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First-Trimester Antihistamine Exposure and Risk of Spontaneous Abortion or Preterm Birth

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Abstract

Purpose—We tested whether antihistamine exposure during early pregnancy is associated with spontaneous abortion (SAB) or preterm birth (PTB).

Methods—Women were enrolled in *Right from the Start* (2004-2010), a prospective pregnancy cohort. Data about first-trimester antihistamine use were obtained from screening and first-trimester interviews. Self-reported outcomes included spontaneous abortion and preterm birth and were verified by medical records. Cox proportional hazards models were used to test for an association between antihistamine use and each outcome, both performed adjusting for confounders.

Results—Among the 2,685 pregnancies analyzed, 14% (n=377) reported use of antihistamines. Among antihistamine users, 12% (n=44) experienced SABs, and 6% (n=21) had PTBs. Antihistamine exposure was not associated with SAB (adjusted hazard ratio [aHR]=0.88, 95% confidence interval [CI] 0.64, 1.21) or PTB, which was modified by maternal race (aHR=1.03, 95% CI 0.61,1.72 among White women and aHR=0.43, 95% CI 0.14, 1.34 among Black women).

Conclusions—Despite biologic plausibility that antihistamine use may influence pregnancy outcomes, we did not detect evidence of an association with SAB. These data demonstrate the utility of large prospective cohorts for evaluating drug safety in pregnancy when concerns are raised from animal models.

Keywords

Pregnancy; pharmacoepidemiology; histamine antagonists; prospective studies

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Introduction

Approximately 85% of women report using one or more medications during pregnancy.[1] Antihistamines are among the most commonly reported medications used, with studies showing up to 15% of pregnant women reporting use of over-the-counter antihistamines.[2] Women take antihistamines for several reasons, including allergies, motion sickness, and acid reflux and they may take one or more of the following types (classes): first or second generation H1 receptor antagonists or H2 receptor blockers. In a retrospective study using a clinical population, Matok and colleagues[3] described H2 receptor blockers (e.g. famotidine, ranitidine, and cimetidine) as a common class used during pregnancy. H2 receptor antagonists inhibit gastric acid secretion and are commonly used to treat gastroesophageal reflux, which impacts 30%-50% of pregnant women. Because 50% of pregnancies are unplanned, the authors estimate that millions of women are exposed to H2 receptor antagonists early in pregnancy.[3] Despite the high frequency of antihistamine use during pregnancy, there is limited knowledge regarding the effects of exposure on pregnancy outcomes.

The biologic mechanism through which antihistamines inhibit the actions of histamine may effect both implantation and uterine contraction. Histamine is a monoamine that impacts several cellular pathways in the female reproductive system, as it is produced by uterine mast cells, uterine epithelial cells, and the placenta.[4-7] The action of histamine is mediated through four subtypes of histamine receptors:H1, H2, H3, and H4 receptors.[4] Of particular interest are the H1 and H2 receptors, which are expressed in the uterus[5-6, 8], placenta[4, 9], and blastocysts.[7] Stimulation of H1 receptors by agonists leads to smooth muscle contraction, nitric oxide formation for endothelial vasodilation, and increased vascular permeability.[5-6,8-11] These effects are inhibited by first and second generation H1 receptor antagonists. First generation H1 receptor antagonists have the side effect of diminishing central nervous system arousal due to inhibition of central H1 receptors on the blood-brain barrier. Second generation H1 receptor antagonists are devoid of this effect. This is largely due to a difference in brain penetration properties between the two classes.[12] Activation of H2 receptors by agonists influences gastric acid secretion, smooth muscle relaxation, and stimulation of adenylyl cyclase, while H2 receptor antagonists inhibit these effects.[3, 7, 10, 13]

Several studies suggest that H1 and H2 receptors have significant implications in pregnancy. Histamine receptors are found on the trophoblast and help mediate the implantation of the blastocyst.[4,7] Receptors are also found on uterine smooth muscle cells where they play a role in contraction (H1) and relaxation (H2).[5, 8, 13-14] Both implantation and contractile pathways are inhibited when antihistamines were tested in animal studies.[8] Due to the role of histamine and its receptors in these processes, it is reasonable to conclude that antihistamine use may be associated with pregnancy outcomes such as spontaneous abortion (SAB) and preterm birth (PTB).

Currently, there are no safety guidelines for the use of antihistamines during pregnancy. Using *Right from the Start* (RFTS, 2004-2010), a prospective community-based pregnancy cohort, we examined the association between first-trimester antihistamine use and risk for both PTB and SAB.

Methods

Study population

Right from the Start (RFTS) is a community-based pregnancy cohort study that enrolled women who were pregnant or planning to become pregnant between 2000 and 2012. The study included three phases (RFTS 1, 2, and 3), and participants were recruited from several metropolitan areas in North Carolina, Texas, and Tennessee. Participants were 18 years of age and older and did not use assisted reproductive technologies to conceive. Details regarding RFTS recruitment have been previously published.[15] The study population for these analyses consisted of women in the second and third study phases because those in RFTS1 did not provide information on over-the-counter medication use.

Participants underwent an early pregnancy ultrasound to assess fetal viability and confirm the gestational age of the fetus. The self-reported date of the last menstrual period (LMP) was used to calculate gestational age; if self-reported information on LMP was unavailable, the ultrasound-based LMP date was used. Gestational age at end of pregnancy was calculated in days and is presented in weeks for descriptive purposes in Table 1.

Participants completed screening interviews after they had positive pregnancy tests, and first-trimester interviews were targeted for 13 weeks gestation. In these interviews, information regarding maternal characteristics, medical history, reproductive history, and health behaviors during pregnancy was collected. The questions asked about medication use (both prescription and over-the-counter) are provided in Supplemental Table 1. Outcomes were self-reported and prenatal records were obtained to verify the outcome. Considered for these analyses were 3,262 first-enrollment pregnancies (women can enroll in RFTS for multiple pregnancies) recruited during the second and third study phases (2004-2010). Population exclusions included: missing gestational age at enrollment (none), missing gestational age at pregnancy outcome or censor date (n=5), missing enrollment dates (none), unknown pregnancy outcome (n=335), ectopic or molar pregnancy (n=18), failure to complete the first-trimester interview (n=154), and did not provide any information on antihistamine use (n=63). For the analyses on SAB risk, an additional two women were excluded who indicated losses on their enrollment days, leaving a final population of 2,685 women. Three hundred thirty five women did not have an ultrasound-based estimate for LMP, but self-reported dates were available and used, as described above. Women who had SABs (n=353) or stillbirths (n=10) were not considered to be at risk for PTB and therefore not included in these analyses. The final population for our investigation of PTB risk consisted of 2,322 participants (n=2,089 when limiting to non-Hispanic White and Black women). The institutional review board of Vanderbilt University approved study procedures and all participants gave informed consent.

Variable Definitions

The primary exposure was classified as any self-reported antihistamine use versus no use. Once becoming pregnant, participants were queried about all medications used during the screening and first-trimester interviews. Both interviews included questions about medication use during the periconceptional period (i.e., from LMP through six weeks

gestation). In the first trimester interview, women were also asked whether they were currently taking or had taken any medications since becoming pregnant (in the case of SAB, whether they had taken any medications during pregnancy). Across the study population, the exposure period ranged from LMP date to the first trimester interview date (See Table 1). From these self-reported medications, we grouped antihistamines by class, generic name, and brand name. The primary resource used to classify drugs was the Food and Drug Administration drug classification on Lexi-Comp ONLINE[16] and DailyMed.[17] Those over-the-counter medications that could not be classified with the previously listed resources were identified with drugs.com.[18]

SAB was defined as loss of a recognized pregnancy prior to 20 completed weeks of gestation. PTB was defined as a live birth at less than 37 weeks of gestation, but not before 20 weeks.

Other data collected during interviews and used in these analyses included maternal demographic factors (age, race/ethnicity, marital status, and household income), body mass index (BMI, measured during ultrasounds or self-reported), morbidities (diabetes), behaviors (smoking), and previous obstetric history (parity, gravidity, multiple gestations, history of SAB, induced abortion, or PTB). If self-reported information on race was unavailable, vital records were used (n=3).

Statistical Analysis

Descriptive statistics and analyses were generated using Stata 12 SE (StataCorp, College Station, TX). Descriptive statistics were expressed as frequencies and proportions for categorical variables.

We used Cox proportional hazards survival models with ragged study entry to characterize the rate of SAB in relation to antihistamine exposure (any versus none) both unadjusted and adjusted for confounders. Ragged study entry will correctly estimate the risk of SAB conditioning on the fact that each subject had not had pregnancy loss before they were recruited into the cohort.[19] Schoenfeld residuals were tested and Kaplan-Meier curves were visually examined to assess proportionality of hazards for the final Cox models (results not shown). The Efron method was used to handle ties. Time at risk for SAB began at gestational age at enrollment (conditional on not experiencing a loss prior to enrollment) and ended at 19 and 6/7 weeks gestation from the LMP date (≤ 139 days gestation). Pregnancy outcomes occurring at or after 20 weeks (stillbirths or live births) were censored at this time point and considered non-SABs. We used Cox proportional hazard models to generate hazard ratios (HR) and 95% confidence intervals (CI) for SAB associated with antihistamine exposure.

We used similar adjusted and unadjusted Cox regression models to examine the association between PTB and antihistamine exposure (any versus none). The at risk period for PTB began at or after 20 and ended at 37 weeks gestation.

A priori we identified candidate confounders based on suspected associations with antihistamine exposure and our outcomes. A change-in-estimate approach was used to select

from these factors and build parsimonious models for SAB or PTB associated with antihistamine use (using a 1% criterion). Candidate confounders for the SAB analyses included: maternal age (years in quartiles: < 27 [reference], ≥ 27 and < 30, ≥ 30 and < 33, ≥ 33), race (non-Hispanic White [reference, referred to as White], non-Hispanic Black [referred to as Black], Hispanic, Other), BMI (< 18.5, ≥ 18.5 and < 25.0 [reference], ≥ 25.0 and < 30.0, ≥ 30.0),[20] diabetes status (no prior diagnosis [reference], diagnosis of any type), parity (nulliparous [reference], 1, 2+), gravidity (0 [reference], 1+) , therapeutic abortion history (0 [reference], 1, 2+), smoking status (not smoking during index pregnancy or quit at least four months prior to the first-trimester interview or unknown when quit [reference], smoking during pregnancy or quit within four months prior to the first-trimester interview). For the PTB models, the following were assessed for confounding: age, race, BMI, multiple gestations (singleton [reference], yes), parity, gravidity, therapeutic abortion history, smoking status, history of SAB (0 [reference], 1, 2+).

For each outcome we also tested for effect modification of antihistamine use by race/ethnicity (limiting to White and Black women). A Wald test was used to test the contribution of a race and antihistamine use interaction term. Race stratified analyses were only presented if these tests suggested heterogeneity ($p<0.2$). Race was not included as a covariate in stratified models, but it was assessed as a potential confounder (all race groups included) for our non-stratified models.

Results

Compared to women who did not, women who used antihistamines were more likely to be 30 to 33 years of age (27% vs. 24%), make more than $80,000 (42% vs. 37%), and be overweight (25% vs. 22%; Table 1). No maternal characteristics were associated with antihistamine use with the exception of enrollment site and gestational age among women with SABs. The timing of the screening and first trimester interviews was similar between antihistamine users and non-users.

The overall prevalence of first-trimester antihistamine use among women in RFTS was 14% (Table 2). The most common class of antihistamines taken were first generation H1 receptor antagonists (n=265). Women also reported taking second generation H1 receptor antagonists (n=101) and H2 receptor antagonists (n=30). First generation H1 receptor antagonists remain the most commonly reported antihistamine used in the first-trimester when use is qualified by race/ethnicity. Among White antihistamine users, 67% reported use of first generation H1 receptor antagonists. Among Black antihistamine users, 81% reported use of first generation H1 receptor antagonists. Among Hispanic users or users of other races/ethnicities, 82% reported use of first generation H1 receptor antagonists. Second generation H1 receptor antagonists were the next most commonly reported antihistamine used among all race/ethnicity groups, and H2 receptor antagonists were least commonly reported. Among all study participants, 20 women used both first generation H1 receptor and second generation H1 receptor antagonists, five used both first generation H1 receptor and H2 receptor antagonists, two used second generation H1 receptor and H2 receptor antagonists; no women used all three classes of antihistamines (results not shown).

Visual inspection of Kaplan-Meier curves suggested a protective effect for antihistamine use on SAB risk (not shown). We did not find evidence of effect modification by maternal race for the association between antihistamine use and risk of SAB. After assessing the potential confounders for inclusion, our final models were adjusted for maternal BMI and diabetes history (Table 3). A protective effect was suggested for the risk of having a pregnancy loss before 20 weeks (140 days), but the association was null (HR 0.88, 95%CI 0.64, 1.21, adjusted). Results from the proportional hazards test suggest that this HR should be interpreted cautiously, as an average hazard rather than a risk that remains constant over the first 20 weeks of gestation (p=0.066 for antihistamine use and p=0.122 for the adjusted [global] model). After stratifying our results on timing of loss (before or after 10 weeks/70 days), the strongest protective effect of antihistamine use was suggested among those with early losses (HR 0.79, 95%CI 0.50, 1.24, adjusted; proportional hazards test, p=0.267). Proportional hazards violations were strongest among later losses (p=0.075), where a null association was also possible (HR 0.98, 95%CI 0.63, 1.55, adjusted).

We observed effect modification by race for the effect of antihistamine use on risk of PTB. Our final models were adjusted for multiple gestation, BMI, and history of therapeutic abortions. For race-stratified analyses, we limited to non-Hispanic White or Black women and did not include race as a confounder. Overall, a null association was suggested for antihistamine use and PTB among White (OR 1.03, 95%CI 0.61, 1.72, adjusted) and Black women (OR 0.43, 95%CI 0.14, 1.34, adjusted; Table 4). The strongest proportional hazards violations were observed for White women (p=0.092 for antihistamine use and p=0.094 for the adjusted model, compared to p=0.217 and p=0.345, respectively, among Black women).

Discussion

The pharmacologic properties of antihistamines suggest they may influence pregnancy implantation and uterine contraction, which may have implications for pregnancy outcome. We examined the relationship between first-trimester antihistamine exposure and SAB and PTB. We did not detect evidence of association with SAB or PTB.

Several studies examined the effects of agonists and antagonists on histamine receptors during pregnancy. For example, animal models have investigated the role of histamine in implantation because histamine receptors are found on syncytiotrophoblast cells, cytotrophoblast cells, and the developing blastocyst. Antihistamines were found to inhibit the implantation process.[4,7] Martinez-Mir and colleagues[8] showed that H1 histamine receptors produced concentration-dependent contractions of the human uterus when stimulated by an agonist, while antagonistic action blocked this effect. H2 receptors mediated uterine relaxation upon stimulation with agonists. Predictably, this relaxant effect was reduced under the influence of an antagonist, such as ranitidine. Pennefather and colleagues[5] reported similar findings by comparing medication effects in uterine segments from pregnant and non-pregnant women; they saw a pregnancy-related increase in the myometrial response when stimulated by histamine. Several animal studies have confirmed these findings.[13-14] Antihistamines may interfere with these uterine contractile or early-pregnancy processes and contribute to adverse pregnancy outcomes, such as SAB and PTB.

There is conflicting data among epidemiological studies regarding the impact of antihistamine use on pregnancy. A retrospective cohort study by Ruigomez and colleagues[1] examined cimetidine (H2 receptor antagonist), omeprazole (proton pump inhibitor), and ranitidine (H2 receptor antagonist) use among pregnant women. Using data from 1,179 pregnancies in the United Kingdom and 1,057 pregnancies in Italy, they evaluated the association between first-trimester exposure and PTB. Within the United Kingdom cohort, 6% of those exposed to cimetidine (n=227) and 10% of those exposed to ranitidine (n=229) experienced PTB (compared to 7% among the control group, n=651). Within the Italy cohort, none of those exposed to cimetidine (n=10) and 6% of those exposed to ranitidine (n=101) experienced preterm birth (compared to 7% among the control group, n=924). Ultimately, they found no association with PTB. Antihistamine exposure in this study was based on filled prescriptions and not self-report.[3]

A prospective study by Garbis and colleagues[21] observed an increased risk for PTB among women exposed to H2-blockers any time during pregnancy. All information concerning exposure was reported by participants or their care providers. The researchers evaluated the outcome of 553 pregnancies with reported exposure to H2 receptor antagonists, with 91% reporting exposure in the first-trimester (the control group in the study consisted of 1,390 pregnant women). The H2 receptor antagonists reported in the study included ranitidine (n=335), cimetidine (n=113), famotidine (n=75), nizatidine (n=15), and roxatidine (N=15). Overall, the incidence of PTB was higher in the exposed group (9%) compared to the unexposed group (6%) (RR 1.67, 95% CI 1.18, 2.35); however, within the exposed group, five of the women reported use throughout pregnancy and 10 reported use only in the second or third trimester. The study also examined SAB risk due to antihistamine use any time during pregnancy and found the incidence of SABs was lower among the exposed (3%) than among the unexposed (6%), with a protective effect for antihistamine use (RR=0.52, 95% CI 0.31,0.86).

In contrast with prior studies, our evaluation of antihistamine use was limited to early first-trimester use. As a result, the distribution of types of antihistamines used may differ because medication use may vary as pregnancy symptoms change. We found H1 receptor antagonists were the most commonly reported antihistamine used, which is inconsistent with prior work suggesting that H2 receptor antagonists are more common. This may be due to the time-of-onset of gastric symptoms during pregnancy—symptoms often treated with H2 receptor antagonists. Our questionnaire focused on the first-trimester periconceptional period which may be outside of the timeframe when gastric symptoms are strongest. Our results could have implications for women who take antihistamines for allergies or symptoms such as nausea/vomiting.

Our study is unique in that we analyzed both prescribed and over-the-counter antihistamines, allowing us to capture a greater population of women at risk for adverse pregnancy outcomes associated with first-trimester antihistamine use. Our findings suggest that there is no increased risk for adverse outcomes. We were not able to examine the effect of dose on this risk. An adverse or protective effect may be seen at a particular dose threshold. Further investigation of exposure risks during other periods and of dose or duration effects is needed in order to understand the safety of antihistamine use throughout gestation.

Given the limitations of conducting clinical trials in pregnant women, our study demonstrates the utility of large prospective cohorts for evaluating drug safety in pregnancy when animal studies have raised concerns. RFTS can serve as a model for future studies examining medication exposures during pregnancy.

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Table 1

Maternal characteristics and antihistamine use among *Right from the Start* study participants

Characteristic	No Antihistamine Use (N=2,308)		Antihistamine Use (N=377)		OR	95% CI
	N	%	N	%		
Age (yrs, quartiles)						
<27	555	24.1	80	21.2	Ref	
≥27 and <30	578	25.0	97	25.7	1.16	0.85, 1.60
≥30 and <33	544	23.6	101	26.8	1.29	0.94, 1.77
≥33	631	27.3	99	26.3	1.09	0.79, 1.49
Missing	0		0			
Gravidity						
1	863	37.5	140	37.2	0.99	0.79, 1.24
>1	1,439	62.5	236	62.8	Ref	-
Missing	6		1			
Parity						
0	1,127	49.0	180	47.9	Ref	-
1	823	35.8	142	37.8	1.08	0.85, 1.37
≥2	352	15.3	54	14.4	0.96	0.69, 1.33
Missing	6		1			
BMI						
Underweight (<18.5)	57	2.5	3	0.8	0.35	0.11, 1.12
Normal weight (≥18.5 and <25.0)	1,316	58.0	200	53.5	Ref	-
Overweight (≥25.0 and <30.0)	495	21.8	94	25.1	1.25	0.96, 1.63
Obese (≥30.0)	403	17.8	77	20.6	1.26	0.94, 1.67
Missing	37		3			
Race/Ethnicity						
Non-Hispanic White	1,818	78.8	301	79.8	Ref	-
Non-Hispanic Black	246	10.7	43	11.4	1.06	0.75, 1.49
Hispanic	125	5.4	17	4.5	0.82	0.49, 1.38
Other	118	5.1	16	4.2	0.82	0.48, 1.40
Missing	1		0			

Characteristic	No Antihistamine Use (N=2,308)		Antihistamine Use (N=377)		OR	95% CI
	N	%	N	%		
Household Income						
≤$40,000	520	23.2	73	19.8	0.88	0.65, 1.20
$40,001-$80,000	895	40.0	142	38.5	Ref	-
>$80,000	824	36.8	154	41.7	1.18	0.92, 1.51
Missing	69		8			
Marital Status						
Married/Cohabitating	2,183	94.6	362	96.0	Ref	-
Other	125	5.4	15	4.0	0.72	0.42, 1.25
Missing	0		0			
Smoking Status						
Non-smokers/quit prior to first trimester/unknown when quit	2,119	92.2	341	90.9	Ref	-
Current smokers/possible first trimester use	179	7.8	34	9.1	1.18	0.80, 1.73
Missing	10		2			
Diabetes						
None	2,237	97.4	368	97.9	Ref	-
Any	60	2.6	8	2.1	0.81	0.38, 1.71
Missing	11		1			
Study site[1]						
North Carolina	1,673	72.5	255	67.6	Ref	-
Tennessee	635	27.5	122	32.4	1.26	1.00, 1.60
Missing	0		0			
History of preterm birth						
0	2,129	92.5	346	92.0	Ref	-
≥1	173	7.5	30	8.0	1.07	0.71, 1.60
Missing	6		1			
History of spontaneous abortions						
0	1,771	76.9	290	77.1	Ref	-
≥1	531	23.1	86	22.9	0.99	0.76, 1.28
Missing	6		1			
History of induced abortions						

Characteristic	No Antihistamine Use (N=2,308)		Antihistamine Use (N=377)		OR	95% CI
	N	%	N	%		
0	2,017	87.6	334	88.8	Ref	-
≥1	285	12.4	42	11.2	0.89	0.63, 1.26
Missing	6		1			
Multiple gestation in current pregnancy						
No	2,197	95.2	357	94.7	Ref	-
Yes	36	1.6	5	1.3	0.85	0.33, 2.19
Unknown due to early loss	75	3.3	15	4.0	1.23	0.70, 2.17
Missing	0		0			
Pregnancy outcome						
Live birth	1,990	86.2	332	88.1	Ref	-
Spontaneous abortion	309	13.4	44	11.7	0.85	0.61, 1.20
Stillbirth	9	0.4	1	0.3	0.67	0.08, 5.27
Missing	0		0			
Preterm Birth (Index pregnancy)						
No	1,845	92.7	311	93.7	Ref	-
Yes	146	7.3	21	6.3	0.85	0.53, 1.37
Loss before 20 weeks or stillbirth	318		45			
Gestational Age at end of pregnancy (weeks, live births only)						
median[range]	1,990	39.7 [23.0-45.0]	332	39.5 [29.7-45.0]	1.00	0.94, 1.06
Gestational age at end of pregnancy (weeks, SAB only)						
median[range]	309	9.4 [2.6-19.0]	44	10.1 [5.7-19.3]	1.12	1.01, 1.24
Gestational age at enrollment (weeks)						
median[range]	2308	6 [1.9-13.6]	377	6 [1.4-9.9]	0.97	0.91, 1.05
Gestational age at first trimester interview (weeks)						
median[range]	2308	14 [5.4-22.7]	377	14 [6.4-22.3]	0.99	0.92, 1.06
Weeks between enrollment and interview						
median[range]	2308	8 [0.4-16.3]	377	8 [1.0-17.9]	1.01	0.95, 1.06

yrs=years, OR=odds ratio (unadjusted), CI=confidence interval, ref=reference group

[1] Participants from Texas were removed when applying our exclusion criteria. Most were enrolled during the first study phase (RFTS1).

Table 2

Antihistamine use during the first-trimester in *Right from the Start*

Antihistamine Class	Generic Names	All Women (n=2,684)		White (n=2,119)		Black (n=289)		Hispanic or Other (n=276)	
		N	% users[1] (n=377)	N	% users[1] (n=301)	N	% users[1] (n=43)	N	% users[1] (n=33)
Any first generation H1 receptor antagonist use	diphenhydramine brompheniramine doxylamine pheniramine chlorpheniramine dimenhydrinate promethazine triprolidine	265	70.3	203	67.4	35	81.4	27	81.8
Any second generation H1 receptor antagonist use	loratadine cetirizine azelastine fexofenadine	101	26.8	88	29.2	9	20.9	4	12.1
Any H2 receptor antagonist use	ranitidine famotidine cimetidine	30	8.0	25	8.3	2	4.7	3	9.1
Missing information on drug class		8	2.1	7	2.3	1	2.3	0	0

N=number

[1]Some women used multiple antihistamines of different classes

Table 3

First-trimester antihistamine use and risk of SAB in *Right from the Start*

First-Trimester Antihistamine Exposure	N	Unadjusted HR	95% CI	Adjusted[1] HR	95% CI
No use	2,308	Ref	-	-	-
Any use	377	0.85	0.62, 1.17	0.88	0.64, 1.21
Any use, women with early SAB (< 70 days)[2]	195	0.73	0.46, 1.14	0.79	0.50, 1.24
Any use, women with late SAB (≥ 70 days)[2]	158	1.02	0.66, 1.58	0.98	0.63, 1.55

N=number, HR=hazard ratio, CI=confidence interval

Reference group is non-antihistamine users

[1] Adjusted for maternal BMI and diabetes status

[2] Women with late SAB (users and non-users) were excluded from the early SAB analysis and those with early SAB excluded from the late SAB analysis

Table 4

First-trimester antihistamine use and risk of PTB in *Right from the Start*

First-Trimester Antihistamine Exposure	N	Unadjusted HR	95% CI	Adjusted[1] HR	95% CI
No use among Non-Hispanic White women	1,571	Ref	-	-	-
Any use among Non-Hispanic White women	264	1.02	0.61, 1.71	1.03	0.61, 1.72
No use among African Americans	214	Ref	-	-	-
Any use among African Americans	40	0.39	0.12, 1.23	0.43	0.14, 1.34

N=number, CI=confidence interval

[1] Adjusted for maternal multiple gestation, BMI, and history of induced abortion; non-users of each respective race served as the reference groups