

Is periconceptual opioid use safe?

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Abstract

Question A patient in my practice who takes buprenorphine for chronic pain would like to conceive. Is it safe for her to continue taking her medication?

Answer The literature regarding periconceptual opioid use is conflicted as to whether opioids pose an elevated risk of birth defects. Confounding factors such as socioeconomic status, stress, and alcohol consumption might play a role. The first trimester of pregnancy is the critical period of development for many organ systems in the embryo. A chemical or environmental insult is more likely to produce major congenital malformations such as neural tube defects or mental retardation if it occurs within this window. Medical practitioners should judiciously consider a risk-benefit analysis before making their decisions.

L'utilisation des opioïdes est-elle sécuritaire avant la conception?

Résumé

Question Une patiente de ma pratique prend de la buprénorphine pour des douleurs chroniques et elle planifie une grossesse. Est-il sécuritaire pour elle de continuer à prendre ces médicaments?

Réponse Les ouvrages scientifiques concernant l'utilisation des opioïdes durant la période entourant la conception donnent des renseignements contradictoires quant à la possibilité que les opioïdes augmentent le risque d'anomalies à la naissance. Des facteurs de confusion comme la situation socioéconomique, le stress et la consommation d'alcool pourraient avoir une influence. Le premier trimestre de la grossesse est la période critique dans le développement de nombreux organes chez l'embryon. Il est plus probable qu'une agression chimique ou environnementale provoque des malformations congénitales comme des défauts du tube neural ou un retard du développement mental si elle se produit durant cette période. Les médecins devraient envisager de faire une judicieuse analyse des risques et des avantages avant de prendre une décision.

Opioids act on the μ , κ , and δ opioid receptors in the central nervous system (CNS) and some peripheral tissue, including vascular, cardiac, lung, and gut tissue.¹ This class collectively includes natural opiates derived from *Papaver somniferum*, as well as semisynthetic and synthetic opioids. In addition, endogenous opioid peptides, known as enkephalins, endorphins, and endomorphins, have been isolated.² Opioids are well known for their potent antinociceptive effects and produce euphoria, sedation, miosis, gastrointestinal (GI) hypomotility, and respiratory depression owing to their inhibitory mechanism of action.^{1,2} Some common opioid medications include morphine, codeine, oxycodone, hydrocodone, heroin, methadone, fentanyl, and buprenorphine.

Physical and psychological dependence on opioids has been well described, and abrupt discontinuation is characterized by withdrawal symptoms that manifest as CNS irritability, autonomic overreactivity, and GI dysfunction.² Owing to their low molecular weight and lipophilicity,² opioids are able to rapidly cross the placenta

and blood-brain barrier, as well as pass into breast milk.³ The prevalence of neonatal abstinence syndrome has been well documented in the literature and will not be further discussed in this article.^{2,4} Manifestations of neonatal abstinence syndrome are similar to adult withdrawal symptoms, involving irritability, poor feeding, respiratory distress, hyperthermia, and hypertonia.⁴

Evidence concerning periconceptual opioid use

A pressing concern is the paucity of information concerning the safety of periconceptual opioid use. The first trimester of pregnancy is the critical period of development for many organ systems in the embryo. Organogenesis, cell division, cell differentiation, and morphogenesis occur at their highest rates; as a result, the embryo is most sensitive to teratogens during this time.⁵ For instance, the critical period of development for the CNS occurs between weeks 3 and 16 of gestation.⁵ A chemical or environmental insult is more likely

to produce major congenital malformations such as neural tube defects (NTDs) or mental retardation if it occurs within this window. Organs continue to develop after this critical period but become less sensitive to teratogenic exposure.

The current body of literature regarding periconceptual opioid use is conflicted as to whether opioids pose an elevated risk of birth defects. Broussard et al performed a case-control study based on data from the National Birth Defects Prevention Study.⁶ Focusing on opioid exposures between 1 month before and 3 months after conception, the study found that therapeutic maternal opioid treatment within this time frame was significantly associated with some types of congenital heart defects (CHDs), including conoventricular septal defects (odds ratio [OR]=2.7; 95% CI 1.1 to 6.3), atrioventricular septal defects (OR=2.4; 95% CI 1.2 to 4.8), hypoplastic left heart syndrome (OR=2.4; 95% CI 1.4 to 4.1), tetralogy of Fallot (OR=1.7; 95% CI 1.1 to 2.8), and pulmonary valve stenosis (OR=1.7; 95% CI 1.2 to 2.6).⁶ Furthermore, spina bifida (OR=2.0; 95% CI 1.3 to 3.2), hydrocephaly (OR=2.0; 95% CI 1.0 to 3.7), glaucoma or anterior chamber defects (OR=2.6; 95% CI 1.0 to 6.6), and gastroschisis (OR=1.8; 95% CI 1.1 to 2.9) were also linked with maternal opioid use.⁶ When the exposure period was defined as only the first 2 months after conception, the same associations of these congenital defects with maternal opioid use were evident, albeit at an elevated magnitude. The elevated risk of congenital defects during this limited exposure period is consistent with the heightened sensitivity to teratogens during critical periods of development.⁶ Codeine and hydrocodone use was involved in most of the statistically significant associations, and they were also the most frequently reported drug exposures (69%).⁶ While the study did have a large sample size, its statistical power was close to the limit of detection for rarer CHD categories.⁷

Broussard et al did not observe an association with anencephaly. However, a case-control study by Yazdy et al based on data from the Slone Epidemiology Center birth defects study from 1998 to 2010 reported an increased risk of NTDs, mostly as spina bifida, anencephaly, and encephalocele.⁸ The study compared the infants of mothers who used opioids within 2 months after their last menstrual period with infants in non-malformed (OR=2.2) and malformed control groups (OR=1.9).⁸ When adjusted specifically for codeine, a larger risk for all NTDs was evident compared with the non-malformed (OR=2.5) and malformed (OR=2.0) groups. Non-codeine opioids were found to be slightly more strongly associated with spina bifida (OR=2.8 and OR=2.5 for non-malformed and malformed groups, respectively) compared with codeine (OR=2.5 and OR=2.0, respectively).⁸

These findings are further corroborated by a retrospective study by Fishman et al based on data obtained

from Clalit Health Services in southern Israel between 2000 and 2009.⁹ A 4-fold increase in risk of spina bifida was found in newborns and abortuses exposed to intra-uterine codeine compared with an unexposed group (OR=4.375).⁹ However, neither codeine nor propoxyphene exposure was significantly associated with total major malformations (OR=0.920 and OR=0.965, respectively).⁹ The authors also found no increased risk of total major malformations and specific malformations, including cardiovascular, CNS, NTD, GI, genitourinary, and cleft palate types, with opioid exposure.⁹

Likewise, a large population-based cohort study in Norway comparing women who had used codeine during pregnancy with those who had not found no significant association between maternal codeine use and survival (OR=0.9), congenital malformation (OR=0.9), or neonatal respiratory depression (OR=0.9).¹⁰ Other literature has also found no increased risk of NTDs with maternal codeine use.¹¹

Critical review

The study by Broussard et al⁶ was criticized for the possibility of recall bias owing to self-reporting,^{12,13} especially as there was an average time interval of 9 to 11 months between delivery and interview, with patients being asked about exposures up to 3 years in the past. The 3 other studies were less prone to this form of error.^{8,10,11} In the case study by Shaw et al, interviews were done on average between 4.6 and 4.9 months postpartum.¹¹ In the study by Nezvalová-Henriksen et al, information was collected from the patients at 3 set points during their pregnancies,¹⁰ which would limit the incidence of recall error. Yazdy et al used an additional control group of women whose offspring had non-NTD congenital malformations⁸; this was a prudent choice in the experimental design to prevent selection bias, as women whose children have congenital malformations would more likely remember details of their pregnancies, including exposures, compared with women with healthy children.¹²

Morphine has also been known to increase apoptosis in human fetal microglia and neurons, and research suggests that opioid exposure in rat embryos might adversely affect neurogenesis and myelination.^{3,14} Hence, inhibition of neural pathfinding might explain the relationship between opioid use and NTDs. Likewise, as opioid receptor density is high in both the CNS and the GI tract,² both of these organ systems could be affected.

Confounding factors such as socioeconomic status, stress, and alcohol consumption might play a role. Also, maternal opioid use was associated with lower levels of education, prepregnancy obesity, and periconceptual smoking.^{6,9} The potential adverse neonatal outcomes could have been related to concomitant conditions or polypharmacy. In the study by Nezvalová-Henriksen et al,¹⁰ 13% of exposed women had chronic conditions such

as arthritis, systemic lupus erythematosus, and fibromyalgia; moreover, 98.3% of the exposed group took codeine in a fixed combination with acetaminophen. The Broussard et al study excluded illicit drug users,⁶ while Yazdy et al did not make an effort to identify them.⁸ Meanwhile, the studies by Nezvalová-Henriksen et al and Shaw et al only reported codeine exposures.^{10,11}

Even if taking opioids results in increased risk of birth defects, the heightened relative risk might lead to a small magnitude of absolute risk.¹² In the study by Broussard et al, only 2.6% of the 17449 case mothers and 2.0% of the 6701 control mothers reported opioid use.⁶ Maternal opioid use in the other studies ranged from 1.6% to 3.9%.^{8,10,11} Furthermore, some of these congenital defects are quite rare to begin with. Hypoplastic left heart syndrome has an incidence of 2.4 per 10000 live births; a 2.4-fold increase in risk would still only translate to an incidence of 5.8 per 10000 live births (0.06%).⁶

Conclusion

To date, the knowledge concerning the safety of periconceptional opioid use is still limited and inconclusive. It is possible that maternal opioid use is merely indicative of underlying concomitant conditions that might adversely affect the fetus. Medical practitioners should judiciously consider a risk-benefit analysis before making their decisions.

Motherisk is conducting a prospective cohort study that aims to compare the safety of opioid medications relative to nonopioid analgesics during pregnancy. This will allow us to add to the body of literature concerning both classes of pain medications so that future treatment schedules can be optimized to lower the incidence of adverse outcomes.

Competing interests

None declared

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in

Toronto, Ont. Mr Chan was a student in the Motherisk program at the time of writing and Dr Koren is Director of the Motherisk Program.

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