

Obstetrics and gynaecology

Are prescription opioids safe to use in pregnancy?

Prescription opioids used in early pregnancy are not associated with a substantial increase in the risk of most congenital malformations, although a small increase in the risk of oral clefts associated with their use is possible, a large US study has found.

The study used two sources of information: pregnancy cohorts nested in the Medicaid Analytic eXtract (MAX), which includes data on healthcare use for Medicaid beneficiaries across the US, from 2000 to 2014; and the IBM Health MarketScan Research Database (MarketScan), which includes data on healthcare use from a nationwide sample of commercially insured beneficiaries, from 2003 to 2015.

The definition of opioid exposure was based on two filled prescriptions during the first trimester, on the assumption that if a woman refilled her prescription for opioids, she was probably taking them. Pregnancies were considered unexposed if women did not fill an opioid prescription from 90 days before the date of the estimated last menstrual period to the end of the first trimester.

Based on congenital malformations found to have a possible association with opioid exposure in previous studies the primary study outcomes included: congenital malformations overall, cardiovascular malformations overall, ventricular septal defect, secundum atrial septal defect/non-prematurity related patent foramen ovale, neural tube defect, clubfoot, and oral cleft (cleft lip and/or cleft palate).

Overall, the study included 82,901 pregnant women exposed to prescription opioids during the first

trimester drawn from more than 2.7 million pregnancies. Of those in the MAX cohort 4.4% were dispensed two or more opioid prescriptions during the first trimester, compared with 1.1% in the MarketScan group.

Women prescribed opioids were more likely to be diagnosed with pain conditions, to have comorbid psychiatric and medical conditions, to be dispensed other drugs in the first trimester, and to have higher measures of general comorbidity.

Relative risk (RR) values were adjusted for the following potential confounders: indications for opioids, maternal demographic characteristics, chronic comorbidities, concomitant medication use, and general markers of illness.

Pooled estimates did not suggest a substantially increased risk for congenital malformations with opioid exposure:

- Overall risk for congenital malformations, RR 1.06 (95% CI: 1.02-1.10)
- Cardiovascular malformations overall, RR 1.09 (95% CI: 1.00-1.18)
- Ventricular septal defect, RR 1.07 (95% CI: 0.95-1.21)
- Atrial septal defect/patent foramen ovale, RR 1.04 (95% CI: 0.88-1.24)
- Neural tube defect, RR 0.82 (95% CI: 0.53-1.27)
- Clubfoot, RR 1.06 (95% CI: 0.88-1.28)

However, the pooled risk estimate for oral cleft remained high after adjustment:

- RR 1.21 (95% CI: 0.98-1.50). This increase was explained by a higher risk of cleft palate, RR 1.62 (95% CI: 1.23-2.14)

Estimates were close to null for cleft lip, RR 1.02 (95% CI: 0.69-1.51) and cleft palate with cleft lip, RR 1.08 (95% CI: 0.79-1.47).

Because of the role of endogenous opioids as regulators of growth and development, a teratogenic effect for prescribed opioids is plausible. However, evidence of this from epidemiological studies is limited and conflicting and there has been considerable uncertainty as to whether or not there is an association between opioid use and congenital malformations.

The study authors conclude: 'Overall, our findings suggest that prescription opioids used in early pregnancy are not associated with a substantial increase in risk for most of the malformation types considered, although clinicians should be aware of the potential for a small increase in the risk of oral clefts, and counsel patients about this risk.'

DR JEZ THOMPSON

Bateman BT, Hernandez-Diaz S, Straub L et al. Association of first trimester prescription opioid use with congenital malformations in the offspring: population based cohort study. *BMJ* 2021;372:n102