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Periconceptional antibiotic use and spontaneous abortion: a prospective cohort study

Holly Michelle Crowe[1,2], **Elizabeth Elliott Hatch**[1], **Tanran R. Wang**[1], **Charles Robert Horsburgh**[1], **Ellen Margrethe Mikkelsen**[3], **Wendy Kuohung**[4], **Lauren Anne Wise**[1], **Amelia Kent Wesselink**[1]

[1]Boston University School of Public Health, Department of Epidemiology, 715 Albany Street, Boston, MA, 02118, USA.

[2]Author's present address: Department of Epidemiology, Harvard T.H. Chan School of Public health, Department of Epidemiology, 677 Huntington Ave, Boston, MA 02115, USA.

[3]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Olof Palmes alle 43-45, 8200 Aarhus N, Denmark.

[4]Boston University School of Medicine, Department of Obstetrics and Gynecology, 72 E. Concord Street, Boston, MA 02118, USA.

Abstract

Background: Many reproductive-aged North Americans use antibiotics in the weeks preceding conception or during early pregnancy. Antibiotic use may influence risk of spontaneous abortion (SAB) by disrupting the reproductive tract microbiome or treating harmful infections. However, this association has not been extensively studied.

Objective: To determine the extent to which periconceptional antibiotic use is associated with the risk of SAB.

Methods: We analyzed data from an internet-based preconception cohort study of pregnancy planners. Eligible participants self-identified as female, were aged 21–45 years, resided in the USA or Canada, and conceived during 12 months of follow-up (n=7,890). Participants completed an enrollment questionnaire during June 2013-September 2021 and bimonthly follow-up questionnaires for up to 12 months or until a reported pregnancy, whichever came first. Pregnant participants completed questionnaires in early (~8–9 weeks) and late (~32 weeks) gestation. We assessed antibiotic use, including type (penicillins, nitrofurantoin, cephalosporins, macrolides) and indication for use, during the previous four weeks on preconception questionnaires. Participants reported pregnancies and SAB on follow-up and pregnancy questionnaires. We used Cox proportional hazards regression models with gestational weeks as the time scale to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between periconceptional antibiotic use and SAB, controlling for potential demographic, medical, and lifestyle confounders.

Corresponding author: Holly M. Crowe, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA USA, hcrowe@hsph.harvard.edu.

Author contributions

EEH and LAW designed the study. EEH, EEM, EEH, and LAW planned and initiated Pregnancy Online. HMC and TRW analyzed the data. All authors interpreted the results. HMC drafted the manuscript. All authors approved the final version of the manuscript.

Results: Nineteen percent (n=1537) of pregnancies ended in SAB. Participants reported periconceptional antibiotic use in 8% of pregnancies ending in SAB and 7% not ending in SAB. Periconceptional antibiotic use was not appreciably associated with SAB (adjusted HR 1.06, 95% CI: 0.88, 1.28). We observed no strong associations between antibiotic type, indication for use, or recency of exposure and SAB risk.

Conclusions: Periconceptional antibiotic use was not appreciably associated with SAB in this study. This association is likely complicated by antibiotic type and dosage, timing of conception, and the individual's overall health.

Keywords

antibiotics; infection; penicillin; miscarriage; spontaneous abortion

Background

Antibiotic use is common among reproductive-aged North Americans. Approximately 40–45% of pregnant individuals are prescribed antibiotics in the six months before conception.[1,2] Although the majority of antibiotics are considered safe for use during pregnancy, certain classes of macrolides (especially clarithromycin), sulfonamides, quinolones, and tetracyclines have been associated with adverse pregnancy outcomes, including congenital malformations and spontaneous abortion (SAB).[3–6]

SAB is defined as pregnancy loss occurring before 20 completed weeks gestation and occurs in an estimated 20% of recognized pregnancies.[7,8] SAB is a significant physical and psychological stressor and has been associated with future obstetric complications, cardiovascular disease, anxiety, depression, and post-traumatic stress.[9] Given the widespread use of antibiotics among reproductive age individuals, the unobservable nature of the exact timing of conception, and the high population burden of SAB, quantifying the association between periconceptional antibiotic use and SAB is of great public health importance.

Antibiotic use overall may be associated with disruption of the reproductive tract microbiome, which may be a risk factor for SAB.[10–12] The biologic mechanisms through which specific antibiotics may be related to SAB vary by antibiotic type and are not well explicated. Although the half-life of antibiotics is generally hours to days, short-term disruptions in the periconceptional period may impact early fetal development. Clarithromycin may inhibit cardiac rhythm regulation in early embryonic development[3,4], quinolones may inhibit DNA replication[3,4,13], tetracyclines may suppress proinflammatory cytokines necessary for implantation[3], and sulfonamides may inhibit folic acid synthesis, critical for fetal development.[3,14]

Previous studies of the association between antibiotic use and SAB have yielded inconsistent results.[2–4,13] A 2020 systematic review and meta-analysis of eleven observational studies on the association between antibiotic use during pregnancy and SAB (7 cohort studies and 4 population-based case-control studies) found an increased risk of SAB among individuals using macrolides (RR 1.42, 95% CI: 1.04, 1.93), quinolones (RR 2.48, 95% CI: 1.46, 4.20), and tetracyclines (RR 2.57, 95% CI 1.95, 3.38)

during pregnancy, compared with those who did not use antibiotics.[3] Ten antibiotics (sulfamethizole, clarithromycin, azithromycin, ciprofloxacin, norfloxacin, levofloxacin, doxycycline, minocycline, trimethoprim, metronidazole) were associated with SAB in various included studies, while amoxicillin and nitrofurantoin were associated with a decreased risk of SAB.[3] Most studies focused on antibiotic use in the first trimester of pregnancy and ascertained antibiotic use from hospital registries, prescription registries, or teratology information services.

Despite several large registry studies investigating the association between antibiotic use and SAB, confounding by indication, reverse causation, and inconsistent exposure windows continue to present challenges to ascertaining the true association.[4,15–17] Registry studies have little to no information on relevant confounding lifestyle factors. In addition, registries are unable to identify early SABs that do not require medical care; >50% of all SABs occur before 8 weeks of gestation and are unlikely to be registered.[8,18]

Antibiotic use during the preconception period has not been extensively studied but is highly relevant to pregnancy planners and their clinicians. Because the precise timing of conception is unknown, there is little practical difference between preconception exposures occurring close to conception and very early pregnancy exposures. In the present study, we analyzed data from a preconception cohort study to examine the association between periconceptional antibiotic use and risk of SAB.

Methods

Pregnancy Study Online (PRESTO) is an ongoing, web-based cohort study of couples trying to conceive. Study methods have been described in detail elsewhere.[19] Eligible participants self-identify as female, are aged 21–45 years, reside in the United States or Canada, and are not using contraception or fertility treatment. Participants complete a baseline questionnaire and follow-up questionnaires every 8 weeks for 12 months or until pregnancy, whichever comes first. On baseline and follow-up questionnaires, we ascertain data on demographics, lifestyle factors, and reproductive and medical history. Participants who report conception are invited to complete two additional questionnaires in early (~8–9 gestational weeks) and late pregnancy (~32 gestational weeks).

From June 2013 to September 2021, 15,319 eligible female participants enrolled in PRESTO and completed the baseline questionnaire. Of these, 3,910 (25%) were lost to follow-up before reporting a conception and 3,519 (23%) did not conceive during the follow-up period. The final analytic sample included 7,890 pregnant participants. We added questions pertaining to antibiotic type and indication to the questionnaires in March 2016; thus, we restricted the analyses of antibiotic type and indication to participants completing the baseline questionnaire after March 1st, 2016 (77% of pregnant participants).

Assessment of exposure

We asked participants at baseline and follow-up if they had taken antibiotics in the previous four weeks. If a participant indicated taking antibiotics, we asked them to provide the name of the antibiotic and the reason it was prescribed in open text boxes. We classified antibiotic

names by active ingredient, (penicillins, nitrofurantoin, cephalosporins, macrolides, other) and classified indications for use by type of infection (respiratory, urinary tract, pelvic/vaginal, or other). Indication categories were not mutually exclusive, and some participants reported more than one indication for a given antibiotic prescription.

We assessed antibiotic use in the prior four weeks every eight weeks during the preconception period using follow-up questionnaires. Many participants reported antibiotic use during some follow-up periods and non-use during others. We hypothesized that a potential association between antibiotics and SAB would likely be transient.[20,21] Therefore, we considered antibiotic use at the most recent questionnaire before conception to be the most etiologically relevant exposure period. We estimated the date of conception as the last menstrual period (LMP) before pregnancy + 14 days and assessed exposure from the most recent questionnaire completed before conception. If the participant was unknowingly pregnant at enrollment, exposure was assessed from the baseline questionnaire. We categorized the timing of exposure assessment relative to conception as: after conception, but before pregnancy detection (10% of participants), 1–4 weeks before conception (50%), 5–8 weeks before conception (25%), and >8 weeks before conception (15%). We hypothesized that 1–8 weeks before conception would be the most etiologically relevant exposure window.

Assessment of outcome

On follow-up questionnaires, we asked participants to report the dates and outcomes of all pregnancy tests. We asked participants who reported a pregnancy during follow-up how they detected their pregnancy (home pregnancy test, urine test at doctor's appointment, etc.) and the date. We defined SAB as pregnancy loss before 20 completed weeks gestation, ascertained through follow-up and pregnancy questionnaires. SAB included the responses "miscarriage," "chemical pregnancy," and "blighted ovum". If a participant reported a pregnancy loss, we asked them to provide the date of the loss, which we used to calculate completed gestational weeks at loss. We calculated gestational weeks from the date of the pregnancy LMP.

We attempted to determine pregnancy outcomes among participants lost to follow-up by contacting them by email or phone, searching social media and baby registries, using data shared by participants from fertility tracking apps, and linking participant data to birth registries in states with a high proportion of PRESTO participants (California, Florida, Massachusetts, Michigan, Ohio, Pennsylvania, Texas, and New York). If we were able to contact a participant, we asked them to provide information on pregnancy status, including date of pregnancy loss, if applicable.

Assessment of covariates

We selected potential confounders *a priori* based on available literature. Covariates assessed on the baseline questionnaire included: partner's age, household income, education, geographic region of residence, body mass index (BMI), parity, irregular menstrual cycles, smoking history, efforts to improve the chances of conception (e.g. charting menstrual cycles, ovulation testing), intercourse frequency, last method of contraception (hormonal,

barrier, etc.), history of SAB, history of infertility (defined as trying to conceive for 12 or more months without becoming pregnant), and history of diagnosed chlamydia. Covariates assessed at the most recent follow-up prior to the date of conception include: age, physical activity (total metabolic equivalents of task (MET)-hours per week),[22,23] prenatal vitamin or multivitamin use, current smoking, alcohol and caffeine intake, and pain medication use in the four weeks prior to the questionnaire.

Statistical analysis

We used Andersen-Gill data structure with one observation per week of gestation to account for left truncation due to differential timing of pregnancy detection.[24] We began follow-up at the gestational week of pregnancy detection, if available (95% of SABs), or at four weeks of gestation (the median gestation at first pregnancy detection in the cohort), and ended at SAB, 20 weeks of gestation, or other censoring event (date of ectopic pregnancy or induced abortion, withdrawal from study). There were 11% of participants lost to follow-up after reporting a pregnancy. As their pregnancy outcome was unknown, we censored these individuals at their date of last contact.

We used life-table methods to estimate the percentage of pregnancies ending in SAB, after accounting for censoring events. We used Cox proportional hazards regression models with gestational weeks as the time scale to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between antibiotic use and SAB, controlling for potential confounders. Results were adjusted for age (years), income (<$50,000, $50,000-$99,000, $100,000-$149,000, >$150,000), education (high school or less, some college, college, graduate school), BMI (kg/m^2, continuous), multivitamin use (yes, no), ever smoker (yes, no), parity (parous, nulliparous), irregular cycles (yes, no), doing something to improve the chances of conception (yes, no), intercourse frequency (<1, 1, 2–3, >3 times per week), history of SAB (yes, no), history of infertility (yes, no), alcohol use (drinks per week), caffeine consumption (mg/day), smoking status (never, former, current occasional, current regular smoker), pain medication use (yes, no), history of pelvic inflammatory disease (yes, no), history of chlamydia (yes, no), use of hormonal birth control as last method of contraception (yes, no), and geography (Midwestern U.S., Northeastern U.S., Southern U.S., Western U.S., Canada).

We conducted a summary-level probabilistic bias analysis[25] to examine the impact of non-differential misclassification of exposure on our results. We defined distributions of bias parameters using data from an external validation study on self-reported antibiotics,[26] using a range of sensitivities (0.27–0.92) and specificities (0.93–0.95, the lowest plausible range given the data we observed). We performed 10,000 simulations in which we randomly drew sensitivity from a trapezoidal distribution (min=0.27, mode 1=0.60, mode 2=0.73, max=0.92) and specificity from a triangular distribution (mine=0.93, mode=0.94, upper=0.95). We calculated corrected risk ratios (to approximate hazard ratios) given the parameters and reported the median corrected risk ratio as the point estimate and the 2.5^{th} and 97.5^{th} percentiles of the distribution as the simulation interval.

In addition to the main analysis, we stratified by early (<8 weeks) and late (8–20 weeks) gestation, as periconceptional exposures may be more likely to be associated with earlier

losses.[27] We also stratified by timing of exposure assessment relative to conception (after conception, but before pregnancy detection; 1–4 weeks before conception; 5–8 weeks before conception; >8 weeks before conception) to determine the extent to which antibiotic use more proximal to conception was more strongly associated with SAB. For antibiotic type and indication analyses, we classified participant-provided antibiotic names and indication for use.

Missing data

We used multiple imputation to generate values for missing baseline and follow-up data using fully-conditional specification methods.[28] We created twenty imputed datasets and statistically combined coefficients and standard errors across datasets. The proportion of participants missing covariate information was generally low. Household income data were missing for 3% of participants, while all other covariates were missing for <1% of participants. Missingness for antibiotic use was less than 1%.

Ethics Approval

This study was approved by the Institutional Review Board at the Boston University Medical Campus and online informed consent was obtained from all participants.

Results

Of the 7,890 pregnancies analyzed, we identified 1,537 SABs (19%) during 95,933 weeks of gestation. Overall, 7% of participants reported antibiotic use in the past four weeks on the questionnaire closest to conception, including 8% of pregnancies ending in SAB and 7% of pregnancies not ending in SAB. Participants who reported use of an antibiotic tended to have lower income and educational attainment (Table 1). They were also more likely to report irregular menstrual cycles (17% vs. 13%), a hormonal last method of contraception (41% vs. 36%), a history of SAB (32% vs. 25%), and a history of infertility (12% vs. 8%) at baseline. Antibiotic users were slightly less likely to report multivitamin use (82% vs. 86%), and more likely to report current regular smoking (7% vs. 4%), and pain medication use (77% vs. 68%) on the follow-up questionnaire closest to conception.

Any antibiotic use in the past four weeks on the most recent follow-up questionnaire before a recognized conception was not appreciably associated with SAB (adjusted HR 1.06, 95% CI: 0.88, 1.28). The results of the quantitative bias analysis correcting for systematic error due to misclassification of antibiotic use showed a modest positive association between antibiotic use and SAB (corrected RR 1.34, 95% simulation interval: 1.11,1.79). There was no meaningful association between antibiotic use and SAB when stratifying by early (<8 weeks; adjusted HR 1.03, 95% CI: 0.82, 1.30) or later gestation (8–20 weeks; adjusted HR, 1.11, 95% CI: 0.80, 1.54).

There was a modest association when antibiotic use was measured 1–4 weeks prior to conception (HR 1.20, 95% CI: 0.92, 1.56) or 5–8 weeks prior to conception (HR 1.22, 95% CI: 0.85, 1.75), compared with those who did not use an antibiotic (Table 3). The HR for antibiotic use after conception, but before pregnancy detection was 1.46 (0.86,2.47) and the HR for antibiotic use >8 weeks before conception was 0.82 (0.50, 1.35). When we excluded

individuals who conceived prior to exposure assessment from the main analysis, there was little change in the overall association between antibiotic use and SAB (HR 1.03, 95% CI: 0.84, 1.25).

Antibiotic type

Penicillins were the most frequently reported antibiotic type, comprising one third of antibiotic prescriptions, followed by nitrofurantoin (15%), cephalosporins (11%), and macrolides (9%) (Supplemental Table 1). We did not find strong associations between any specific type of antibiotics and SAB risk. The adjusted HR for use of penicillins, cephalosporins, nitrofurantoin, and macrolides were 0.95 (95% CI: 0.65, 1.39), 1.37 (95% CI: 0.78, 2.42), 1.14 (95% CI: 0.66, 1.96), and 1.16 (95% CI: 0.63, 2.17), respectively. We were unable to analyze other medication types due to the small number of users.

Antibiotic indication

The most common indication for antibiotic use was respiratory infections (25%), followed by urinary tract infections (24%), and pelvic or vaginal infections (13%). The remaining 38% of participants reported other indications such as surgery, dental infection, and preventive antibiotics, and other infections which could not be classified into one of the above categories (Supplemental Table 2). There were enough antibiotic users to reasonably estimate the association between use of an antibiotic for respiratory, urinary tract, or pelvic/vaginal infections and SAB. The HRs for use of an antibiotic for each these infections, compared with no antibiotic use were very similar (Table 2).

Comment

Principal findings

In this North American prospective cohort study, we found that female antibiotic use in the periconceptional period was not appreciably associated with risk of SAB. These findings were consistent when examining SAB in earlier (<8 weeks) and later (8–20 weeks) gestation. There was also no clear relationship between the timing of exposure assessment and the association between antibiotic use and SAB.

Strengths of the study

This prospective study of pregnancy planners addresses existing gaps in the literature by capturing robust data on potential confounding factors, and identifying a greater share of SABs, including those occurring early in gestation which do not result in medical treatment. In addition, the present study is less likely to be vulnerable to reverse causation, as most participants reported antibiotic use in the preconception period.

Limitations of the data

Although antibiotics are commonly prescribed in the periconceptional period, the diversity of antibiotic types and indications led to few individuals in subcategories of antibiotic users, which precluded analysis of type and indication jointly and limited the precision of our findings.

Additionally, we used self-reported exposure information for our analyses. Misclassification of exposure is possible if participants misreport antibiotic use. Previous literature on the validity of antibiotic self-report is limited to a study of veterans. The validation study found low sensitivity and high specificity when comparing self-report of antibiotic use to a Veteran's Administration national pharmacy database.[26] While the PRESTO and veterans study populations may not be comparable with regards to medication recall, there is likely under-ascertainment and potentially some over-ascertainment of exposure in our study. When correcting for a similar magnitude of exposure classification as the veteran's study, we found that, as expected, low sensitivity and high specificity may have biased our results towards the null. However, the bimonthly follow-up questionnaires and four-week recall period reduced the likelihood of a large degree of misclassification due to this mechanism.

We did not collect information on the exact timing of medication use, so there may be some of the same reverse causation as noted in previous studies, wherein an SAB had already begun prior to initiation of antibiotics.[15–17] However, excluding these individuals had no impact on the overall results. The confidence intervals for the analyses stratified by timing of exposure assessment were wide, and these findings may also be due to chance.

Exposure misclassification due to misspecification of the etiologically relevant time window is also possible in this study. Proposed biological mechanisms for potential effects of antibiotics on SAB, as well as the etiologically relevant period for exposure, vary by antibiotic type. Differences in the timing of exposure assessment and specific antibiotics studies may explain some of the discrepancies between our null findings and previous literature, including a meta-analyses showing an increased risk of SAB among individuals using certain types of antibiotics in the first trimester.[3]

Additionally, the conflicting potential mechanisms of disruption of the reproductive tract microbiome from repeated antibiotic use (which may increase the risk of SAB), and treatment of harmful infections (which should decrease the risk of SAB) may contribute to the null results.[11,30–33] However, we are unable to analyze these mechanisms in the present study. While we did not consider duration of antibiotic use in this study, the vaginal microbiome changes in a matter of hours under antibiotic exposure[34], but is known to be quite resilient and for the most part rebounds to its original state within one to three weeks of cessation of treatment.[20] Therefore, it is unlikely that exposure to antibiotics 8 weeks or more preceding pregnancy would be relevant to the risk of spontaneous abortion, although further research on this topic is warranted.[35]

Misclassification of outcome is also possible in this study, as we ascertained SAB from self-report and were unable to capture losses occurring prior to pregnancy detection. However, more than 95% of PRESTO participants reported use of home pregnancy tests (mean timing of first pregnancy test was 2 days before expected menses), and the median timing of first pregnancy detection in the cohort was four weeks, suggesting that this study was able to capture losses very early in gestation. Non-differential misclassification of SAB would likely lead to bias towards the null, unless there was perfect specificity (which is possible, given the nature of the outcome), in which case there would be no bias. The proportion

of recognized pregnancies ending in SAB in our study was similar to national estimates,[7] indicating that a high degree of outcome misclassification is unlikely.

Although we collected robust participant data at multiple time points to control for a range of potential demographic, lifestyle, and medical confounders, residual confounding from unmeasured or inaccurately measured factors is possible. In addition to confounding by infection severity and indication, residual confounding by unmeasured factors such as immune or inflammatory conditions is possible.

Selection bias due to differential loss to follow-up is unlikely, as loss to follow-up after a reported pregnancy was low (11.5%) and similar across antibiotic users (13.7%) and non-users (11.3%). If periconceptional antibiotic use is a strong predictor of pregnancy, our findings would be biased since our analysis conditions on recognized pregnancy.[36,37] However, we previously no association between antibiotic use and the probability of pregnancy in this cohort.[38] Therefore, this is unlikely an important source of bias in the present study.

Interpretation

Previous studies have shown a positive association between some antibiotics and SAB, and an inverse association between others when examining prenatal antibiotic use and SABs occurring after eight weeks of gestation. However, our study found no strong associations between antibiotics and SAB, when examining by type, indication, or timing relative to conception. Our study concentrated on the period before pregnancy detection and captured very early losses. As individuals may initiate lifestyle changes and seek to decrease medication use after pregnancy detection, and early losses make up the majority of SAB, this study provides additional information on periconceptional antibiotic use and SAB.

We also observed little association between use of cephalosporins, nitrofurantoin or macrolides and increased risk of SAB. Previous literature has shown no association between female use of cephalosporins and SAB.[3] Any increased risk of SAB among nitrofurantoin users may be attributable to confounding by indication, as nitrofurantoin is commonly used to treat urinary tract infections, which may have a modest association with increased risk of SAB independent of antibiotic class.[29] While previous studies have shown an association between macrolides, specifically clarithromycin, and SAB, there were too few clarithromycin users in the present study to examine the association with SAB.

We did not observe a strong association between respiratory, pelvic, or vaginal infection and SAB. While pelvic or vaginal infections may be more biologically plausibly related to SAB than respiratory infections, the absence of strong associations implies that confounding by indication (infection type) did not have a strong impact on our findings. Confounding by infection in general cannot be ruled out in this study. While some participants reported preventive antibiotic use (e.g. to prevent infection following a routine medical or dental procedure, to prevent diarrhea when traveling), there were too few preventive antibiotic users to allow for comparison between preventive antibiotic use and use to treat an active infection. We also did not have data on the severity of infection, and more severe maternal infections have been found to be associated with an increased risk of SAB.[30]

Conclusions

In summary, antibiotic use in the periconceptional period or very early in gestation was not appreciably associated with SAB. The relationship between antibiotic use in the periconceptional period and SAB is likely complicated by the nature and timing of the infection for which the antibiotic was prescribed, type, dosage, and frequency of medication, timing of conception, and the participant's overall health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Research data are not shared to protect the privacy of participants

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Synopsis:

Study question:

To what extent is periconceptional antibiotic use associated with spontaneous abortion?

What's already known:

Use of clarithromycin, sulfonamides, quinolones, and tetracycline antibiotics early in pregnancy has been associated with an increased risk of spontaneous abortion in some studies.

What this study adds:

This study examines antibiotic use in the periconceptional period overall and by type (penicillins, nitrofurantoin, cephalosporins, macrolides), indication for use, and recency of exposure. This study adjusts for confounding by medical, reproductive, and lifestyle factors and captures spontaneous abortions occurring early in gestation. In this study, periconceptional antibiotic use was not appreciably associated with spontaneous abortion.

Table 1.

Baseline characteristics by periconceptional antibiotic use, Pregnancy Study Online, 2013–2021

Characteristic[a]	Antibiotic Use	
	Non-use	Use
Number of participants (%)	7,293 (92%)	585 (7%)
Age (years, mean)	30.1	30.1
Partner's age (years, mean)	31.8	32.2
White, non-Hispanic (%)	85.9	84.6
Annual household income, USD (%)		
<$50,000	13.8	18.7
$50,000-$99,000	35.5	36.9
$100,000-$149,000	27.7	25.0
≥$150,000	20.3	16.6
Education (%)		
High school or less	3.0	5.1
Some college	17.0	19.8
College	34.7	34.8
Graduate school	45.3	40.3
Geographic Region (%)		
Midwest	21.8	23.5
Northeast	24.3	20.7
South	22.1	25.2
West	16.0	17.6
Canada	15.8	13.4
BMI (kg/m^2, mean)	26.8	27.5
Parous (%)	32.9	33.9
Irregular menstrual cycles (%)	13.4	17.0
Doing something to improve chances of conceiving (%)	81.0	81.3
Intercourse Frequency (%)		
<1 time per week	20.0	19.2
≥4 times per week	14.8	20.1
Hormonal last method of contraception (%)	36.0	40.5
History of spontaneous abortion (%)	25.0	31.6
History of infertility (%)	7.6	11.9
History of chlamydia (%)	7.1	8.0
Physical activity (MET-hrs/wk, mean)[b]	35.5	33.5
Multivitamin use (%)[b]	85.7	82.4
Smoking Status (%)[b]		
Never	80.8	74.9
Former	12.6	14.9
Current Occasional	2.7	3.2

Characteristic[a]	Antibiotic Use	
	Non-use	Use
Current Regular	4.0	7.0
Alcohol intake (drinks/week, mean)[b]	3.1	2.6
Caffeine intake (mg/day, mean)[b]	121.3	119.8
Pain medication use (%)[b]	67.6	76.7
Perceived stress score (mean)[b]	15.9	16.3

Abbreviations: USD = United States Dollar. Notes: Conception defined as 14 days after date of last menstrual period.

[a]All characteristics except for age are standardized to the age distribution of cohort at baseline.

[b]Assessed at follow-up closest to conception

Table 2.

Association between periconceptional[a] antibiotic use and spontaneous abortion, by weeks of gestation, antibiotic type and indication for use

	No. of SABs	No. of pregnancies	Unadjusted HR (95% CI)	Adjusted HR[b] (95% CI)
Periconceptional antibiotic use				
Yes	121	585	1.06 (0.88, 1.28)	1.06 (0.88, 1.28)[c]
No	1416	7305	1.00 (Reference)	1.00 (Reference)
Antibiotic use and gestational age				
<8 weeks gestation				
Yes	81	540	1.05 (0.83, 1.32)	1.03 (0.82, 1.30)
No	955	6688	1.00 (Reference)	1.00 (Reference)
8–20 weeks gestation				
Yes	40	467	1.10 (0.79, 1.53)	1.11 (0.80, 1.54)
No	461	5700	1.00 (Reference)	1.00 (Reference)
Antibiotic type				
None	1128	5599	1.00 (Reference)	1.00 (Reference)
Penicillins	28	148	0.93 (0.64, 1.36)	0.95 (0.65, 1.39)
Nitrofurantoin	15	66	1.17 (0.67, 2.03)	1.14 (0.66, 1.96)
Cephalosporins	14	49	1.43 (0.81, 2.52)	1.37 (0.78, 2.42)
Macrolides	10	41	1.22 (0.66, 2.27)	1.16 (0.63, 2.17)
Antibiotic indication for use				
No antibiotic use	1128	5599	1.00 (Reference)	1.00 (Reference)
Urinary tract infection	30	130	1.13 (0.75, 1.70)	1.14 (0.77, 1.70)
Respiratory infection	32	134	1.14 (0.80, 1.62)	1.14 (0.79, 1.63)
Pelvic/vaginal infection	16	71	1.19 (0.73, 1.94)	1.15 (0.71, 1.89)

[a] Assessed on the questionnaire closest to conception

[b] Adjusted for age, income, education, BMI, multivitamin use, parity, irregular menstrual cycles, doing something to improve chances of conception, intercourse frequency, history of SAB, alcohol intake closest to conception, smoking status closest to conception, pain medication closest to conception, history of pelvic inflammatory disease, history of chlamydia, last method of birth control, geographic region

[c] Bias corrected estimate 1.34 (95% simulation interval 1.11–1.79)

Table 3.

Association between periconceptional[a] antibiotic use and spontaneous abortion, by recency of exposure

	No. of SABs	No. of pregnancies	Unadjusted HR (95% CI)	Adjusted HR[c] (95% CI)
Never use of antibiotics	1223	6848	1.00 (Reference)	1.00 (Reference)
Antibiotic use				
1–4 weeks before conception	60	276	1.25 (0.95, 1.60)	1.20 (0.92, 1.56)
5–8 weeks before conception	32	148	1.24 (0.87, 1.77)	1.22 (0.85, 1.74)
>8 weeks before conception	17	112	0.81 (0.49, 1.32)	0.82 (0.50, 1.35)
Up to 5 weeks after conception[b]	15	58	1.41 (0.83, 2.38)	1.46 (0.86–2.47)

[a] Assessed on the questionnaire closest to conception

[b] Participant was pregnant, but unaware at study enrollment

[c] Adjusted for age, income, education, BMI, multivitamin use, parity, irregular menstrual cycles, doing something to improve chances of conception, intercourse frequency, history of SAB, alcohol intake closest to conception, smoking status closest to conception, pain medication closest to conception, history of pelvic inflammatory disease, history of chlamydia, last method of birth control, geographic region