Current Obstetrics and Gynecology Reports (2019) 8:9–14
https://doi.org/10.1007/s13669-019-0255-9

HIGH-RISK OBSTETRICS (T MCELRATH, SECTION EDITOR)

Caring for Pregnant Women with Opioid Use Disorder

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Published online: 6 March 2019

Abstract

Purpose of Review The US opioid epidemic continues historic trends of disproportionately affecting women. However, attention to the rise in neonatal opioid withdrawal syndrome (NOWS) and other types of neonatal care often overshadow the urgent need for improved and more wide-ranging maternal treatment in the peripartum period.

Recent Findings This review aims to highlight the trends in maternal morbidity and mortality related to substance use disorder (SUD), to discuss the under-funding of woman-focused interventions, and to discuss medication-assisted treatment (MAT) options for women with SUD. We found that the rates of pregnancy-related mortality are highest for SUD-related deaths and remains at crisis levels.

Summary Women continue to face barriers to treatment access, and there is a critical need to provide new mothers in recovery with more comprehensive and supportive care in the peripartum period.

Keywords Maternal mortality · Substance use disorder · Opioid use disorder · Postpartum · Drug overdose · Pregnancy-related mortality

Introduction

The opioid epidemic in the USA has become one of the deadliest and most stigmatized healthcare crises in our recent history. Nearly 30,000 Americans died of opioid drug overdoses in 2017, largely due to the illicit availability of the potent opioid, fentanyl [1]. The financial burden of the opioid epidemic on the US economy is nearly 80 billion dollars annually, which includes the cost of medical care, drug treatment, and law enforcement intervention [2]. Despite national attention and increased funding to address this devastating disease, the epidemic shows little signs of slowing [3–6].

Historically, women have been quietly and disproportionately affected by opioid overprescribing. In the late 1800s, American doctors routinely prescribed opium to women for all types of gynecologic-related pain and "female ailments," including dysmenorrhea, hyperemesis, and "hysteria." Almost all opioid formulations were explicitly marketed to women and children [7]. During this period, an estimated 60% of Americans dependent on opium were women [8, 9] and this pattern of gender-specific overprescribing continues today [10, 11]. Even during pregnancy, women are commonly prescribed opioids. In 2007, one in five pregnant women in the USA filled a prescription for opioid pain medication [12]. By 2010, 90% of admissions for opioid use disorder (OUD) treatment were among women [13]. Furthermore, the rate of opioid overdose mortality has been increasing more rapidly for women than for men; between 1999 and 2010, there was a fivefold increase in opioid overdose mortality for US women [14].

The majority of women affected by the opioid epidemic are young and of reproductive age. Women with OUD and are less likely to use reliable contraception than women who do not use opioids [15, 16] and unplanned pregnancies in this population reach 80%, considerably higher than the general population [17]. The rise in OUD combined with high rates of unplanned pregnancies in this population has culminated in the current obstetric and pediatric care crises of treating perinatal OUD.

The standard of care for pregnant women with OUD is medication-assisted treatment (MAT) using methadone or buprenorphine, combined with behavioral healthcare and relapse prevention throughout the pregnancy [18, 19]. Maternal engagement in prenatal MAT treatment, while lifesaving, has increased the incidence of neonatal abstinence syndrome (NAS) or more specifically neonatal opioid withdrawal

This article is part of the Topical Collection on *High-risk Obstetrics*

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syndrome (NOWS) [13, 20]. NAS/ NOWS is a newborn neurobiological withdrawal response to transitioning from in utero maternal medication exposure to extra-uterine life. Depending on exposure type, the onset of NAS/ NOWS symptoms ranges from 48 h to 4 days and can require up to 3 weeks of in-hospital treatment [21]. Advances in non-pharmacologic care including swaddling, rooming-in, and breastfeeding have decreased length of in-hospital stay for the newborn, severity of NAS/ NOWS symptoms, and need for medication treatment [22–24].

National attention to the rise in NAS and associated neonatal care required in the wake of the opioid epidemic often overshadows the urgent need for improved maternal treatment. Between 2008 and 2018, the National Institute of Health (NIH) funded 21 projects focused on perinatal OUD in the USA, totaling $11.7 million in grants. Seven projects focused on both maternal and neonatal outcomes, receiving $4.4 million in funding (37%). Ten projects investigating NAS and neonatal outcomes received $6.1 million, 52% of total funding. The remaining four projects that focused solely on maternal interventions and outcomes received $1.2 million, 10% of total funding. New estimates of maternal mortality in the opioid epidemic create urgency for national attention and the need for more robust funding to develop innovative approaches to caring for pregnant and parenting women with OUD (Table 1) [25].

Opioid Use Disorder and Pregnancy-Associated Mortality

In 2000, the estimated US maternal mortality rate (deaths per 100,000 live births) was 18.8; in 2014, this estimate increased to 23.8 [26]. Conventionally, pregnancy-related hypertension, thrombotic events, sepsis, hemorrhage, and more recently cardiovascular etiologies have been the leading causes of maternal morbidity and mortality [27]. Recent reports outlining etiologies of maternal morbidity and mortality show a striking rise in trauma, self-harm, and drug overdose. Accurate estimates of maternal mortality can be difficult to ascertain and is reflective of the definitions employed to extract the data. An "obstetric-related death" refers to mortality occurring 6 weeks or less from date of delivery and "pregnancy-related mortality" refers to deaths of pregnant women within 1 year of delivery. Traditionally, trauma-related deaths during the postpartum period were not included under the "pregnancy-related mortality" umbrella. In response, the category of "pregnancy-related deaths" was designed to capture trauma-related deaths within 365 days of delivery. In a 2017 analysis by Kilpatrick et al., the author laments "many if not most trauma-related deaths remain uncaptured" [28•]. Despite the expanded terminology, estimates of maternal mortality from trauma remain inaccurate [29]. In 2005, Chang et al. outlined the previously under-reported pregnancy-related injuries and deaths in the USA and showed that homicide was the leading cause of these fatalities [30]. Newer data highlights an emerging trend of drug overdose deaths as the highest risk of pregnancy-related mortality.

In 2013, Hardt et al. tracked "pregnancy-associated, non-natural deaths" in Florida from 1995 to 2005 using "Florida's Pregnancy-Related Mortality Review"; 415 pregnancy-associated deaths were recorded with 385 associated toxicology reports. Drug overdose was the leading cause of pregnancy-associated deaths. Toxicology results showed prescription medications, particularly opioids, were more common than illicit drugs (54% vs. 45%) [31].

Mehta et al. (2016) described the increase in pregnancy-related mortality noted in Philadelphia, PA from 2010 to 2014. Of the 85 pregnancy-related deaths, nearly half (42 out of 85) were related to unintentional injury, suicide, or homicide, and 31 were due to unintentional injury (e.g., drug overdose and motor vehicle accident). The leading cause of death (58% of unintentional deaths) was directly attributable to drug overdose. High rates of maternal mental health disorders and intimate partner violence were also noted [32].

Metz et al. published a case series in 2016 on maternal mortality in Colorado which found "self-harm," defined as accidental overdose or suicide, was the leading cause of

Table 1 Total and average funding given to projects by the National Institute of Health (NIH) focusing on maternal and neonatal outcomes between 2008 and 2018

	Projects focusing on maternal outcomes	Projects focusing on neonatal outcomes	Projects focusing on both neonatal and maternal outcomes
# projects	4*	10‡	7◊
Average funding given	$1,183,636.00	$6,142,298.00	$4,400,523.00
Total funding given	$295,909.00	$558,390.73	$628,646.14

*NIH project numbers: 1R01CE002996-01, 5K23DA038789-03, 1R34DA045831-01A1, 1R03HD092825-01A1

‡ NIH project numbers: 3R01DA043519-02S1, 271201700065C-0-0-1, 271201700021C-0-0-1, 1R01DA043678-01A1, 2R01HD070795-06A1, 1R01DA047867-01, 5R01DA042074-03, 4R01DA029076-05, 5R21DA041706-02, 5K23DA038720-05

◊ NIH project numbers: 5R01DA044293-02, 1R01HD096796-01, 3R01DA041328-02S1, 1R01HD096800-01, 1R01DA047867-01, 1R01DA045675-01A1, 1R01HD096798-01

pregnancy-related mortality. From 2004 to 2012, Colorado experienced 211 maternal deaths, 63 of which (30%) were determined to be from drug overdose or suicide. Data were collected from state vital records, prenatal documentation, and delivery records. The pregnancy-associated death ratio (defined as deaths per 100,000 live births) for drug overdose was 5.0 (95% confidence interval [CI] 3.4–7.2) and 4.6 (95% CI 3.0–6.6) for suicide. 90% of fatalities occurred in the postpartum period and were equally distributed from 0 months to 1 year after delivery. 81% of women had engaged in and were compliant with prenatal care. 43% of women attended a postpartum visit. 16.9% of women were identified with a diagnosis of substance use disorder, 54% with a mental health disorder (majority of which were depression), and 10% with a history of prior suicide attempts. Nearly half of the women who were prescribed an antidepressant prior to pregnancy discontinued it in the antepartum period. 84.7% of the cases had toxicology results available in which opioids were detected most frequently, of which 42% were prescription pain medications. Social stressors including financial stress, single parenting, homelessness, and intimate partner violence were commonly found. While the authors stressed the need for improved prenatal screening, they recognized that 22% of the deaths were among women with no identifiable risks for self-harm [33•].

Between 2005 and 2014, the Massachusetts Department of Public Health data highlights a near fivefold increase in pregnancy-related mortality due to drug overdose with 90% of these deaths occurring between 42 and 365 days postpartum [34]. Schiff et al. analyzed this data for opioid overdose events in women with OUD documented in the year prior to delivery of a live-born infant between 2012 and 2014. A total of 4,154 live-born deliveries to women with OUD (2.3% of state total) were identified. A total of 242 opioid overdose events occurred in the 1-year window prior to and after delivery, 11 of which were fatal events. The overall rate of opioid overdose events was noted to be 8.0 per 100,000 person-days; the rate nadired in the third trimester at 3.0 per 100,000 person-days and peaked at 12.3 per 100,000 person-days in the 7–12-month postpartum period. Younger women who were unmarried, unemployed, homeless, poorly engaged in prenatal care, and had comorbid mental health disorders were at highest risk for overdose events. Opioid pharmacotherapy, with methadone or buprenorphine, was protective in lowering the rates of overdose events. However, women with OUD and concurrent anxiety or depression, regardless of whether they received medication-assisted therapy, showed higher rates of overdose events than for women without mental health diagnoses [35••].

The shifting maternal mortality landscape in the context of the opioid epidemic requires obstetric providers to expand their understanding of the disease of addiction and their scope of practice. Access to medication-assisted treatment for pregnant women with opioid use disorder is the vital first step to engaging this population in long-term recovery treatment.

Medication-Assisted Treatment Options for Perinatal Opioid Use Disorder

Methadone

Methadone, a full opioid receptor agonist, has been an accepted treatment option for perinatal OUD for decades in the USA [36, 37]. Methadone maintenance therapy (MMT), combined with recovery support services, is recommended by the American College of Obstetrics and Gynecology (ACOG) and Substance Abuse and Mental Health Services Administration (SAMHSA) for treatment of OUD during pregnancy [38, 39]. MMT has been shown to improve maternal and newborn outcomes when compared to methadone detoxification and recovery support services alone in pregnancy [40]. Pregnant women with OUD who engage in methadone treatment are more likely to attend prenatal care visits and more likely to have an in-hospital delivery than women who stop or taper off methadone during pregnancy [41].

Harm reduction models favor MMT stabilization for pregnant women regardless of gestational age. Initiating MAT treatment, even late in pregnancy, reduces maternal overdose risks [35••]. This harm reduction model also conveys neonatal benefit. A study in Ontario, Canada, of 1,842 pregnancies found no differences in "small for gestational age, preterm birth, congenital anomalies, severe maternal morbidity, caesarean section, and induced labour" between women who were stable on methadone prior to conception and those who began methadone treatment after conception. Women who began MMT after conception, however, had a fourfold increased risk of losing child custody than women stable on MMT prior to pregnancy [42]. Methadone remains a lifesaving treatment option for pregnant women with opioid use disorder by decreasing risks of drug overdose and promoting positive fetal outcomes.

Buprenorphine

Buprenorphine, a partial opioid receptor agonist, has gained first-line treatment status for perinatal OUD. It has been shown to be a safe and effective treatment of OUD in pregnancy [43]. Data on newborn outcomes show buprenorphine to be superior to methadone when comparing NAS/ NOWS symptom severity, duration of newborn hospital stays, and need for medication treatment for

NAS/ NOWS [44]. Compared to methadone, buprenorphine-exposed pregnancies have lower rates of preterm delivery, increased newborn head circumference, and increased birth weights [45]. Observational studies using the buprenorphine/naloxone formulation in pregnancy are now being conducted and show promising preliminary results with few risks associated with the mother or fetus [46, 47].

While still limited, the data showing safety of injectable and implantable naltrexone during pregnancy is growing [48–50]. Many treatment centers have implemented the use of buprenorphine/naloxone therapy for pregnant women citing the high risk of diversion with monotherapy and preliminary safety data [46]. SAMHSA's 2018 "Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants" states that although there is a growing body of evidence of safety in pregnancy, there is still insufficient evidence to recommend the combination buprenorphine/naloxone formulation use in pregnancy [51]. The experts cite concern for intravenous diversion of the combination product and risk of precipitated pre- and post-natal withdrawal given the intravenous bioavailability of naloxone. While further research investigating buprenorphine formulations in pregnancy is needed, the decision to include buprenorphine as a treatment option to pregnant women with OUD is clear. Expanding access to buprenorphine treatment for pregnant and postpartum women is vital. Obstetric providers can make a dramatic change in access to care for this vulnerable population by becoming waivered, or certified, to prescribe buprenorphine, which will allow for the collocation of prenatal care and addiction recovery treatment.

Discussion

The US opioid epidemic continues historic trends of disproportionately affecting women. National data show pregnant and postpartum women with OUD are experiencing a dramatic rise in pregnancy-related mortality. Review of data from Mehta et al. (2016), Metz et al. (2016), and Schiff et al. (2018) highlight three common themes regarding pregnancy-related mortality for this population: (1) they suffer from high rates of untreated or undertreated mental health disease, (2) they have high social stressors with minimal social supports, and (3) their risk of death peaks outside the traditional postpartum window.

Pregnant women with OUD continue to face barriers to treatment access and those who are able to find a comprehensive treatment program during pregnancy are routinely subject to a major transition of care postpartum. The standard of care in the USA for postpartum follow-up ends 42 days following delivery. This critical and vulnerable time for new mothers with OUD marks a dangerous intersection of increasing maternal mortality risk and programmed postpartum healthcare gaps.

While healthcare providers across the country struggle to engage pregnant women in treatment, we often lose sight of the tremendous risk of overdose mortality in the postpartum period. Approaching OUD in pregnancy as an acute disease, rather than the first step in the journey to long-term recovery and motherhood, has contributed to current situation of OUD as the leading cause of pregnancy-related mortality. Over the past decade, while we debated the particulars of acute treatment options, we lost sight of the chronicity of the disease. The intensity of medical care that patients receive during pregnancy is rarely continued after delivery—a period of time when new mothers in early recovery need us the most.

Optimizing treatment of NAS is of vital importance and there have been significant advances in improving the acute treatment of these newborns in recent years [52]. As crucial as it is to medically manage NAS/ NOWS in the acute transition period, the long-term outcomes for these infants rely heavily on the mental health and recovery stability of the mother. Developing treatment centers for perinatal substance use disorders and improving access to care for pregnant and postpartum women continues to require attention and funding. Obstetric providers struggle to meet this treatment need within the traditional prenatal care paradigms due to limited knowledge of local and regional resources, and lack of appropriate referral services and community-based systems for continuation of care [53]. Increased investments in research focused on improving maternal recovery engagement and long-term care for the mother benefits both her and her newborn. Our new mission should be focused on extending prenatal treatment programs and maternal recovery supports through the first two or more years of the baby's life with particular attention on treating maternal mental health disorders and strengthening community supports for new mothers in recovery. Without comprehensive, long-term, and sustainable recovery programs, pregnant and postpartum women with OUD will continue to struggle to survive.

Compliance with Ethical Standards

Conflict of Interest Yeon Woo Lee and Kelley Saia declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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