Objectives: To compare maternal characteristics, prenatal care, and newborn outcomes in a cohort of opioid-dependent pregnant women treated with methadone versus buprenorphine.

Methods: In a retrospective cohort study, 609 pregnant, opioid-dependent women were treated with methadone (n = 248) or buprenorphine (n = 361) between 2000 and 2012 at a single institution.

Results: Mothers treated with buprenorphine were more likely to start medication before or earlier in pregnancy, had longer gestation, and gave birth to larger infants. Newborns of buprenorphine- versus methadone-maintained mothers required treatment for neonatal abstinence significantly less often and for a shorter duration.

Conclusions: These data suggest pregnancy outcomes with buprenorphine to treat opioid dependence during pregnancy in clinical practice are as good and often better than outcomes with methadone. These results are consistent with efficacy data from randomized clinical trials and further support the use of buprenorphine for the treatment of opioid dependence during pregnancy.

Key Words: buprenorphine, methadone, opioid dependence, pregnancy


Opioid dependence during pregnancy is often compounded by multiple risk factors contributing to adverse maternal and newborn consequences (Kandall et al., 1977; Lifschitz et al., 1985; Hulse et al., 1997; Lester et al., 2004; Messinger et al., 2004; Winklbaur et al., 2008). For more than 4 decades, methadone has been the recommended standard for treating opioid-dependent pregnant patients. In the context of comprehensive care, methadone maintenance improves maternal and newborn outcomes relative to no treatment or medication-assisted withdrawal (Kaltenbach et al., 1998; Jones et al., 2008; Winklbaur et al., 2008).

Despite numerous small studies that have examined the safety and efficacy of buprenorphine for the treatment of opioid dependence during pregnancy (Jones et al., 2012), only a few studies compared treatment with methadone to buprenorphine (Jones et al., 2005; Fischer et al., 2006; Lejune et al., 2006; Binder & Vavrinkova, 2008; Kakko et al., 2008; Bakstad et al., 2009; Jones et al., 2010; Lacroix et al., 2011). Most data suggest that newborns exposed to buprenorphine in utero demonstrate milder, more limited neonatal abstinence symptoms than those exposed to methadone. The most rigorous comparison conducted was the MOTHER study, a multisite randomized controlled trial in which maternal participants received study medication in a double-blind, double-dummy manner (Jones et al., 2010). The rigorous trial requirements of the MOTHER study specifically addressed the efficacy of buprenorphine versus methadone for the treatment of opioid dependence during pregnancy.

In everyday practice, however, treatment allocation is not randomized. Development of a treatment plan for substance abuse includes addressing a myriad of social factors, including housing, family drug use, and often prior treatment failures. In this regard, the tightly controlled environment of randomized trials may not provide sufficient information for general use.

The goal of this study is to compare maternal characteristics, prenatal care, and newborn outcomes in women treated with buprenorphine versus methadone for opioid dependence during pregnancy in a setting in which treatment allocation was clinically determined. To our knowledge, this is the largest study to date comparing the effectiveness of these 2 opioid agonist therapies (OATs) during pregnancy as prescribed in clinical practice.

METHODS

Participants

Study subjects were identified retrospectively from a database of newborns with a known in utero opioid exposure maintained for quality assurance purposes. A total of 806 mother–newborn dyads were identified in the database for potential study inclusion. Mother–newborn dyads were excluded from the study if the mother was treated with an OAT for reasons other than opioid dependence (n = 47), the mother was treated as part of the MOTHER study (n = 25), the mother had
a known opioid dependence but was not prescribed an OAT (n = 78), the mother delivered at an outside institution (n = 40), or the newborn had an Apgar score of 0 (n = 7). A total of 609 mother–newborn dyads treated for opioid dependence during pregnancy with methadone or buprenorphine and delivered at a single institution between August 2000 and June 2012 were included in this study. The study was reviewed and approved by the Committees on Human Research at the University of Vermont.

**Obstetric Care**

Women were treated at the tertiary care obstetric clinic with an onsite social worker and a single provider for both obstetrics and buprenorphine maintenance or at community obstetric practices. Ultrasound for viability was performed before the initiation of medication for opioid dependence. Subsequently, routine prenatal care was provided. Decisions regarding pregnancy management, analgesia, timing and mode of delivery, and postpartum care were per standard obstetric practice. For mothers who were not on OAT at the time of conception, estimated gestational age (EGA) at the initiation of treatment was recorded.

Newborn outcomes included sex (male/female), EGA at delivery, preterm delivery (EGA less than 37 weeks), birth weight in grams, birth weight standardized for sex and EGA (z-score), birth weight less than the fifth percentile (yes/no), head circumference in centimeters, head circumference standardized for sex and EGA (z-score), nonpreterm newborn length of hospital stay in days, the newborn receiving any breast milk at discharge (yes/no), and if the newborn was discharged in the care of the mother or family (yes/no). In addition, newborns were classified as neonatal abstinence syndrome (NAS) positive if the newborn required pharmacologic treatment was initiated for withdrawal symptoms. For NAS-positive newborns, NAS treatment duration in days was also measured.

**Opioid Medication Management**

Opioid agonist therapy medication management was determined by individual assessment, which included success with prior or ongoing treatment, treatment availability, acuity, transportation needs, and patient choice (SAMHSA, 2004). Pregnant women without insurance were eligible for Medicaid, which covered either medication over the course of the pregnancy. In general, women who conceived while participating successfully in an opioid maintenance program were treated through the pharmacy. In each setting, methadone was administered daily. Mothers treated through the pharmacy were referred for counseling in the community. Mothers treated at the opioid treatment program had counseling and mental health assessment within the program. Buprenorphine maintenance was provided by an obstetric provider (n = 190), a treatment center (n = 24), or a community provider (n = 134) (undocumented, n = 13). Counseling was recommended to all women receiving buprenorphine, with social work visits to assist in coordination.

After initial stabilization on selected medication, the medication dose was increased incrementally during pregnancy on the basis of reported withdrawal symptoms and clinical assessment. Urine drug screens were performed weekly at the place of the opioid agonist medication provider and used for clinical decision making but were not available for analysis. Once medication was initiated, there was no medication change without a specific indication. During hospitalization for delivery and postpartum, women remained on their opioid maintenance therapy.

**Newborn Care**

All mothers receiving OATs were referred to the neonatal medical follow-up clinic during pregnancy for consultation. Upon delivery, newborns were hospitalized for assessment of NAS. Breastfeeding was encouraged, except for women actively using cocaine (no patients were HIV positive). While hospitalized, NAS assessments were conducted every 3 to 4 hours for at least the first 4 days postnatal (96 hours) using a 19-item modified Finnegan Scale (Jansson et al., 2009). Pharmacologic treatment was initiated for 2 consecutive total scores ≥9 or one score > 13. The majority of newborns requiring pharmacologic treatment for neonatal abstinence symptoms at our university-affiliated hospital are treated in an outpatient setting using methadone, once stabilized in the inpatient setting.

**Variables**

The 609 mother–newborn dyads included in the study were classified as either methadone or buprenorphine according to the mother’s OAT type at delivery. Variables regarding maternal characteristics, prenatal care, and newborn outcomes were measured and compared for these 2 study groups.
Maternal characteristics included age at delivery (in years), hepatitis C positive (yes/no), nulliparous (yes/no), smoking during pregnancy (yes/no), and number of cigarettes smoked per day during the third trimester.

Prenatal care characteristics included EGA in weeks at initial prenatal care visit, prenatal care initiated in the first trimester (yes/no), adequate prenatal care received (yes/no) according to Kotelchuck index (Kotelchuck, 1994), maternal body mass index (BMI) at initial prenatal care visit, maternal weight change in pounds during pregnancy, and delivery method (cesarean section vs other). Information regarding OAT initiation was measured, categorizing initiation as prior to conception (yes/no).

Statistical Analysis
All analyses were conducted using Stata 12.0 (StatCorp, College Station, TX).

Descriptive statistics were used to describe the characteristics of the mother–newborn dyads included in the study cohort. Both parametric and nonparametric univariate analyses were performed to identify significant differences ($P < 0.05$) between the methadone- and buprenorphine-treated groups. Additional multivariate analyses were conducted using variables that were identified as significant in the univariate analyses to determine whether they remained significant in the multivariate setting.

RESULTS
This study included 609 mother–newborn dyads treated for opioid dependence during pregnancy using methadone or buprenorphine. The distribution of women on OAT at delivery and treatment from 2000 to 2012 are reflected in Figure 1. Maternal characteristics are outlined in Table 1. Nulliparous mothers were more often treated with buprenorphine; hepatitis C was more prevalent in mothers treated with methadone. The prevalence of smoking was greater than 80% in both groups. Differences in nulliparity and hepatitis C status remained significant in the multivariate analysis controlling for year of birth, maternal age, and smoking during pregnancy.

Indices of prenatal care are presented in Table 2; entry into prenatal care was similar between the 2 groups, with more than 65% of mothers initiating prenatal care in the first trimester. Mothers treated with buprenorphine were more likely to receive adequate prenatal care, as defined by Kotelchuck (1994). This significant difference persisted in the multivariate analysis while controlling for EGA at initial visit, BMI, pregnancy weight change, gestational age OAT initiated, year of birth, maternal age, and smoking during pregnancy. Body mass index and pregnancy weight change were similar between the 2 groups. Delivery methods were also similar between the 2 groups, with approximately 30% of women delivering via cesarean section.

Women treated with buprenorphine were more likely to be on an OAT at the time of conception. For those women not in treatment before pregnancy, OAT with buprenorphine was initiated at an earlier gestational age compared with methadone.

Nineteen women changed their OAT type during pregnancy from buprenorphine to methadone. Eleven of these women were transitioned to the more intensive and structured methadone program because of illicit use of other substances ($n = 7$) or noncompliance with appointments or counseling ($n = 4$). Five women requested the change because of suboptimal control of symptoms or other medication-related effects ($n = 3$) or because they could not be certain that buprenorphine would be available for longer than the immediate postpartum period ($n = 2$). Three women were switched for unknown reasons. We identified 4 women who were treated with buprenorphine early in pregnancy but not in treatment at delivery (and not included in the study). Of these women, one weaned (self-directed); one was not compliant with office-based treatment, declined alternative treatment, and left the practice; and 2 were lost to follow-up after buprenorphine initiation. No women were transitioned from methadone to buprenorphine.

Newborn outcomes are shown in Table 3. Maternal treatment with buprenorphine, when compared with methadone, was associated with significantly longer gestational age, reduced incidence of preterm birth, larger birth weight, and head circumference. Differences in gestational age and preterm birth remained significant in the multivariate analysis. Standardized birth weight and head circumference ($z$-scores) were similar between the 2 groups in the univariate analysis.

Buprenorphine-exposed newborns required medication for NAS less frequently and for a shorter duration compared with methadone-exposed newborns. These differences were significant in both the univariate and multivariate settings controlling for EGA at initial prenatal visit, adequacy of prenatal care, nulliparity, maternal BMI, maternal pregnancy weight change, gestational age maternal OAT initiated, year of birth, maternal age, and smoking during pregnancy. Buprenorphine-exposed infants had higher rates of breastfeeding at discharge. More than 95% of newborns in both groups were discharged to the care of the mother and/or family members. Two infants had congenital malformations at birth: one infant born to a mother who conceived while being treated with methadone had an absent hand; another infant born to a mother who conceived...
while being treated with buprenorphine had an isolated cleft palate.

Although not included in the study, it is interesting to note that 7 fetuses born to 6 mothers were stillborn. Of the 5 stillbirths born to 4 mothers (1 twin) treated with methadone, 1 mother had severe pneumonia with septic shock at 26 weeks, 1 mother presented for an ultrasound and was noted to have a fetal demise at 38 weeks with intrauterine growth restriction, 1 mother experienced uterine rupture at 32 weeks after a motor vehicle accident resulting in the birth of stillborn twins, and 1 mother presented in labor with a fetal demise at 26 weeks (she had been evaluated at another institution for a motor vehicle accident 24 hours before presentation). Of the 2 stillbirths born to buprenorphine-treated mothers, 1 mother had a complete abruption at 39 weeks, and the other had preterm rupture of membranes at 21 weeks followed by induction of labor.

**DISCUSSION**

Women treated with buprenorphine during pregnancy were more likely to (1) initiate OAT treatment before pregnancy or begin earlier in pregnancy, (2) deliver at term and have a longer duration of gestation, (3) deliver larger newborns with larger head circumferences, and (4) have newborns who did not require treatment for NAS or required treatment for NAS for a shorter duration compared with newborns exposed to methadone in utero. Overall, these results suggest treatment with buprenorphine during pregnancy in a clinical context (as opposed to a structured randomized trial) provides outcomes that are at least as favorable as methadone. The
significance of this cohort is the finding that office-based treatment during pregnancy can provide comparable pregnancy outcomes outside the confines of a tightly controlled clinical trial.

Comparisons of outcomes from randomized and nonrandomized trials often yield similar outcomes, but larger effect sizes are frequently observed in the nonrandomized studies (Ioannidis et al., 2001). Consistent with this pattern, the present nonrandomized study observed significant differences between medication conditions on a number of outcomes that trended toward significance in the randomized MOTHER study, including significantly longer gestation, lower rate of preterm delivery, and lower proportion of neonates requiring treatment for NAS among buprenorphine- as compared with methadone-treated women (Jones et al., 2010). One trend in the MOTHER study that was not borne out in the present study was a tendency for more women randomized to buprenorphine to drop out of the study prematurely, largely because of reports of dissatisfaction with the medication during the induction period. In our nonrandomized cohort, few women switched from buprenorphine to methadone because of dissatisfaction with buprenorphine; of those women inducted onto buprenorphine during pregnancy, only 3 of the 137 (2.2%) requested a change to methadone because of dissatisfaction with buprenorphine. We did not have any patient leave methadone treatment during pregnancy. These findings suggest that when women are considered candidates for office-based treatment on the basis of the general SAMHSA guidelines, there is a high chance of successful induction and treatment with buprenorphine during pregnancy. Our observations are quite reassuring for those who want to consider a stepped approach to the treatment of opioid dependence during pregnancy: identify patients who may be candidates for office-based treatment and switch only if needed for improved symptom control or a more structured program (Kakko et al., 2007).

Our findings are limited by the lack of randomization and retrospective nature of the data collection. In the practice of treatment, however, multiple issues are considered and multiple outcomes are of importance regarding patient outcomes from a chosen therapy. In this regard, a cohort study that allows for patient treatment selection and assessment of a wide range of outcomes (difficult in tightly controlled settings) and medication effectiveness are quite useful. We recognize the limitations of assessing causality in this study, which is optimally addressed by a randomized trial design (Ioannidis et al., 2001).

Our database may have missed women who initiated treatment but were lost to follow-up before entry into the database. We identified 3 women in whom buprenorphine was initiated but were lost to follow-up. Nonetheless, our findings are reflective of the approach many communities may have in the treatment of opioid-dependent women during pregnancy. Overall, our data demonstrated a high degree of compliance with prenatal care and continuation of treatment for women initiated or maintained on buprenorphine during pregnancy. It is of note that a large majority of our neonates were discharged into the care of a family member at birth. This is possible in part because of close follow-up of all families for at least a year after birth in a state-supported program.

The present study is the largest cohort comparing pregnancy outcomes in women treated with methadone versus buprenorphine in the United States. Our findings are reassuring for opioid treatment in general, as both groups demonstrated good compliance with prenatal care and more than 95% of infants were discharged to the care of the mother or family. Because of the cohort size and reassuring outcomes, these data add significantly to the literature examining the efficacy and clinical effectiveness of buprenorphine for the treatment of opioid dependence during pregnancy and strongly support its use on the basis of standard clinical criteria for office-based treatment of opioid dependence.

CONCLUSIONS

Pregnancy outcomes of office-based treatment for opioid dependence during pregnancy with buprenorphine are at least comparable to outcomes observed with daily dosing with methadone. Neonatal abstinence is reduced in the patients treated with buprenorphine in this cohort.

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