GYNECOLOGY

Use of nonsteroidal antiinflammatory drugs during pregnancy and the risk of miscarriage

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BACKGROUND: Nonsteroidal antiinflammatory drugs are among the medications most widely used by pregnant women, and previous studies have reported an increased risk of miscarriage that is associated with nonsteroidal antiinflammatory drug use during pregnancy. Although the findings have not always been consistent, there is a well-established mechanism for the association: nonsteroidal antiinflammatory drugs inhibit the production of prostaglandin, which is essential for successful embryonic implantation. Abnormal implantation increases the risk of miscarriage.

OBJECTIVE: The purpose of this study was to examine the impact of nonsteroidal antiinflammatory drug use in early pregnancy on the risk of miscarriage, especially regarding the timing and duration of use.

STUDY DESIGN: We conducted a cohort study among pregnant members of Kaiser Permanente Northern California, an integrated healthcare delivery system. Pregnant Kaiser Permanente Northern California members (N=1097) were recruited very early in pregnancy (median gestational age at enrollment, 39 days) to achieve optimal ascertainment of miscarriage, including early miscarriages, which are often missed in studies of miscarriages. Based on the use of nonsteroidal antiinflammatory drugs and acetaminophen, which has similar indication as nonsteroidal antiinflammatory drugs, 3 cohorts were formed: (1) women who used nonsteroidal antiinflammatory drugs only, (2) women who used acetaminophen only (to control for indication), and (3) women who used neither nonsteroidal antiinflammatory drugs nor acetaminophen (unexposed control subjects). Among all eligible women contacted, 63% participated in the study. Miscarriages were ascertained from both electronic medical record data and directly from interviews with participants. The Cox proportional hazards model with accommodation for left truncation was used to examine the risk of miscarriage associated with the use of nonsteroidal antiinflammatory drugs and acetaminophen during pregnancy; we controlled for potential confounders.

RESULTS: After an adjustment for multiple confounders that included maternal age, previous miscarriage, multivitamin use, caffeine drinking, and smoking during pregnancy, we found that nonsteroidal antiinflammatory drug use during pregnancy was associated with a statistically significant increased risk of miscarriage compared with both unexposed control subjects (adjusted hazard ratio, 1.59; 95% confidence interval, 1.13–2.24) and acetaminophen users (indication control subjects; adjusted hazard ratio, 1.45; 95% confidence interval, 1.01–2.08). The risk was largely due to nonsteroidal antiinflammatory drug use around conception (adjusted hazard ratio, 1.89; 95% confidence interval, 1.31–2.71) with a statistically significant dose-response relationship: adjusted hazard ratio, 1.37 (95% confidence interval, 0.70–2.71) for nonsteroidal antiinflammatory drug use of ≤14 days; adjusted hazard ratio, 1.85 (95% confidence interval, 1.24–2.78) for nonsteroidal antiinflammatory drug use of ≥15 days. The association was stronger for early miscarriage (<8 weeks gestational age): adjusted hazard ratio, 4.08 (95% confidence interval, 2.25–7.41). Women with lower body mass index (<25 kg/m^2) appeared to be more susceptible to the effect of nonsteroidal antiinflammatory drug use around conception (adjusted hazard ratio, 3.78; 95% confidence interval, 2.04–6.99) than women with high body mass index (≥25 kg/m^2; adjusted hazard ratio, 1.03; 95% confidence interval, 0.61–1.72).

CONCLUSION: After we controlled for confounding by indication, nonsteroidal antiinflammatory drug use around conception was associated with an increased risk of miscarriage with a dose-response relationship. In addition, women with lower body mass index could be especially vulnerable to the effects of nonsteroidal antiinflammatory drug use around the time of embryonic implantation, although this new observation must be confirmed in future studies.

Key words: miscarriage, NSAID, pregnancy

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most commonly used over-the-counter medications among pregnant women.[1] The main pharmacologic effect of NSAIDs is to inhibit the biosynthesis of prostaglandin. However, the presence of a sufficient amount of prostaglandin is crucial for successful embryonic implantation in early pregnancy.[2–5] Thus, there is a well-established biologic plausibility that exposure to NSAIDs during pregnancy, especially in early pregnancy, could impact normal implantation adversely, thereby increasing the risk of miscarriage. Given this biologic mechanism, the risk is expected to be higher for early miscarriage because of malimplantation. In fact, selective NSAIDs (cyclooxygenase 2 inhibitors) have been classified as pregnancy category C by the US Food and Drug Administration because of the increased pregnancy losses observed in experimental animal studies. A few human studies have reported an increased risk of miscarriage that is associated with NSAID use during pregnancy, especially around the time of conception.[6–9] However, the results have not been consistent, with 2 other studies reporting no increased risk.[10,11] Thus, the risk of NSAID use around conception remains largely ignored by both pregnant women and clinicians, as demonstrated by the fact that NSAIDs remain among the medications most widely used by pregnant women.[1,12]

The current study was designed to overcome some of the weaknesses of

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AJOG at a Glance

Why was this study conducted?

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the medications most widely used by pregnant women; previous studies have reported an increased risk of miscarriage associated with NSAID use during pregnancy. Although the findings have not always been consistent, there is a well-established mechanism for the association: NSAIDs inhibit the production of prostaglandin, which is essential for successful embryonic implantation.

Key Findings

NSAID use around the time of conception increases the risk of miscarriage, and there is a dose-response relationship.

What does this add to what is known?

In addition to a comparison of NSAID users with unexposed control subjects, this study further confirmed the finding by comparing them with acetaminophen-exposed control subjects to remove confounding by indication. Consistent results were found with both control groups, which strengthens the evidence of an underlying association. The study also adds a new finding that the association appears to be stronger among women with a low body mass index (<25 kg/m^2).

previous studies so that more robust results could be provided to determine whether NSAID use during pregnancy, especially around conception, is indeed associated with the risk of miscarriage. Most previous studies were based on linkages of existing records only, with limited ability to control for confounders. The study in which information on confounders was ascertained through in-person interviews had a relatively small number of NSAID-exposed pregnant women because the study was not designed originally to examine NSAID exposure during pregnancy.[7] To examine this important association more thoroughly, the current study designed a natural indication-control cohort by including pregnant women who used acetaminophen only, which has similar indications as, but different pharmacologic effects from, NSAIDs (it does not inhibit prostaglandin biosynthesis in peripheral tissues).

Materials and Methods

The study was approved by the Kaiser Permanente Northern California (KPNC) Institutional Review Board. The study design consisted of an NSAID-exposed cohort, an acetaminophen cohort (indication control subjects), and an unexposed control cohort (used neither NSAIDs nor acetaminophen) among pregnant KPNC members, aged $\geq$18 years old, who lived in the greater San Francisco Bay Area. KPNC women who were pregnant from 2005–2012 and resided in the participating areas were eligible for inclusion in the study. KPNC is an integrated healthcare delivery system that provides healthcare to approximately 28–30% of the underlying service area population. KPNC membership is socioeconomically and racially/ethnically representative of the broader population in the catchment area. All potentially eligible women ($\geq$18 years old) were identified based on positive pregnancy test results from KPNC's Electronic Medical Record (EMR) databases. Women suspected to be pregnant were required by KPNC to have a pregnancy test done at a KPNC laboratory or clinic for confirmation, which ensured complete ascertainment of pregnant members. KPNC pharmacy databases were queried for dispensing and over-the-counter purchases of NSAID and acetaminophen medications among identified pregnant women to form cohorts based on their exposure to NSAIDs or acetaminophen during pregnancy. Based on the pharmacy records, we classified all eligible women from the KPNC EMR database into 3 cohorts. Only 1 pregnancy from each participating woman was included in the study to avoid nonindependence of pregnancy outcomes.

Invitational flyers describing the purposes and procedures of the study were distributed to participating facilities and given to pregnant women who submitted a urine sample for a pregnancy test. The flyer included a postage-paid and self-addressed return refusal postcard for those who did not wish to be contacted for participation. Women with positive tests from whom we did not receive the refusal postcard were contacted by a well-trained female interviewer to determine their eligibility and to ask for their consent to participate in the study.

In this study, women were recruited as soon as possible after their positive pregnancy test so that we could ascertain early miscarriages that are often missed in studies of miscarriage. The median gestational age at recruitment was 39 days (range, 4–91 days), much earlier in pregnancy than most published studies of miscarriage. This enabled the study to identify miscarriages that would have otherwise been missed.

Given that the number of eligible pregnant women in any given week was much greater than our ability to recruit, we randomly selected for recruitment from all eligible women separately from each of the following cohorts: (1) exposed to NSAIDs only, (2) exposed to acetaminophen only (indication matched control subjects), and (3) exposed to neither NSAIDs nor acetaminophen (unexposed control subjects). Women who reported use of NSAIDs immediately before pregnancy (but not during pregnancy) were excluded from the acetaminophen only and unexposed control subjects to avoid any possible misclassification. We excluded those who used both NSAIDs and acetaminophen during pregnancy because the combined exposures made it difficult to separate the individual main effects. In addition, we excluded those who used aspirin, which may possess a somewhat similar pharmacologic effect and pathway to NSAIDs, and who were therefore not suitable for inclusion in either the exposed or the unexposed groups. Selected women were contacted