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Original article

Racial differences in risk of spontaneous abortions associated with periconceptional over-the-counter nonsteroidal anti-inflammatory drug exposure

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ABSTRACT

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most common medications reported in pregnancy. NSAIDs directly impact prostaglandin pathways and have been proposed as potential risk factors for spontaneous abortions (SABs, gestation <20 weeks). SAB risk and drug response across several medications differ by race; therefore, we evaluated whether associations between NSAIDs and SAB risk differ by race.

Methods: Women were enrolled in the *Right from the Start* (2004–2010) prospective cohort. Data regarding over-the-counter NSAIDs up to the sixth week of pregnancy were obtained from interviews. Race was self-reported. Cox proportional hazards regression models were used to estimate the association between NSAID exposure and SAB, adjusted for confounders.

Results: Among 2493 pregnancies, 12% were African American and 88% were Caucasian. NSAID exposure was reported by 40% ($n = 124$) of African Americans and 43% ($n = 945$) of Caucasians. Race-stratified analyses showed protection from SAB among African Americans (adjusted hazard ratio [aHR], 0.84; 95% confidence interval [CI], 0.73–0.96) but no effect in Caucasians (aHR, 1.01; 95% CI 0.88–1.16).

Conclusions: Our findings suggest that risk for SAB due to over-the-counter NSAIDs in early pregnancy is modified by race. Further investigation of dose, timing in gestation, and indication may help to further reconcile the relationship between race, NSAIDs, and SAB.

Introduction

In the United States, each year, at least 1.5 million women use nonsteroidal anti-inflammatory drugs (NSAIDs) around the time of conception, implantation, and early embryonic development [1–3], making them the most common medication exposure reported in the first trimester [4]. NSAIDs are primarily used to relieve pain and reduce inflammation and their effects generally result from inhibition of cyclooxygenase (COX)-2. Three population-based observational cohort studies have previously implicated first-trimester NSAID use as a risk factor for miscarriage (spontaneous abortions [SABs], <20 weeks' gestation) primarily using data obtained from administrative databases or study interviews that limited drug exposure to a subset of NSAIDs [5–7]. These studies were conducted in either multiethnic populations or among individuals of European descent, as a result we do not know if there are racial differences in the association between NSAIDs and SAB. There are known racial disparities in drug response that are primarily driven by racial genetic differences in drug metabolism [8–11]. Furthermore, there are also known racial difference in reproductive outcomes, including the risk for SAB [12–19]. Inconsistent risk estimates and level of association across prior studies of NSAIDs and SAB may be due to these racial differences in study populations. Further understanding of the relationship between race and NSAID is important due to the currently limited knowledge regarding the role of drug exposures during pregnancy.

The biological basis for suspecting a link between NSAIDs and risk of SAB rests on the multiple stages in development that involve prostaglandin (PG) synthesis in early pregnancy, such as prostaglandin E (PGE) synthases, that may be essential for establishing the implantation and early placentation. NSAIDs inhibit COX enzymes, which catalyze the formation of PGs from arachidonic acid and thus NSAIDs reduce PG synthesis. Altering PG levels has direct effects on conception, implantation, and maintenance of pregnancy in animal models [20–30]. Because NSAIDs inhibit PG synthesis, they may influence embryo transport, implantation, placental development,

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and maintenance of pregnancy and have been shown to lead to embryonic demise in animal models [31]. This suggests that NSAID use during early pregnancy is a plausible biological candidate for causing SABs.

Women and their care providers currently lack clear empirical evidence to inform clinical care regarding the consequences of NSAID use during pregnancy and whether race differentially impacts their response to NSAIDs. Prior research has shown inconsistent results regarding the associations between NSAIDs and miscarriage risk, including our prior study that showed no effect by NSAIDs on miscarriage (adjusted hazard ratio [aHR], 1.01; 95% confidence interval [CI], 0.82–1.24) [32]. However, these inconsistencies across studies may be due to racial differences in risk for SAB due to NSAIDs to racial differences in risk among the populations due to racial. In this study, we build upon our prior work and use data from the *Right from the Start* (RFTS) study (2004–2010), a nonclinical community-based pregnancy cohort, to examine the racial disparities in periconceptional NSAID use during pregnancy as it relates to risk for SAB. This study tests whether there are racial disparities in periconceptional over-the-counter (OTC) NSAIDs used associated with SAB risk.

Materials and methods

Study population and data collection protocol

RFTS is an ongoing community-based cohort that began enrolling study participants in 2000. Over time, RFTS has been funded through three major phases with distinctive research questions (RFTS 1, 2, and 3) and has enrolled participants in Galveston, TX; Memphis, Nashville, Knoxville, and Chattanooga, TN; and the Research Triangle region (Raleigh, Durham, and Chapel Hill) in NC. RFTS participants are 18 years or older and did not use assisted reproductive technologies to conceive. Consent was obtained to review all records pertaining to the study pregnancy. Participants were actively recruited and followed from preconception or very early pregnancy through the end of pregnancy (mean and standard error of gestational age at enrollment was 44.0 ± 10.8 days). Follow-up was conducted to document outcomes. Participants completed an intake interview at enrollment and a computer-assisted telephone interview at the end of the first trimester. The computer-assisted telephone interview was conducted at a mean gestational age of 98.0 days $\pm$ 12.8 days, providing information on history of bleeding or pain, medication use, and exposure to potential confounders in the time since last menstrual period (LMP). The institutional review boards of Vanderbilt University, Nashville, TN and the University of North Carolina, Chapel Hill, NC approved this study.

Pregnancy outcomes were self-reported and abstraction of medical records was used to verify outcomes. Live births were linked to state vital records to assist in verifying the pregnancy outcomes for ongoing pregnancies. SABs were defined as a loss before 20 completed weeks' gestation. Those without losses included both live births and stillbirths, excluding ectopic pregnancies ($n = 9$) and induced abortions ($n = 14$). Gestational age was estimated from self-reported LMP. Women could enroll in RFTS during more than one pregnancy, but only the first enrollment was included ($n = 251$ subsequent pregnancies excluded). Also excluded were those with incomplete race information ($n = 4$) and those whose self-reported race was not African American or Caucasian ($n = 283$).

NSAID assessment and other variables

Participants were queried about medications in the intake and first-trimester interviews (Supplementary Table 1). Both interviews included NSAID exposures during the periconceptional period (e.g., from LMP through 6 weeks' gestation) before pregnancy outcome. The primary exposure was classified as any NSAID use versus no NSAID use based on whether the participant reported NSAID use in either interview. NSAIDs were further grouped by drug class, generic name, and brand name. The primary resource used to classify drugs was the Food and Drug Administration drug classification database and our drug classes were assigned based on published drug class categories [33]. Other resources also used include the following: Micromedex 2.0, Lexi-Comp ONLINE, Epocrates Online Premium, and DailyMed [34–37]. OTC drugs that were reported according to their store brands and could not be classified with the previously listed resources were identified with drugstore.com to identify the generic name [38]. We did not include acetaminophen use in the NSAID definition, with the exception of drugs that included acetaminophen and an NSAID as the active ingredients.

RFTS 1 participants were excluded from the analyses ($n = 1956$) because OTC NSAID use was not ascertained during the interview. RFTS also includes information on prescription NSAIDs in the first-trimester interview regarding prescription medications taken for pain, bleeding, and other reasons. However, the number of women reporting prescription NSAID use was too small to perform statistical analyses ($n = 10$). We, therefore, excluded women who used prescription NSAIDs from the analysis.

Maternal characteristics and obstetric history were also recorded. These included maternal age, height, weight, body mass index (BMI), race/ethnicity, diabetes status, parity, gravidity, induced abortion history, study site, and smoking status (current or not current smokers). Information on these characteristics was obtained from either the first-trimester interview or in person during the study ultrasound visits.

Statistical analysis

Analyses were conducted with STATA statistical software version 11.0 (StataCorp LP, College Station, TX). We used Cox proportional hazards survival models with variable gestational age at study entry to characterize the rate of pregnancy loss in relation to NSAID exposure (any vs. none) and test for effect modification by race, both unadjusted and adjusted for confounders. Allowing for variability for study participant, gestational age at study entry will correctly estimate the risk of SAB conditional on the fact that each subject had not had pregnancy loss before they were recruited into the cohort, this should allow less bias in estimates of error compared with other methods such as logistic regression [39,40]. Longitudinal data from each woman starts at enrollment or after they confirm they are pregnant through a positive pregnancy test if they enrolled while they were still trying to get pregnant and continues through 20 completed weeks' gestation or the occurrence of a pregnancy loss. Those lost before 20 weeks (<1%) were excluded from the analyses. We used a two-sided alpha = 0.05 significance level for all tests of statistical significance.

All analyses are performed stratified by race. Candidate confounders included maternal age (years), BMI (kg/m^2), income ($\leq$\$40,000, \$40,000–\$80,000 [referent], >\$80,000), diabetes status (no diabetes [referent] vs. any [type 1, type 2, gestational, or multiple]), parity (none [referent] vs. ≥ 1), gravidity (none [referent] vs. ≥ 1), induced abortion history (none [referent] vs. ≥ 1), and smoking status (not current [referent] vs. current). Candidate confounders were analyzed for independent association with both NSAID exposure and SAB outcome. We also analyzed demographic data with logistic regression to compare Caucasian and African American demographic characteristics. Those that were independently associated with NSAID exposure and SAB outcome and that