Taking NSAIDs during pregnancy

Is it safe?

Karen Jackson-Northey Michael F. Evans, MD, CCFP

Nielsen GL, Sorensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observation study and case-control study. BMJ **2001;322(7281):266-70.**

Research question

Are nonsteroidal anti-inflammatory drugs (NSAIDs) associated with adverse fetal outcomes when taken during pregnancy? Specifically, is there risk of miscarriage, congenital abnormalities, low birth weight, or prematurity?

Type of article and design

Population-based primary research article using both cohort and case-control designs.

Relevance to family physicians

Anti-inflammatories are thought to be one of the most commonly prescribed drugs during pregnancy.[1] A recent study of 101 newborns in Michigan showed that 49.5% had NSAIDS detected in their meconium.[2] Given the high use of both prescription and over-the-counter NSAIDs, knowledge of any adverse effects of taking them during pregnancy is important for family doctors.

To date, acetylsalicylic acid (ASA) has been the most thoroughly studied NSAID. The general (but not unanimous) consensus is that low-dose (<3 g/d) ASA is not associated with increased risk of congenital anomalies, prematurity, low birth weight, or miscarriages.[3] Research on other NSAIDs, however, particularly the newer cyclooxygenase-2 inhibitors, is scant, with very few population-based studies.

Some current articles in the literature recommend stopping NSAIDS 6 to 8 weeks before delivery.[4,5] This reduces the possible risk of early closure or constriction of the ductus arteriosus, persistent fetal pulmonary hypertension, intracranial hemorrhages, and renal toxicity in fetuses.[2,4] This study did not address these end points.

Overview of study and outcomes

The study was based in a Danish community, where a central pharmacy database kept records of all reimbursed prescription drugs (including NSAIDs equivalent to >400 to 600 mg of indomethacin). The local birth registry and hospital discharge summaries were the sources of the rest of the raw data.

The cohort study compared pregnancies where mothers had used NSAIDs (n = 1462) with pregnancies where they had not (n = 17 259) and looked at the incidence of birth defects, prematurity, and low birth weight. Pregnancies where mothers had used NSAIDs early (30 days before conception until end of first trimester) were analyzed for risk of congenital anomalies; pregnancies where mothers had used NSAIDs late (ie, during second or third trimester) were analyzed for low birth weight (<2500 g) or prematurity (birth at <37 weeks). Logistic analysis was used to calculate odds ratios (OR), and adjustments were made for mothers' age, smoking status, and birth order.

In the case-control study, miscarriages in pregnancies with or without NSAID use in the first trimester (63/4268) were compared with live births with or without NSAID use in the third trimester (318/29 750). Data were grouped according to time between NSAID purchase and discharge from hospital (1, 2 to 3, 4 to 6, 7 to 9, and 10 to 12 weeks). Again, logistic analysis was used to calculate ORs, and adjustments were made for mothers' age.

Results

In the cohort study, there was no statistical association between filling NSAID prescriptions and risk of congenital abnormalities, low birth weight, or preterm birth. In fact, no specific trend in anomalies was noted. The case-control study, however, showed significant risk of miscarriage. A general trend

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail michael.evans@utoronto.ca or by fax (416) 603-5821.

Ms Jackson-Northey *is a fourth-year medical student at the University of Toronto.* **Dr Evans** *practises in the Department of Family and Community Medicine at the Toronto Western Hospital, University Health Network, and teaches in the Department of Family and Community Medicine at the University of Toronto.*

← FOR PRESCRIBING INFORMATION SEE PAGE 628

indicated higher risk associated with filling prescriptions closer to time of miscarriage. The OR for 1 week between NSAID purchase and discharge after miscarriage was 6.99 (95% confidence interval [CI] 2.75 to 17.54); the OR for 10 to 12 weeks between purchase and discharge was 1.26 (95% CI 0.85 to 1.87).

Analysis of methodology

This type of trial is lower in the hierarchy of scientific investigation, but the only method available in this case. It would be impossible ethically to investigate adverse fetal effects using a randomized controlled trial. The strengths of this study included a large population sample with no selection bias and pharmacy and discharge summary databases validated through other studies.

Because the study was done retrospectively, the authors were confined to hard end points and database constraints. This meant that over-the-counter purchases of NSAIDs were not accounted for; the various types of NSAIDs were not differentiated; and prescription filling, rather than actual consumption of drugs, was the independent variable. Researchers assumed that, once a prescription was filled, the drug was taken.

Regarding the observation of a higher incidence of miscarriages with NSAID use closer to time of miscarriage, it is unclear whether the pain of miscarriage increased use of NSAIDs or whether the drug itself caused the event. It is possible that women with disease requiring NSAIDs during pregnancy have a higher incidence of miscarriages regardless of drug use. Last, the database in this study did not include mothers' smoking status, which could confound results.

Application to clinical practice

While this study showed an association between miscarriage and NSAID use, there are several alternative explanations of the observed correlation and several possible confounding factors. As the authors conclude, the result is a new observation and needs further research to investigate a possible causative link. It is worth our noting NSAID use by patients

who have miscarriages and informing them of this recently published observation.

The cohort study lends additional support to the safety of NSAIDS regarding teratogenicity and risk of prematurity or low birth weight. Patients can be reassured on this issue.

The study did not investigate incidence of persistent pulmonary hypertension of newborns, ductus arteriosus constriction, renal dysfunction or toxicity, or bleeding, all of which have been linked with NSAID use during pregnancy.

Bottom line

- Using NSAIDs during early or late stages of pregnancy is not associated with congenital anomalies, prematurity, or low birth weight.
- There is a significant link between NSAID use and miscarriage in the first trimester. This association could be secondary to underlying disease caused by NSAID use or caused by the pain of miscarriage.
- Further research is needed.

Points saillants

- Le recours aux AINS durant les premières ou les dernières étapes de la grossesse n'est pas associé à des anomalies congénitales, à une naissance prématurée ou à un faible poids à la naissance.
- Il existe une association significative entre l'utilisation d'AINS et les avortements spontanés durant le premier trimestre. Cette association pourrait être secondaire à une maladie sous-jacente causée par l'utilisation d'AINS ou par la douleur occasionnée par la fausse-couche.
- Il est nécessaire d'effectuer plus de recherches.

References

1. Bonati M, Bortolus R, Marchetti F, Romero M, Tognoni G. Drug use in pregnancy: an overview of epidemiological (drug utilization) studies. *Eur J Clin Parmacol* 1990;38(4):325-8.
2. Alano MA, Ngougmna E, Ostrea EM Jr, Konduri GG. Analysis of nonsteroidal antiinflamatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. *Pediatrics* 2001;107(3):519-23.
3. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. *Lancet* 1994;343(8898):619-29.
4. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy and lactation. *Arch Intern Med* 2000;160(5):610-9.
5. Ostensen M, Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? *Drug Saf* 1998;19(5):389-410.