

Spontaneous abortion and NSAIDs

Nakhai-Pour and colleagues¹ reported a possible increased risk of spontaneous abortion associated with any type or dose of nonsteroidal anti-inflammatory drug (NSAID). This finding supports earlier work by Nielsen and colleagues² — which is not surprising, given that a combination of population-based prescription drug registries and pregnancy outcome databases was used in both studies. A criticism of the design of the earlier study³ can also be made of the later study. Filling a prescription does not adequately represent actual use of the drug prescribed, thereby rendering the findings unreliable. Nakhai-Pour and colleagues¹ do provide a reference that supports the validation of risk-assessment studies using the Régie de l'assurance maladie du Québec prescription drug database for pregnant women, but the citation is from their own institution and includes one of their coauthors,⁴ thus raising the possibility that the validation is lacking the necessary degree of independence or objectivity.

The authors stated that “to their knowledge,” neither smoking nor body mass index (BMI) are risk factors for spontaneous abortion and therefore neither needed to be considered as a confounding factor in their analyses. They cite their own work as the source for this statement.⁵ Not only maternal, but also paternal and environmental exposure to smoking have been reported to be associated with an increased incidence of spontaneous miscarriage.⁶

A recent meta-analysis of the effect of BMI on spontaneous abortion reported that patients with a BMI greater than 25 kg/m² have significantly higher odds of miscarriage regardless of the method of conception,⁷ and evidence-based guidelines for the investigation and treatment of recurrent miscarriage include BMI as a risk factor.⁸ Nakhai-Pour and colleagues¹ were not able to ascertain the smoking and BMI status of their cohorts because of their study

design, but we suggest that not considering these factors puts their findings further in question.

We believe that it would be interesting if the authors were to compare the obstetric histories and pre-existing comorbidities of the subgroup of women who filled prescriptions for nonaspirin NSAID and had a live birth ($n = 1213$) with the subgroup that filled the same prescriptions but had a spontaneous abortion ($n = 352$). This might reveal a distinct demographic at increased risk of miscarriage.

Because this was a population-based study, the authors were unable to assess usage of over-the-counter NSAIDs. In 2005, Werler and colleagues⁹ reported that the use of over-the-counter medications is extremely common during pregnancy. That an association between a common occurrence and a rare marker cannot be shown may be an epidemiologic truism. However, if an association between two common events, such as NSAID use and spontaneous abortion, exists it should be possible to find. A study is required that includes the use of both over-the-counter and prescription NSAIDs during pregnancy and, the analysis must control for all known confounding factors for each event. Until then, we are left with studies such as this one — that provide subsets of data that suggest an association but do not adequately support their claims.

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The authors respond:

We disagree with Clark and colleagues.¹ Given that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is on an acute basis, even when used for chronic conditions, women who took the time to go to the pharmacy most likely took at least one pill. Glover and colleagues² have shown that most pregnant women who fill a prescription take it, and Daniels and colleagues³ have shown that self-reporting measures of medication use do not provide accurate measurements when compared with electronic monitoring, as was done in our study.⁴

Data on maternal smoking and body mass index (BMI) were available only for a subset of women included in our registry. However, these variables would need to confound the effect to bias our results. For smoking and BMI to be confounders, they would need to be associated with both outcome and exposure. Delaney and colleagues⁵ have shown that smoking and BMI are not associated with use of NSAIDs that are prescribed or over the counter.

The registry includes data on the use of prescription medication during gestation. We looked at over-the-counter ibuprofen obtained with a prescription; however, the number of women who used over-the-counter ibuprofen with-