Major malformations after first-trimester exposure to aspirin and NSAIDs

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CRD summary
The authors concluded that exposure to aspirin or NSAIDs during the first trimester of pregnancy was associated with the risk of gastroschisis (aspirin), cardiac malformations (NSAIDs) and orofacial malformations (naproxen). The authors' conclusion reflected the evidence presented. However, due to a lack of validity assessment and reliance upon observational studies, the reliability of the authors conclusions is unclear.

Authors' objectives
To determine if there is an association between aspirin and non-steroidal anti-inflammatory drug (NSAID) use and the risk of congenital malformations

Searching
MEDLINE (1966-2008), EMBASE (1980-2008), EBM reviews, DARE and Cochrane Database of Systematic Reviews were searched for studies in any language with an English abstract. Internet sources, including Google Scholar, and citations in selected articles were searched. Search terms were reported.

Study selection
Eligible studies were controlled prospective or retrospective studies on human populations that examined maternal exposure to aspirin or NSAIDs during the first trimester of pregnancy and reported congenital malformations. Studies that reported only premature closure of the ductus arteriosus as a primary outcome were excluded from the review.

Included studies were either case-control or cohort studies, with the exception of one randomised controlled trial. Data sources used in the studies included registries (malformation, prescription and health registries), interviews, surveys, tests and medical records. NSAIDs included both cyclo-oxygenase-1 (COX-1) and COX-2 inhibitors. Types of NSAID included in the review were: ibuprofen, naproxen, diclofenac, ketoprofen, tenoxicam, rofecoxib, celecoxib. Types of congenital malformations reported were: all malformations; cardiac (transpulmonary gradient), ventricular and atrial septal defects; central nervous system; facial; cardiac; respiratory; digestive; urogenital; musculoskeletal; endocardial cushion defects; all muscular defects; orofacial clefts; pulmonary hypertension of the new born; gastroschisis; cardiac malformations; aortic stenosis; coarctation; hypoplastic left ventricle; transposition of the great arteries; conotruncal defects; neural tube defect; cleft lip with or without cleft palate; and posterior cleft palate.

Two reviewers independently selected the studies for inclusion in the review. Any disagreement was resolved by consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Odds ratios (ORs) and 95% confidence intervals (CI) were extracted for from the studies or calculated from the numbers of events. Details of any variables used to adjust the analyses of the case-control studies, such as maternal age or parity, were extracted.

Two reviewers independently extracted data. Any discrepancies were resolved by discussion.

Methods of synthesis
For all outcomes, odds ratios and 95% CIs were presented for each study.

Results of the review
Thirty studies were included in the review (22 case control studies, seven cohort studies and one RCT). Sample sizes
ranged from 22 to 582,745.

**Overall congenital malformation:**

Aspirin (11 studies). Three studies found that use of aspirin in the first trimester of pregnancy was associated with a statistically significant increased risk of overall congenital malformation. Eight studies found no statistically significant association between the use of aspirin and risk of overall congenital malformations. Only case control studies (two studies) showed a statistically significant association between the use of aspirin and the risk of overall congenital malformations (OR 1.64, 95% CI 1.30 to 2.04).

NSAIDs (three studies). One study found that use of NSAIDs in the first trimester of pregnancy was associated with a statistically significant increased risk of overall congenital malformations. Two studies found no association between the use of NSAIDs and the risk of overall congenital malformations.

**Gastrochisis:**

Aspirin (eight studies). Six studies found that the use of aspirin during the first trimester of pregnancy was associated with a statistically significant increased risk of gastrochisis. Two studies found no association between the use of aspirin and the risk of gastrochisis.

NSAIDs (three studies). All three studies found no association between the use of the NSAID ibuprofen during the first trimester of pregnancy and the risk of gastrochisis.

**Cardiac malformations:**

Aspirin (eight studies). All eight studies found no association between the use of aspirin during the first trimester of pregnancy and the risk of cardiac malformations.

NSAIDs (eight studies). Three studies found that the use of NSAIDs during the first trimester of pregnancy was associated with an increased risk of cardiac malformations. Five studies found no association between the use of NSAIDs and the risk of cardiac malformations.

**Orofacial malformations:**

Aspirin (three studies). All three studies found no association between the use of aspirin during the first trimester of pregnancy and the risk of orofacial malformation.

NSAIDs (two studies). Both studies found a statistically significant association between the use of NSAIDs (including naproxen, ibuprofen and diclofenac) during the first trimester of pregnancy and the risk of orofacial malformations.

**Authors' conclusions**

Exposure to aspirin or NSAIDs during the first trimester of pregnancy was associated with an increased risk of gastrochisis (aspirin), cardiac malformations (NSAIDs) and orofacial malformations (naproxen).

**CRD commentary**

This review addressed a clear research question and was supported by adequate inclusion criteria. The search strategy was adequate. However, there was no attempt to search for unpublished material, which meant that relevant articles may have been missed. There was no assessment of validity, which meant that the reliability of the findings could not be assessed. The conclusions reflected the evidence presented. However, the reliance upon observational studies (although representing the best available evidence) together with the lack of study quality assessment means that the reliability of the authors conclusions is unclear.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.
Research: The authors stated that further studies on the teratogenicity of aspirin and NSAIDs were needed. In particular, such studies were needed with larger sample sizes, with full data on time and length of exposure, dosage and types of drug and with appropriate control groups, with all participants matched or adjusted for maternal age, comorbidities and tobacco and alcohol use. Studies were also needed to identify candidate genes that might be associated with higher prenatal toxicity of aspirin and NSAID use.

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