

# Safety of the newer class of opioid antagonists in pregnancy

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## Abstract

**Question** I have a patient recently confirmed to be 6 weeks pregnant. For the past 6 months she has been treated for an opioid addiction with buprenorphine-naloxone combination. Should I be concerned about her exposure to this drug combination up to this point of the pregnancy? Should I switch her medication to methadone now that she is pregnant?

**Answer** The limited data on buprenorphine exposure during pregnancy show no increased risk of adverse outcomes in the newborn. There are limited data on naloxone exposure during pregnancy; however, oral use is not expected to be associated with an increased risk of adverse pregnancy outcomes. Physicians treating pregnant women or women who become pregnant while they are stable taking buprenorphine-naloxone treatment are advised to continue this treatment but to consider transition to buprenorphine monotherapy.



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There are limited prevalence data on substance abuse in pregnant women in Canada. In the United States there has been an increase in the prevalence of substance abuse among women, and up to 90% of women who abuse substances are of reproductive age.<sup>1</sup> Further, the proportion of pregnancies that are unintended among opioid-dependent women ranges between 80% and 90%.<sup>2</sup> This makes opioid use and dependence in pregnancy an important health problem. While little information exists about the incidence of treatment of opioid addiction in pregnant women, more than 550 000 women were admitted to US treatment programs in 2007, with roughly 4% being pregnant at the time of admission. In 8.6% of these pregnant women, opioids were the primary substance of abuse at admission.<sup>3</sup>

Although it would be ideal to abstain from taking opioids throughout the course of pregnancy, most opioid-dependent women are unable to do so even under close medical supervision and are at risk of relapse. The pressure from rapid detoxification might cause maternal stress, withdrawal, and fetal stress, which are associated with poor fetal growth, preterm delivery, and fetal death.<sup>4</sup> Abrupt opioid withdrawal in pregnancy might also increase the likelihood of abortion, premature labour, miscarriage, and stillbirth.<sup>5</sup> The current criterion standard for managing opioid dependence in pregnant women is methadone maintenance.<sup>6</sup>

## Buprenorphine use during pregnancy

A comprehensive 2003 review covering 309 pregnancies

across several cohorts (case series, prospective studies, controlled studies) reported overall equal or lower incidence of neonatal abstinence syndrome (NAS) with buprenorphine exposure compared with methadone exposure.<sup>7</sup>

A comprehensive 2012 review covering several hundred pregnancies across various cohorts (case series, prospective studies, controlled studies; N=31 studies) reported no increased risk of malformations in infants prenatally exposed to buprenorphine.<sup>8</sup> Other neonatal outcomes (gestational age, weight, length, head circumference) were generally unremarkable and within normal limits. Within the various cohorts, the unweighted mean incidence of NAS was 44% to 48%, with approximately 50% of neonates being treated for NAS. The mean time to NAS onset was 52.7 hours.<sup>8</sup> Other studies have reported similar results.<sup>9,10</sup> This review also discussed several small studies (n=9) examining various developmental outcomes, such as sleep patterns, stress signs, visual maturation, and neurodevelopment, in infants exposed prenatally to buprenorphine. Most studies reported no abnormal adverse outcomes with the exception of 1 showing significantly lower scores in the emotional availability ( $P<.05$ ) and language scales ( $P<.001$ ) when compared with a nonexposed group.<sup>8,11</sup> It should be noted that in most cases the children were exposed to other drugs in addition to buprenorphine, with such multiple exposures making it difficult to ascertain whether reported effects on cognitive function were the result of prenatal exposure to buprenorphine or whether they were caused by genetic and environmental factors

and the mother's intake of additional drugs, including alcohol and tobacco.

The MOTHER (Maternal Opioid Treatment: Human Experimental Research) study, a multicentre randomized controlled trial included in the above review, compared 58 newborns exposed to buprenorphine with 73 newborns exposed to methadone; in both groups, their mothers had been treated for opioid dependence during pregnancy.<sup>12</sup> The authors reported no difference in the incidence of NAS between the groups of infants; however, the infants exposed to buprenorphine required significantly less morphine for treatment of NAS (mean dose 1.1 mg vs 10.4 mg,  $P<.009$ ), had significantly shorter hospital stays (10.0 days vs 17.5 days,  $P<.009$ ), and had significantly shorter durations of treatment for NAS (4.1 days vs 9.9 days,  $P<.003$ ).<sup>12</sup>

### Buprenorphine-naloxone use during pregnancy

Rodent reproductive studies on naloxone use during pregnancy fail to show evidence of embryotoxicity or teratogenicity at dosages several times higher than those recommended for humans.<sup>13,14</sup> When naloxone is taken orally it is not detected in the blood, and with sublingual use systemic levels are low.<sup>15</sup> Thus, with proper use no adverse effects are expected. However, when it is used intravenously or intranasally, such as when it is abused, it causes severe withdrawal in opioid-dependent patients.<sup>15</sup>

A retrospective chart review of opioid-dependent mothers treated with buprenorphine-naloxone film started either before pregnancy ( $n=8$ ) or during the first trimester ( $n=2$ ) reported no significant adverse maternal or neonatal outcomes when compared with mothers treated with buprenorphine only. Of their newborns ( $n=10$ ), 80% were full term with normal birth parameters (Apgar scores, head circumference, birth weight, infant length). Four neonates were treated for NAS, and this rate of occurrence is similar to that in neonates exposed to buprenorphine monotherapy. Likewise, length of treatment and number of days in hospital were also comparable to those for infants exposed to buprenorphine monotherapy.<sup>16</sup> A recent review compared the outcomes of these 10 pregnancies to outcomes from 7 previously published studies examining treatment of opioid-dependent pregnant women. There were no significant differences in maternal or neonatal outcomes for buprenorphine-naloxone compared with buprenorphine, methadone, or methadone-assisted withdrawal.<sup>17</sup>

### Conclusion

Evidence has shown buprenorphine maintenance therapy during pregnancy to be an effective treatment for opioid dependence. It has not been associated with increased risk of adverse pregnancy outcomes and it might be considered an alternative to methadone. In Canada, buprenorphine is available as a single-agent product through Health Canada's Special Access Programme<sup>6</sup> and in a sublingual combined formulation with naloxone,

an opioid antagonist used to reduce addiction relapse.<sup>15</sup> Women who become pregnant while they are stable taking buprenorphine-naloxone treatment are advised to continue their treatment but to transition to buprenorphine monotherapy<sup>6,18</sup> owing to concerns about withdrawal if used improperly (eg, injection). However, when choosing a treatment for opioid dependence during pregnancy, the benefits and risks of buprenorphine and methadone should be considered. If buprenorphine is taken near term, infants should be observed for NAS at birth. 🌸

#### Competing interests

None declared

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## MOTHERISK

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Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the *Canadian Family Physician* website ([www.cfp.ca](http://www.cfp.ca)) and also on the Motherisk website ([www.motherisk.org](http://www.motherisk.org)).