Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature

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Abstract

Prescription opioids are used prenatally for the management of pain, as well as for opiate dependency. Opioids are known to cross the placenta and despite the evidence of possible adverse effects on fetal development, studies have consistently shown prescription opioids are among the most commonly prescribed medications and the prevalence of use is increasing among pregnant women. This article summarizes the available literature documenting potential harms associated with prescription opioid use during pregnancy, including poor fetal growth, preterm birth, birth defects, and neonatal abstinence syndrome.

Keywords
► opioids
► pregnancy
► fetal growth
► birth weight
► birth defects
► neonatal abstinence syndrome

Therapeutic Use and Prescribing Patterns of Opioids

Opioids include a broad range of natural and synthetic alkaloid derivatives that act as agonists of at least one of the three types (mu [µ], lambda [δ], and kappa [κ]) of characterized opioid receptors.1 Activation of opioid receptors in both the central and the peripheral nervous system is responsible for the analgesic properties of opioids.2 Currently, marketed prescription opioids include codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocin, propoxyphene, buprenorphine, tapentadol, and tramadol. Based on their abuse potential, opioids are classified by the U.S. Drug Enforcement Agency as schedule II, III, or IV.3

Prescription opioid therapy is regarded as a valuable tool in physicians’ armamentarium for control of acute pain and for chronic pain due to various conditions, including cancer and terminal diseases.4 Guidelines from the American Pain Society and the American Academy of Pain Medicine, however, recommend careful consideration of benefits and risks associated with chronic opioid therapy for chronic noncancer pain before initiation.5 Nonetheless, chronic prescription opioid use for noncancer pain conditions has been on the rise in the United States over the last two decades. According to one estimate, the proportion of noncancer pain patients using chronic opioid therapy increased to 16% in 2005 from 9% in 2000 among Arkansas Medicaid enrollees.6 Another study reported a doubling in the rates of chronic opioid therapy between 1997 and 2005 among enrollees of two commercial health plans in Washington and California, United States.7 National estimates for the total number of opioid prescriptions dispensed also showed a 35% increase between 2000 and 2010.8 This increasing trend of prescription opioids in chronic noncancer pain is concerning because evidence for their effectiveness against chronic pain is weak9–12 and there is the potential risk of side effects (e.g., constipation, nausea, cardiac complications, respiratory depression, drug dependence) with long-term use.1
Two opioid agonists, methadone and buprenorphine, are indicated for the management of opioid dependence in pregnancy. Utilization rates of medication-assisted maintenance therapy with methadone and buprenorphine have increased over the last decade. However, according to Substance Abuse and Mental Health Services Administration, medication-assisted maintenance therapy is still underutilized, with only 40% of the opioid-abusing or dependent Americans who are 12 years or older receiving it in 2012.

### Prescription Opioid Use in Pregnancy

Opioid medications are used for a variety of conditions in pregnancy. Pain is a commonly reported indication in pregnancy; for example, the prevalence of low back and pelvic pain during pregnancy ranges from 68 to 72%. Additionally, other pain conditions such as myalgia, joint pain, and migraine are frequently reported. Pharmacologic treatment is frequently used for pain management during pregnancy. In addition to the nonsteroidal anti-inflammatory drugs, prescription opioids may provide an important option for managing acute pain during pregnancy. For chronic pain, however, American Pain Society guidelines suggest counseling women about the benefits and risks of chronic opioid therapy and recommend no use or minimal use in pregnancy, if possible.

As with many treatments used prenatally, fetal safety of opioid exposure during pregnancy is not well understood because clinical trials typically exclude pregnant women for ethical reasons and postmarketing data generated from observational studies are limited. As a result, most prescription opioids are currently classified by the Food and Drug Administration under category C for use in pregnancy, indicating evidence of potential harm to the fetus from animal studies and the absence of well-controlled human studies. One exception is oxycodone, which is currently classified in category B, indicating no evidence of harm to the fetus from animal studies and the absence of well-controlled human studies. For drugs approved after 2001, the newly issued Food and Drug Administration pregnancy label rule will replace the category designation with a narrative describing the available data on a given drug's risks and safety. It is hoped that this information will assist providers and their patients in making informed decisions about treatment options.

Despite evidence of adverse effects on fetal development from prescription opioids, studies from both Europe and the United States have consistently documented high rates of prescription opioid use during pregnancy, whether for medical indications or opioid dependency. Data from a population-based registry in Norway showed that 6% of the pregnant women filled at least one opioid prescription between 2004 and 2006. Results of numerous studies from the United States are more concerning. Analysis of prescription claims data for women enrolled in Tennessee Medicaid found that 29% of pregnant women filled a prescription for an opioid analgesic from 1995 to 2009. Similarly, another study using data from Medicaid-enrolled pregnant women from 47 states in the United States reported that 21.6% of the women filled at least one opioid prescription during their pregnancy. An increasing trend was also observed in this study, with the proportion of women filling prescription opioids during pregnancy increasing from 18.5% in 2000 to 22.8% in 2007. Data from pregnant women enrolled in commercial health plans across the United States also showed high rates (14.4%) of prescription opioid dispensing between 2005 and 2011. Some of the most commonly filled opioid agents reported in these studies were codeine, hydrocodone, oxycodone, and propoxyphene.

Fewer studies have described rates of chronic prescription opioid use (use ≥ 1 month) during pregnancy. In a cohort study of all deliveries at the Mayo Clinic from 1998 through 2009, <1% of the women were chronic opioid therapy users (167 of 26,314 total pregnancies). The corresponding rate from the study using nationwide Medicaid data was 2.5% (28,118 of 1,106,757 total pregnancies). Thus, the majority of prescription opioid use during pregnancy appears to be for management of acute pain.

For management of opioid dependence during pregnancy, maintenance therapy with methadone or buprenorphine is considered the standard of care; however, in 2012, only 37% of pregnant women reporting any prescription opioid abuse at admission to a substance abuse treatment received medication-assisted maintenance therapy.

In summary, use of opioids is common and increasing among pregnant women. It is imperative to understand the risks associated with both short- and long-term use of these agents during pregnancy. In this review, we summarize the evidence available in the literature documenting potential harms associated with prescription opioid use during pregnancy. Prescription opioids encompass a variety of medications and it cannot be assumed that the potential effects on the fetus are the same for all medications within a drug class. For this reason, we present the study results for individual opioids, when available in the original studies; however, in many studies opioids were assessed as a group due to small numbers and concerns over loss of statistical power.

### Fetal Growth

Altered fetal growth can be an indicator of harmful exposures during pregnancy. Several markers for fetal growth, such as birth length and birth weight, have been identified as strong predictors of mortality and adult health outcomes. Independent of birth weight, birth length is thought to be a unique measure of leanness and growth that is not fully captured by other measures. However, birth length is often not studied because the data are frequently unavailable, can be less reliable in certain situations (e.g., for ailing newborns) and are prone to measurement error. A study that examined birth length in relation to opioid use in pregnancy did not identify an association between the two. Head circumference, another marker of fetal growth, has also not been associated with opioid use.

Multiple birth weight measures are often employed to assess fetal growth restriction. Low birth weight (LBW), often...
Maternal codeine use was analyzed in another study, but no association was identified with all malformations examined as a group, and the authors were unable to assess individual malformations due to small numbers (40 exposed cases).\textsuperscript{44}

One of the largest studies published on opioid use in pregnancy used the Michigan Medicaid data and included 229,101 pregnancies from 1985 to 1992. For exposure to hydrocodone, 332 newborns were exposed in the first trimester and only cardiovascular defects had more cases than expected (five observed and three expected).\textsuperscript{47} Using data from the Swedish birth registry, investigators found an overall association of any malformation in the offspring with buprenorphine use early in pregnancy (OR: 3.0; 95% CI: 1.1–6.5) and specifically, an elevated OR was reported for clubfoot and trisomy 18 in early pregnancy (OR: 3.6; 95% CI: 1.7–6.6).\textsuperscript{43,48}

Given the rarity of birth defects, cohort studies have limited power both for birth defects overall and more importantly, for specific birth defects. For this reason, case–control studies are often more informative. The case–control design allows for efficient accrual of a large number of cases, which in turn allows investigators to classify cases into homogeneous groups (e.g., individual heart defects) based on pathogenetic and embryologic mechanisms.\textsuperscript{49} Proper classification of birth defects is essential to not only understanding the underlying etiology,\textsuperscript{49} but studying birth defects as a heterogeneous group could potentially obscure any associations, as it is unlikely an exposure will be linked to all types of birth defects. Independent of study design, it is necessary to assess maternal opioid use in the etiologically relevant time period, which for most birth defects occurs in the first trimester. Several case–control studies have focused on opioid use in early pregnancy and birth defects. The largest to date is the National Birth Defects Prevention Study (NBDPS), a population-based multisite case–control study.\textsuperscript{25} One of the major strengths of the NBDPS was the rigorous case classification conducted by clinical geneticists. Of the 17,499 mothers of cases with a birth defect, 454 (2.6%) reported opioid use. For exposure to this drug class, elevated ORs were identified for atrial septal defects, not otherwise specified (OR: 2.0; 95% CI: 1.2–3.6), atrioventricular septal defects (OR: 2.4; 95% CI: 1.2–4.8), conoventricular septal defects (OR: 2.7; 95% CI: 1.1–6.3), gastrochisis (OR: 1.8; 95% CI: 1.1–2.9), glaucoma/anterior chamber defects (OR: 2.6; 95% CI: 1.0–6.6), hydrocephaly (OR: 2.0; 95% CI: 1.0–3.7), hypoplastic left heart syndrome (OR: 2.4; 95% CI: 1.4–4.1), and spina bifida (OR: 2.0; 95% CI: 1.3–3.2). Associations were identified specifically for maternal codeine use in early pregnancy and atrioventricular septal defects (OR: 3.6; 95% CI: 1.3–10.2), left ventricular outflow tract obstruction defects (OR: 2.0; 95% CI: 1.1–3.5) and hypoplastic left heart syndrome (OR: 3.1; 95% CI: 1.4–6.9); maternal hydrocodone use and spina bifida (OR: 2.5; 95% CI: 1.3–4.8), atrioventricular septal defects (OR: 3.7; 95% CI: 1.3–10.4), tetralogy of Fallot (OR: 2.4; 95% CI: 1.2–4.8), hypoplastic left heart syndrome (OR: 3.2; 95% CI: 1.4–7.1), pulmonary valve stenosis (OR: 2.2; 95% CI: 1.2, 4.3), cleft palate (OR: 2.1; 95% CI: 1.1–3.9), and gastrochisis (OR: 3.3; 95% CI: 1.8–6.1);
| Reference         | Study design        | Location/study site                  | Outcomes studied                      | Exposure                  | Number of participants | Number exposed | Effect estimates (if available)                                                                 |
|-------------------|---------------------|--------------------------------------|---------------------------------------|---------------------------|------------------------|----------------|---------------------------------------------------------------------------------------------|
| Hadi et al (2006) | Case study, 1999–2002 | Ontario, Canada                      | Birth length, head circumference, and birth weight | Opioids                   | Mother–neonate pairs: 13 | Neonates: 13 | Growth markers were within normal ranges on standard growth charts                           |
| Källén et al (2013) | Cohort, 1996–2011   | Sweden                               | Birth weight and preterm delivery     | Opioids as a group, codeine, propoxyphene, and tramadol | Mother–neonate pairs: 1,575,847 | Neonates: 13,805 | Preterm delivery was associated with tramadol (OR: 1.3; 95% CI: 1.0, 1.6), but very preterm birth (< 32 wk) was not associated with opioid use. No association was observed for SGA or low birth weight; however, an association was identified for LGA and propoxyphene (OR: 1.4; 95% CI: 1.3, 1.7) and codeine (OR: 1.3; 95% CI: 1.1, 1.4) |
| Kelly et al (2011) | Chart review, 2009–2010 | Ontario, Canada                      | Birth length, head circumference, birth weight, and preterm delivery | Oxycodone                 | Mother–neonate pairs: 482 | Neonates: 61 | No significant difference between exposed and unexposed neonates for birth length (mean length: 51.1 cm in both groups), head circumference (mean circumference: 34.9 cm in both groups), and birth weight (mean weight: 3,516 and 3,591 g, respectively). Prevalence of preterm birth was higher in exposed (8.2%) than unexposed (2.3%) neonates |
| Nezvalová-Henriksen et al (2011) | Cohort, 1967–2008 | Norway                               | Birth weight and preterm delivery     | Codeine                   | Mother–neonate pairs: 67,982 | Neonates: 2,666 | No elevated estimate for codeine and low birth weight (OR: 1.1; 95% CI: 0.9, 1.3) or preterm delivery (OR: 1.1; 95% CI: 0.9, 1.3) |
| Smith et al (2014) | Cohort, 2005–2009   | Connecticut and Massachusetts, United States | SGA and preterm delivery             | Opioids, of which the majority was acetaminophen with oxycodone, codeine, or hydrocodone | Mother–neonate pairs: 2,748 | Neonates: 165 | No association was identified between opioid use and preterm birth (prevalence of preterm in both exposed and unexposed group was 11.5%). Neonates exposed to opioids in pregnancy were more likely to be SGA (11.5%) than unexposed neonates (7.8%) |

Abbreviations: CI, confidence interval; LGA, large for gestational age; NA, not available; OR, odds ratio; SGA, small for gestational age.
| Reference                  | Study design               | Location/study site                      | Outcomes studied                      | Exposure                          | Number of participants | Number exposed in first trimester | Effect estimates (if available)                                                                 |
|----------------------------|----------------------------|------------------------------------------|---------------------------------------|-----------------------------------|------------------------|----------------------------------|---------------------------------------------------------------------------------------------|
| Bracken and Holford (1981) | Case-control, 1974–1976   | Five major hospitals in Connecticut, United States | A spectrum of birth defects           | Opioids as a group and codeine    | Cases: 1,427 Controls: 3,001   | Neonates: 18                       | Opioids and inguinal hernia (OR: 4), central system anomalies/spina bifida (OR: 2.9), VSD/ASD (OR: 5.8), other heart and circulatory defects (OR: 8.4), cleft lip, palate (OR: 12.8), and dislocated hip/musculoskeletal defects (OR: 7.2) |
| Bracken (1986)             | Case-control, 1974–1976   | Five major hospitals in Connecticut, United States | CHDs                                  | Codeine                           | Cases: 330 Controls: 3,002    | Not available                     | Codeine and CHDs (OR: 2.4; 95% CI: 1.1, 5.2)                                               |
| Broussard et al (2011)     | Case-control, 1997–2005   | Ten states in the United States          | A spectrum of birth defects           | Opioids as a group, codeine, hydrocodone, oxycodeine, and meperidine | Cases: 17,449 Controls: 6,701 | Cases: 454 Controls: 134           | Opioids and conoventricular septal defects (OR: 2.7; 95% CI: 1.1, 6.3), atriovenous septal defects (OR: 2.0; 95% CI: 1.2, 3.6), hypoplastic left heart syndrome (OR: 2.4; 95% CI: 1.4, 4.1), spina bifida (OR: 2.0; 95% CI: 1.3, 3.2), or gastroschisis (OR: 1.8; 95% CI: 1.1, 2.9) in infants |
| Heinonen et al., 1977–1980 | Cohort, 1959–1965         | 12 sites in the US                       | A spectrum of birth defects           | Opioids as a group, propoxyphene, and codeine | 50,282 mother-neonate pair   | Neonates: 1,564 (of which 75 had a major birth defect) | Codeine and respiratory defects (SRR: 2.6; 95% CI: 1.1, 5.1) and genitourinary defects (SRR: 2.1; 95% CI: 0.8, 4.2), Propoxyphene and clubfoot (SRR: 1.8; 95% CI: 0.7, 3.8) |
| Källén (2009)              | Cohort, 1996–2006         | Sweden                                   | A spectrum of birth defects           | Opioids as a group, codeine, dextropropoxyphene, morphine, ketobemidone, and buprenorphine | Mother–neonate pair: 1,015,537 | Neonates: 4,725 (of which 177 had a birth defect) | Buprenorphine and birth defects overall (OR: 3.0; 95% CI: 1.1, 6.5) |
| Källén et al (2013)        | Cohort, 1996–2011         | Sweden                                   | A spectrum of birth defects           | Opioids as a group, codeine, dextropropoxyphene, and tramadol | Mother–neonate pair: 1,575,847 | Neonates: 7,780 (of which 401 had a birth defect) | Clubfoot and opioids (OR: 1.7; 95% CI: 1.1, 2.6) and tramadol (OR: 3.6; 95% CI: 1.7, 6.6) |
| Reference                  | Study design            | Location/study site          | Outcomes studied                          | Exposure | Number of participants | Number exposed in first trimester | Effect estimates (if available)                                                                 |
|---------------------------|-------------------------|------------------------------|-------------------------------------------|----------|------------------------|-----------------------------------|---------------------------------------------------------------------------------------------|
| Nezvalová-Henrikson et al (2011) | Cohort, 1967–2008       | Norway                       | Birth defects as a group                  | Codeine  | 67,982                 | Neonates: 1,693 (of which 40 had a major birth defect) | No elevated estimate for codeine and birth defects (OR: 0.8; 95% CI: 0.5, 1.1) |
| Rosa (1993)               | Cohort, 1985–1992      | Michigan Medicaid data, United States | Cardiovascular defects, OFC, spina bifida, polydactyly, limb reduction defects, and hypospadias | Hydrocodone | 229,101                | Neonates: 332                     | Overall, 24 major birth defects were observed (14 expected), 5 of which were cardiovascular defects (3 expected) |
| Rothman et al (1979)      | Case–control, 1973–1975 | Massachusetts, United States | CHDs                                      | Codeine  | 390 cases: 1,254       | Cases: 5, Controls: 4              | Codeine and CHDs (POR: 4.1; 95% CI: 1.3, 13)                                                |
| Saxén (1975)              | Case–control, 1967–1971 | Finland                      | OFC                                       | Opioids as a group | 599 cases: 590 | Cases: 40, Controls: 13 | Opioids and OFCs (chi-square test p-value: < 0.001)                                      |
| Shaw et al (1992)         | Case–control, 1981–1983 | California, United States   | CHDs                                      | Codeine  | 141 cases: 176        | Cases: 4, Controls: 7              | Codeine and CHDs (OR: 0.7; 95% CI: 0.2, 2.4)                                                 |
| Shaw et al (1998)         | Case–control, 1989–1991 | California, United States   | NTDs                                      | Codeine  | 538 cases: 539        | Cases: 8, Controls: 9              | Codeine and NTDs (OR: 0.9; 95% CI: 0.4, 2.2)                                                  |
| Werler et al (2014)       | Case–control, 2006–2012 | Massachusetts, North Carolina, and New York, United States | Clubfoot                                  | Opioids as a group | 646 cases: 2,037 | Cases: 25, Controls: 47 | Opioids and clubfoot (OR: 1.6; 95% CI: 0.9, 2.7)                                               |
| Yazdy et al (2013)        | Case–control, 1998–2010 | Five centers in the United States and Canada | NTDs                                      | Opioids as a group, codeine, and non-codeine opioids as a group | 305 cases: 7,125 Malformed controls: 13,405 | Cases: 12, Nonmalformed controls: 114 | Opioids and NTDs (OR: 2.2; 95% CI: 1.2, 4.2) and spina bifida (OR: 2.5; 95% CI: 1.3, 5.0), Spina bifida and codeine (OR: 2.5; 95% CI: 0.9, 7.4) and noncodeine (OR: 2.8; 95% CI: 1.3, 6.3) |
| Zierler and Rothman (1985) | Case–control, 1980–1983 | Massachusetts, United States | CHDs                                      | Codeine  | 298 cases: 929        | Cases: 14, Controls: 18             | Codeine and CHDs overall (POR: 2.0; 90% CI: 1.1, 3.6), VSD (POR: 2.5; 90% CI: 1.2, 5.2), and double-outlet right ventricle (POR: 5.7; 90% CI: 1.2, 19.7) |

Abbreviations: ASD, atrial septal defect; CHD, congenital heart defects; CI, confidence interval; NTD, neural tube defect; OR, odds ratio; OFC, orofacial cleft; POR, prevalence odds ratio; SRR, standard rate ratio; VSD, ventricular septal defect.
and maternal oxycodone use and pulmonary valve stenosis (OR: 2.4; 95% CI: 1.1–5.4).

Consistent with the findings from the NBDPS, several earlier case–control studies have identified positive associations between opioid use and congenital heart defects (CHDs). As a group, CHDs have been associated with codeine in three studies, with ORs ranging from 2.0 to 4.1 and all lower bounds of the 95% CIs excluded. However, one study was not able to replicate these findings. In two studies, individual heart defects were assessed and increased risks were observed for atrial septal defects, ventricular septal defects, and double-outlet right ventricle (ORs ranged from 2.5 to 5.8 and 95% CIs excluded 1).

Associations between neural tube defects (NTDs) and opioids have been identified in some studies, but not all. When specific NTDs were examined, an elevated association was identified for spina bifida and codeine (OR: 2.5; 95% CI: 0.9–7.4) and noncodeine opioids (OR: 2.8; 95% CI: 1.3–6.3). Associations have also been found with opioids, clubfoot, and orofacial clefts, though not consistently across studies.

Thus, there is a growing evidence to suggest opioids may be associated with some birth defects, particularly CHDs, NTDs, and clubfoot. Many of the findings come from case–control studies, which are not without their challenges and limitations (e.g., misclassification of opioid exposure, confounding). The retrospective nature of case–control studies and reliance on maternal recall raises concerns about possible recall bias, which is differential recall of exposure in cases and controls. A few of the cited studies have attempted to address this concern. Yazdy et al. and Zierler and Rothman used a second control group consisting of mothers of infants with malformations other than the case group and found the results did not differ substantially. Zierler and Rothman also conducted a secondary analysis using opioid exposure based on medical records and found results were of similar magnitude or larger than when maternal reports were used for the exposure.

Opioid Use in Pregnancy

Opioid use disorders in women in the United States can be traced to the 1870s, when morphine and heroin became available for analgesic use. The majority of opioid addicts during this period were women, which shifted to men with the passage of the Harrison Anti-Narcotic Act in 1914. In recent years the escalating use of opioids, therapeutic and illicit, in the Unites States, has produced a marked increase in the prevalence of opioid dependency in women and subsequently, in pregnancy. Prenatal opioid agonist therapy can prevent illicit opioid use and withdrawal in opioid dependent pregnant women. Prenatal methadone maintenance therapy (MMT) has been used in the United States since the late 1960s. Compared with pregnant women who use heroin alone, women treated with MMT have better prenatal care adherence, reduced fetal death rates, and higher infant birth weights (Table 3). Yet, neonatal abstinence syndrome (NAS) is more severe in neonates exposed to MMT than heroin. Buprenorphine maintenance therapy (BMT) has been used to treat prenatal opioid dependency since the mid-2000s. Buprenorphine is a partial µ-opioid agonist that binds primarily to µ-opioid receptors with higher affinity but lower activity than a full agonist such as methadone or heroin. In the United States, BMT is prescribed for opioid dependence in an outpatient setting, while MMT is generally prescribed for use at an observed daily dosing clinic and as such, women must attend daily dispensing clinics.

BMT has been associated with lower birth weights when compared with national standards and more buprenorphine-exposed neonates fall below the 10th percentile for population standardized growth curves. MMT has also been associated with LBW, as well as with SGA, reduced head circumference, and preterm delivery when compared with pregnancies where no opioids were used. When studying treatments for opioid dependency, it can be difficult to separate the social and behavioral differences (e.g., poor nutrition, alcohol or cigarette use, housing instability) between women on opioid agonist therapy and women who use no opioids at all (formally termed as confounding by indication). To address potential confounding, Sharpe and Kusche explored neonatal outcomes where pregnancies using methadone for pain (the pain group) were compared with pregnancies using methadone for opiate dependency (the maintenance group). Neonates in the pain group had significantly improved markers of fetal growth measures (birth weight and head circumference) than the maintenance group, suggesting that the pharmacological actions of methadone itself may not be responsible for altered fetal growth. However, higher rates of preterm delivery were observed in the pain group compared with the maintenance group. Of note, in the pain group, 81% of the preterm deliveries were induced, with “pain” commonly cited as the reason for induction, indicating the underlying indication for methadone may explain the higher preterm delivery rate. Nevertheless, the results of this study should be interpreted cautiously due to small numbers (n = 43) and dosing differences in the two groups.

There is accumulating data to suggest that prenatal BMT versus MMT exposure may improve neonatal outcomes. Birth weights tended to be higher for BMT compared with MMT-exposed neonates in several studies but not all. Neonates exposed to BMT in pregnancy had head circumferences that were larger and closer to the 50th percentile of World Health Organization standards and greater birth length than neonates exposed to MMT. Rates of preterm delivery were lower among BMT-exposed infants compared with MMT, in fact, it has been hypothesized that the lower rate of preterm birth associated with BMT may explain, in part, the better growth outcomes observed for BMT-exposed infants.

Physicians have long recognized the problem of neonatal opioid withdrawal from prenatal exposure to opioids. NAS is a constellation of gastrointestinal, respiratory, autonomic and central nervous system disturbances that affect postnatal life adaptation in critical areas of sleep, feeding and
| Reference          | Study design      | Location/study site | Outcomes studied                                                                 | Exposure                  | Number of participants | Number exposed in first trimester | Study results                                                                                                                                 |
|--------------------|-------------------|---------------------|-----------------------------------------------------------------------------------|---------------------------|------------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Kandall et al (1977) | Cohort, 1971–1974 | New York, United States | Birth weight and NAS severity                                                    | Methadone and heroin     | Mother–neonate pairs: 296 | Exposed methadone neonates: 230  | Compared with heroin-exposed neonates, methadone-exposed neonates had higher birth weights, longer gestations, and required larger doses of medications for a longer time. |
| Bakstad et al (2009) | Cohort, 2005–2007  | Norway              | Birth weight, length, head circumference, and NAS treatment                     | Methadone and buprenorphine | Mother–neonate pairs: 38 | Methadone-exposed neonates: 26 Buprenorphine-exposed neonates: 12 | Birth outcomes were similar for both groups and no significant differences were observed for NAS treatment (58% in the methadone group and 67% in the buprenorphine group). A significant association was identified between increased daily cigarette consumption and length of NAS in the methadone group. |
| Cleary et al (2011) | Cohort, 2000–2007  | Ireland             | Preterm delivery and small for gestational age                                  | Methadone                | Mother–neonate pairs: 61,030 | Exposed neonates: 618             | Methadone was associated with preterm birth (OR: 2.5; 95% CI: 2.0, 3.1), very preterm birth (OR: 2.3; 95% CI: 1.4, 3.7) and infants that were small for gestational age (OR: 2.2; 95% CI: 1.9, 2.6) |
| Cleary et al (2012) | Cohort, 2009–2010  | Ireland             | Preterm delivery and small for gestational age                                  | Methadone                | Mother–neonate pairs: 114   | Exposed neonates: 114            | Methadone-exposed neonates fell below the 10th percentile for birth weight (38%), head circumference (30%), and birth length (26%) |

(Continued)
| Reference                  | Study design     | Location/study site | Outcomes studied                           | Exposure          | Number of participants | Number exposed in first trimester | Study results                                                                                                                                                                                                 |
|----------------------------|------------------|---------------------|--------------------------------------------|-------------------|------------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dryden et al (2009)        | Cohort, 2004–2006| United Kingdom      | Preterm delivery, birth weight, head circumference | Methadone         | Mother–neonate pairs: 450 | Mother–neonate pairs: 450          | Compared with all births at the hospital, methadone-exposed neonates were more likely to be delivered preterm (9 vs. 20%, respectively), have smaller head circumference, and weigh less |
| Johnson et al (2003)       | Chart review, 1991–2001 | United Kingdom    | Birth weight, head circumference, and NAS severity | Methadone and illicit opiates | Mother–neonate pairs: 41 | Exposed methadone neonates: 14    | Compared with neonates exposed to illicit opiates, methadone-exposed neonates had higher birth weights, required longer durations of treatment for NAS, and their mothers were more likely to receive antenatal care |
| Jones et al (2005)         | RCT, 2000–2003   | Baltimore, Maryland, United States | NAS severity | Methadone and buprenorphine | Mother–neonate pairs: 30 | Exposed neonates: 30               | Methadone-exposed neonates had longer hospital stays (8.1 vs. 6.8 d) and required three times as much morphine than buprenorphine-exposed infants |
| Jones et al (2010)         | RCT, 2005–2008   | Six sites in the United States, Canada and Austria | Birth weight, length, preterm delivery, and NAS severity | Methadone and buprenorphine | Mother–neonate pairs: 175 | Women assigned buprenorphine: 86 Assigned methadone: 89 | Buprenorphine-exposed neonates had higher birth weights (mean: 3,093.7 vs. 2,878.5 g), had longer birth lengths (mean: 49.8 vs. 47.8 cm), were less likely to be preterm (OR: 0.3; 95% CI: 0.1, 2.0), required less morphine (mean dose: 1.1 vs. 10.4 mg),
| Reference                  | Study design          | Location/study site | Outcomes studied                      | Exposure                          | Number of participants | Number exposed in first trimester | Study results                                                                                                                                                                                                 |
|---------------------------|-----------------------|---------------------|---------------------------------------|-----------------------------------|------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kahila et al (2007)67     | Cohort, 2002–2005     | Finland             | Birth length                          | Buprenorphine                     | Exposed neonates: 67   |                                  | had shorter hospital stays (10.0 vs. 17.5 d), and had a shorter durations of NAS treatment (4.1 vs. 9.9 d) than methadone-exposed neonates                                    |
| Kakko et al (2008)78      | Cohort, 1982–2006     | Sweden              | Birth weight, length, and head circumference | Methadone and buprenorphine       | Methadone-exposed neonates: 36  
Buprenorphine-exposed neonates: 49 |                                  | Methadone-exposed neonates had lower birth weights (mean: 2,941 g) and lower gestational ages (mean: 38.6 wks) than buprenorphine-exposed neonates (3,250 g and 39.5 wks, respectively) |
| Kaltenbach and Finnegan (1987)72 | Cohort               | Philadelphia, Pennsylvania, United States | Birth weight and head circumference | Methadone                          | Exposed neonates: 141  |                                  | Methadone-exposed neonates had lower birth weights compared with nonexposed neonates                                                                                   |
| Lacroix et al (2011)85    | Cohort, 1998–2006     | France              | NAS severity                          | Methadone and buprenorphine       | Methadone-exposed neonates: 45  
Buprenorphine-exposed neonates: 90 |                                  | Methadone-exposed neonates required NAS treatment more frequently (84%) than buprenorphine-exposed neonates (57%)                                                                                     |
| Lejeune et al (2006)68    | Cohort, 1998–1999     | France              | Birth weight and length                | Methadone and buprenorphine       | Methadone-exposed neonates: 101  
Buprenorphine-exposed neonates: 159 |                                  | Birth weights and length were higher for buprenorphine-exposed neonates, though not significantly                                                                 |
| Reference                  | Study design                         | Location/study site | Outcomes studied                                      | Exposure                        | Number of participants | Number exposed in first trimester | Study results                                                                                                                                 |
|----------------------------|--------------------------------------|---------------------|--------------------------------------------------------|---------------------------------|------------------------|------------------------------|----------------------------------------------------------------------------------|
| Metz et al (2011)76        | Cohort, 2005–2009                    | Austria             | Birth weight, length, gestational age at birth, and NAS severity | Methadone and buprenorphine     | Mother–neonate pairs: 114 | Methadone-exposed neonates: 70 Buprenorphine-exposed neonates: 44 | Compared with methadone-exposed neonates, buprenorphine-exposed neonates were older at birth, weighted, required less morphine, had shorter durations of NAS treatment, and shorter lengths of stay |
| Pritham et al (2012)71     | Cohort, 2005–2007                    | Maine, United States | Birth weight, head circumference, and size for gestational age | Methadone and buprenorphine     | Mother–neonate pairs: 152 | Methadone-exposed neonates: 136 Buprenorphine-exposed neonates: 16 | Methadone-exposed neonates had smaller head circumferences (mean: 32.9 cm) and were SGA (10.5%) than buprenorphine-exposed infants (33.8 cm and 0%, respectively) |
| Sharpe and Kuschel (2004)75| Chart review, 1997–2000               | New Zealand         | Birth weight, head circumference, birth length, and pre-term delivery | Methadone                       | Mother–neonate pairs: 43  | Exposed neonates: 43            | Mothers who took methadone for pain had neonates that were heavier (median z score: −0.04) and with larger head circumferences (median z score: +0.75) compared with mothers who took methadone for opiate dependency (−0.69 and −0.75, respectively). Rates of pre-term birth were higher for mothers who took methadone for opiate dependency |
| Wachman et al (2011)83     | Chart review, 2003–2009               | Boston, United States | NAS severity                                          | Methadone and buprenorphine     | Mother–neonate pairs: 273 | Methadone-exposed neonates: 158 Buprenorphine-exposed neonates: 22 | Length of hospitalization was shorter for buprenorphine exposed (15.5 d) vs. methadone exposed (23.66 d) babies |
| Reference                  | Study design | Location/study site | Outcomes studied                        | Exposure                   | Number of participants | Number exposed in first trimester | Study results                                                                 |
|----------------------------|--------------|---------------------|-----------------------------------------|----------------------------|------------------------|----------------------------------|--------------------------------------------------------------------------------|
| Welle-Strand et al (2013)  | Cohort       | Norway              | Birth weight, birth length, and head circumference | Methadone and buprenorphine | Mother–neonate pairs: 139 | Methadone-exposed neonates: 90 Buprenorphine-exposed neonates: 49 | Buprenorphine-exposed infants were heavier (mean birth weight 3,254 g), had larger head circumferences (mean: 34.7 cm), and greater birth length (mean: 48.8 cm) than methadone-exposed infants (2,944 g, 33.7 cm, and 47.4 cm, respectively) |
| Wouldes et al (2010)       | Cohort       | New Zealand         | Birth weight, head circumference, birth length, and pre-term delivery | Methadone                   | Mother–neonate pairs: 74 | Methadone-exposed neonates: 32 | Methadone-exposed neonates had smaller birth lengths, head circumference, and lower birth weights compared with nonexposed neonates |

Abbreviations: NAS, neonatal abstinence syndrome; RCT, randomized control trial; SGA, small for gestational age.
autonomic function.\textsuperscript{59,81} Neonates with severe NAS symptoms require prolonged hospitalization and pharmacotherapy, usually with morphine, with unknown long-term effects.\textsuperscript{82} NAS is not limited to infants of mothers addicted to opioids; use of prescription opioids for long periods during pregnancy in non-addicted mothers can also produce NAS. In the Kellogg et al\textsuperscript{33} study of 167 women with chronic prescription opioid use in pregnancy, 5\% of the newborns were noted to have symptoms of NAS.

Some cohort studies and randomized controlled trials have observed decreased NAS severity\textsuperscript{76,79,83,84} and lower risk of NAS treatment,\textsuperscript{85} in BMT relative to MMT exposed neonates. A recent meta-analysis of the published literature, however, showed that the apparent protective effect of BMT relative to MMT on neonatal outcomes may be affected by maternal risk factors (e.g., maternal severity of opioid addiction) that independently affect the type of prenatal treatment and neonatal outcomes.\textsuperscript{80} Indeed, studies have shown that BMT is typically used in more stable opioid-dependent pregnant women who do not need the structure of observed daily dosing required for MMT in the United States.\textsuperscript{68,76,78,85,86} This imbalance in maternal risk factors across treatment groups can produce confounding bias (i.e., confounding by indication) in studies of the comparative safety of BMT relative to MMT.

In summary, additional studies are needed to improve our understanding of the risks associated with prenatal treatment for opioid dependency and to optimize care for opioid-dependent pregnant women and their infants. The number of newborns with NAS in the United States is approximately 14,000 annually and continues to increase.\textsuperscript{87} Around 40 to 80\% of exposed neonates develop NAS, requiring prolonged hospitalization and pharmacotherapy with potential adverse effects.

**Conclusion**

In this review, we summarize the available literature on opioid use in pregnancy and birth outcomes. The limited studies that have assessed head circumference and birth length, have found no association with opioid use. These markers of fetal growth have been well studied in the context of dependency and for BMT-exposed neonates, both head circumference and birth length fall within normal ranges, further demonstrating that opioid medications may not affect fetal growth. On the other hand, results for birth weight and preterm birth have been inconclusive and further studies are needed to assess if opioids pose a risk for preterm birth or LBW. There is a growing body of evidence to suggest that opioids may be associated with specific birth defects. To date, five studies have identified an association with CHDs and three studies have found elevated estimates with NTDs and clubfoot. Codeine has been implicated in several of the studies but additional studies that consider individual opioids are needed to evaluate if the risk of some opioids may be lower than others.

Studying opioid use in pregnancy presents multiple methodological challenges. Studies are vulnerable to confounding by indication, as women who take opioids—or who take a particular opioid versus another—may be different from women who do not. Additionally, it can be difficult to differentiate whether the underlying condition for opioid use (e.g., migraine) or the medication itself is responsible for any observed elevated risk. Future studies should consider the nature and severity of the underlying condition and address the potential for confounding by indication. Due to small numbers, studies often consider opioid medications as a homogeneous group and by doing so any effect for specific medications may be missed. As it is unlikely that all medications within the class of opioid medications have the same mechanism of action on the fetus, we recommend future studies assess individual opioid medications. Larger studies are needed, especially to allow for assessment of individual opioids. Furthermore, studies should focus on precise exposure measurements, with dose and duration information and accurate outcome ascertainment.

Prenatal prescription of opioids has dramatically increased in the United States and elsewhere.\textsuperscript{32,87} To prescribe safe and effective prenatal medications, health care providers must carefully consider both the medical concerns of the pregnant woman and the potential harms to the developing fetus. In situations where opioids are not necessary, health care providers should discuss the potential risks with women and consider the possibility of alternative medications. Prenatal opioid therapy is used for a wide range of conditions that include both medical indications (e.g., pain, migraines) and opioid dependency. Studies of in utero opioid exposure for these two broad categories suggest different levels of risk for the neonate. Further research is needed on adverse effects on birth outcomes and longer term child development that may result from in utero exposure to opioids or the conditions for which these drugs are used.

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