the mean duration of treatment for the NAS after exposure to oral methadone and slow-release oral morphine was 18 days.

It has been shown that there is a significant improvement in maternal and birth outcomes when pregnant opioid-dependent women are maintained on methadone and provided comprehensive prenatal care (Kandall et al., 1976; Connaughton et al., 1977; Finnegan, 1991b; Svikis et al., 1997). Whether this improvement is due directly to the pharmacologic effects of methadone (i.e., consistent opioid blood levels, decreased withdrawal symptoms, etc.) or due primarily to better prenatal care (i.e., improved nutrition, medical care, etc.) is not clear. Although outcomes are improved when opioid-dependent women are maintained on methadone and receive prenatal care, the NAS in infants born to mothers maintained on methadone is not trivial. This fact has caused much debate over the appropriate use of methadone (i.e., dose taper or maintenance, dose reduction or increase or split dose, etc.) in pregnant opioid-dependent women. There are those who advocate dose taper to limit fetal exposure to exogenous opioids, and there are situations where women may need to be withdrawn (Jarvis and Schnoll, 1994). Most addiction specialists advocate maintenance therapy with a dose sufficient to eliminate and prevent withdrawal symptoms and craving. This dose generally ranges for 50–150 mg per day (Substance Abuse and Mental Health Services Administration, 1995). Appropriate treatment of the opioid dependence will assist in retaining women in treatment and help ensure continuous prenatal care. Overall, the cost-benefit ratio seems to be greater when the mother is maintained on opioid substitution therapy and she receives prenatal care than when her dose is tapered to zero or receives no drug abuse treatment (Svikis et al., 1997).

The availability of new medications for the treatment of opioid dependence may provide valuable alternatives to improve both maternal and infant outcomes (i.e., less NAS). One new pharmacotherapy that holds promise is buprenorphine, a partial mu-opioid agonist. Studies of buprenorphine in adults (that did not include pregnant subjects) generally report little or no autonomic signs or symptoms of opioid withdrawal following the abrupt termination of buprenorphine (Jasinski et al., 1978; Mello and Mendelson, 1980; Mello et al., 1982; Reisinger, 1985; Seow et al., 1986; Fudala et al., 1990); this is in contrast to reports for methadone and heroin. From these and other data, it has been concluded that the abstinence syndrome associated with buprenorphine is quantitatively different from full mu-opioid agonists such as morphine or methadone. Using these data, it has been hypothesized that the neonate born to buprenorphine-maintained mothers will experience a shorter and milder withdrawal syndrome than that observed with methadone or heroin.

One concern with the use of any new medication during pregnancy is the possibility of toxic or teratogenic effects. Buprenorphine has been reported to lack physical teratogenic effects in rodents (Mori et al., 1982a). No teratogenic effects were observed in the rat and rabbit, respectively, after oral doses (most comparative to sublingual route) 150 and 50 times greater than the daily recommended dose (16 mg/m²) for the treatment of opioid dependence. Although significant increases in skeletal abnormalities have been observed in rats after subcutaneous administration of 1 mg/kg per day and greater, these effects were not observed after oral doses 95 times greater than the daily recommended dose for human (personal communication, Reckitt Benckiser Pharmaceuticals, Inc., 2002). Fertility and peri- and post-natal animal toxicity studies with buprenorphine have reported difficult parturition and high neonatal mortality, particularly at high oral dose levels (i.e., 50 times the daily recommended dose) but there was no evidence that buprenorphine had adverse effects on pregnancy rates or fertility. It is possible that the difficulty in parturition and the high neonatal mortality may be due to the sedative effects of buprenorphine or buprenorphine’s effect on maternal endocrine function. A slight decrease in growth rate occurred in offspring whose mothers were treated with buprenorphine during lactation and there was a slightly higher mean post-implantation loss at oral doses 6 and 50 times the recommended daily dose for treating opioid dependence in the rat and rabbit, respectively (personal communication, Reckitt Benckiser Pharmaceuticals, Inc., 2002).

Teratology studies in rodents and rabbits have shown either no difference or mixed effects on maternal water intake, maternal weight gain, external defects, internal
anomalies, skeletal defects, intra-uterine deaths, litter and mean fetal weights, litter size, crown-rump length, survival, weight gain, or early post-natal behavior of buprenorphine-exposed offspring compared with non-exposed controls (Hutchings et al., 1995; Evans et al., 1989; Mori et al., 1982b; Robinson and Wallace, 2001).

Overall, it appears that buprenorphine is associated with pre-implantation loss in the rodent and rabbit. The doses of buprenorphine associated with this loss have ranged from 1.25 to 50, and 12.5 times the daily recommended dose for the treatment of opioid dependence for the rabbit and rodent, respectively.

Unlike methadone, prenatal exposure with buprenorphine does not appear to affect activity, cycles of rest-activity, or developmental milestones (Enters et al., 1991; Zagon and McLaughlin, 1984; Zagon et al., 1979; Hutchings et al., 1979, 1996). However, at relatively high doses, buprenorphine, like other opioids, has been reported to alter sexually dimorphic non-reproductive (spontaneous parental behavior and saccharin consumption) behaviors (Barron and Chung, 1997). Buprenorphine has been shown to reduce both striatal nerve growth factor (Robinson, 2000; Wu et al., 2001), and transiently affect acetylcholine content (Robinson, 2002) and to produce toxic effects (Mori et al., 1982b) similar to methadone. Specific to acetylcholine content, buprenorphine effects varied across a wide dose range which could be explained by it being a partial agonist at the mu-opioid receptor. Additionally, it has been reported that, unlike methadone, prenatal exposure to buprenorphine does not reduce encephaline levels in the rat brain (Tiong and Olley, 1988). The exact implication of this difference between methadone and buprenorphine on post-natal development is not currently known.

Overall, any deleterious effect observed with buprenorphine during pregnancy do not appear greater or to differ significantly from methadone and other opioids. Although the evidence is limited comparing buprenorphine and methadone, the effects of buprenorphine during pregnancy do not seem to be significantly different from methadone and other opioids based on their pharmacologic, teratogenic, fertility, reproductive, and safety profile. Thus, the general consensus is that exposure of pregnant women to buprenorphine will not expose them or their fetus to greater risk than expected for methadone or other opioids.

The purpose of this paper is to review the current literature describing the use of buprenorphine (Subutex®) in pregnant opioid-dependent women as it relates to patient management and effects on the neonate. Although a combination tablet of buprenorphine plus naloxone 4:1 (Suboxone®) has recently been approved by the Food and Drug Administration in the United States for the treatment of opioid dependence, there have been no reports of Suboxone® being administered to opioid-dependent women during pregnancy. Therefore, the combination of buprenorphine plus naloxone 4:1 will not be discussed in this review.

2. Review of literature

To date, there have been a total of 21 published reports (see Table 1) of buprenorphine use during pregnancy. Fourteen are a series of case reports, five are reports of prospective studies and two are reports from planned open-labeled controlled studies. Seven of the case reports published in the literature are summarized as three reports (see Table 1) for the purpose of this review. Seven reports have been combined into three reports due to the fact that multiple reports appear to have been published on the same cohort of subjects; thus, there are 10 valuable case reports. Also, there have been unpublished case reports of infants born to buprenorphine-maintained mothers in France since its introduction there in February 1996; however, only those reports that have been published are reviewed here. The five valuable prospective reports include cohorts from three studies (i.e., data from one study has been published three times). Most of the results from the prospective studies are from France where more than 15,000 women are treated annually with buprenorphine and 10–20% of these women become pregnant (Auriacombe and Loustauneau, 2001). The two open-labeled controlled studies were designed to obtain pilot data for conducting future clinical trials (Fischer et al., 2000; Johnson et al., 2001). Each case report and prospective study is briefly summarized with expanded emphasis given to the two open-labeled controlled studies conducted by the authors (R.E.J., H.E.J., and G.F.) and their colleagues.

2.1. Case reports

The first report came from Belgium where four women who became pregnant while abusing buprenorphine were maintained on buprenorphine throughout their pregnancy (Reisinger, 1995). Patients were maintained on low dose (range 0.8–1.5 mg) buprenorphine sublingual tablets throughout the duration of their pregnancy. The age of the patients ranged from 25 to 35 years (mean: 28.3 years). Their history of heroin use ranged from 1.5 to 12 years (mean: 6.9 years). The mothers delivered healthy normal infants (one male and three females) ranging in gestational age from 39 to 41 weeks (mean: 40 weeks); birth weights ranged from 2.9 to 3.7 kg (mean: 3.2 kg) and Apgar scores for all four neonates were 9, 10, and 10 at 1, 5, and 10 min, respectively. One neonate was reported to have increased agitation at 13 days post-delivery so that opioid withdrawal could not be ruled out. This infant did not
require medication to treat the symptom(s). These infants have reportedly developed normally.

The second report was a series of six case reports (Mazurier et al., 1996). The mothers were at gestational week 12 or greater when they began taking buprenorphine. The dose of buprenorphine ranged from 1 to 10 mg per day. No complications were reported in the infants. All six neonates exhibited, and were treated for, an opioid withdrawal syndrome. Other drug use was reported in one of the mothers. Withdrawal signs were reported to appear between 6 and 48 h and the average length of treatment was 11.5 days. The authors concluded that buprenorphine was a useful alternative to methadone.

The third and fourth reports are from Marquet and his colleagues in France (Marquet et al., 1997, 1998). These two reports included six infants exposed to buprenorphine in utero. The third report (Marquet et al., 1997) was a 24-year-old woman who had been addicted to heroin for several years. She was treated with buprenorphine due to the non-availability of methadone in her hometown. She was maintained on a daily sublingual tablet dose of 4 mg. Random urine toxicology screens were negative for illicit opioids. She delivered an apparently healthy baby girl at gestational week 39. The infant’s Apgar scores were 10 at 1 and 10 min. An opioid withdrawal syndrome was reported with an onset at 48 h, a peak modified Finnegan Scale score of 12 (maximum possible = 40), and symptoms of agitation, sleep disturbance, tremor and yawning, noisy breathing, and slight fever which resulted in the infant being admitted to the NICU. No medication was required to treat the infant’s withdrawal symptoms and the infant was discharged from the NICU on day 6. Blood, urine, meconium, and maternal milk were measured for parent drug and metabolite in the mother and infant. The

Table 1
Published case reports on the use of buprenorphine in pregnancy

<table>
<thead>
<tr>
<th>Report number</th>
<th>Number of evaluable reports</th>
<th>Author(s)</th>
<th>Number of NAS</th>
<th>Number treated</th>
<th>Percent other drug use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Reisinger (1995)</td>
<td>4</td>
<td>1</td>
<td>0 n = 0 (0%)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Mazurier et al. (1996)</td>
<td>6</td>
<td>6</td>
<td>6 n = 1 (17%)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Marquet et al. (1997)*</td>
<td>6</td>
<td>4</td>
<td>2 n = 2 (33%)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Marquet et al. (1998)*</td>
<td>12</td>
<td>11</td>
<td>11 n = 7 (58%)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>Regini et al. (1998)</td>
<td>1</td>
<td>1</td>
<td>1 n = 1 (100%)</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>Hervé and Quernum (1998)</td>
<td>1</td>
<td>1</td>
<td>1 n = 1 (100%)</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>Jernite et al. (1998)*</td>
<td>24</td>
<td>16</td>
<td>15 n = 9 (38%)</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>Jernite et al. (1999)*</td>
<td>14</td>
<td>9</td>
<td>8 n = 5 (36%)</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>Auriaimo et al. (1999)*</td>
<td>16</td>
<td>7</td>
<td>5 n = 2 (13%)</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>Burlet et al. (1999)</td>
<td>14</td>
<td>9</td>
<td>8 n = 5 (36%)</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>Auriaimo and Loustauneau (2001)*</td>
<td>16</td>
<td>7</td>
<td>5 n = 2 (13%)</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>Loustauneau et al. (2000)*</td>
<td>21</td>
<td>13</td>
<td>10 n = 12 (57%)</td>
</tr>
<tr>
<td>Prospective studies</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>1</td>
<td>Gourarier et al. (2001)*</td>
<td>153</td>
<td>99</td>
<td>79 n = UNKOverall (19–38%)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Lejeune et al. (2001)*</td>
<td>31</td>
<td>13</td>
<td>8 UNK</td>
</tr>
<tr>
<td>Open-label controlled studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Fischer et al. (2000)</td>
<td>15</td>
<td>7</td>
<td>3 n = 15 (100%)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Johnson et al. (2001)</td>
<td>3</td>
<td>3</td>
<td>0 n = 0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>309</td>
<td>193 (62%)</td>
<td>149 (48%)</td>
</tr>
</tbody>
</table>

UNK = unknown. Value in bold indicates some or all of these infants may be duplicate reports.

a Number of reports published in the literature.
b Number of evaluable reports (i.e., when multiple reports of the same infants are combined).
c Number of infants reported.
d Number of infants reported to have neonatal abstinence signs.
e Number of infants treated for neonatal abstinence signs.
f Other drug use verified by either urine toxicology or self-report.
g Multiple publications of the same infants combined as one report.
fourth report (Marquet et al., 1998) included five women maintained on buprenorphine (range: 4–8 mg) sublingual tablets during their pregnancy. Two of the infants, whose mothers were positive at delivery for morphine and/or codeine, had severe NAS. Two of the remaining three infants had no NAS while the other infant was reported to have slight to mild signs of opioid withdrawal.

The fifth series of case reports (Dos Santos, 1998) included 12 infants exposed to buprenorphine in utero. 11 of the 12 infants were reported to have an NAS that required treatment. Seven (58%) of the women were reported to have used other drugs during their pregnancy.

The sixth case report was a 30-year-old patient maintained on buprenorphine (Regini et al., 1998). The patient had a 3-year history of heroin use and 10-year history of generalized idiopathic epilepsy. She was taking “4 tablets per day” (the assumed dose is 0.8 mg since the authors describe a 0.2 mg tablet available in Italy) at conception and decreased her dose to “2 tablets per day” after her third month of pregnancy (assumed dose of 0.4 mg) which she continued until delivery. She delivered a male infant weighing 2.6 kg at week 35 by cesarean section due to fetal deceleration of heart rate. The Apgar score was 3 and 7 at 1 and 5 min, respectively. The infant developed an NAS that the authors reported responded poorly to treatment with methadone. On the second post-delivery day, the infant was treated initially with methadone “1 ml/kg three times a day” (exact dose in mg was not stated) for symptoms of hypothermia, spontaneous tremors, muscular hypertonia, continuous acute crying, polypnoea, and feeding difficulties. The dose of methadone was gradually increased to “1.3 ml/kg three times a day” whereupon on the third day the infant experienced apnea and bradycardia that responded to naloxone. A total of 41 days of withdrawal was reported. At 5 months, the infant was diagnosed with infantile cerebral paralysis with malformation of the central nervous system (CNS), dystonic tetraparesis, epilepsy, and dystrophy. The authors concluded that the initial NAS but not the other complications observed were due to exposure to buprenorphine.

The seventh report was a case report of one newborn (Hervé and Quernum, 1998). The mother reportedly took one buprenorphine 2-mg tablet per day. Birth outcome measures were normal at delivery. Withdrawal symptoms began to appear on the third post-delivery day and gradually increased until the sixth day at which time the infant was admitted to the neonatal unit with diarrhea, tremors, hyper-excitability, hypertonia, and disturbed sleep. Treatment was continued with paregoric (opium tincture camphorated; each 5 ml contains morphine, 2 mg; anise oil, 0.2 ml; benzoic acid, 20 mg; camphor, 20 mg; glycerin, 0.2 ml; and ethanol to make 5 ml) for 10 weeks. There was no report of other drug use by the mother prior to delivery. The authors caution that treatment of withdrawal symptoms in infants exposed to buprenorphine in utero can be expected.

The eighth and ninth reports came from Jernite and colleagues. These two reports included a total of 24 infants exposed to buprenorphine during gestation. The first case report by Jernite et al. (1998) included 6 of the 24 total infants. Three of the women were receiving buprenorphine sublingual tablets of 2, 4 and 16 mg, respectively. One woman was injecting buprenorphine (8 mg per injection), another was abusing cocaine and benzodiazepines, and the third was reported taking buprenorphine but was not an opiate addict. All six neonates were reported to have opioid withdrawal symptoms. Five of the infants required standard treatment for the NAS. One infant who showed symptoms of hypotonia and somnolence was treated with clorazepate and paregoric. Of the 24 women treated with, and infants exposed to, buprenorphine during pregnancy, 13 were assessed retrospectively through chart review and 11 were followed prospectively in collaboration with OB/GYN, mental health, and drug abuse treatment specialists using a comprehensive care model (Jernite et al., 1999). Complications were fewer in the group followed prospectively using the comprehensive care model. A high rate of ancillary drug use (e.g., benzodiazepines) was reported. An NAS was reported in 69 and 63% of the infants born to the groups assessed retrospectively and prospectively, respectively. The average length of treatment was 16 and 9 days for the retrospective sample and prospective sample, respectively. A post-withdrawal syndrome was reported in two of the infants that lasted 8–10 weeks but required no treatment. The NAS with buprenorphine was reported to appear to be less severe than with methadone except when combined with high doses of other medications particularly benzodiazepines. The importance of having a comprehensive treatment model for pregnant opioid-dependent women was evident by the fact that 1 of 11 and 4 of 13 infants were born premature in the group receiving comprehensive and non-comprehensive care, respectively. Further, the non-comprehensive treatment group infants had six with intrauterine growth retardation, three with acute fetal stress, and one with convulsions compared with 1, 0, and 0, respectively, for the comprehensive treatment group.

The 10th report included 14 women who were treated with buprenorphine during pregnancy (Burlet et al., 1999). The appearance of an NAS was reported in 9 of 14 infants with 8 of the infants requiring treatment for withdrawal. The authors divided the 14 women into those taking buprenorphine and their infant had withdrawal symptoms (n = 4), those taking buprenorphine and their infant had no withdrawal symptoms (n = 5), and those supposedly taking buprenorphine but had
urine specimens negative for buprenorphine (n = 3/5) and were also positive for other drugs (n = 5/5) at delivery. Overall, only 3 of 9 infants whose mothers were taking buprenorphine alone required treatment for signs of opioid withdrawal. This was in contrast to the infants whose mothers were negative for buprenorphine but positive for other drugs at delivery, where all five required treatment for withdrawal signs. In the group whose mothers were taking buprenorphine and the infants showed signs of withdrawal, the highest Finnegan score of 15 occurred at 72 h after delivery. In the five infants whose mothers were taking buprenorphine but no withdrawal signs were observed, the highest Finnegan score was 3 at 12 h after delivery. Finally, for those infants whose mothers’ urine samples were negative for buprenorphine but positive for other drugs at delivery, the highest Finnegan score was 13 at 36 h after delivery.

The 11th, 12th, and 13th reports by Auriacombe et al. (1999), Auriacombe and Loustauneau (2001) and Loustauneau et al. (2000), respectively, appear to include 16 births. The Auriacombe et al. (1999) report included 4 women (3 of whom delivered) who were taking buprenorphine and 12 women (9 of whom delivered) who were receiving methadone during pregnancy. The authors report that, from their limited data, it appeared that the women receiving buprenorphine had fewer problems than those receiving methadone. They further concluded that treatment of pregnant women with methadone or buprenorphine was “non-toxic” to the infant. The 12th report (Loustauneau et al., 2000) included 18 women (14 deliveries). Loustauneau et al. reported the mean weight of the 14 newborns was 3.0 kg, and they delivered between gestational weeks 37 and 41. In the Auriacombe and Loustauneau (2001) report, it was stated that 7 of the 16 neonates were reported to have had opioid withdrawal symptoms within 48 h. Of these 16, five required treatment for their NAS. The average length of hospital stay was reported to be 15 days (Loustauneau et al., 2000). However, the authors concluded that, compared with methadone, buprenorphine-exposed infants had less frequent and less severe opioid withdrawal symptoms that persisted for a shorter period of time.

The 14th and final report by Marquet et al. (2002) included 23 subjects, but NAS data were available for only 21 subjects (see Table 1). It is difficult to determine if these 21 births are new cases or have been previously reported. From a personal communication (Dr. Michel Mallaret, Director, Centre d’Evaluation et d’Information sur la Pharmacodépendance, Grenoble, France, August 19, 2002), we believe that outcomes for some of these infants have been reported previously; however, for the purpose of this summary the 21 births reported are considered new reports (see Table 1). 12 (57%) of 21 mothers had other drugs including alcohol, benzodiazepines, cannabinoids, opiates, and cocaine in their urine at birth. The birth weight of the neonates ranged from 1.7 to 3.9 kg (mean: 2.8 kg). Apgar scores were 9 or above for 20 of the neonates and 8 for one neonate. Of the 21 neonates, 8, 3, and 10 were reported to have no, mild, or severe NAS, respectively. The mean duration of treatment was 16.5 days. There was a slight trend (P = 0.17) for the mothers of neonates who experienced NAS to have a higher mean daily dose of buprenorphine. The authors point out the need for frequent urine collection to assess other drug use and concluded that future studies should assess the relationship of the NAS in mothers who take buprenorphine alone versus mothers who take buprenorphine and still use other illicit opioids.

As with all case reports, those presented here are generally confounded by small sample size, lack of adequate control comparison groups, limited measurement, or control for potential confounds (i.e., drug use, prenatal care, nutritional care, domestic environment, maternal and fetal/neonatal medical histories pre- and post-delivery, etc.). The cases with the most negative birth outcomes are fraught with these factors. For example, in the severe case reported by Regini et al. (1998), the mother had not received routine prenatal care, and other substances including alcohol, amphetamines, and cocaine may have been used during her pregnancy. Secondly, the effects of asphyxia at delivery and the severe hypoxia following the use of high dose methadone to treat the purported NAS could have actually prolonged the withdrawal; however, this cannot be determined from our review of the report. Even the authors contradict themselves by attributing observed symptoms to buprenorphine and later stating that it is difficult to absolutely rule out the role the use of alcohol, amphetamine, or cocaine had in this patient. To our knowledge, this case is the most severe NAS purportedly due to in utero exposure to buprenorphine. It also represents the most extensive report of post-delivery neurological and behavioral complications to date. However, it must be noted that this case report is on one infant and a similar clinical course can be found for infants born to opioid-maintained or other mothers with similar medical histories. These factors cannot be discounted in the Jernite report given the high rate and high doses of other medications given or taken during pregnancy. The post-withdrawal syndrome of 8–10 weeks for two of the infants was not described in detail. The cases reported by Regini et al. (1998) (n = 1), Jernite et al. (1999) (n = 2), and Hervé and Quernum (1998) (n = 1) appear to be the most protracted withdrawal syndromes reported to date in buprenorphine-exposed infants.

This array of clinical cases with reported differences in outcome points to the need to conduct well-designed, well-controlled studies with buprenorphine. To address
some of these issues and to extend the collection of safety data with buprenorphine in this special population, the Groupe d’Etudes Grossesse et Addictions in France has followed the use of buprenorphine in pregnant women for the past several years. The two largest prospective studies emanating from this group and reported to date are reviewed next followed by a report of two women who have delivered two children each while being maintained on buprenorphine. The summary review of these prospective studies is followed by a more extensive review of two open-labeled controlled prospective studies conducted by the authors (R.E.J., H.E.J., and G.F.) and their colleagues. These open-labeled controlled studies used stringent methodologies and systematic collection of data for the purpose of collecting pilot data to design, implement, and execute a randomized, double-blind controlled study comparing methadone and buprenorphine generally lacking in other prospective studies (except for the Schindler et al., 2003). The three prospective and two open-labeled controlled studies are summarized below.

3. Prospective study

The largest prospective study reported to date included 246 pregnant women with 153 of these women receiving buprenorphine (Gourarier et al., 2001; Lejeune et al., 2001, 2002). Comparisons between methadone and buprenorphine were made on medical, social, perinatal, birth outcome, and the NAS. Only the results from buprenorphine are presented here. 130 (85%) of the 153 women conceived while on buprenorphine. Approximately 10% of the women receiving buprenorphine delivered prior to gestational week 37. Approximately 99 (65%) of the neonates had LIPSITZ scores (a measure of NAS; Lipsitz, 1975) greater than zero with 79 (52%) requiring treatment for NAS for a mean duration of 16 days. The authors reported a significant correlation between dose of methadone and buprenorphine at delivery and maximum LIPSITZ score. Significant differences between the methadone and buprenorphine groups included: (1) a greater number of women received buprenorphine prior to conception, (2) a greater number of women received methadone through specialized treatment centers and buprenorphine through general practitioners, (3) a higher number of premature (<37 weeks) births in the methadone group, and (4) maximum withdrawal scores were reported later for methadone compared with buprenorphine (i.e., 92 h vs. 70 h). By self-report, there was higher cocaine use in the methadone (14%) vs. buprenorphine (9%) group. Although no overall differences in self-reported illicit drug use were observed between groups, high levels of other drug use was reported with 19, 38, 31, and 29% of the women (not reported by group) using heroin, hashish, alcohol, and benzodiazepines, respectively, during treatment. There were no differences observed between methadone and buprenorphine for acute fetal stress, percentage treated for NAS, duration of treatment, hospital stay, intra-uterine growth retardation, height, head circumference, weight, or Apgar scores. 34 buprenorphine- and 22 methadone-maintained mothers were reported to have breast-fed; however, no kinetic data were reported nor was there a discussion regarding the potential effects of the medication on the NAS or withdrawal following weaning. The authors stated that the withdrawal syndrome appeared “to be a bit more severe and longer lasting in the methadone group”.

The authors point out that the two major weaknesses of this large prospective study was the lack of randomization and sole reliance on a self-report measure of illicit drug use. Sole reliance on self-report, without objective drug use measures, is a major weakness in this report given that self-report can be biased by numerous factors. Both urinalysis and self-report are accepted as surrogate measures of drug-taking behavior; however, they differ in their sensitivity for detecting abstinence. Self-reported drug use is open to over- or under-reporting, often depending on the patient’s perceived demand characteristics of the situation (Darke, 1998).

A second prospective study is ongoing and designed to include 100 methadone- and 100 buprenorphine-maintained women (Lacroix et al., 2002). To be in the study, the women have to commence methadone or buprenorphine before the end of their eighth month of pregnancy. This multi-site study is collecting an array of data from both the mother and neonate. This preliminary report included 34 pregnancies of which there were 31 births of infants exposed to buprenorphine in utero. There was one stillborn birth, one spontaneous, and one voluntary abortion. An NAS occurred in 13 (42%) of the infants with 8 (26%) requiring treatment for it. Data on the use of other drugs were collected but not reported. The mean time to appearance of the NAS was 72 h (range: 24–192 h).

A third prospective report by Schindler et al. (2003) is the first to describe the outcomes from two infants whose mothers had previously delivered buprenorphine-exposed infants (Fischer et al., 2000) and who conceived while continuing to be maintained on buprenorphine (Eder et al., 2001). During the initial pregnancy, the women were transferred from oral methadone 30 mg and slow-release oral morphine hydrochloride 400 mg daily to buprenorphine at gestational weeks 21 and 25, respectively. At delivery, the women were receiving buprenorphine 8 and 10 mg daily. Neither infant required treatment for NAS. These same women became pregnant a second time while being maintained on buprenorphine and elected to continue buprenorphine rather than transfer to methadone. Their doses of
buprenorphine at conception and delivery during their second pregnancy were 6 and 12 mg daily. Both women were free of illicit drugs throughout the second pregnancy. One woman delivered a boy by cesarean section at 38 weeks and the second a girl by vaginal delivery at 40 weeks. Birth outcomes including length, weight, and Apgar scores were within normal limits. The maximum Finnegan withdrawal scores were 5 and 8, with neither neonate requiring treatment for NAS. The authors concluded that buprenorphine has a good safety profile in women who are receiving buprenorphine before and at conception.

4. Open-label controlled studies

4.1. Vienna study

The largest open-label controlled study reported to date was by Fischer et al. (2000). They studied 15 pregnant opioid-dependent women maintained on buprenorphine for 4–21 weeks. Additional methodological details are provided in that report, with some of the key findings summarized here along with an expanded data presentation.

Strict inclusion and exclusion criteria were used in the study and all women were generally healthy as determined by history, physical examination, and laboratory evaluation (Fischer et al., 2000). Prior to induction onto buprenorphine, 14 of the women were maintained on long-acting opioids (either oral methadone or slow-release oral morphine), and one was injecting “street” heroin. The first dose of buprenorphine was administered 24–36 or 14–16 h after last dose of either oral methadone or slow-release oral morphine, respectively. Reckitt Benckiser Healthcare (UK) Ltd. supplied buprenorphine sublingual tablets 2 and 8 mg for the study. The women were provided regular routine prenatal and perinatal care, psychiatric and social services, and opioid-dependent partners were also offered treatment. A flexible dosing regimen was used with doses increasing during a 3-day induction period until the patient was stabilized or until a dose of 10 mg was attained. The authors reported that the 10 mg upper dose limit was mandated by the human subjects ethics committee based on earlier published reports (Johnson et al., 1992; Strain et al., 1994; Walter et al., 1997). During the 3-day induction period, 4 mg of buprenorphine (2 × 2 mg sublingual tablets) was given twice a day, with the option of an additional 2 mg dose at night during the first 2 days; ratings of maternal opioid withdrawal and fetal distress were measured systematically. After discharge, sublingual buprenorphine tablets were taken once daily in the morning and take-home doses of buprenorphine were provided for Tuesday, Thursday, Saturday, and Sunday. Supervised urine specimens were collected twice weekly and tested for illicit drug use and safety was assessed throughout the study. At delivery, birth outcomes were measured and the presence of an NAS was assessed every 4 h for the next 2–15 days. Additionally, following delivery, polysomnographic electromyogram (EMG) and electroencephalogram (EEG) examinations were conducted to evaluate neonatal sleep, breathing patterns, airway flow, thoracic impedance, heart rate, carbon dioxide, and oxygen saturation.

Specific demographic and dosing data for the study participants have been published (Fischer et al., 2000). During induction, the major complaint of all women transferred from oral methadone and slow-release oral morphine was a dysphoric mood state for 3 days with minor complaints of restlessness for 2 days. The one woman inducted directly from “street heroin” did not complain of dysphoric symptoms or restlessness. Oxazepam was administered on four occasions for the treatment of sleeplessness. Maternal opioid withdrawal symptom scores (Wang et al., 1974) never exceeded 4 (maximum = 45), reflecting minimal discomfort and acceptance of the induction procedure (Fischer et al., 2000). These observations are consistent with findings of other investigators who have studied the transition of individuals from methadone to buprenorphine (Levin et al., 1997) and “street heroin” to buprenorphine (Law et al., 1997). The transition from methadone to buprenorphine has been associated with dysphoria (Law et al., 1997).

During the study, six women requested their dose to be reduced and two women requested a dose increase. With the exception of one patient (reduced from 10 to 1 mg), five of the six women reduced their dose by 2 mg during maintenance. A total of 259 urine samples was collected and assayed for illicit drug use during the study (Fischer et al., 2000). Twenty-four samples were positive for opiates only. The 91% opioid-negative urine rate observed in the outpatient phase of this study is higher than that observed in most large clinical trials (e.g., Johnson et al., 1992; Kosten et al., 1993; Strain et al., 1994; Ling et al., 1996; Schottenfeld et al., 1997) that have not included pregnant women. Only four women relapsed to opiate use suggesting acceptance and effectiveness of buprenorphine treatment in this special population. At delivery, two maternal urine samples were positive for opiates and all urine samples were positive for cannabinoids. Birth outcome measures of Apgar scores, birth weights, length, and head circumference were all within normal limits (Fischer et al., 2000), adding to the evidence that buprenorphine is safe in this population.

Additionally, exposure to buprenorphine during pregnancy appeared to be safe as evidenced by maternal clinical laboratory data. Observed changes in clinical and laboratory data were either not clinically significant.
or to be expected during pregnancy (e.g., elevation of alkaline phosphatase). Sonographic examinations performed during induction onto buprenorphine to assess fetal stress showed that the induction procedure was not detrimental to the fetus. There were 10 vaginal and 5 cesarean deliveries. Average maternal weight gain during the course of pregnancy was 11.9 kg (range: 5–18) and two women breast-fed their infants. None of the infants were pre-term or small for gestational age at delivery, although all women were moderate to heavy smokers. No severe adverse events were observed in the mothers or their neonates. The post-delivery polysomnographic records revealed no severe complications in the neonates. However, one neonate showed slight bradycardia 2 days post-delivery with decreased acceleration and decreased variability.

Overall, an NAS was observed in 7 of 15 infants. A moderate NAS appeared in three neonates that required treatment with low dose morphine, a mild NAS appeared in four (requiring no treatment) and no NAS was observed in eight of the neonates. The main symptoms observed were tremor and hyperreflexia. The NAS appeared to peak between days 2 and 5, which is consistent with withdrawal time-course data from adult studies (Fudala et al., 1990; San et al., 1992). Where appropriate, the NAS was treated with morphine drops according to a standard protocol. The dose of morphine was dependent on body weight and total NAS score (Pacifico et al., 1989). The total dose of oral morphine received by the three neonates who were treated was 0.15, 0.45, and 1.20 mg (mean: 0.6 mg). The mean duration of pharmacologic treatment for NAS was 5.33 days (±3.21 S.D.) (range: 3–9 days). Of the three neonates who required treatment for NAS, two were born to mothers who had relapsed to heroin use the week prior to delivery. The authors could not assign a specific causality of the two major withdrawal symptoms (tremor and hyperreflexia). However, these symptoms have been reported in infants whose mothers are heavy smokers with a positive correlation reported between maternal cigarette consumption, neonatal restlessness, and other vegetative symptoms (Mullen et al., 1991). It is interesting that in this study, mothers of the neonates that required treatment for NAS smoked a higher number of cigarettes per day (mean: 17.5) compared with the mothers whose neonates required no treatment (mean: 9.4). The relationship between signs reported for the NAS (now believed to be specific to the withdrawal of an opioid) and number of cigarettes smoked (i.e., nicotine consumption) by the mother during her pregnancy needs additional investigation. The authors were not able to find a correlation between the mean total buprenorphine dose in the mothers whose neonates required treatment and mothers whose neonates required no treatment for NAS.

A confound in this study is the high use of cannabis by the mothers. All mothers were positive for cannabinoids at delivery as confirmed by urine analyses. Active smoking of marijuana cigarettes generally results in cannabinoid urine level of >100 ng/ml (i.e., the cutoff used in this study) for less than 24 h (Mulé et al., 1988). Thus, it appears that women in this study may have used cannabinoids within 24 h of delivery. The effects of this apparent chronic and persistent use of cannabinoids on the NAS are unknown and also needs further investigation.

In summary, buprenorphine was well tolerated by the mothers as assessed by self-reports, urine toxicology, and safety data. Overall, the NAS was absent or mild in the majority of infants with only three infants requiring treatment with low-dose morphine drops.

4.2. Baltimore study

A second open-label, flexible dosing study was conducted in three opioid-dependent pregnant women and reported by Johnson et al. (2001). The essential components of that report are included here, including some additional details not reported earlier. Again, strict inclusion and exclusionary criteria were followed (Johnson et al., 2001). However, unlike the Fisher et al. (2000) study, prior to enrollment all three women were using “street heroin” and the first two women remained inpatient (except for day passes) throughout their pregnancy.

All three women were healthy as determined by history, physical, and laboratory evaluations. Reckitt Benckiser Healthcare (UK) Ltd. provided sublingual tablets containing 2 and 8 mg of buprenorphine. Regular and routine prenatal, obstetrical and gynecological, psychosocial, and counseling care were provided. The Human Subjects Ethics Committee approved the study.

The women were admitted to a domiciliary unit of the Center for Addiction and Pregnancy (CAP) at Johns Hopkins Bayview Medical Center for a 3-day induction onto buprenorphine. Biophysical Profiles and Non-Stress Tests of the fetus were obtained pre- and post-dosing of buprenorphine during the first 4 days of induction. The women were dosed daily and maintained on sublingual buprenorphine tablets throughout their pregnancy. After the study was completed, the women could choose between a 21-day inpatient and a 10-week outpatient dose taper with buprenorphine.

Urine samples were collected each morning (i.e., tested randomly) while inpatient and prior to and after day trips (i.e., all were tested) and analyzed for illicit drugs. One woman (#3) provided urine samples on
Monday, Wednesday, and Friday while an outpatient. A full screen (i.e., opiates, methadone, cocaine, ampheta-
mamine, barbiturates, benzodiazepines, cannabinoids, and PCP) was done on 84 samples (women #2 and #3) and 63 samples were screened only for opiates, methadone, cocaine, and benzodiazepines (woman #1). The women completed visual analog scales weekly that assessed dose adequacy. For safety purposes, blood chemistries and other laboratory evaluations were performed prior to induction (baseline) and every 4 weeks during pregnancy and again at delivery. Blood, urine, and hair (data not reported) samples were obtained for pharmacokinetic data at pre- and post-delivery. Breast milk was also obtained from woman #1. Birth outcomes were evaluated at delivery. In this study, the newborn was assessed for the presence of NAS every 12 h for 10 days using a modified Finnegan Scale (Finnegan and Kaltenbach, 1992). Additionally, during the first 10 days of life, infants were evaluated using the NICU Network Neurobehavioral Scale (NNNS; Bouk ydis and Lester, 1999) and Infant Acoustic Cry Analysis (Corwin et al., 1992; Lester et al., 1991, 2002).

Gestational age at admission ranged from 24 to 26 weeks (mean: 25 weeks). All three women had used heroin and nicotine daily for the past 30 days, and only one had used cocaine 4 days during the past month. Only one woman had a history of previous treatment for opioid dependence. Demographic data for the three women have been published (Johnson et al., 2001). Induction onto buprenorphine 8 (women #2 and #3) and 10 mg (woman #1) sublingual tablets was accomplished over 3 days without difficulty. Woman #1 had her dose of 10 mg increased to 12 mg on day 15 after admission and she was maintained on this dose from gestation week 26 throughout her pregnancy. Women #2 and #3 were maintained on 8 mg buprenorphine tablets from gestation weeks 24 and 26, respectively, throughout their pregnancy. None of the women complained of withdrawal or requested dose increases during this time. The authors reported that results from Biophysical Profiles and Non-Stress Tests of the fetus obtained pre- and post-dosing of buprenorphine during the first 4 days and periodically throughout the study were unremarkable (Johnson et al., 2001). Of the 147 urine samples collected and assayed over a mean investigational period of 14 weeks, 146 urine samples were negative for all illicit substances. Only one sample (i.e., 9 weeks predelivery) was positive for both opiates and cannabinoids. No urine samples were positive for opiates or any other licit or illicit drug at delivery. The authors reported that dose adequacy was acceptable with all three women reporting that they liked the medication and felt low levels of craving for heroin. Most blood and urine chemistry values were within normal limits. Those outside normal limits were explained by the pregnancy or other medical reasons unrelated to buprenorphine attesting to the safety of buprenorphine in this population.

All three women developed spontaneous labor with two having normal vaginal deliveries and one delivered by cesarean section due to failure to progress. Birth outcomes including gestational age, birth weight, length, head circumference, Apgar score at 1 and 5 min, and Cord pH were all within normal limits. Apgar scores and Cord pH were not reported for neonate #3 due to being born at home. There were no signs of meconium staining indicative of fetal stress. Two infants remained in the newborn nursery for 4 days (minimum allowed by hospital policy) and one remained for an additional day to observe for weight gain (i.e., mother was nursing) and none was admitted to the NICU.

Maternal and neonatal pharmacokinetic data were collected from one woman and her infant. In the one maternal and infant pair from which pharmacokinetic data were obtained, levels from maternal, cord, and infant plasma were comparable. Analysis of breast milk and plasma revealed a ratio of approximately 1. Additionally, mean trough buprenorphine plasma levels pre- and post-delivery were comparable in two of the women while the third woman’s levels were 3–4 times lower, possibly due to her increased weight.

The authors reported that all three infants exhibited signs of opioid withdrawal (Johnson et al., 2001). The onset of symptoms was within the first 12 h following delivery. Observed symptoms increased over time, peaked by 72 h, and returned to below pre-12 h levels by 120 h. Tremors (disturbed), hyperactive moro, and sleep less than 3 h after feeding were the three most predominant symptoms observed in the neonates.

Results from the NNNS, a measure of behavioral states, were unremarkable. Finally, the Infant Acoustic Cry analysis that has been used to show differences between in utero drug-exposed and non-drug-exposed infants showed no evidence that these three babies experienced opioid withdrawal.

In summary, the results from this study were in general agreement with the observations made in the Fischer et al. (2000) open-labeled, controlled study and provides further impetus for the assessment of buprenorphine for the treatment of pregnant opioid-dependent women.

5. Discussion

There have been a total of approximately 309 infants born to mothers maintained on buprenorphine as reported in the literature. From these data, there appears to be a wide range of doses that is effective in treating this population. The dose of buprenorphine reported to date has ranged from 0.4 to 24 mg sublingual tablets per day.
The mothers’ pregnancies have generally progressed normally with low rates of prematurity. From the limited data reported to date, the maternal safety and effectiveness of buprenorphine is positive. Maternal and infant laboratory data reported have generally been within normal limits. Those results outside normal limits were deemed clinically non-significant, normal during pregnancy, or due to factors other than the medication.

To date, pharmacokinetic data in pregnant women are extremely sparse (Marquet et al., 1997; Johnson et al., 2001). In animals, buprenorphine plasma and tissue levels appear to remain similar and constant throughout pregnancy when compared to the non-pregnant state with minimal metabolism in the fetus and high levels in the gastrointestinal tract consistent with lack of enterohepatic circulation. Additionally, buprenorphine is excreted in breast milk and levels are similar or higher than levels observed in the blood. The limited human pharmacokinetic data appear consistent with the animal data in that buprenorphine is present in breast milk with an apparent plasma to milk ratio of approximately 1. Furthermore, the nor-buprenorphine to buprenorphine plasma ratio appears to be 6:1 in the mother and approximately 1:1 in the neonate suggesting the lack of development of metabolic pathways in the neonate. A threefold difference in plasma levels of buprenorphine has been observed in women reported on to date. The high inter- and low intra-individual variability in plasma drug levels observed here is not uncommon and has been reported previously (e.g., Mendelson et al., 1997; Kuhlman et al., 1996).

The fact that the plasma to breast milk ratio approximates 1 is an important observation. The knowledge that buprenorphine is detectable in breast milk and that the plasma to breast milk ratio is approximately 1 provides clinicians with the ability to estimate the total daily amount of buprenorphine consumed by the infant. Because buprenorphine has poor oral bioavailability, the infant will be exposed to only 1/5 to 1/10 of the total amount of buprenorphine available. Accordingly, the infant should be exposed proportionally to less of an active dose with buprenorphine than other opioid agonist medications found in breast milk with similar plasma to breast milk ratios. Approximately 15% of the women maintained on buprenorphine have been reported to breastfeed with 8 reported by Auriacome and Loustaueneau (2001) and 34 reported by Lejeune et al. (2002). The NAS does not appear to be suppressed by the buprenorphine in breast milk nor has an NAS been reported following the cessation of breast milk feeding (Auriacome and Loustaueneau, 2001). Thus, buprenorphine may have significant advantages over opioid agonist medications used to treat this special population. Although controversial, it has been suggested that extradural buprenorphine administered in analgesic doses after cesarean section suppresses breast-feeding (Hirose et al., 1997). However, it should be noted that this effect has also been seen with other opioids such as meperidine (Wittels et al., 1997). The effect of buprenorphine on breast-feeding at the higher doses used to treat opioid dependence needs further investigation.

From current non-controlled data, there does appear to be an NAS in infants born to buprenorphine-maintained mothers that has been described as mild to severe. An NAS has been reported in 193 of 309 infants (62%). Of these, 149 (48%) required treatment for opioid withdrawal and, of these infants, the NAS was confounded by other drug use in greater than 40% of the cases. Of the 309 infants, it appears that less than 10% have required admission into a NICU. These results appear favorable when compared with methadone for the treatment of pregnant opioid-dependent women. Although variable between infants, the NAS observed to date has an apparent onset within the first 12–48 h, peaks within approximately 72–96 h, with a duration of approximately 120–168 h. The exception to this has been the few infants who were reported to have had withdrawal symptoms for 6–10 weeks. It should be noted that this duration of withdrawal symptoms is inconsistent with data to date in adults. This duration of withdrawal symptoms has not been reported in adults with documented histories of no other drug use, even at doses higher than doses taken by patients reported here. To date, only one report has found a correlation between dose and the severity of the NAS (Marquet et al., 2002) and this was only on the maximum LIPSITZ score while other reports have reported no correlation (Jernite et al., 1999; Fischer et al., 2000; Auriacome, 2001). A wide range of medications including chlorpromazine, phenobarbital, benzodiazepine, paregoric elixir, and morphine drops have been used successfully to treat the NAS in these infants.

The NAS associated with buprenorphine has been reported to be less intense than that observed with methadone. This difference in the NAS may be explained by: (1) the difference in receptor affinity (high) and intrinsic activity (low) of buprenorphine compared to other opioids and/or (2) possible differences in fetal adaptation and expression of opioid receptors within the CNS (Belcheva et al., 1994, 1998), or (3) the low transplacental transfer of buprenorphine to the fetus (Nanovskaya et al., 2002). Buprenorphine is different from oral methadone or slow-release oral morphine (currently used for maintenance therapy) with regard to receptor affinity and activity. The second explanation (see above) may explain differences in pharmacologic efficacy of opioid agonists, partial-agonist or mixed agonists/antagonists previously reported in premature neonates (Barrett et al., 1993).
6. Conclusion

In summary, results from the two open-labeled controlled studies designed to assess the NAS in buprenorphine-exposed infants and a majority of the case reports (both prospective and retrospective) provide initial safety and effectiveness data that should allow for the continued study of buprenorphine in pregnant opioid-dependent women. With the introduction of buprenorphine in France in 1996, there has been significant scientific attention paid to the use of buprenorphine during pregnancy. During this same period, several studies have documented the effectiveness of buprenorphine and ancillary services for the treatment of this special population. While great strides have been made, there still remain significant questions about the optimal effectiveness of buprenorphine in pregnant opioid-dependent women. Additional medications that benefit the pregnant opioid-dependent female and her newborn are needed. It appears that treatment with buprenorphine provides the same benefits to the mother as other opioid agonist medications (i.e., cessation of smoking generally observed in infants born to mothers enrolled in maintenance treatment programs, etc.), but, more importantly, may attenuate the NAS. Although these results are promising, they should be interpreted with caution given the lack of appropriate controls. Going forward, the problems observed with the case reports and many prospective studies could be avoided or minimized through the collaborative development of standardized prospective protocols that systematically utilize the same maternal and neonatal outcome measures and definitions. Ultimately, well-designed, well-controlled studies are needed to determine if there is a difference in the NAS observed following fetal exposure to buprenorphine in utero. Without controlled clinical trials, clinicians will rely upon uncontrolled case reports and prospective open-label studies. Reliance on these uncontrolled case reports and prospective studies will inevitably lead to controversy regarding the potential benefits of buprenorphine when it is used to treat pregnant opioid-dependent women.

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