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COMMENTARY

Risk of spontaneous abortion after periconceptional medication use: Time to tackle the methodological challenges

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Spontaneous abortion (SAB) is a common complication in early pregnancy affecting approximately 1 out of 7 recognised pregnancies and may have a profound impact on maternal psychological and long-term health, as well as obstetrical complications in future pregnancies.[1] Risk factors include sociodemographic characteristics, lifestyle, medical and obstetric history, environmental pollutants and occupational exposures. Although some medications, such as retinoids, misoprostol, methotrexate, and non-steroidal anti-inflammatory drugs, have been associated with an increased risk of SAB,[2] little is known about the role of many medications in the aetiology of SAB. Gaining more insight into the risks of medication use in relation to SAB is of vital importance for prospective parents and prescribing physicians, as well as from a regulatory perspective.[3] SAB, however, is one of the most challenging outcomes to study in perinatal pharmacoepidemiology for several methodological reasons, including outcome assessment, immortal time bias, selection bias, protopathic bias (reverse causation) and confounding (specifically confounding by indication).

Using data from 7890 participants in the web-based preconception cohort study Pregnancy Study Online (PRESTO), Crowe et al.[4] explored associations between periconceptional use of antibiotics and SAB, skilfully tackling several methodological challenges related to this outcome. Antibiotic use in the periconceptional period is hypothesised to increase the risk of SAB by disrupting the microbiome of the reproductive tract, but also to decrease SAB risk by treating harmful infections. Females trying to conceive were asked about antibiotic use in the previous 4 weeks in the baseline questionnaire and follow-up questionnaires every 8 weeks for 12 months or until pregnancy. Timing of antibiotic use relative to conception was categorised into four mutually exclusive categories: after conception, but before pregnancy detection; 1–4 weeks before conception; 5–8 weeks before conception; and >8 weeks before conception. The outcome (SAB) was ascertained using questionnaires at 8 and 32 weeks of gestation. The authors estimated hazard ratios (HR) for the association between periconceptional antibiotic use and SAB, controlling for a wide range of potential confounders. For 7% of pregnancies ($N = 585$), antibiotic use in the past 4 weeks was reported in the questionnaire closest to conception. The results indicated no strong association between any periconceptional antibiotic use and SAB (HR 1.06, 95% confidence interval [CI] 0.88, 1.28), with HRs varying from 0.82 (95% CI 0.50, 1.35) for antibiotic use >8 weeks prior to conception to 1.46 (95% CI 0.86, 2.47) for antibiotic use after conception, but before pregnancy detection. No strong associations between types of antibiotics or indications for antibiotic use and the risk of SAB were observed either. These reassuring results may contribute to fewer concerns about the safety of antibiotics in the periconceptional period. This may possibly lead to increased adherence to antibiotics, which is known to be suboptimal among pregnant women due to these concerns. On the other hand, it is critical that additional studies with larger sample sizes replicate these null associations.

This study nicely illustrates the value of observational studies with primary data collection starting enrolment before pregnancy when studying SAB as an outcome. PRESTO also captures SABs occurring in early gestation and those not resulting in medical encounters, in contrast to administrative claims databases, registries and prospective cohort studies with enrolment during pregnancy. Bias due to this left-truncation (i.e., participants are enrolled into the study at different gestational ages and an unknown proportion of

the source population is missing due to SABs prior to enrolment) may lead to substantial underestimation or overestimation of effect estimates, depending on the direction and magnitude of the difference in gestational age at enrolment of exposed and unexposed participants.[5] Left truncation can be corrected for using Cox regression, but this requires data on the gestational age at which the SAB occurs. Many administrative claims databases and registries lack this information, indicating the need for the development of valid algorithms to detect and date SABs in secondary data sources.[6] Additionally, quantitative bias analyses to quantify the influence of exposure and outcome misclassification as well as the application of alternative study designs are necessary to address some of the methodological limitations associated with evaluating SAB risks. The latter may include case-crossover studies and emulation of sequential target trials. Irrespective of the data source, elective terminations of pregnancy (induced abortions) are an important competing event of SAB and should be right-censored, as Crowe et al. have implemented.

As far as we know, the aetiologically relevant exposure window when studying SAB as an outcome remains to be elucidated. It has become clear, however, that there is a strong potential for protopathic bias when evaluating exposures occurring in the days before the SAB. As outlined by Sundermann et al.,[7] using gestational age at SAB instead of the estimated gestational age at arrest of development (which is seldom observed) overestimates the duration of exposure and time at risk. This may lead to an overestimation of SAB risks when the medication is used to treat signs and symptoms (e.g., abdominal pain, nausea, fever and cramping) of the yet undiagnosed SAB, which may be the case for analgesics and antibiotics. As such, previous studies finding a positive association between antibiotic use in the first trimester and SAB may be prone to reverse causation if the lag time between arrest of development and SAB (median: 23 days)[7] is not taken into account. By focusing on preconception exposure, Crowe et al. avoided protopathic bias, but it remains questionable whether the interval between the exposure and outcome did not become too large since the vaginal microbiome returns to its original state within 1–3 weeks after discontinuation of antibiotic treatment.[8] There is, however, growing evidence that preconception exposures may be associated with various pregnancy outcomes, for example, associations between preconception exposure to bisphenols and a decrease in offspring birth size.[9] Considering the mechanism of action and half-life of medications, preconception exposure to some medications might exert similar effects and is an interesting area for future research.

As discussed by the authors, frequent administration of questionnaires may reduce the potential for exposure misclassification, that is, increase the sensitivity of the ascertainment of antibiotic use. Although the PRESTO follow-up questionnaires were administered as frequently as every 8 weeks, they only assessed antibiotic use in the previous 4 weeks. Therefore, antibiotic exposure ascertainment may not be accurate only due to the low sensitivity of self-report of antibiotic use but also due to the questionnaire design. For example, if the most recent follow-up questionnaire was completed 1 week before conception and antibiotics were taken 6 weeks before conception, this would result in a false-negative exposure status for antibiotic use 5–8 weeks before conception and possibly also any antibiotic use if no antibiotics were reported in other relevant questionnaires. If non-differential, this misclassification may have led to underestimation of the effect estimates, which coincides with the results of the quantitative bias analyses presented in the results section (corrected risk ratio 1.34, 95% simulation interval 1.11, 1.79). This suggests a slightly increased risk of SAB after periconceptional antibiotic use, which cannot be explained by protopathic bias as only a small proportion of pregnancies (10%) was exposed after conception, but before pregnancy detection. Unmeasured confounding, however, cannot be excluded despite the extensive set of potential confounders adjusted for. This particularly concerns confounding by indication, partially adjusted for in the analyses on indication for use (site of infection), but an active comparator or diseased control group is deemed preferable.[10] These approaches may also be of increased relevance for clinical practice as they enable a comparative safety profile of several therapeutic options. Unfortunately, this study was underpowered to compare the safety profiles of the individual antibiotics.

Wilson's fifth principle of teratology, published in 1959 but still current, states that the four manifestations of teratogenicity are fetal death, malformation, growth restriction and functional deficit.[11] It should not come as a surprise that we cannot conclude on the reproductive safety of medications before having studied SAB risk. Therefore, we urgently need well-designed studies, such as the study by Crowe et al., to assess the safety of medication use preconceptionally and in early pregnancy regarding SAB risk. These studies, whether based on primary or secondary collected data, need to tackle the many methodological challenges associated with studying SAB as an outcome, including time-related biases such as left truncation, protopathic bias, confounding and sample size. A well-informed benefit-risk assessment for pregnant persons and pregnancy planners includes evidence-based knowledge on all important maternal and child health outcomes. It goes without saying that this includes SAB.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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