Clinical Research in Practice: The Journal of Team Hippocrates

Volume 5 | Issue 2 Article 12

2019

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Recommended Citation
DURUDOGAN L. NSAID use increases risk of miscarriage in early pregnancy. Clin. Res. Prac. 2019 Sep 18;5(2):eP1946. doi: 10.22237/crp/1567555860

Clinical Research in Practice
The Journal of Team Hippocrates
VOL 5 ISS 2 / eP1946 / SEPTEMBER 18, 2019
doi: 10.22237/crp/1567555860

NSAID use increases risk of miscarriage in early pregnancy

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ABSTRACT A critical appraisal and clinical application of Li D, Ferber J, Odouli R, Quesenberry C. Use of nonsteroidal anti-inflammatory drugs during pregnancy and the risk of miscarriage. *Am J Ob Gyn.* 2018; 219(3): 275.e1–275.e8. doi: 10.1016/j.ajog.2018.06.002.

Keywords: *NSAIDs, nonsteroidal anti-inflammatory drugs, ibuprofen, acetaminophen, pregnancy, miscarriage, spontaneous abortion*

Clinical Context

Jessica Lewis (pseudonym), a 31 year old G0P0 African American woman with past medical history of hypertension, well-controlled with labetalol, presents to clinic to discuss the possibility of having a baby. She and her husband have been attempting to conceive for the last 3 months. She is currently "hopeful" and without many concerns as the "women in my family haven't had problems getting pregnant." Current BMI is 28 and she has no history of diabetes. Pertinent social determinants of health discussed during the visit include Midwestern residence, college degree recipient, non-smoker, and minimal caffeine consumption. In review of medications, she states that she takes prenatal vitamins and ibuprofen regularly for low back pain, occasional tension headaches, and other generalized aches. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are among the most commonly used over-the-counter medications in the first trimester of pregnancy.[1] Our patient sought guidance on the following question: "A friend told me (that her doctor said) not to take NSAIDs while trying to get pregnant because it can cause miscarriages. Should I not be taking ibuprofen? What do I do about my pain?" The association of NSAID use with miscarriage risk has been a long-debated topic. Prostaglandins are essential for successful implantation and NSAIDs inhibit their production.[2] Although this mechanism provides support to the hypothesis that NSAIDs increase risk of miscarriage early in pregnancy, conflicting conclusions have been drawn from multiple studies. The controversial nature of this topic has made it unclear whether physicians should be warning patients of this risk in the periconceptional period. We sought out an answer for Mrs. Lewis.

Clinical Question

Does NSAID use increase risk of miscarriage in early pregnancy?

Research Article

Li D, Ferber J, Odouli R, Quesenberry C. Use of nonsteroidal anti-inflammatory drugs during pregnancy and the risk of miscarriage. *Am J Ob Gyn.* 2018; 219(3): 275.e1–275.e8. doi: 10.1016/j.ajog.2018.06.002

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ISSN: 2379-4550
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Related Literature

An advanced search using keywords “NSAIDs”, “pregnancy”, and “miscarriage” was conducted through PubMed and Google Scholar and sorted by best match. This generated 483 results on PubMed. Based on title relevance, abstracts were reviewed and papers further assessed for their ability to answer our clinical question. Articles on UpToDate regarding spontaneous abortion risk factors and NSAID safety in pregnancy were read and their listed references taken into account. After narrowing down the most applicable and valid studies, seven papers were chosen for consideration.

A paper by Edwards utilized a prospective cohort design of 2780 pregnant women who were interviewed regarding NSAID use and concluded no increased risk of miscarriage.[3] The study did not analyze patients taking prescription NSAIDs due to insufficient sample size and power, and therefore does not provide any information on the miscarriage risk associated with these medications. In addition, the study does not include an indication control (see below for additional discussion).

A paper by Keim conducted a case-control study that obtained data from a previous prospective cohort study where 3129 pregnant women were interviewed regarding aspirin use and concluded no increased risk of miscarriage.[4] While aspirin is considered an NSAID, our patient is taking ibuprofen and therefore it is uncertain whether the results would apply. The original prospective cohort study took place from 1959 to 1965. In comparison to more recent studies, there were less reports of miscarriages very early in pregnancy possibly due to delayed practices of receiving prenatal care at that time. The consideration of miscarriages early in pregnancy is integral to our patient’s concern as she is not currently pregnant and NSAIDs may adversely affect implantation.

A paper by Daniel conducted a retrospective cohort study analyzing data from online databases on 4495 pregnant women exposed to NSAIDs during the designated time period and concluded no increased risk of miscarriage.[5]

A paper by Nakhai-Pour employed a nested case-control design that looked at data from the Quebec Pregnancy Registry for 4705 women who had a reported miscarriage and concluded an increased risk of miscarriage.[6] A paper by Nielsen included both a population based cohort study of 1462 pregnant women who had filled prescriptions for NSAIDs within a set period of time and a case-control study of 4268 women who had a recorded miscarriage. Data was derived from the Danish birth registry and a prescription registry and an increased risk of miscarriage was concluded.[7]

Reliance on registries for determination of NSAID use and presence or absence of confounding variables is an important limitation of the studies by Daniel, Nakhai-Pour, and Nielsen. Filling a prescription as indicated on the registry is not an accurate measurement of actual use of the drug, nor does it consider over-the-counter NSAIDs.

A feature absent from all of the above studies is an indication control. The indication for which the participants are taking the medication may also be a confounding variable. While certain papers made efforts to consider indication, such as the paper by Nakhai-Pour stratifying based on Systemic Lupus Erythematosus and Rheumatoid Arthritis diagnoses and the paper by Nielsen mentioning that prescriptions were “mostly for benign conditions of the muscles and skeleton”, the lack of a clearly defined indication control allows for possible underlying confounders.[7] For example, a patient taking NSAIDs for a febrile illness may result in a miscarriage due to the underlying medical condition. By adding an indication control such as acetaminophen, which can also be used for fever, a study is better able to control for the indication in which the medication was taken. This ultimately demonstrates a clearer link between NSAIDs and miscarriage.

A 2003 paper by Li discussed their population based cohort study on 1055 interviewed pregnant women and concluded an increased risk of miscarriage.[8] Conducting interviews is a welcomed departure from the strictly registry-based methodology. However, the primary interest of the study was not to determine whether an association between NSAID use and miscarriage exists, and rather the consequences of prenatal magnetic field exposure. This undoubtedly affected the quality of interview techniques to elicit accurate measurements of NSAID use from the participants. The same critique applies to the study’s ability to obtain accurate data on the acetaminophen exposed cohort, their indication control.

A 2018 paper by Li conducted a prospective cohort study created from 1097 pregnant women within the Kaiser Permanente Northern California healthcare system.[2] The study included targeted and thorough interview techniques and an indication control (i.e. acetaminophen exposed cohort), making it the ideal selection for critical appraisal.

ISSN: 2379-4550

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Critical Appraisal

This study looked at 3 cohorts created from 1097 pregnant women within the Kaiser Permanente Northern California (KPNC) healthcare system: 241 who used NSAIDs only, 391 who used acetaminophen only, and 465 who used neither. Centre for Evidence-Based Medicine level of evidence is 2b.[9] Participants eligible for the study were 18 and older, pregnant at some time from 2005 – 2012, and lived in the greater San Francisco Bay Area. A positive pregnancy test within the KPNC records was followed up with a review of the pharmacy database for medication use, both filled prescriptions and over-the-counter purchases. This allowed for initial cohort divisions. Invitational flyers were given to eligible participants in addition to a return refusal postcard for those who did not wish to be contacted. Those who did not return the refusal cards were contacted by an interviewer to assess willingness to participate and obtain consent. Although not addressed explicitly in the paper, participation bias may be present, as 37% of the eligible women contacted did not agree to participate. Over the phone interviews of all consented participants provided confirmation or clarification of eligibility and medication use and cohort assignment was updated accordingly. In person interviews included in-depth assessments of timing and frequency of medication use and visual aids to assist with recall. In addition, information on possible confounding variables was collected at this time. The authors determined pregnancy outcome via KPNC records and ensured that this was consistent with information presented in the initial interview and a follow up interview at 20 weeks gestation.

The paper did report a difference at baseline among the 3 cohorts. These variables included race/ethnicity and education level. The NSAID exposed cohort also reported less multivitamin use at conception. However, the study chose to select confounding variables based on the standard change-in-estimate criterion. This criterion establishes a variable as a confounder if the miscarriage hazard ratio for NSAID use changed by >10%. Given that race/ethnicity, education level, and multivitamin use at conception did not meet this criterion, the authors believe these differences to be minimal. It is possible that the combination of NSAID use and lack of multivitamin use may have contributed to the results more than the NSAID use alone.

An important factor in answering our patient's question is how well she is represented by the participants of the study. Confounders that were controlled for in the study include age, race/ethnicity, education level, smoking during pregnancy, number of previous miscarriages, average daily caffeine intake during pregnancy, multivitamin use at conception, number of previous pregnancies, fever during pregnancy, history of diabetes mellitus, and history of fertility problems. The majority of the participants fall in the 30 – 34 age group and our patient is 31. On the other hand, our patient is African American, which is the second lowest represented race/ethnicity among 5 categories. In order to be eligible for the study, participants had to reside in the greater San Francisco Bay area. It is therefore called into question whether this population adequately parallels our patient's Midwestern home city. Our patient received a college degree, while most participants did not complete college. She is a non-smoker, consumes minimal caffeine, has had no previous miscarriages or history of fertility problems, has a prepregnancy BMI > 25, and does not have diabetes. The majority of the participants share these characteristics. However, our patient does have a history of medically managed hypertension, which was not taken into account in this study. It would be of interest in future studies to consider hypertension as a possible confounder.

There are several components of the methods of this study that set it apart from other relevant studies. Instead of relying on online databases which limit ascertainment of medication use to filled prescriptions, both phone and in person interviews were conducted for a more accurate measure. During these interviews, more detailed information regarding possible confounders was obtained as well. With NSAIDs' possible adverse effect on implantation in mind, the study devised ways to assess miscarriages early in pregnancy. Early recruitment, with a median gestational age of 39 days, aimed to maximize capturing of miscarriages often missed by other studies that analyze data retrospectively. Stratification techniques based on timing and duration of NSAID exposure as well as timing of miscarriage further specified the increased risk found in previous studies. These techniques were able to demonstrate the greatest strength of association for NSAIDs taken for longer duration around the time of conception with early miscarriage. Another unique element of design in this study was the inclusion of an indication control. Not only does this help to eliminate the possible confounding variable of indication for taking the medication (i.e. fever, headache, joint or muscle pain, pain associated with miscarriage, etc.), it also provides women with a potential alternative medication. Acetaminophen can be taken for similar indications as NSAIDs but does not inhibit prostaglandin production. The addition of an acetaminophen exposed cohort helps to establish a more clear association between NSAID use and miscarriage versus studies that may have just picked up on NSAID use around the time of miscarriage being taken for pelvic pain.

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However, the methodology is not without certain flaws and biases. Interviewing participants on prior events can result in recall bias. Although the study used visual aids to assist with recall of medication packaging, brands, etc., it can still be difficult to recall the exact days when a medication was taken or the exact dose. In addition, due to the possible social implications of taking certain medications during or around the time of pregnancy, participants may experience response bias in that they will underreport use of medications because they feel it will reflect negatively on them. Another pitfall of the study is that it does not stratify based on individual NSAIDs. Prescription strength NSAIDs could have a greater association with miscarriage risk. For instance, the Daniel paper concluded that NSAID use is not associated with increased miscarriage risk with the exception of indomethacin, which showed a significantly increased risk.[5] This is an important point of interest given that our patient specifically takes ibuprofen. The chosen study did stratify based on timing of NSAID exposure, however, the categories consisted of "started around conception" meaning within the first 2 weeks of gestation and "started after conception" meaning after the first 2 weeks of gestation. It is not stated in the paper if they excluded patients who had been taking NSAIDs regularly before attempting to conceive, like our patient, rather than starting medication use at the indicated time intervals. Only one pregnancy per participant during the designated time period (2005 - 2012) was considered, however, determination of which pregnancy to include was not clearly stated.

It was concluded that NSAID use around the time of conception (within the first 2 weeks of gestation) increases risk of miscarriage in a dose-dependent manner. 27.2% of women who started NSAID use around conception had a miscarriage (adjusted Hazards Ratio (aHR) = 1.89), while 14% of women who started NSAID use after conception had a miscarriage (aHR = 0.89). 21.7% of women who used NSAIDs around the time of conception for 1-14 days had a miscarriage (aHR = 1.36), while 29% of women who used NSAIDs around the time of conception for > 14 days had a miscarriage (aHR = 2.10). Also, a greater strength of association was observed for NSAID use around the time of conception and early miscarriage (< 8 weeks of gestation). 4.3% of women who were not taking NSAIDs had a miscarriage at < 8 weeks gestation, while 15.8% of women who were taking NSAIDs had a miscarriage at < 8 weeks gestation (aHR = 4.08). There was no statistically significant association with miscarriage when analyzing the acetaminophen exposed and unexposed cohorts. 16.1% of acetaminophen exposed women had a miscarriage, 17% of unexposed women had a miscarriage, and 24.1% of NSAID exposed women had a miscarriage. The Number Needed to Harm (NNH) is 14.

A concept to consider when reviewing these conclusions is reverse causality. It is reasonable to suspect that women with symptoms of miscarriage will take more anti-inflammatory medications and that this could influence the results. This concern is mitigated by the fact that the strongest association was found for NSAID use within the first 2 weeks of gestation, while the majority of miscarriages occurred around 7 weeks gestation. The dose-response nature of the conclusion must be interpreted carefully since this is based on durations of 1-14 day use and > 14 day use rather than exact doses.

Clinical Application

Mrs. Lewis's primary concerns during her office visit included the potential risk of miscarriage with NSAID use and how else to manage her pain. Despite the limitations and flaws of the 2018 Li study, we believe the strength of the evidence balanced with risk-benefit analysis is sufficient to recommend that our patient refrain from taking NSAIDS in the periconceptional period. As supported by the paper, acetaminophen's low risk profile and similar indications for use as NSAIDs make it a reasonable alternative medication for our patient. Although the literature remains divided, we feel that most women would be open to avoiding the potential risk by attempting to treat their symptoms with an alternative medication. The recommendation should still be considered in a case-by-case fashion, as some patients are not good candidates for acetaminophen therapy (e.g. liver disease). Mrs. Lewis agreed that this was a change she would like to make to increase her chances of a successful pregnancy. This relatively simple change of these readily accessible medications may be able to positively influence pregnancy outcome.

Learning points:

1. NSAID use likely increases risk of miscarriage in early pregnancy.

2. Acetaminophen may serve as a safe alternative medication in the periconceptional period for indications such as fever, headache, and joint or muscle aches.

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The Journal of Team Hippocrates
VOL 5 ISS 2 / eP1946 / SEPTEMBER 18, 2019
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3. Physicians should educate women about NSAID use early in their attempt to conceive in order to maximize positive pregnancy outcomes.

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