Opioid analgesic use during pregnancy and risk of adverse outcomes

Bianca Varney[1,2], Malcolm B Gillies[1], Duong Tran[2], Ximena Camacho[1], Jonathan Brett[1,3], Sonia Hernandez-Diaz[4], Krista Huybrechts[4,5], Timothy Dobbins[1], Antonia Shand[6,7], Sallie-Anne Pearson[1], Helga Zoega[8*], Alys Havard[1,2*]

The Difference is Research

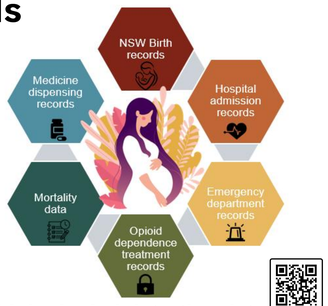
Background

- There is little evidence on the safety of opioids used to treat pain (*analgesics*) during pregnancy.
- To address this gap, we applied a method called ***target trial emulation***, which uses real-world data to replicate the design of a randomised clinical trial.

Objective

To investigate whether prescribed opioid analgesic exposure during pregnancy increases the risks of adverse maternal and neonatal outcomes employing a target trial emulation.

Methods



Linked administrative data
All pregnancies resulting in a birth in NSW

Study Cohort:
- Conception: July 2013 – March 2019
- Aged 12 to 60 years
- NSW resident
- No opioids dispensed in 90 days pre-pregnancy or during pregnancy

No diagnosis or treatment of:
- Cancer (past year)
- Opioid dependence (past 2 years)

Exposure:
Exposed: Pregnant people dispensed opioids subsidised under the Pharmaceutical Benefits Scheme.
Unexposed: No opioid dispensed.

Outcomes:
Maternal: preterm premature rupture of membranes, preterm birth, placental abruption, postpartum haemorrhage, severe maternal morbidity complications.

Neonatal: stillbirth, neonatal death, severe neonatal morbidity complications, low Apgar score, small for gestational age, neonatal abstinence syndrome.

Statistical Analysis:
Estimated the intention-to-treat effect:
- Preterm birth, placental abruption, preterm premature rupture of membranes: Pooled logistic regression used to calculate hazard ratios.
- Remaining outcomes: Marginal structural models used to calculate odds ratios
- 95% confidence intervals (CI) were obtained using 200 bootstrap samples.

Confounding:
Inverse probability of treatment weighting was used to reweight unexposed to make them comparable to opioid exposed across baseline characteristics.

This adjustment was important because pregnancies exposed to opioids were more likely to involve mothers who had:
- Smoked during pregnancy
- Mental health conditions
- Used medicines (e.g., pain medicines)

The weighting accounted for
- Sociodemographic
- Obstetric history
- Maternal conditions
- Maternal medicine use
- Healthcare utilisation

Results

Maternal and Neonatal Outcomes	Opioid exposed	Unexposed	Risks
	n* (%)	n* (%)	
Preterm premature rupture of membranes	525 (0.13)	9690 (0.06)	Increased risk
Preterm birth	2147 (10.2)	17974 (8.5)	Increased risk
Stillbirth	148 (0.5)	74246 (0.4)	Increased risk
Neonatal death	86 (0.3)	31627 (0.2)	Increased risk
Placental abruption	166 (0.05%)	2597 (0.03)	No risk
Postpartum haemorrhage	3154 (11.7)	210415 (11.5)	No risk
Severe maternal morbidity complications	1873 (6.9)	996421 (5.4)	No risk
Severe neonatal morbidity complications	1304 (4.7)	665457 (3.6)	No risk
Low Apgar score	690 (2.5)	373426 (2.0)	No risk
Small for gestational age	1965 (7.2)	1449985 (7.8)	No risk
Neonatal abstinence syndrome	83 (0.3)	25951 (0.1)	No risk

*number reflects the number of target trials, not the number of pregnancies

Cautious Interpretation

We are exploring whether *increased risks* are due to opioid exposure itself or the underlying conditions that led to treatment.

An **example** of how an underlying condition could cause an *increased risk*

What we don't see in the data	Intrauterine death → Outpatient induction of labour → Opioid dispensed for pain → Stillbirth → Increased risk
What we see in the data	

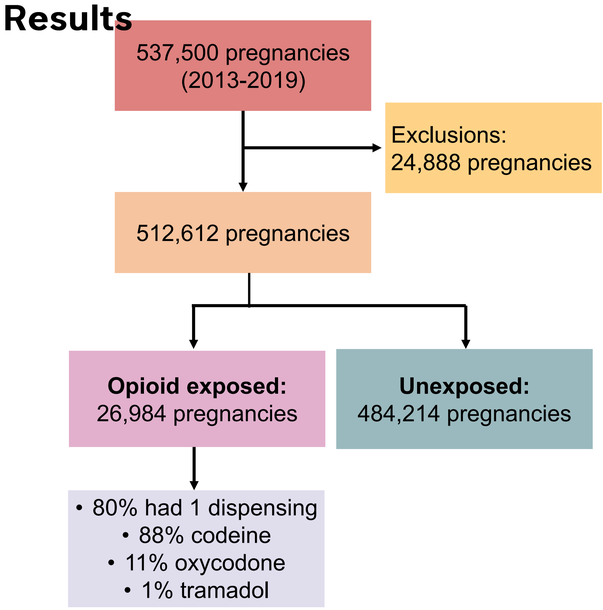
Conclusion

Key Findings:
- We observed a small increase in the risk of certain maternal and neonatal outcomes among pregnant people exposed to opioids.

What This Means:
- More research is needed to understand whether these risks are directly caused by exposure to opioids, or if they are related to other factors, such as existing health conditions that led to the prescription in the first place.

Contact: b.varney@unsw.edu.au

Results



*Contributed equally as senior author. [1] Medicines Intelligence Research Program, School of Population Health, UNSW; [2] National Drug and Alcohol Research Centre, UNSW; [3] St Vincent's Hospital Clinical School, 390 Victoria Street, Darlinghurst NSW 2010, Australia; [4] Department of Epidemiology, Harvard T.H. Chan School of Public Health; [5] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; [6] Department of Maternal Fetal Medicine, Royal Hospital for Women, Randwick, Sydney, Australia; [7] Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, Sydney, Australia; [8] Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland