

Prenatal Treatment and Outcomes of Women With Opioid Use Disorder

Susan B. Brogly, PhD, MSc, Kelley E. Saia, MD, Martha M. Werler, ScD, Emily Regan, BA, and Sonia Hernández-Díaz, DrPH, MD

OBJECTIVE: To describe the characteristics, treatment, and outcomes of pregnant women with opioid use disorder.

METHODS: Women attending an obstetric and addiction recovery clinic in Boston from 2015 to 2016 were enrolled in a prospective cohort study and followed through delivery (N=113). Buprenorphine or methadone was initiated clinically. The Addiction Severity Index was administered at enrollment. Prenatal and delivery data were systematically abstracted from medical charts.

RESULTS: Most women in the cohort were non-Hispanic white (80.5%) with a mean age of 28 years. Few women were married (8.9%). More than half of the cohort had been incarcerated, 29.2% had current legal involvement, and 15.0% generally had unstable housing. A majority (70.8%) were infected with hepatitis C and histories of sexual (56.6%) and physical (65.5%) abuse were prevalent. Regular substance used included heroin (92.0%), injection heroin (83.2%), other opioids (69.0%), marijuana (73.5%), alcohol (56.6%), and cocaine (62.8%).

Fifty-nine women (52.2%) were treated initially with prenatal buprenorphine and 54 (47.8%) with methadone; 49.6% also were taking concomitant psychotropic medications. Employment (0.766 ± 0.289) and psychological (0.375 ± 0.187) Addiction Severity Index scores were the highest, indicating the most severe problems in these areas. Opioid use relapse did not differ by treatment (44.7% overall). Thirteen (22.5%) of 59 women treated with buprenorphine transitioned to methadone mainly because of positive opioid screens. Overall, 23.0% (n=26) of the cohort discontinued clinical care. The number of pregnancy losses was small (three therapeutic abortions, four miscarriages, one stillbirth), with an overall live birth rate of 90.8% (95% CI 82.7–95.9).

CONCLUSION: These data on the social circumstances, substance use, treatment, and treatment outcomes of pregnant women with opioid use disorder may help clinicians to understand and treat this clinically complex population.

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From the Department of Surgery, Queen's University, Kingston, Ontario, Canada; and the Department of Obstetrics & Gynecology, Boston University, the Department of Epidemiology, Boston University School of Public Health, and the Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

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Corresponding author: Susan B. Brogly, PhD, MSc, Department of Surgery, Queen's University, 76 Stuart Street, Victory 3, Kingston, ON, Canada K7L 2V7; email: susan.brogly@queensu.ca.

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The opioid crisis is an ongoing public health issue in the United States and Canada. Of the 2.1 million initiators of opioid misuse annually in the United States, 1.2 million (57%) are women.^{1,2} Increases in opioid use among pregnant women also have been documented.³ Among pregnant women enrolled in Medicaid, 18.5% filled a prescription for an opioid during pregnancy in 2000 rising to 22.8% in 2007. Although women are increasingly affected by the opioid crisis, public health responses have not been geared toward women or pregnant women.^{1,4}

In a population-based survey of pregnant and nonpregnant women in the United States, less than 20% of these women with substance use disorder received any treatment.⁵ Furthermore, 39% of pregnant women with opioid use disorder admitted to a federally funded U.S. treatment facility in 2012 received opioid agonist therapies such as buprenorphine or methadone.⁶



Similarly, only 41% of pregnant women with a diagnosis of opioid dependence enrolled in Medicaid in Massachusetts had any opioid agonist therapy prescription in the year before delivery.⁷ Health care providers who care for women must be prepared to assess and evaluate opioid use, misuse, and addiction.¹ A recent survey of the American College of Obstetricians and Gynecologists fellows and junior fellows identified a need to improve obstetrician–gynecologists’ knowledge of opioid use, misuse, and best prescribing practices.⁸

Although ample research has focused on the outcomes of neonates born to women with opioid use disorder, less attention has been given to the women themselves. To provide insight to the characteristics, treatment, and outcomes of this growing population, we describe a prospective cohort of pregnant women with opioid use disorder. We recruited this contemporary cohort from patients attending the largest volume clinic of pregnant women with opioid use disorder in New England.

MATERIALS AND METHODS

We conducted a prospective cohort study of pregnant women and their neonates. The study population was recruited from pregnant women attending the Project RESPECT (Recovery–Empowerment–Social Services–Prenatal Care–Education–Community–Treatment) Clinic in 2015 and 2016. Project RESPECT is a multidisciplinary treatment team at Boston Medical Center consisting of three obstetric care providers, a psychiatrist, a psychiatry nurse practitioner, and a licensed independent clinical social worker. Boston Medical Center is an urban safety net hospital with a labor and delivery unit, high-risk maternal-fetal medicine inpatient service, a level 3 neonatal intensive care unit, and a pediatric inpatient ward for neonates with neonatal abstinence syndrome. Project RESPECT operates in conjunction with local and regional methadone clinics, counseling centers, and residential treatment programs for pregnant women. Maternal criteria for opioid agonist therapy at Project RESPECT included being 18 years of age or older (the Boston Medical Center adolescent clinic cares for pregnant patients with opioid use disorder who are younger than 18 years of age), *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* diagnosis of substance dependence for opioids, laboratory or ultrasonographic documentation of pregnancy, and voluntary consent to engage in Project RESPECT’s comprehensive treatment program. The clinical protocol generally followed at the study site was to initiate the type of opioid agonist therapy chosen by the patient unless medically contraindicated.

Clinical providers generally did not recommend methadone over buprenorphine (ie, buprenorphine alone, Subutex) for pregnant women unless the patient preferring buprenorphine was previously or recently was unsuccessful with buprenorphine treatment. Per the clinical practice protocol, women were scheduled for prenatal care and relapse prevention visits every 1–3 weeks through delivery. Observed urine drug tests were done at each prenatal visit and on admission to labor and delivery. If an appointment was missed, women were contacted and requested to come in for a urine drug test within 48 hours.

Women attending Project RESPECT were eligible for study participation if they were not in legal detention at enrollment, were 18 years of age or older, intended to carry the pregnancy to term, intended to receive prenatal care and deliver at Project RESPECT, and were able to provide informed consent. Women were recruited at opioid agonist treatment initiation or at the first prenatal visit (for women who were on treatment at conception); some women were recruited at subsequent visits if they presented for care on a weekend or could not be interviewed at the first prenatal visit. This study was approved by the Boston University Medical Center institutional review board.

A research assistant administered the Addiction Severity Index, 5th Edition Lite—which has been widely used in patients with substance use disorders since the 1980s⁹—to women at study enrollment. The Addiction Severity Index included questions pertaining to seven domains: medical status, employment and support, drug use, alcohol use, legal status, family–social status, and psychiatric status. Interviewer ratings were summed across particular domain questions to indicate the degree of patient-reported problems in each domain.⁹ The composite scores in each domain ranged from 0 (no problems) to 1 (severe problems). Prenatal data including opioid agonist treatment use (date of initiation, starting dose, and dosing changes), urine toxicology screen results, concomitant prenatal medication use, and pregnancy outcomes were systematically abstracted from maternal medical charts from enrollment through delivery.

Differences in treatment outcomes (eg, adherence to clinical care, urine screen results, opioid agonist therapy cessation) by first prenatal treatment with buprenorphine or methadone were assessed statistically using the Fisher exact test. The Wilcoxon signed-rank test was used to statistically assess changes in opioid agonist therapy dose from early pregnancy to delivery. The proportion of pregnancies that ended in miscarriage (defined as an unintended pregnancy loss



at less than 23 5/7 weeks of gestation) or therapeutic abortion was calculated among women enrolled in the cohort in the first trimester of pregnancy. The proportion of pregnancies that ended in stillbirth (defined as a pregnancy loss at 23 5/7 weeks of gestation or greater) was calculated by dividing the number of stillbirths by the total number of stillbirths and live births. The proportion of pregnancies that ended in a live birth was calculated by dividing the number of live births by the total number of pregnancies that had a known outcomes (ie, women lost to follow-up in clinical care were excluded). These were reported as the proportion \times 100% with the corresponding exact binomial 95% CI. Analyses were performed using SAS 9.3 and Stata Intercooled 11.0.

RESULTS

From February 2015 through April 2016, 115 pregnant women with opioid use disorder attending the study clinic were enrolled in the cohort. Seven women (5.7%) who were approached declined to participate. An additional seven eligible women who were approached were not enrolled because they did not complete opioid agonist therapy titration or were admitted and discharged on a weekend and did not present for prenatal care again. Of the 115 women enrolled, two were subsequently found to be ineligible and were excluded, leaving 113 women in the study cohort.

The sociodemographic and clinical characteristics of the 113 women in the cohort are shown in Table 1. Most women were non-Hispanic white (80.5%) with a mean age of 28 years. Women had, on average, 12 years of education, and few were married (8.9%). More than half of the cohort had ever been incarcerated, 29.2% had current legal involvement (were on parole, had charges pending, or were incarcerated in the past 30 days), and 15% generally had unstable housing. Most women were multiparous and multigravida. A majority of the cohort (70.8%) was infected with hepatitis C. Histories of sexual abuse (56.6%) and physical abuse (65.5%) were prevalent. Fifty-nine women (52.2%) were treated initially with buprenorphine and 54 (47.8%) with methadone, and 49.6% also were taking concomitant psychotropic medications.

Polysubstance use was common among the cohort (Table 2). Almost all women smoked (86.7%) and had ever regularly used heroin (92.0%) and injection heroin (83.2%). Women also reported ever having regularly used marijuana (73.5%), opioids other than heroin (69.0%), alcohol (56.6%), and cocaine (62.8%). A history of methadone treatment was reported by 59.3% of the women.

Table 1. Demographic and Clinical Characteristics of 113 Pregnant Women With Opioid Use Disorder in the Study Cohort

Characteristic	Distribution
Age (y)	28.3 \pm 4.4
Race	
Non-Hispanic white	91 (80.5)
Non-Hispanic black	11 (9.7)
Hispanic	11 (9.7)
Years of education	12.0 \pm 1.7
Employment income	30 (26.5)
Income from illegal activity	21 (18.6)
Income from social assistance	69 (61.1)
Trimester of cohort enrollment	
1st	48 (42.5)
2nd	45 (39.8)
3rd	20 (17.7)
Married	10 (8.9)
Ever incarcerated	58 (51.3)
Parole, charges pending or incarcerated 30 d before enrollment	33 (29.2)
Generally had unstable housing in the past 3 y	17 (15.0)
Gravida*	
1	22 (19.5)
2–3	49 (43.4)
4 or greater	42 (37.2)
Parity	
0	43 (38.1)
1	33 (29.2)
2–3	34 (30.1)
4 or greater	3 (2.7)
Singleton pregnancy	108 (95.6)
Hepatitis C infection	80 (70.8)
Ever been sexually abused	64 (56.6)
Ever been physically abused	74 (65.5)
Initial prenatal opioid agonist therapy	
Buprenorphine	59 (52.2)
Methadone	54 (47.8)
Psychotropic medications	
Any	56 (49.6)
SSRI	23 (20.4)
Benzodiazepines	27 (23.9)
Anticonvulsant	26 (23.0)
Other	33 (29.2)

SSRI, selective serotonin reuptake inhibitor.

Data are mean \pm SD or n (%).

* Includes current pregnancy.

The prenatal treatment of the 59 women initially treated with buprenorphine and the 54 with methadone is detailed in Table 3. Within each treatment group, women who were on treatment at conception had a significantly higher daily dose at conception than the initiation dose for those who started treatment prenatally. More women in the buprenorphine group than in the methadone group had at least one urine toxicology screen after opioid agonist therapy initiation (98.3% vs 87.0%, $P=.027$). The mean total



Table 2. Substance Use Histories of 113 Pregnant Women With Opioid Use Disorder in the Study Cohort*

Characteristic	Distribution
Smoking recorded in medical record	98 (86.7)
Self-reported ever regularly used*	
Alcohol	64 (56.6)
Heroin	104 (92.0)
Heroin injection	94 (83.2)
Methadone	67 (59.3)
Other opioids	78 (69.0)
Cocaine use	71 (62.8)
Cocaine injection	30 (26.5)
Marijuana	83 (73.5)
Self-reported age at first use (y)	
Alcohol	13.9±2.6
Heroin	20.4±4.3
Other opioids	17.7±3.5
Cocaine	17.5±3.9
Marijuana	13.7±1.9
Self-reported lifetime y of regular use*	
Alcohol	5.3±4.6
Heroin	6.0±4.1
Methadone	2.3±2.5
Other opioids	3.3±3.1
Cocaine	4.1±3.9
Marijuana	6.5±5.3
ASI scores	
Alcohol	0.027±0.121
Drug use	0.217±0.142
Employment	0.766±0.289
Family and social	0.190±0.226
Medical	0.171±0.260
Legal	0.156±0.241
Psychologic	0.375±0.187

ASI, Addiction Severity Index.

Data are n (%) or mean±SD.

* Regular use on the ASI refers to use three or more times per week, binges, or problematic irregular use in which normal activities are compromised.

number of toxicology screens was higher in the buprenorphine than methadone group (12.7 vs 7.6, $P<.001$). Among women with at least one urine toxicology screen, the proportion with continued opioid use or relapse did not differ by prenatal treatment (44.7% overall). Buprenorphine-treated women, however, were less likely to have urine screens positive for cocaine than methadone-treated women (12.1% vs 27.7%, $P=.049$).

Of the 59 women in the buprenorphine group, 13 (22.0%) were transitioned to methadone treatment because of urine screens positive for opioids ($n=9$), incarceration ($n=3$, all of whom also had positive urines screens before incarceration), or adverse treatment effects ($n=1$). Three women transitioned to methadone in the first trimester of pregnancy, five

in the second trimester, and five in the third trimester. One woman who initiated treatment with buprenorphine was transitioned to methadone for 12 days while incarcerated and then resumed care at the study clinic and transitioned back to buprenorphine. Finally, one woman in the buprenorphine group was initially treated with methadone at the study site, but 3 days after treatment initiation, she transitioned to buprenorphine at another clinic and subsequently continued to be cared for at the study site on buprenorphine.

A small proportion of women had interruptions in their opioid agonist therapy during pregnancy or were weaned off treatment before delivery (one woman treated with buprenorphine and two treated with methadone; Table 3). The daily dose significantly increased from early pregnancy to delivery in both the buprenorphine and methadone groups. Finally, 23.0% of women did not continue clinical care and thus were lost to follow-up. Compared with women who continued clinical care, those who were lost to follow-up were more likely to have legal involvement 30 days before cohort enrollment (46.2% vs 24.1%, $P=.048$), less likely to use other opioids (53.9% vs 73.6%, $P=.089$), and more likely to have greater mean Addiction Severity Index drug (0.288 vs 0.195, $P=.004$), family (0.308 vs 0.155, $P=.008$), and legal (0.234 vs 0.133, $P=.017$) scores.

The absolute number of pregnancy losses was small (Table 4). Among women who enrolled in the study cohort in the first trimester, two women in the buprenorphine group and one in the methadone group underwent therapeutic abortions, and four women the buprenorphine group miscarried. One woman in the methadone group had a stillbirth at 35 5/7 weeks of gestation. The remaining pregnancies were live births. Five women delivered at a site other than the study clinic because of admission to a residential treatment program outside of the area and a coordinated transfer of prenatal-obstetric care ($n=2$), overdose and cardiac arrest ($n=1$), withdrawal from residential treatment and clinical care ($N=1$), ambulance transport to the closest hospital at delivery ($n=1$), and unknown ($n=1$). Finally, in terms of neonatal outcomes, among liveborn neonates, 20.3% were born preterm and 73.1% were pharmacologically treated for neonatal withdrawal.

DISCUSSION

We describe a contemporary cohort of pregnant women treated for opioid use disorder enrolled and followed at a high-volume obstetric and addiction recovery clinic in Boston. The complexity of this



Table 3. Treatment and Outcomes of Pregnant Women With Opioid Use Disorder by Initial Opioid Agonist Therapy

Treatment or Outcome	Buprenorphine (n=59)	Methadone (n=54)	P
Time of opioid agonist therapy initiation			.158
Before conception	20 (33.9)	18 (33.3)	
1st trimester	20 (33.9)	15 (27.8)	
2nd trimester	16 (27.1)	11 (20.4)	
3rd trimester	3 (5.1)	10 (18.5)	
Dose among women on opioid agonist therapy at conception	16.2±4.4	79.2±34.9	—
Dose at prenatal initiation among pregnancy initiators	10.4±4.3	55.6±22.0	—
1 or more urine toxicology screens after opioid agonist therapy initiation	58 (98.3)	47 (87.0)	.027
No. of urine toxicology screens after opioid agonist therapy initiation*	12.7±6.9	7.6±5.1	<.001
1 or more urine toxicology screen positive after opioid agonist therapy initiation*			
Opioids	27 (46.6)	20 (42.6)	.698
Cocaine	7 (12.1)	13 (27.7)	.049
Other nonprescribed licit or illicit drugs	9 (15.5)	11 (23.4)	.329
Lost to follow-up in clinical care	11 (18.6)	15 (27.8)	.271
Stopped opioid agonist therapy			
1 time or more	6 (10.2)	4 (7.4)	.745
Not on opioid agonist therapy at delivery [†]	1 (2.1)	2 (5.1)	
Dose at delivery [†]	14.7±5.4	97.9±39.1	—

Data are n (%) or mean±SD unless otherwise specified.

* Women with at least one urine toxicology screen after treatment initiation.

[†] Women with delivery information and includes those who underwent therapeutic abortion or miscarried.

patient population in terms of their social and living conditions, their addiction and its treatment, and their treatment outcomes is presented.

As evident from our data, obstetric care providers have the challenge of addressing multiple substance use and the effects of these substances on both the pregnant women and the fetus. Opioid exposure is associated with preterm birth, neonatal abstinence syndrome, and vision abnormalities.^{10,11} Prenatal cocaine use has been associated preterm birth, low birth weight, small head circumference, fetal growth restriction, placental abruption, prelabor rupture of membranes, and maternal migraines and seizures.^{12,13} Similarly, pregnant women who smoke have an increased risk for ectopic pregnancy,

prelabor rupture of membranes, placental abruption, placenta previa, and stillbirth.¹⁴ Risks to the fetus include preterm birth, low birth weight, intrauterine growth restriction, birth defects such as cleft lip or palate, and sudden infant death syndrome.¹⁴ This polysubstance exposure, in addition to prescribed psychotropic medications, may exacerbate the assessment, treatment, and risk of neonatal opioid withdrawal.^{15,16} The risks of poor pregnancy outcomes in women who use substances likely reflect not just the substances themselves, but also the social and environmental circumstances that surround substance use.¹⁷

A majority of women in our cohort had experienced physical abuse and sexual abuse. Studies have

Table 4. Pregnancy Outcomes of Women With Opioid Use Disorder

	Initial Prenatal Opioid Agonist Therapy		Overall Rate (95% CI)*
	Buprenorphine	Methadone	
Therapeutic abortion	2	1	6.3 (1.3–17.2)
Miscarriage	4	0	8.3 (2.3–20.0)
Stillbirth	0	1	1.4 (0.0–7.7)
Live birth	42	37	90.8 (82.7–95.9)

* Denominator for miscarriage and therapeutic abortion is women who enrolled in the cohort in the first trimester of pregnancy only; denominator for live births is pregnancies with a known outcome; denominator for stillbirths is stillbirth plus live births; rate is the proportion×100%.



shown deleterious sequelae of abuse including cognitive deficits, depression, dissociative symptoms, maladaptive sexual development, high rates of obesity, dropping out of high school, persistent posttraumatic stress disorder, self-mutilation, physical and sexual revictimization, premature delivery, drug and alcohol use disorders, and domestic violence among others.¹⁸ Obstetricians are in a unique position to respond to sexual abuse disclosure, even when a woman declines mental health referral.¹⁹ Guidelines exist so that obstetricians can make preparations and modifications to help the patient cope with stressors that may arise during prenatal care or delivery.^{20,21} Long-term counseling and the involvement of expertise in abuse counseling for these pregnant women with opioid use disorder are recommended.¹⁹

The multitude of issues faced by these women in pregnancy likely cannot be addressed and resolved in the prenatal period alone. Comprehensive, postnatal medical care, counseling, and social support should be accessible for all women. Few women in our study had legal employment and employment problems were significant as measured by the Addiction Severity Index. Evolving current treatment approaches to address employment, financial insecurity, and safe housing should be considered. With the growth of this population, it is critical to create a compassionate comprehensive care model for women to address the complex physical, emotional, social, and environmental characteristics of addiction.^{22,23} Although the obstetric care provider appropriately manages the medical and obstetric consequences that may arise from these many issues, a multidisciplinary team is needed.

Although fewer methadone- than buprenorphine-treated women had a urine toxicology screen after opioid agonist therapy initiation and there were fewer tests per woman in the methadone group, we observed higher continued cocaine use or relapse—as detected by urine screens—in women treated with methadone than buprenorphine. This likely reflects the higher prevalence of concomitant cocaine dependence in women treated with methadone at our site. Importantly, we found no clinically or statistically significant difference between the buprenorphine- and methadone-treated groups in opioid use, consistent with observations in a prior randomized controlled trial (RCT) of pregnant women.²⁴ The rate of continued opioid use or relapse overall in our clinical cohort was 44.7%, which is higher than the rate among women in the RCT (9% buprenorphine, 15% methadone). This is expected given that 84% of opioid-

dependent pregnant women receiving care at the RCT sites were excluded from the RCT as a result of eligibility criteria or nonparticipation,¹² whereas few women who presented for care at our study site during the recruitment period did not enroll in our study cohort. Compared with women in the RCT, more women in our cohort were Hispanic and fewer were white, and the duration of heroin and cocaine use was considerably longer; Addiction Severity Index drug and alcohol scores were similar among women in the two studies.

Buprenorphine treatment failure, described as transition to methadone because of continued opioid use or relapse, occurred in 22.0% of the study cohort, which is higher than the rate of 1.5% observed at our clinic from 2006 through 2010.²⁵ This may reflect changes in the clinic protocol to offer buprenorphine as a treatment option, even for women with higher risk profiles, in an effort to expand buprenorphine access and increase patient autonomy. Some women with opioid use disorder may not have been adequately treated by the partial agonist effects of buprenorphine and required transitioned to the full opioid agonist effects of methadone to adequately manage symptoms.

The complex needs of these pregnant women pose challenges for both the patient and obstetrician. Even at a dedicated high-risk obstetric and addiction recovery clinic with a multidisciplinary treatment team, 23.0% discontinued prenatal care and were lost to follow-up. The challenging circumstances of pregnant women with opioid use disorder observed in our cohort may have contributed to discontinuation of clinical care. In addition, although some women continued prenatal care at the study site, delivery sometimes occurred at other sites as a result of the need for urgent care or changes in residential treatment programs.

The problem of opioid use and addiction during pregnancy has become prominent in recent years.^{26,27} Our study provides insight on the clinical complexity of pregnant women with opioid use disorder treated at a leading U.S. clinic that serves the largest population of Medicaid patients in Massachusetts.²⁸ Compared with other settings in the United States, our clinic may have more women with high Addiction Severity Index scores arising from low socioeconomic status, urban environment, or social determinants of health (ie, women with a longer history of substance use). In addition, patient choice and access to treatment with buprenorphine or methadone may differ in other prenatal settings. These data may, however, provide insight to prenatal care providers.



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