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Opioid analgesic use during pregnancy and risk of adverse outcomes: a target trial emulation

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Abstract

Background and Aims: Evidence on opioid analgesic safety during pregnancy remains inconclusive. We employed a sequential target trial emulation (TTE) to generate real-world evidence on the risks of adverse maternal and neonatal outcomes following opioid analgesic exposure during pregnancy.

Design and Methods: We linked records of all pregnancies resulting in a birth in NSW (2013-2019) to prescription medicine dispensing, hospital admissions, and death records. We created a new trial for each gestational week, assigning eligible women as opioid initiators or non-initiators based on whether

they were dispensed a prescription opioid that week. We employed inverse probability weighting to balance baseline covariates for each trial and incorporated treatment weights in logistic regression models to estimate odds ratio for neonatal outcomes, postpartum haemorrhage, and severe maternal morbidity, and pooled logistic regression to estimate the hazard ratios for the remaining maternal outcomes. Bootstrapping was used to calculate 95% confidence intervals (CI).

Results: The TTE yielded 18,360,776 trials (511,357 pregnancies; 398,944 women), consisting of 26,984 opioid initiators and 18,333,792 non-initiators. Compared with non-initiators, opioid initiators had a higher risk of preterm premature rupture of membranes (OR 1.12, 95% CI 1.00–1.26), preterm birth (HR 1.27, 95% CI 1.20–1.35), severe maternal morbidity (OR 1.05, 95% CI 0.99–1.12), severe neonatal morbidity (OR 1.08, 95% CI 1.00–1.17), stillbirth (OR 1.28, 95% CI 1.04–1.59) and neonatal death (OR 1.29, 95% CI 0.94–1.79). There was no increased risk of placental abruption, postpartum haemorrhage, low Apgar score, small for gestational age or neonatal abstinence syndrome.

Conclusions: We found a slight increase in the risk of certain maternal and neonatal outcomes among opioid initiators. However, further research is needed to determine whether these risks are directly attributable to opioid initiation or instead reflect reverse causation or unmeasured confounding factors, such as underlying maternal health conditions that led to prescription opioid use.