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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 (SAB, 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 the *Right from the Start* (2004–2010) prospective cohort. Data regarding over-the-counter (OTC) 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 2,493 pregnancies, 12% were African American (AA) and 88% were Caucasian (CA). NSAID exposure was reported by 40% (n=124) of AAs, and 43% (n=945) of CAs. Race stratified analyses showed protection from SAB among AAs (adjusted hazard ratio [aHR]=0.84, 95% CI 0.73, 0.96), but no effect in CAs (aHR=1.01, 95% CI 0.88, 1.16).

CONCLUSIONS—Our findings suggest that risk for SAB due to OTC 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.

Keywords

Nonsteroidal anti-inflammatory drugs; pregnancy; toxicology; miscarriage; disparity

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CONFLICTS OF INTEREST

None of the authors have conflicts of interest to report.

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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 [SAB], less than 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 multi-ethnic 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 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 PG E synthases (PGE), that may be essential for establishing the implantation and early placentation. NSAIDs inhibit cyclooxygenase (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, 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 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 (hazard ratio [HR] = 1.01, 95% confidence interval [CI] 0.82–1.24).[32] However, this may be due to racial differences in risk among the populations due to racial. In this study we build upon our prior work and used data from the *Right from the Start* (RFTS) study (2004–2010), a non-clinical 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 (RFTS1, 2, 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 pre-conception or very early pregnancy through the end of pregnancy (mean and standard error of gestational age at enrollment was 44.0 days $\pm$ 10.8). Follow-up was conducted to document outcomes. Participants completed an intake interview at enrollment and a computer assisted telephone interview (CATI) at the end of the first trimester. The CATI 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 (IRB) 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 last menstrual period (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 (Supplemental Table 1). Both interviews included NSAID exposures during the preconceptional period (e.g. from LMP through 6 weeks gestation) prior to 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 utilized include: 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 = 1,956) 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, USA). 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 versus none) and to 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 to 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/m²), income (< \$40,000, \$40,000–\$80,000 [referent], > \$80,000), diabetes status (no diabetes [referent] versus any [type 1, type 2, gestational, or multiple]), parity (none [referent] versus 1), gravidity (none [referent] versus 1), induced abortion history (none [referent], 1), and smoking status (not current [referent] versus current). Candidate confounders were analyzed for independent association with both NSAID exposure and SAB outcome. For descriptive purposes, we also analyzed demographic data with logistic regression in order to compare Caucasian and African American demographic characteristics. Those that were independently associated with NSAID exposure and SAB outcome and that resulted in a 5% relative change in NSAID effect size estimates, in individual race stratified analyses, were retained in the model. No candidate confounders met inclusion criteria. However, analyses were adjusted for maternal age because this covariate was commonly included in previous studies of NSAID use and SAB risk.[5–7] We also performed regression analyses with robust standard errors clustering by study site (North Carolina [referent], Tennessee, Texas). We also ran the analyses with bootstrapping with 1,000 replications for African Americans due to the smaller sample sizes (data not shown and the results were consistent). Using Cox regression, we estimated adjusted hazard ratios (HR) with 95 percent confidence intervals (CI) for risk of miscarriage with NSAID exposure. In order to compare our findings with those from studies that used different definitions for NSAID exposure, we also performed Cox regression analyses excluding aspirin from the NSAID exposure definition.

RESULTS

We included a total of 2,185 Caucasian and 308 African American women who enrolled in the study between 2004 and 2010 (Table 1). African Americans, compared to Caucasians, were more likely to be less than 26 years old, have more than one previous pregnancy, have a BMI over 26, have a household income at or below \$40,000, not be married or living as married, have a history of preterm birth and SAB, be diabetic, and from Tennessee.

The overall prevalence of periconceptional NSAID use among Caucasian women was 43% and 40% among African American women (Table 2). The most common NSAIDs reported were propionic acid derivatives, followed by non-aspirin NSAIDs, and aspirin NSAIDs. When comparing racial groups, use of aspirin NSAIDs was similar across racial groups. However, Caucasians reported higher use of non-aspirin NSAIDs (Caucasians 36%, African American 32%) and NSAIDs that were classified as propionic acid derivatives (Caucasians 41%, African American 36%).

The overall prevalence of SAB is 13%, with a prevalence of 13% among Caucasians and among African Americans 12%. Overall NSAID use was more common among Caucasians who experienced a loss (43%) compared to African Americans (36%) who experienced a loss (Table 3). Because of an interaction between race and NSAID use ($p < 0.0001$) analyses were performed stratified by race (Table 4).

Among Caucasians there were associations between NSAIDs and SAB (Table 4). There was a nominally significant association in Caucasian analyses excluding aspirin users, with an aHR = 0.89 (95% CI 0.79, 1.01), $p = 0.078$. However, among African Americans we observed a significant association with decreased risk of SAB when participants had used NSAIDs regardless of class (aHR = 0.84 [95% CI 0.73, 0.96], $p = 0.013$) and non-aspirin NSAID users (aHR = 0.74 [95% CI 0.61, 0.90], $p = 0.003$).

DISCUSSION

NSAIDs are the most commonly reported drug taken during early pregnancy,[4] and prior studies have suggested that NSAIDs used during pregnancy may increase SAB risk. We observed evidence suggesting risk for SABs due to NSAIDs differed significantly by race, with null effects observed among Caucasians. There were consistent patterns of inverse risk for African Americans and similar patterns of inverse risk for non-aspirin users across racial groups. However, only the inverse effect among African Americans was significant. While we found no overall effect for NSAID these data suggest a protective effect among a subset of the population, which may suggest that response to NSAIDs during pregnancy may have a different etiology in African Americans compared to Caucasians.

Biological differences in infection and inflammatory response pathways may explain racial differences. NSAIDs have direct roles in downregulating infection and inflammatory response pathways and have been shown to interact with gene polymorphisms in these pathways. Examples include several studies of cancer where NSAID interactions with cytokine polymorphisms have been shown to result in an inverse risk for cancer.[9,41,42] There are multiple known biological differences between African Americans and Caucasians with regards to infection and inflammatory response and gene polymorphisms particularly with regards to pregnancy traits.[13–19] For example, expression levels and individual polymorphisms in inflammatory response genes have associated with preterm birth (gestation < 37 weeks) risk and have been shown to significantly differ between African Americans and Caucasians.[13–15,17,18] Further detailed analysis of the relationship between NSAIDs and SAB in the context of infection and inflammatory response pathways are needed to further resolve this relationship.

Racial differences in miscarriage risk due to NSAIDs may be explained by differences in drug response as a result of genetic factors.[10] Polymorphisms that differ by race have been shown to modify drug metabolism enzymes, receptor proteins, and proteins involved in drug progression. A notable example among these is a study by Lin et al. (2002), specifically looking at genetic differences in drug response by race, observed that a prostaglandin H Synthase 2 (COX-2) variant (Val511Ala), a gene involved in NSAID metabolism, was present among African Americans at approximately 5% but absent among Caucasians and Hispanics.[9] This variant resulted in an inverse risk for colorectal cancer among African Americans but not Caucasians or Hispanics. Similar, but not necessarily identical, mechanisms may be involved among African American women who take NSAIDs, where an allele present among African Americans but not Caucasians is contributing to protection from spontaneous abortions.

The protective effect observed Among African Americans may have similar mechanistic effects as those involved in vitro fertilization and low dose aspirin treatment. These studies have hypothesized that low dose aspirin treatment enhances uterine and ovarian blood flow and tissue perfusion by decreasing platelet aggregation and inhibiting vasoconstriction; therefore, having favorable effects on pregnancy.[43,44] It may be that among African Americans there is a similar mechanism involved for NSAID use.

Our study improves the understanding of NSAID use during early pregnancy as we had a large sample of NSAID-exposed pregnant women, limited to OTC NSAID use, which should better represent common NSAID during pregnancy, and examined NSAID use across racial groups.[32] Prior studies primarily examined pharmacy-filled NSAID prescriptions. [6,7] The sample sizes for NSAID exposed miscarriages in these studies were smaller (SABs NSAID exposed ranged between 13 to 352). We observed significantly higher rates of NSAID exposure in our cohort, which is due to inclusion for OTC NSAID exposure data. [5–7] None of the previous studies tested for racial disparities or effect modification by race in SAB risk due to NSAIDs. We do note however, that we had a limited sample size among our African American women evaluated in this study and therefore results should be interpreted with caution and do require replication of study findings. A potential reason why we did not observe associations in Caucasians despite other studies observing an association between NSAIDs and SABs in Caucasian populations is due to our population consisting of OTC NSAIDs. It may be that the majority of the risk for SABs by NSAIDs is due to higher dosages more common in prescription forms of NSAIDs.

While we have documented no overall affect for increased SAB risk due to NSAIDs,[32] we did show evidence for racial difference in NSAID use during pregnancy. We observed that African Americans had overall lower NSAID use compared to Caucasians, and there were significant racial difference in SAB risk due to NSAID exposure. Although the protection in African Americans was unexpected, biologically these data may indicate that there are differences in NSAID drug response by race that may be explain the inconsistent findings across studies of NSAIDs and SAB. These data also suggest overall differences in the underlying etiology of NSAID pathways by race and that NSAIDs may be beneficial to African Americans. It may be that NSAID use among African Americans is treating some other underlying condition that involves infection or inflammatory pathways, which are known to have strong racial differences. Further investigation needs to be conducted to determine gene polymorphisms and biologic mechanisms that determine the race-specific relationships between NSAIDs and SAB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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LIST OF ABBREVIATIONS AND ACRONYMS

aHR	adjusted Hazard Ratio
BMI	body mass index

CI	confidence interval
COX-2	cyclooxygenase 2
IL-6	interleukin 6
IRB	Institutional Review Board
NSAID	nonsteroidal anti-inflammatory drugs
OTC	over-the-counter
PGE	prostaglandin E synthase
RFTS	<i>Right from the Start</i>
SAB	spontaneous abortion
S.D	standard deviation
TNF-α	<i>Tumor necrosis factor alpha</i>

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Table 1Characteristics of participants by race in the *Right from the Start* study

Variable	Total N	Caucasian (n=2,185)	African American (n=308)
Maternal age (mean yrs $\pm$ S.D.)		30 $\pm$ 4	28 $\pm$ 5 [†]
<26	439	15	35 [†]
26–29	555	23	19
29–32	665	28	20
32	834	35	26
Gravidity (%)			
1	902	38	26
>1	1,591	62	74 [†]
Parity (%)			
0	1,170	49	48
1	1,224	51	52
BMI (mean $\pm$ S.D.)		25 $\pm$ 6	30 $\pm$ 8 [†]
Underweight (less than 20)	218	9	6
Normal weight (Greater than 20 and less than 26)	1,409	61	32
Overweight (Greater than 26 and less than 29)	315	12	17 [†]
Obese (29 and above)	512	17	46 [†]
Household income (%)			
\$40,000	490	17	49 [†]
\$40,001–\$80,000	952	42	30
>\$80,000	893	41	21
Marital status (%)			
Married/Living as Married	2,341	97	73
Other	152	3	27 [†]
History of preterm birth (%)			
0	2,219	93	89
1	175	7	11 [†]
History of spontaneous abortions (%)			
0	1,848	78	73
1	546	22	27 [†]
History of induced abortions (%)			
0	2,110	91	70
1	284	9	30 [†]
Smoking status (%)			
Not current smokers	2,326	98	94
Current	62	2	6 [†]
Diabetes (%)			
None	2,330	98	95

Variable	Total N	Caucasian (n=2,185)	African American (n=308)
Any	58	2	5 [†]
Study site (%)			
North Carolina	1,755	69	78
Tennessee	726	30	22 [†]
Texas	12	1	0

[†] Variables with statistically significant differences ($p < 0.05$) between Caucasians and African Americans in univariate logistic regression or linear regression

Table 2

Comparison of NSAID exposure by race in *Right from the Start*

NSAID Exposure	Total N [†]	Caucasian (n=2,185)		African American (n=308)	
		NSAID Exposed n (%)		NSAID Exposed n (%)	
Any NSAID	1,069	945 (43)		124 (40)	
Propionic acid derivatives*	919	818 (37)		101 (33)	
Non-salicylates	801	713 (33)		88 (29)	
Salicylates*	268	232 (11)		36 (12)	
Acetic acid derivatives	3	3 (0.14)		0 (0)	
Enolic acid derivatives (Oxicams)	1	1 (0.0005)		0 (0)	

* Salicylates included products with aspirin as an active ingredient as well as those that include aspirin and other medications as well as diflunisal, disalcid, and trilisate; propionic acid derivatives included Ibuprofen, naproxen, ketoprofen, fenoprofen, flubiprofen, suprofen, oxaprozin.

† Participants could have reported more than 1 NSAID class and therefore could be included in more than one NSAID class. Percentages are proportions of NSAID class by race.

Table 3
Pregnancy outcome by race, pregnancy outcome, and NSAID exposure in *Right from the Start*

Pregnancy Outcome	Total N	Caucasian (n=2,185)				African American (n=308)	
		No NSAIDs (%)	NSAIDs (%)	No NSAIDs (%)	NSAIDs (%)	No NSAIDs (%)	NSAIDs (%)
Without Losses	2,171	1078 (57)	821 (43)	161 (59)	111 (41)		
SAB	322	162 (57)	124 (43)	23 (64)	13 (36)		

Table 4

Adjusted association analysis of periconceptional NSAID exposure and risk of spontaneous abortions in *Right from the Start*

Periconceptional NSAID Exposure	Total N Exposed/Unexposed	aHR [†]	95% CI	P
Race x NSAID interaction				<0.0001
Caucasian				
None		1.00		
Any NSAID	821/1078	1.01	0.88, 1.16	0.865
Excluding salicylates NSAID users (Non-aspirin)	713/1241	0.89	0.79, 1.01	0.078
African American				
None		1.00		
Any NSAID	124/184	0.84	0.73, 0.96	0.013
Excluding salicylates NSAID users (Non-aspirin)	88/184	0.74	0.61, 0.90	0.003

[†]aHR-Adjusted HR for maternal age, clustering by study site.