

## Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: cohort study of 151,141 singleton pregnancies

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### Study question:

Is *in utero* exposure to five over-the-counter (non-prescription) analgesics (paracetamol, ibuprofen, aspirin, diclofenac, naproxen) associated with offspring health outcomes?

### Summary answer:

Consumption of over-the-counter analgesics during pregnancy, either as single compounds or in combinations, is significantly associated with a variety of adverse offspring health outcomes.

### What is known already:

A high percentage of pregnant women use over-the-counter analgesics during pregnancy globally. Some of these compounds such as paracetamol are considered safe to use, while contraindications exist for others, such as NSAIDs use beyond gestational week 30. Current evidence regarding the safety of use during pregnancy in humans is largely conflicting. Results from many published human studies on the topic suffer from limitations including use of small cohorts, short study time or failure to adjust for important confounders. These may explain conflicting results that cause significant concern regarding evidence-based prenatal guidance on use during pregnancy.

### Study design, size, duration:

Retrospective cohort study using the Aberdeen Maternity and Neonatal Databank. Data from 151,141 singleton pregnancies over 30 years (between 1985 and 2015) were used. Consumption of paracetamol, ibuprofen, aspirin, diclofenac and naproxen during pregnancy was recorded in medical notes of each woman. In our analysis, the control group was pregnancies where no analgesic was consumed, and the exposure groups included pregnancies with over-the-counter analgesic consumption either in combinations or as single compound use.

### Participants/materials, setting, methods:

Maternal baseline characteristics were compared using  $\chi^2$  tests for categorical variables and Mann-Whitney for continuous variables (significance at  $<0.05$ ). Premature delivery, stillbirth, neonatal death, baby weight, neonatal unit admission, APGAR score at 1 and 5 minutes, neural tube defects, amniotic band defects, gastroschisis, and, in males only, hypospadias and cryptorchidism, were the outcomes assessed. Crude (cORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated using logistic regression to control for confounders.

### Main results and the role of chance:

The overall prevalence of over-the-counter analgesics use during pregnancy was 29.1%, increasing over the 30-year study period, to over 60% of women in the last seven years of the study. 83.7% of those women reported first trimester use when specifically asked at their first antenatal clinic visit. Pregnancies exposed to at least one of the five analgesics were independently associated with increased risks for premature delivery  $<37$  weeks (aOR=1.50, 95%CI 1.43-1.58), stillbirth (aOR=1.33, 95%CI 1.15-1.54), neonatal death (aOR=1.56, 95%CI 1.27-1.93), birthweight  $<2,500$ g (aOR=1.28, 95%CI 1.20-1.37), birthweight  $>4,000$ g (aOR=1.09, 95%CI 1.05-1.13), admission to neonatal unit (aOR=1.57, 95%CI 1.51-1.64), APGAR score  $<7$  at 1 minute (aOR=1.18, 95%CI 1.13-1.23) and 5 minutes (aOR=1.48, 95%CI 1.35-1.62), neural tube defects (aOR=1.64, 95%CI 1.08-2.47) and hypospadias (aOR=1.27, 95%CI 1.05-1.54 males only). Associations of paracetamol alone with high birth weight, neural tube defects and hypospadias were not significant in the adjusted analysis. Diclofenac consumption was associated with significantly decreased odds of stillbirth (aOR=0.59, 95%CI 0.41-0.87).

### Limitations, reasons for caution:

Our data were based on medical notes; however, consumption is self-reported, and details on the timing, dosage, product type (single-ingredient vs combination) and administration type were not available in the database. Our study only considered neonatal health outcomes and longer-term follow-up of the offspring was not available at this time.

### Wider implications of the findings:

This is one of the largest and most comprehensive studies into analgesic use in pregnancy. The increased risks of adverse neonatal outcomes associated with non-prescribed, over-the-counter, analgesics use during pregnancy indicate that healthcare guidance for pregnant women regarding analgesic use should be re-assessed.

**Trial registration number:** N/A

**Study funding:** Yes

**Funding source:** Funding by national/international organization(s)