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 weak[9–12] and there is the potential risk of side effects (e.g., constipation, nausea, cardiac complications, respiratory depression, drug dependence) with long-term use.[1]

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Two opioid agonists, methadone and buprenorphine, are indicated for the management of opioid dependence in pregnancy.[13] Utilization rates of medication-assisted maintenance therapy with methadone and buprenorphine have increased over the last decade.[14,15] 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.[16]

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%.[17,18] Additionally, other pain conditions such as myalgia, joint pain, and migraine are frequently reported.[19] 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.[20] 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.[5]

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.[21,22] 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.[23] 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.[24]

Despite evidence of adverse effects on fetal development from prescription opioids,[25–29] 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.[30] 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.[31] 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.[32] 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.[19] Some of the most commonly filled opioid agents reported in these studies were codeine, hydrocodone, oxycodone, and propoxyphene.[19,32]

Fewer studies have described rates of chronic prescription opioid use (use $\geq$ 1 month) during pregnancy. In a cohort study of all deliveries at the Mayo Clinic from 1998 through 2009,[33] $<$ 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).[32] 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.[34]

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.[22] 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.[35–39] 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.[40] 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.[41] Head circumference, another marker of fetal growth, has also not been associated with opioid use.[41,42]

Multiple birth weight measures are often employed to assess fetal growth restriction. Low birth weight (LBW), often

categorized as < 2,500 g, is one such measure; however, LBW does not incorporate gestational age and can include a mix of preterm and growth-restricted neonates. For this reason, investigators will often choose to use small for gestational age (SGA) instead, as gestational age is incorporated into the definition (SGA is defined as birth weights that fall into the lowest 10th percentile at each gestational age) and can be useful at detecting exposures that restrict fetal growth on a population level.[40] Both LBW and SGA have been explored in relation to opioid use, but study results have varied (►**Table 1**). Several studies have identified no association between LBW and oxycodone, codeine, and opioids overall.[41,43,44] SGA has been associated with opioid use in one study where the majority of exposed women reported acetaminophen with oxycodone, codeine, or hydrocodone (11.5% among opioid exposed compared with 7.8% nonexposed neonates).[45] However, another study observed no increased rates of SGA or birth weight, but instead identified an elevated rate of large for gestational age for mothers who used propoxyphene (odds ratio [OR]: 1.4; 95% confidence interval [CI]: 1.3–1.7) or codeine (OR: 1.3; 95% CI: 1.1–1.4).[43]

Preterm Birth

Preterm birth (defined as delivery before 37 weeks' gestation) may be indicative of fetal distress or impaired fetal development that triggers early labor.[40] Study results have been inconsistent for opioids and preterm delivery. Compared with neonates unexposed prenatally to opioids, a study from the first nations population in northwestern Ontario found that preterm birth was associated with maternal oxycodone use in pregnancy (8.2% among opioid exposed compared with 2.3% nonexposed neonates).[41] Another study from the Swedish Medical Birth Register, found a modest, but significant, association between maternal tramadol use and preterm birth (OR: 1.3; 95% CI: 1.04–1.62).[43] However, the latter association was not observed for very preterm birth (< 32 weeks) in the same study.[43] No elevated risk for preterm delivery was identified either in a study which assessed codeine use in pregnancy[44] or in another study where the majority of opioid use was acetaminophen with oxycodone, codeine, or hydrocodone.[45]

Birth Defects

To date, only a few large cohorts have examined the use of opioids in early pregnancy and birth defects (►**Table 2**). One of the earliest studies was the U. S. Collaborative Perinatal Project, a prospective study from 1959 to 1965 that included 50,282 pregnant women.[46] A total of 1,564 women reported use of narcotic analgesics in lunar months 1 to 4 and no association was identified for malformations overall. When drug-specific estimates were considered, elevated standardized relative risks (SRR) were identified for 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), as well as for propoxyphene and clubfoot (SRR: 1.8; 95% CI: 0.7–3.8).[46] 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).[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).[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 tramadol use in early pregnancy (OR: 3.6; 95% CI: 1.7–6.6).[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.[49] Proper classification of birth defects is essential to not only understanding the underlying etiology,[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.[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), gastroschisis (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 gastroschisis (OR: 3.3; 95% CI: 1.8–6.1);

Table 1 Studies of opioid use and fetal growth

Reference	Study design	Location/study site	Outcomes studied	Exposure	Number of participants	Number exposed	Effect estimates (if available)
Hadi et al (2006)[42]	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)[43]	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)[41]	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)[44]	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)[45]	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.

Table 2 Studies of opioid use and birth defects

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)[26]	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)[50]	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)[25]	Case–control, 1997–2005	Ten states in the United States	A spectrum of birth defects	Opioids as a group, codeine, hydrocodone, oxycodone, 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), atrioventricular 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,[46]	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)[48]	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)[43]	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)

Table 2 (*Continued*)

Reference	Study design	Location/study site	Outcomes studied	Exposure	Number of participants	Number exposed in first trimester	Effect estimates (if available)
Nezvalová-Henriksen et al (2011)[44]	Cohort, 1967–2008	Norway	Birth defects as a group	Codeine	Mother–neonate pair: 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)[47]	Cohort, 1985–1992	Michigan Medicaid data, United States	Cardiovascular defects, OFC, spina bifida, polydactyly, limb reduction defects, and hypospadias	Hydrocodone	Pregnancies: 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)[27]	Case–control, 1973–1975	Massachusetts, United States	CHDs	Codeine	Cases: 390 Controls: 1,254	Cases: 5 Controls: 4	Codeine and CHDs (POR: 4.1; 95% CI 1.3, 13)
Saxén (1975)[53]	Case–control, 1967–1971	Finland	OFC	Opioids as a group	Cases: 599 Controls: 590	Cases: 40 Controls: 13	Opioids and OFCs (chi-square test p-value: < 0.001)
Shaw et al (1992)[51]	Case–control, 1981–1983	California, United States	CHDs	Codeine	Cases: 141 Controls: 176	Cases: 4 Controls: 7	Codeine and CHDs (OR: 0.7; 95% CI: 0.2, 2.4)
Shaw et al (1998)[52]	Case–control, 1989–1991	California, United States	NTDs	Codeine	Cases: 538 Controls: 539	Cases: 8 Controls: 9	Codeine and NTDs (OR: 0.9; 95% CI: 0.4, 2.2)
Werler et al (2014)[54]	Case–control, 2006–2012	Massachusetts, North Carolina, and New York, United States	Clubfoot	Opioids as a group	Cases: 646 Controls: 2,037	Cases: 25 Controls: 47	Opioids and clubfoot (OR: 1.6; 95% CI: 0.9, 2.7)
Yazdy et al (2013)[29]	Case–control, 1998–2010	Five centers in the United States and Canada	NTDs	Opioids as a group, codeine, and noncodeine opioids as a group	Cases: 305 Nonmalformed controls: 7,125 Malformed controls: 13,405	Cases: 12 Nonmalformed controls: 114 Malformed controls: 281	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)[28]	Case–control, 1980–1983	Massachusetts, United States	CHDs	Codeine	Cases: 298 Controls: 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 1.[27,28,50] However, one study was not able to replicate these findings.[51] 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).[26,28]

Associations between neural tube defects (NTDs) and opioids have been identified in some studies,[25,26,29] but not all.[52] 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).[29] Associations have also been found with opioids, clubfoot, and orofacial clefts,[26,53,54] 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,[29] and Zierler and Rothman[28] 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[28] 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 Dependency and Neonatal Withdrawal

Opioid use disorders in women in the United States can be traced to the 1870s, when morphine and heroin became available for analgesic use.[55] 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.[56] 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.[57–60] 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**).[61–63] Yet, neonatal abstinence syndrome (NAS) is more severe in neonates exposed to MMT than heroin.[61,63] 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.[64] In the United States, BMT is prescribed for opioid dependence in an outpatient setting,[65] while MMT is generally prescribed for use at an observed daily dosing clinic and as such, women must attend daily dispensing clinics.[66]

BMT has been associated with lower birth weights when compared with national standards[67] and more buprenorphine-exposed neonates fall below the 10th percentile for population standardized growth curves.[68] 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.[69–74] 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 Kuschel[75] 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.[75]

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,[76–79] but not all.[68] Neonates exposed to BMT in pregnancy had head circumferences that were larger and closer to the 50th percentile of World Health Organization standards[71,77–79] and greater birth length than neonates exposed to MMT.[77–79] Rates of preterm delivery were lower among BMT-exposed infants compared with MMT[76,79,80]; 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.[78]

Physicians have long recognized the problem of neonatal opioid withdrawal from prenatal exposure to opioids.[55] 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

Table 3 Studies of opioid maintenance treatment and neonatal outcomes

Reference	Study design	Location/study site	Outcomes studied	Exposure	Number of participants	Number exposed in first trimester	Study results
Kandall et al (1977)[61]	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)[86]	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)[69]	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)[70]	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*)

Table 3 (*Continued*)

Reference	Study design	Location/study site	Outcomes studied	Exposure	Number of participants	Number exposed in first trimester	Study results
Dryden et al (2009)[74]	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)[63]	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)[84]	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)[79]	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),

Table 3 (*Continued*)

Reference	Study design	Location/study site	Outcomes studied	Exposure	Number of participants	Number exposed in first trimester	Study results
							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
Kahila et al (2007)[67]	Cohort, 2002–2005	Finland	Birth length	Buprenorphine	Mother–neonate pairs: 67	Exposed neonates: 67	No difference in birth length among buprenorphine-exposed infants and Finnish general population
Kakko et al (2008)[78]	Cohort, 1982–2006	Sweden	Birth weight, length, and head circumference	Methadone and buprenorphine	Mother–neonate pairs: 85	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	Mother–neonate pairs: 268	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	Mother–neonate pairs: 135	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	Mother–neonate pairs: 260	Methadone-exposed neonates: 101 Buprenorphine-exposed neonates: 159	Birth weights and length were higher for buprenorphine-exposed neonates, though not significantly

(*Continued*)

Table 3 (*Continued*)

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 preterm 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 preterm 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

Table 3 (*Continued*)

Reference	Study design	Location/study site	Outcomes studied	Exposure	Number of participants	Number exposed in first trimester	Study results
Welle-Strand et al (2013)[77]	Cohort, 1996–2009	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: 34.7cm), 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)[73]	Cohort	New Zealand	Birth weight, head circumference, birth length, and preterm 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.[59,81] Neonates with severe NAS symptoms require prolonged hospitalization and pharmacotherapy, usually with morphine, with unknown long-term effects.[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[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[76,79,83,84] and lower risk of NAS treatment,[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.[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.[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.[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.[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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References

1 Warner EA. Opioids for the treatment of chronic noncancer pain. Am J Med 2012;125(12):1155–1161
2 Vanderah TW. Delta and kappa opioid receptors as suitable drug targets for pain. Clin J Pain 2010;26(Suppl 10):S10–S15
3 U. S. Department of Justice, Drug Enforcement Administration. Drugs of abuse 2011 edition. Available at: http://www.dea.gov/docs/drugs_of_abuse_2011.pdf. Accessed September 15, 2014
4 Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003;349(20):1943–1953
5 Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel.

Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10(2):113–130
6 Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: the TROUP study. Pain 2008;138(2):440–449
7 Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain 2008;24(6):521–527
8 Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. Open Med 2012;6(2):e41–e47
9 Trescot AM, Glaser SE, Hansen H, Benyamin R, Patel S, Manchikanti L. Effectiveness of opioids in the treatment of chronic non-cancer pain. Pain Physician 2008;11(2, Suppl):S181–S200
10 Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. J Pain Symptom Manage 2008;35(2):214–228
11 Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. Ann Intern Med 2007;146(2):116–127
12 Chou R, Deyo R, Devine B, et al. The effectiveness and risks of long-term opioid treatment of chronic pain. In: Agency for Healthcare Research and Quality, ed. Evidence Report/Technology Assessment No. 218 (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290–2012–00014-I.). AHRQ Publication No. 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2014
13 Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs. Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration (US); 2005
14 Riksheim M, Gossop M, Clausen T. From methadone to buprenorphine: changes during a 10 year period within a national opioid maintenance treatment programme. J Subst Abuse Treat 2014; 46(3):291–294
15 Stein BD, Gordon AJ, Sorbero M, Dick AW, Schuster J, Farmer C. The impact of buprenorphine on treatment of opioid dependence in a Medicaid population: recent service utilization trends in the use of buprenorphine and methadone. Drug Alcohol Depend 2012; 123(1-3):72–78
16 Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. N Engl J Med 2014;370(22):2063–2066
17 Wang SM, Dezinno P, Maranets I, Berman MR, Caldwell-Andrews AA, Kain ZN. Low back pain during pregnancy: prevalence, risk factors, and outcomes. Obstet Gynecol 2004;104(1):65–70
18 Mogren IM, Pohjanen AI. Low back pain and pelvic pain during pregnancy: prevalence and risk factors. Spine 2005;30(8):983–991
19 Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. Anesthesiology 2014; 120(5):1216–1224
20 Babb M, Koren G, Einarson A. Treating pain during pregnancy. Can Fam Physician 2010;56(1):25, 27
21 Mann R, Andrews E. Pharmacovigilance. West Sussex, England: John Wiley & Sons; 2007
22 Mitchell AA. Studies of drug-induced birth defects. In: Strom B, Kimmel S, Hennessy S, eds. Pharmacoepidemiology. 5th ed. West Sussex, United Kingdom: Wiley-Blackwell; 2012:487–504
23 Stanhope TJ, Gill LA, Rose C. Chronic opioid use during pregnancy: maternal and fetal implications. Clin Perinatol 2013;40(3): 337–350
24 Food and Drug Administration, HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. Fed Regist 2014;79(233):72063–72103
25 Broussard CS, Rasmussen SA, Reefhuis J, et al; National Birth Defects Prevention Study. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204(4): 314.e1–314.e11
26 Bracken MB, Holford TR. Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstet Gynecol 1981;58(3):336–344
27 Rothman KJ, Fyler DC, Goldblatt A, Kreidberg MB. Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 1979;109(4):433–439
28 Zierler S, Rothman KJ. Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. N Engl J Med 1985;313(6):347–352
29 Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol 2013;122(4):838–844
30 Engeland A, Bramness JG, Daltveit AK, Rønning M, Skurtveit S, Furu K. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106,000 pregnancies in Norway 2004-2006. Br J Clin Pharmacol 2008; 65(5):653–660
31 Epstein RA, Bobo WV, Martin PR, et al. Increasing pregnancy-related use of prescribed opioid analgesics. Ann Epidemiol 2013; 23(8):498–503
32 Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol 2014;123(5):997–1002
33 Kellogg A, Rose CH, Harms RH, Watson WJ. Current trends in narcotic use in pregnancy and neonatal outcomes. Am J Obstet Gynecol 2011;204(3):259.e1–259.e4
34 Martin CE, Longinaker N, Terplan M. Recent trends in treatment admissions for prescription opioid abuse during pregnancy. J Subst Abuse Treat 2015;48(1):37–42
35 Melve KK, Gjessing HK, Skjaerven R, Oyen N. Infants' length at birth: an independent effect on perinatal mortality. Acta Obstet Gynecol Scand 2000;79(6):459–464
36 Morris SS, Victora CG, Barros FC, et al. Length and ponderal index at birth: associations with mortality, hospitalizations, development and post-natal growth in Brazilian infants. Int J Epidemiol 1998;27(2):242–247
37 Kajantie E, Osmond C, Barker DJ, Forsén T, Phillips DI, Eriksson JG. Size at birth as a predictor of mortality in adulthood: a follow-up of 350 000 person-years. Int J Epidemiol 2005;34(3): 655–663
38 Silva IdosS, De Stavola B, McCormack V; Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk of Breast Cancer. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. PLoS Med 2008;5(9):e193
39 Risnes KR, Vatten LJ, Baker JL, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis. Int J Epidemiol 2011;40(3):647–661
40 Wilcox AJ. Fertility and Pregnancy: An Epidemiologic Perspective. New York, NY: Oxford University Press; 2010
41 Kelly L, Dooley J, Cromarty H, et al. Narcotic-exposed neonates in a First Nations population in northwestern Ontario: incidence and implications. Can Fam Physician 2011;57(11):e441–e447
42 Hadi I, da Silva O, Natale R, Boyd D, Morley-Forster PK. Opioids in the parturient with chronic nonmalignant pain: a retrospective review. J Opioid Manag 2006;2(1):31–34
43 Källén B, Borg N, Reis M. The use of central nervous system active drugs during pregnancy. Pharmaceuticals (Basel) 2013;6(10): 1221–1286
44 Nezvalová-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. Eur J Clin Pharmacol 2011;67(12):1253–1261
45 Smith MV, Costello D, Yonkers KA. Clinical correlates of prescription opioid analgesic use in pregnancy. Matern Child Health J 2015;19(3):548–556

46 Analgesics and antipyretic drugs. In: Heinonen OP, Slone D, Shapiro S, eds. Birth Defects and Drugs in Pregnancy. Littleton, MA: Publishing Sciences Group Inc; 1977:286–295
47 Rosa F. Personal communication. In: Briggs GG, Freeman RK, Yaffe SJ, eds. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:691–692
48 Källén B. Drugs during Pregnancy. New York, NY: Nova Biomedical Books; 2009
49 Khoury MJ, James LM, Flanders WD, Erickson JD. Interpretation of recurring weak associations obtained from epidemiologic studies of suspected human teratogens. Teratology 1992;46(1):69–77
50 Bracken MB. Drug use in pregnancy and congenital heart disease in offspring. N Engl J Med 1986;314(17):1120
51 Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. Eur J Epidemiol 1992;8(5): 757–760
52 Shaw GM, Todoroff K, Velie EM, Lammer EJ. Maternal illness, including fever and medication use as risk factors for neural tube defects. Teratology 1998;57(1):1–7
53 Saxén I. Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol 1975;4(1):37–44
54 Werler MM, Yazdy MM, Kasser JR, et al. Medication use in pregnancy in relation to the risk of isolated clubfoot in offspring. Am J Epidemiol 2014;180(1):86–93
55 Kandall SR. Substance and Shadow: Women and Addiction in the United States. Cambridge, MA: Harvard University Press; 1999
56 Jonnes J. The rise of the modern addict. Am J Public Health 1995; 85(8 Pt 1):1157–1162
57 Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: National Findings. Rockville, MD: Office of Applied Studies, NSDUH Series H-30, DHHS Publication No. SMA 06-4194; 2006
58 Knoppert D. The worldwide opioid epidemic: implications for treatment and research in pregnancy and the newborn. Paediatr Drugs 2011;13(5):277–279
59 Hudak ML, Tan RC; Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics 2012;129(2):e540–e560
60 Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers and other drugs among women—United States, 1999-2010. MMWR Morb Mortal Wkly Rep 2013;62(26):537–542
61 Kandall SR, Albin S, Gartner LM, Lee KS, Eidelman A, Lowinson J. The narcotic-dependent mother: fetal and neonatal consequences. Early Hum Dev 1977;1(2):159–169
62 Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. Effects and management. Obstet Gynecol Clin North Am 1998;25(1):139–151
63 Johnson K, Greenough A, Gerada C. Maternal drug use and length of neonatal unit stay. Addiction 2003;98(6):785–789
64 Walsh SL, Preston KL, Bigelow GE, Stitzer ML. Acute administration of buprenorphine in humans: partial agonist and blockade effects. J Pharmacol Exp Ther 1995;274(1):361–372
65 U.S. Government Publishing Office. The Drug Addiction Treatment Act of 2000. Public Law No. 106–310. Available at: http://www.gpo.gov/fdsys/pkg/PLAW-106publ310/pdf/PLAW-106publ310.pdf. Accessed September 15, 2014
66 Rettig RA, Yarmolinsky A, eds. Federal Regulation of Methadone Treatment. Washington, DC: The National Academy Press; 1995
67 Kahila H, Saisto T, Kivitie-Kallio S, Haukkamaa M, Halmesmäki E. A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. Acta Obstet Gynecol Scand 2007;86(2):185–190
68 Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S; Groupe d'Etudes Grossesse et Addictions (GEGA). Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution. Drug Alcohol Depend 2006;82(3):250–257
69 Cleary BJ, Donnelly JM, Strawbridge JD, et al. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol 2011;204(2):139.e1–139.e9
70 Cleary BJ, Eogan M, O'Connell MP, et al. Methadone and perinatal outcomes: a prospective cohort study. Addiction 2012;107(8): 1482–1492
71 Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. J Obstet Gynecol Neonatal Nurs 2012;41(2):180–190
72 Kaltenbach K, Finnegan LP. Perinatal and developmental outcome of infants exposed to methadone in-utero. Neurotoxicol Teratol 1987;9(4):311–313
73 Wouldes TA, Woodward LJ. Maternal methadone dose during pregnancy and infant clinical outcome. Neurotoxicol Teratol 2010;32(3):406–413
74 Dryden C, Young D, Hepburn M, Mactier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. BJOG 2009;116(5):665–671
75 Sharpe C, Kuschel C. Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. Arch Dis Child Fetal Neonatal Ed 2004;89(1):F33–F36
76 Metz V, Jagsch R, Ebner N, et al. Impact of treatment approach on maternal and neonatal outcome in pregnant opioid-maintained women. Hum Psychopharmacol 2011;26(6):412–421
77 Welle-Strand GK, Skurtveit S, Jones HE, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009. Drug Alcohol Depend 2013; 127(1-3):200–206
78 Kakko J, Heilig M, Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. Drug Alcohol Depend 2008;96(1-2):69–78
79 Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010;363(24):2320–2331
80 Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. Am J Epidemiol 2014;180(7):673–686
81 Hayes MJ, Brown MS. Epidemic of prescription opiate abuse and neonatal abstinence. JAMA 2012;307(18):1974–1975
82 Jansson LM, Velez M. Neonatal abstinence syndrome. Curr Opin Pediatr 2012;24(2):252–258
83 Wachman EM, Newby PK, Vreeland J, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. J Addict Med 2011;5(4):293–299
84 Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. Drug Alcohol Depend 2005;79(1):1–10
85 Lacroix I, Berrebi A, Garipuy D, et al. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective multicenter study. Eur J Clin Pharmacol 2011;67(10):1053–1059
86 Bakstad B, Sarfi M, Welle-Strand GK, Ravndal E. Opioid maintenance treatment during pregnancy: occurrence and severity of neonatal abstinence syndrome. A national prospective study. Eur Addict Res 2009;15(3):128–134
87 Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA 2012; 307(18):1934–1940