Time-related Biases in Perinatal Pharmacoepidemiology: A Systematic Review of Observational Studies

Short title: Time-related bias in pregnancy

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ABSTRACT

Background: Time-related biases, such as immortal time and time-window bias, frequently occur in pharmacoepidemiologic research. However, the prevalence of these biases in perinatal pharmacoepidemiology is not well understood.

Objective: To describe the frequency of time-related biases in observational studies of medications commonly used during pregnancy (antibiotic, antifungal, and antiemetic drugs) via systematic review.

Method: We searched Medline and EMBASE for observational studies published, between January 2013 and September 2020, examining the association between antibiotic, antifungal, or antiemetic drugs and adverse pregnancy outcomes, including spontaneous abortion, stillbirth, preterm delivery, small-for-gestational age, pre-eclampsia, and gestational diabetes. The proportion of studies with time-related biases was estimated overall and by type (immortal time bias, time-window bias).

Results: Our systematic review included 20 studies (16 cohort studies, 3 nested case-control studies, and 1 case-control study), of which 12 examined antibiotic, 6 antiemetic, and 2 anti-fungal drugs. Eleven studies (55%) had immortal time bias due to the misclassification of unexposed, event-free person-time between cohort entry and exposure initiation as exposed. No included study had time-window bias. The direction of effect varied for both studies with and without time-related bias, with many studies reporting very wide confidence intervals around the effect estimates, thus making the direction of effect less interpretable. However, studies with time-related bias were more likely to show protective or null associations compared with studies without time-related bias.

Conclusion: Time-related biases occur frequently in observational studies of drug effects during pregnancy. The use of appropriate study design and analytical approaches is needed to prevent time-related biases and ensure study validity.

Keywords: Time-related bias, immortal time bias, time-window bias, pregnancy, pharmacoepidemiology, systematic review.

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KEY POINTS

- Time-related biases, such as immortal time and time-window bias, frequently occur in pharmacoepidemiologic research, but their prevalence in the perinatal pharmacoepidemiologic is unknown.
- Our systematic review suggests that time-related biases are common in the contemporary perinatal pharmacoepidemiology literature, with over 50% of studies on antiemetic and antibiotic medications having immortal time bias.
- Studies affected by time-related biases often produce spuriously protective associations and may provide false reassurance regarding drug safety during pregnancy.
- The use of appropriate study design and analyses, such as emulating a target trial and the use of time-varying analyses, are needed to avoid time-related biases.
- This issue is particularly important in perinatal pharmacoepidemiology as this literature is the primary source of evidence for clinical decision-making given the limited number of trials in this area.

INTRODUCTION

Prescription drug use is common among pregnant women, with nearly 50% of women using multiple drugs at some point during pregnancy.[1,2] While these medications may have short- and long-term benefits to the mother, concerns exist regarding their potential harmful effects on the fetus and mother.[2] Given these safety concerns, the challenges of conducting randomized controlled trials (RCTs) in this population,[3,4] and frequent off-label drug use among pregnant women,[2] observational studies using real-world data play a crucial role in determining drug safety and informing clinical and regulatory decisions regarding prescription drug use during pregnancy.[3,5–7]

Concerns have emerged regarding the potential presence and consequences of time-related biases in perinatal pharmacoepidemiology.[8,9] Briefly, time-related biases occur when person-time of observation is not properly accounted for in the design or analysis of a study.[10] These biases include immortal time bias (mainly in cohort studies) and time-window bias (mainly in case-control studies), which are described below. Daniel *et al*[8] demonstrated how immortal time bias could occur in pregnancy studies through the example of prenatal exposure to non-steroidal anti-inflammatory drugs (NSAIDs) and spontaneous abortion. The use of a time-fixed exposure definition produced a hazard ratio (HR) of 0.70 (95% confidence interval [CI], 0.61, 0.94), whereas the correct time-varying approach resulted in an HR of 1.10 (95% CI, 0.99, 1.12). Similar results were described by Matok *et al*,[9] who examined the association between prenatal exposure to decongestants and preterm delivery, and by Hutcheon *et.al.*,[11] who investigated the association between gestational diabetes and stillbirth.

While it is well established that time-related biases may have substantial implications on the study of medication usage during pregnancy, their frequency in the contemporary perinatal pharmacoepidemiologic literature is unknown. Our objective was therefore to describe and estimate the frequency of time-related biases (focusing on immortal and time-window bias) in perinatal pharmacoepidemiologic studies via a systematic review of pharmacoepidemiologic studies of selected medications commonly used among pregnant women (antibiotic, antifungal, and antiemetic medications). We focused on these medications where the drug exposure is more likely started during pregnancy, so as to be able to clearly define the time frame for drug exposure and follow-up.

Time-related bias assessment

Time-related biases include immortal time bias, time-window bias, time-lag bias, immeasurable time bias, and others.[10,12–15] In this systematic review, we focused on immortal time bias and time-window bias, because we considered these two the most relevant to the study of medications in pregnancy. Immortal time bias occurs when the event-free, unexposed person-time between the cohort entry and the initiation of exposure is either misclassified as exposed (misclassification bias) or excluded (selection bias) (**Figure 1A**).[16] With an unexposed reference group, immortal time bias typically biases the estimate downward for adverse outcomes and may mask increased risks of exposure. Immortal time bias can also occur with an active comparator if the immortal time between cohort entry and drug initiation is differential between treatment groups. Time-window bias usually occurs in case-control studies, when cases and controls have differential opportunities for exposure because the exposure assessment window used in both groups

is not equal (**Figure 1B**),[12] such as when comparing cases to non-cases (people who do not experience the event during the study period) without the use of a fixed exposure assessment window (e.g., 30 days). It may also occur when controls are randomly sampled person-moments, that are not matched on follow-up time, with the different follow-up times resulting in differential exposure assessment windows between cases and controls.

METHODS

We registered the protocol for this systematic review in International Prospective Register of Systematic Reviews (PROSPERO [registration number #136476]) and report its findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines[17] (**eTable 1**). Ethical approval was not required for this study as it was a review of publicly available, aggregate data from already published studies.

Search strategy

We searched Medline (Ovid) and EMBASE (Ovid) for articles published between January 1st, 2013 to September 1st, 2020 that reported the effects of antenatal exposure to antibiotic, antifungal, or antiemetic medications on pregnancy outcomes. With the seminal papers on immortal time bias and time-window bias published in 2007[16] and 2011,[12] respectively, we restricted the beginning of our systematic search to 2013 to ensure that inclusion was restricted to the contemporary literature (i.e., after the causes, implications, and potential solutions to these biases had been established), although immortal time bias had been alluded to in older literature.[18,19] Keywords and subject headings related to "antiemetics",

"antibiotics", and "antifungal" drugs were combined with those for "pregnancy" to identify potentially relevant articles. We restricted our search to articles published in English. The complete search strategy for Medline is provided in **eTable 2**.

Two independent reviewers (UVU, WA) screened the titles and abstracts of articles identified by our electronic search for inclusion. Any article considered potentially relevant by either reviewer was carried forward to full-text review. Two independent reviewers (UVU, WA) conducted the full-text review, with disagreements resolved by consensus or by a third reviewer (RWP or KBF).

Inclusion and exclusion criteria

We included observational studies published in English language journals, including cohort, case-control, and nested case-control studies, on the medications of interest (antibiotic, antifungal, and antiemetic medications) and pregnancy outcomes. We focused on these medications because they are commonly used during pregnancy[20–22] as these have potentially important public health implications. Outcomes of interest were those related to gestational age. Outcomes included adverse fetal outcomes (stillbirth, spontaneous abortion, preterm premature rupture of membranes (PPROM), preterm delivery, small-for-gestational age (SGA), large-for-gestational age (LGA)) and adverse maternal outcomes (pre-eclampsia, gestational hypertension, gestational diabetes mellitus (GDM)). We also included intrauterine growth retardation as fetal growth is a dynamic and continuous process, and drug exposure at any time point during fetal development could conceivably impact on fetal growth.

We excluded randomized controlled trials, case reports and case series, letters to the editor, editorials/commentaries, and previous systematic reviews and meta-analyses. We excluded conference abstracts as they often contain insufficient information to definitely assess their quality and the potential presence of time-related biases. Cross-sectional studies were also excluded as they are less likely to be impacted by time-related biases due to their lack of follow-up time. Studies on congenital malformations only were also excluded to avoid temporality issues between the drug exposure and outcome; it is difficult to differentiate the timing of the occurrence of the malformation versus the timing of its recorded diagnosis. For example, congenital malformations occur early during pregnancy but can often be diagnosed during the first year of life (long after delivery).[23] Given the challenges in identifying the true event date for congenital malformations, the approach described by Hernán et al.[24] is difficult to apply to studies of congenital malformations than for other pregnancy-related outcomes.

Data extraction

For each included study, we extracted the following information using pilot-tested data extraction forms: study characteristics (the first author, year of publication, study design, location, and period, and sample size), exposure information (class of drug exposure, comparator, exposure definition [e.g., time-fixed vs time-varying, current use vs any use], exposure assessment period), and outcome characteristics (outcomes assessed). In addition, we extracted information on the reported adjusted risk estimates (cumulative incidence

proportions, HRs, odds ratios (ORs), risk or rate ratios (RRs)) with corresponding 95% CIs).

Assessment of time-related bias

The presence of time-related biases was assessed independently by two reviewers (UVU, WA), with disagreements resolved by consensus or, when necessary, by a third reviewer (RWP or KBF). This assessment involved the use of signaling questions and suggestions derived from the works of Platt *et al*,[25] Lévesque *et.al.*,[26] and Suissa *et al*.[13] , and time points (cohort entry/eligibility, period of drug exposure, and period of follow-up i.e. time zero) suggested by Hernan et al.[24] The signaling questions used in this assessment are described in detail in **eTable 3**. Consequently, studies that included two or more different exposure definitions were classified as having a time-related bias if one of them likely resulted in bias. Time-related biases in the included studies and the reasons for bias (e.g., the exclusion or misclassification of immortal time or time-window bias) were then summarized and described narratively.

Data synthesis

The frequency of time-related biases among the included studies was quantified as the number of studies with a time-related bias divided by the total number of included studies. These proportions were calculated overall, by type of time-related bias, and by drug class of interest.

RESULTS

Study selection

Our electronic search identified 1,739 potentially relevant articles (**Figure 2**). After removal of duplicates and screening of titles and abstracts, 71 publications underwent full-text review. A total of 20 studies met our inclusion criteria and were included in our systematic review. Six studies were of antiemetic drugs,[27–32] two studies were of antifungal drugs,[33,34] and 12 studies were of antibiotic drugs.[35–46] The most commonly reported outcomes were spontaneous abortion or miscarriage (12 studies),[27–30,32–39] preterm birth or delivery (10 studies),[28,29,31,32,38–43] stillbirth (7 studies),[28,29,31–34,39] and SGA (4 studies).[29,30,32,44] Outcomes reported in individual studies were LGA,[44] GDM,[44] pre-eclampsia,[45] and PPROM.[46]

Study characteristics

The 21 studies included 17 cohort studies, one traditional case-control study, and three nested case-control studies, with sample sizes ranging from 56 to 1,222,503 women (**Table 1**). Four of these studies were conducted in Denmark, three in Korea, two studies each in Canada, United States of America, Norway, Germany, and Israel, and one study each in the United Kingdom, Australia, Brazil, and China.

Time-related bias

Time-related bias appeared to have occurred in 11 (55%) of the 20 included studies (**Tables 2-4 & eTable 4)**. In all 11 studies,[27–29,31,32,35,37,39,42–44] the time-related bias was immortal time bias, which likely arose due to the misclassification of unexposed person-time as exposed time (**eTable 4**). All of the included cohort studies except one[38] used time-fixed

analyses, and person-time was not calculated in 10 of the studies.[27,28,30,31,39–44] Further details on the reasons for classification of time-related biases are provided in **eTable 4**.

Among the four case-control studies (three nested and one traditional),[33,36,45,46] there was no evidence of time-window bias, as all studies matched cases and controls on gestational age, ensuring a similar opportunity for exposure between groups (**eTable 5**).

Antiemetic use in pregnancy

Ondansetron and metoclopramide were the most frequently studied antiemetic medications and were examined in six included studies;[27–32] pyridoxine and doxylamine combination and granisetron were investigated in one study each (**Table 2**). Five of the studies on antiemetic use during pregnancy were considered to have potential time-related bias (83%).[27–29,31,32]

Five studies reported on spontaneous abortion,[27–30,32] three[28,29,32] of which compared use of antiemetics versus non-use while two studies[27,30] had active comparators. In the time-related biased studies, reported associations appeared protective, suggesting a decreased risk of spontaneous abortion with antiemetic use versus non-use[28,29,32] , except for one study which had an active comparator (**eFigure 1**).[27] For studies of stillbirth,[28,29,31,32] all of which had time-related bias, the confidence intervals of the estimates were wide, limiting our ability to make conclusions about the direction of effect although the associations appeared protective in two studies[29,32] and harmful in the other two studies.[28,31] Observed associations were mostly null for studies of preterm delivery (all with time-related

bias).[28,29,31,32] The association was null in the two time-biased studies of SGA that compared antiemetics with non-use, [29,32]

Antifungal use in pregnancy

Fluconazole was the medication of interest in the two studies[33,34] of antifungal use during pregnancy (**Table 3**). One study[33] compared high- or low- dose fluconazole with non-use of fluconazole while the other study[34] compared oral fluconazole to no fluconazole and with use of other topical azoles. Both studies examined the association between drug exposure and the risks of spontaneous abortions and stillbirth.

None of these studies showed evidence of time-related bias **(Table 3 & eTable 5)**. All analyses on fluconazole showed an increased risk of spontaneous abortion, while there was decreased risk or null association for stillbirth **(eFigure 2)**.

Antibiotic use in pregnancy

The 12 studies[35–46] of antibiotic drugs in pregnancy included various antibiotics, including ofloxacin, clindamycin, ampicillin, and penicillin (**Table 4**). Six[35,37,39,42–44] of the included studies were classified as having potential time-related bias (54%).

Five studies[35–39] examined the effect of antibiotic use versus non-use on spontaneous abortion, three of which had time-related bias.[35,37,39] Both the types of antibiotics and the direction of effect varied among these studies (null, protective, and harmful) (**Figure 3**).[36,38] The study of antibiotics and stillbirth had potential time-related bias with wide

confidence intervals around the point estimates, making the direction of effect difficult to interpret.[39] Three[39,42,43] of the six[38–43] studies of preterm delivery had evidence of time-related biases. In the time-related biased studies comparing antibiotic use versus unexposed,[39,41,42] the associations were null in two studies[41,42] and uninterpretable in one.[39] In contrast, they were protective for studies without time-related bias,[38,41] although with wide confidence intervals. Notably, the protective study by Hatanaka *et al* [41] assessed the effectiveness of antibiotic treatment in women at high-risk of pre-term delivery compared with untreated women. All the studies of SGA,[44] LGA,[44] and GDM[44] had potential immortal time bias and reported either null or protective associations. There was no evidence of time-related bias in the studies on PPROM[46] and pre-eclampsia,[45] both of which reported increased risks with antibiotic use versus non-use.

DISCUSSION

Principal findings

In this systematic review of the contemporary perinatal pharmacoepidemiologic literature, we found that time-related biases were frequent (57.1%) in studies of the association between antibiotic, antiemetic, and antifungal drugs and the risk of adverse pregnancy outcomes. Immortal time bias caused by the misclassification of unexposed, event-free person-time as exposed was the type of time-related bias that was present in all affected studies; none of the included studies had time-window bias. Eighty-three percent of antiemetic medication studies and 54% of antibiotic studies included in our systematic review had immortal time bias. There was no evidence of time-related bias in the studies of antifungal medications.

Comparison with existing literature

To our knowledge, our systematic review is the first study to assess the frequency of time-related biases in perinatal pharmacoepidemiology. However, several other studies and reviews have examined its presence in other clinical areas.[14,16,47,48] In a methodological review by Tran and Suissa[49] of studies on anti-acid therapy and survival among patients with idiopathic pulmonary fibrosis, four of 10 observational studies were affected by immortal time bias, while its potential presence was unclear for one additional study. All the studies with immortal time bias had reported protective effects with anti-acid therapy, whereas all other studies reported no association. Suissa *et al*[16] conducted a literature review of studies suggesting a reduction in cardiovascular disease among patients with chronic obstructive pulmonary disease exposed to gastrointestinal and inhaled beta-agonists drugs. All the 20 included studies had immortal time bias (16 studies with misclassified person-time and 4 studies with excluded person-time). A methodological review[47] of 81 observational studies of glucose-lowering drugs and cardiovascular outcomes reported that time-related bias was one of the most encountered methodological issues in this literature. The present study adds important evidence regarding the frequency of time-related bias in the perinatal literature.

Interpretation

Our findings have important clinical and policy implications. Although we were unable to make direct comparisons of the direction of the association among studies with and without time-related bias because of the heterogeneity across studies in exposures and outcomes

assessed, several studies have demonstrated that time-related biases can be conclusion altering, typically producing spuriously protective associations or null associations that mask harmful treatment effects.[8,9,48,49] These implications are particularly important for drug use in pregnancy, where there is a paucity of trial data and the clinical implications of adverse drug reactions are severe. Indeed, given the limited RCT data in this area, clinical decision making, treatment guidelines, and regulatory decisions are often based on the results of observational studies,[4,7] underscoring the importance of methodologically rigorous research in this area.

Our findings also highlight the need for appropriate study design and analytical approaches to avoid time-related biases. Studies of exposures in pregnancy are at high risk for time-related biases because many of the outcome definitions in perinatal studies are gestational-age related, thus longer pregnancies are by definition more likely to be exposed.[25] Strategies on reducing time-related bias, particularly at the study design and analyses stages, have been proposed in the literature.[13,25,50,51] These strategies include designing an observational study that emulates a hypothetical randomized trial such that the cohort entry, treatment assignment, and follow-up all start at the same time.[24,25] At the analytical stage, time-varying or nested-case control analyses, if conducted properly, will prevent time-related biases.[25] Using the study by Pasternak *et al* [29] as an example, immortal time bias may have been avoided in the analyses of preterm delivery if the authors had classified the time before exposure to ondansetron as 'unexposed person-time' in the analyses, or if they had matched the exposed with comparator patients at gestational age of exposure, rather than classifying exposure as "any time before 37 completed weeks" gestation. By grouping

all women who were administered ondansetron in a binary, time-fixed approach as "exposed" vs unexposed, unexposed person-time was misclassified as exposed. We propose matching an exposed person at the gestational age of drug exposure to an unexposed person at the same gestational age and following both persons from that time period until outcome occurrence. This approach is used in both observational studies that emulate target trials[24] as well as Suissa's prevalent new user design.[52] Such matching reduces the likelihood of immortal time bias, as the time between cohort entry and drug exposure (immortal time) would be identical between both exposed and unexposed groups and thus does not result in bias.

Previous studies have demonstrated how the use of a time-varying approach can remove immortal time bias, finding no association in the re-analysis of earlier studies that reported protective associations with a time-fixed approach.[9,51,53] Studies that use active comparators may be at lower risk of immortal time bias if the cohort entry and start of follow-up are not differential for both treatment groups.[54] In addition to decreasing the likelihood of immortal time bias, they also reduce potential confounding by indication and may provide more clinically relevant comparisons. However, active comparators were not frequently reported in the studies included in our systematic review and perhaps should be considered more in the pregnancy literature. The use of appropriate study design and analytical approaches is needed to ensure the validity of study results. In this systematic review, we focused on drugs with short-term use occurring during pregnancy but there is a need for future review of studies reporting different medications use structures (e.g., use of antidepressants in pregnancy).

Strengths

The main strength of our review lies in our assessment of drug classes whose safety during pregnancy has recently been of interest to regulatory agencies.[4,7,20] To our knowledge, we are the first to examine this issue in the perinatal literature and to provide a contemporary view by including more recently published studies. Therefore, our systematic review provides novel evidence, which is important for regulatory and clinical decision-making. Our study used a systematic approach to identify relevant articles and synthesize study findings, with our study protocol registered a priori to ensure transparency and reproducibility. Our use of signaling questions derived from previous studies in this area adds to the reproducibility of results.

Limitations

Our study also has some potential limitations. First, we only included studies of three drug classes commonly used during pregnancy as it was not feasible to assess all pharmacoepidemiologic studies conducted among pregnant women. The generalizability of these results to the larger literature is thus unclear. A follow-up study involving different inclusion/exclusion criteria may be of interest to assess the presence of time-related biases in the broader perinatal pharmacoepidemiologic literature. Our assessment of the exposure definitions used in the included studies was based on the published exposure definitions, which sometimes included insufficient detail to be unambiguously clear. Second, we restricted inclusion to studies published in English, and we cannot rule out the possibility of language bias. Finally, we restricted our assessment to immortal time bias and time-

window bias and did not assess the overall methodological quality of included studies (e.g., using a tool such as the Cochrane Collaboration's Risk Of Bias In Non-randomised Studies - of Interventions [ROBINS-I])[55] or the potential presence of other time-related biases (e.g., time-lag bias, immeasurable time bias). Consequently, our assessment of the amount of potential bias that is present in this literature is a conservative one.

CONCLUSIONS

Time-related biases are frequent in pharmacoepidemiologic studies conducted among pregnant women. In studies with an unexposed reference group, these biases distort the reported treatment effect downward, producing either a spuriously protective association or masking potential harms. The use of appropriate study design and analytical approaches are needed to prevent time-related biases and ensure study validity. Such methods are particularly important in the perinatal literature, where pharmacoepidemiologic studies play a crucial role in generating the evidence needed to inform regulatory decision-making, treatment guidelines, and the clinical care of this patient population.

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Table 1. Characteristics of studies investigating the effects of antibiotic, antiemetic, and antifungal drugs among pregnant women.

Author, year	Study design	Country	Study period	Drug class	Exposure assessment period	Sample size	Outcomes of interest
Antiemetic medications							
Ashkenazi-Hoffnung, 2013	Cohort	Israel	2008 to 2010	Antiemetic	Any trimester	56	Spontaneous abortion
Colvin, 2013	Cohort	Australia	2002 to 2005	Antiemetic	Any trimester	96,968	Preterm birth, stillbirth
Fejzo, 2016	Cohort	U.S.A.	2007 to 2014	Antiemetic	Any trimester	3396	Miscarriage, Preterm birth, stillbirth
Pasternak[a] (Ondansetron), 2013	Cohort	Denmark	2004 to 2011	Antiemetics	Any trimester	608,385	Spontaneous abortion, Stillbirth, Preterm delivery, Small-for-gestational age
Pasternak[b] (Metoclopramide), 2013	Cohort	Denmark	1997 to 2011	Antiemetics	Any trimester	1,222,503	Spontaneous abortion, Stillbirth, Preterm delivery, Small-for-gestational age
Shapira, 2020	Cohort	Israel	2013 to 2015	Antiemetics	1st and/or 2nd trimester	208	Miscarriage, Small-for-gestational age
Antifungal medications							
Bérard, 2019	Nested case-control	Canada	1998 to 2015	Antifungals	Any trimester	320,868	Spontaneous abortion, Stillbirths
Mølgaard-Nielsen, 2016	Cohort	Denmark	1997 to 2013	Antifungal	>7 weeks	16,561	Spontaneous abortion, Stillbirth

Author, year	Study design	Country	Study period	Drug class	Exposure assessment period	Sample size	Outcomes of interest
Antibiotic or antibacterial medications							
Andersen, 2013	Cohort	Denmark	1997 to 2007	Antibiotic	1st trimester	931,504	Miscarriage
Hatanaka, 2019	Cohort	Brazil	2010 to 2015	Antibiotic	16-26 weeks	86	Spontaneous preterm birth delivery
Kim, 2019	Case–control	Korea	2012 to 2016	Antibiotics	≤30 weeks	165	Preterm premature rupture of membranes
Lee, 2016	Cohort	Korea	1993 to 2012	Antibiotics	<34 weeks	314	Spontaneous preterm delivery
Minassian, 2013	Nested case-control	UK	1987 to 2007	Antibiotics	Any trimester	15,769	Preeclampsia
Mission, 2018	Cohort	USA	2012 to 2014	Antibiotics	Any trimester	12,551	Small-for-gestational age, Large-for-gestational age, Gestational diabetes
Muanda, 2017	Nested case–control	Canada	1998 to 2009	Antibiotics	Any trimester	95,722	Spontaneous abortion
Nordeng, 2013	Cohort	Norway	2004 to 2008	Antibiotics	Any trimester	180,120	Preterm delivery

Author, year	Study design	Country	Study period	Drug class	Exposure assessment period	Sample size	Outcomes of interest
Padberg, 2014	Cohort	Germany	1995 to 2012	Antibiotics	1st trimester	4,745	Spontaneous abortion
Philipps, 2020	Cohort	Germany	2000 to 2016	Antibiotics	1st trimester	608	Spontaneous abortion, Preterm birth,
Shin, 2018	Cohort	Korea	2001 to 2014	Antibacterial	Any trimester	143	Spontaneous abortions, Stillbirths, Preterm delivery
Zhang, 2016	Cohort	China	2013 to 2014	Antibacterial	1st and/or 3rd trimester	3767	Preterm delivery

Pasternak[a] = reference 29, Pasternak[b] = reference 32

Table 2. Characteristics of studies of antiemetic medications and pregnancy outcomes.

Author, year	Study design	Time-fixed vs time-varying analyses	Specific drug(s) vs comparator	Measure of Association (95% CIs) or proportion	Time-related bias
Spontaneous abortion, 1st trimester:					
Ashkenazi-Hoffnung, 2013	Cohort	Time-fixed	Pyridoxine and doxylamine vs Metoclopramide	7% vs 3%	Misclassification of person-time
Fejzo, 2016	Cohort	Time-fixed	Ondansetron vs unexposed	OR: 0.09 (0.06, 0.13)	Misclassification of person-time
Pasternak[a], 2013	Cohort	Time-fixed	Ondansetron vs unexposed	HR: 0.49 (0.27, 0.91)	Misclassification of person-time
Spontaneous abortion, 2nd trimester:					
Pasternak[a], 2013	Cohort	Time-fixed	Ondansetron vs unexposed	HR: 0.60 (0.29, 1.21)	Misclassification of person-time
Spontaneous abortion, unspecified trimester:					
Pasternak[b], 2013	Cohort	Time-fixed	Metoclopramide vs unexposed	HR: 0.35 (0.33, 0.38)	Misclassification of person-time
Shapira 2020	Cohort	Time-fixed	Granisetron vs other antiemetics	0 vs 5.5%	None
Stillbirth, unspecified trimester:					
Colvin, 2013	Cohort	Time-fixed	Ondansetron vs unexposed	OR: 1.8 (0.6, 5.5)	Misclassification of person-time
Pasternak[a], 2013	Cohort	Time-fixed	Ondansetron vs unexposed	HR: 0.42 (0.10, 1.73)	Misclassification of person-time
Pasternak[b], 2013	Cohort	Time-fixed	Metoclopramide vs unexposed	HR: 0.90 (0.74, 1.08)	Misclassification of person-time
Stillbirth, 21-36 weeks gestation:					
Fejzo, 2016	Cohort	Time-fixed	Ondansetron vs unexposed	OR: 1.26 (0.32, 5.90)	Misclassification of person-time

Author, year	Study design	Time-fixed vs time-varying analyses	Specific drug(s) vs comparator	Measure of Association (95% CIs) or proportion	Time-related bias
Preterm delivery, 21-36 weeks:					
Fejzo, 2016	Cohort	Time-fixed	Ondansetron vs unexposed	OR: 2.03 (1.36, 3.11)	Misclassification of person-time
Preterm delivery, <37 weeks:					
Colvin, 2013	Cohort	Time-fixed	Ondansetron vs unexposed	OR: 1.4 (0.7, 2.5)	Misclassification of person-time
Preterm delivery, unspecified trimester:					
Pasternak[a], 2013	Cohort	Time-fixed	Ondansetron vs unexposed	HR: 0.90 (0.66, 1.25)	Misclassification of person-time
Pasternak[b], 2013	Cohort	Time-fixed	Metoclopramide vs unexposed	HR: 0.98 (0.93, 1.04)	Misclassification of person-time
Small for gestational age, unspecified trimester:					
Pasternak[a], 2013	Cohort	Time-fixed	Ondansetron vs unexposed	HR: 1.13 (0.89, 1.44)	Misclassification of person-time
Pasternak[b], 2013	Cohort	Time-fixed	Metoclopramide vs unexposed	HR: 1.00 (0.96, 1.04)	Misclassification of person-time
Shapira, 2020	Cohort	Time-fixed	Granisetron vs other antiemetics	7 vs 11%	None

Pasternak[a] = reference 29, Pasternak[b] = reference 32; Abbreviations: OR- Odds ratios, HR- Hazard ratios.

Table 3. Characteristics of studies of antifungal medications and pregnancy outcomes.

Author, year	Study design	Time-fixed vs time-varying analyses	Specific drug(s) vs comparator	Measure of Association (95% CIs) or proportion	Time-related bias
Spontaneous abortion, unspecified trimester:					
Bérard, 2019	Nested case-control	Time-varying	Fluconazole (low dose) vs unexposed	OR: 2.23 (1.96, 2.54)	None
Bérard, 2019	Nested case-control	Time-varying	Fluconazole (high dose) vs unexposed	OR: 3.20 (2.73, 3.75)	None
Mølgaard-Nielsen, 2016	Cohort	Time-fixed	Oral Fluconazole vs unexposed	HR: 1.48 (1.23, 1.77)	None
Mølgaard-Nielsen, 2016	Cohort	Time-fixed	Oral Fluconazole vs topical azoles	HR: 1.62 (1.26, 2.07)	None
Stillbirth:					
Bérard, 2019	Nested case-control	Time-varying	Fluconazole (low dose) vs unexposed	OR: 0.56 (0.13, 2.40)	None
Bérard, 2019	Nested case-control	Time-varying	Fluconazole (high dose) vs unexposed	OR: 0.57 (0.07, 4.50)	None
Mølgaard-Nielsen, 2016	Cohort	Time-fixed	Oral Fluconazole vs unexposed	HR: 1.32 (0.82, 2.14)	None
Mølgaard-Nielsen, 2016	Cohort	Time-fixed	Oral Fluconazole vs topical azoles	HR: 1.18 (0.64, 2.16)	None

Abbreviations: OR- Odds ratios, HR- Hazard ratios.

Table 4. Characteristics of studies of antibiotic or antibacterial medications and pregnancy outcomes.

Author, year	Study design	Time-fixed vs time-varying analyses	Specific drug(s) vs comparator	Measure of Association (95% CIs) or proportion	Time-related bias
Spontaneous abortion, unspecified trimester:					
Andersen, 2013	Cohort	Time-fixed	Clarithromycin vs unexposed	HR: 1.56 (1.14, 2.13)	Misclassification of person-time
Muanda, 2017	Nested case–control	Time-varying	Cephalosporins vs unexposed	OR: 0.90 (0.69, 1.18)	None
Muanda, 2017	Nested case–control	Time-varying	Macrolides vs unexposed	OR: 1.61 (1.41, 1.85)	None
Muanda, 2017	Nested case–control	Time-varying	Penicillins vs unexposed	OR: 0.86 (0.78, 0.95)	None
Muanda, 2017	Nested case–control	Time-varying	Quinolones vs unexposed	OR: 2.72 (2.27, 3.27)	None
Muanda, 2017	Nested case–control	Time-varying	Sulfonamides vs unexposed	OR: 2.01 (1.36, 2.97)	None
Muanda, 2017	Nested case–control	Time-varying	Tetracyclines vs unexposed	OR: 2.59 (1.97, 3.41)	None
Muanda, 2017	Nested case–control	Time-varying	Other antibacterials vs unexposed	OR: 1.25 (0.88, 1.79)	None
Padberg, 2014	Cohort	Time-fixed	Fluoroquinolones vs unexposed	HR: 1.01 (0.80, 1.30)	Misclassification of person-time
Philipps, 2020	Cohort	Time-varying	Fosfomycin vs unexposed	HR: 0.35 (0.14, 0.90)	None
Shin, 2018	Cohort	Time-fixed	Oral Ofloxacin vs unexposed	OR: 0.60 (0.12, 2.76)	Misclassification of person-time
Stillbirth:					
Shin, 2018	Cohort	Time-fixed	Oral Ofloxacin vs no exposure	OR: 1.30 (-1.10, 1.40)	Misclassification of person-time
Preterm delivery, < 32 weeks:					
Lee, 2016	Cohort	Time-fixed	Ampicillin and/or cephalosporins vs ceftriaxone, clarithromycin and metronidazole	OR: 0.11 (0.03, 0.44)	None
Preterm delivery, < 34 weeks:					

Author, year	Study design	Time-fixed vs time-varying analyses	Specific drug(s) vs comparator	Measure of Association (95% CIs) or proportion	Time-related bias
Lee, 2016	Cohort	Time-fixed	Ampicillin and/or cephalosporins vs ceftriaxone, clarithromycin and metronidazole	OR: 0.18 (0.05, 0.62)	None
Hatanaka, 2019	Cohort	Time-fixed	Clindamycin and first-generation cephalosporin vs unexposed	OR: 0.24 (0.06, 0.99)	None
Preterm delivery, unspecified trimester:					
Philipps, 2020	Cohort	Time-varying	Fosfomycin vs unexposed	OR: 0.83 (0.37, 1.87)	None
Preterm delivery, unspecified trimester:					
Nordeng, 2013	Cohort	Time-fixed	Nitrofurantoin vs pivmecillinam	OR: 1.04 (0.78, 1.40)	Misclassification of person-time
Nordeng, 2013	Cohort	Time-fixed	Nitrofurantoin vs unexposed	OR: 1.08 (0.96, 1.22)	Misclassification of person-time
Shin, 2018	Cohort	Time-fixed	Oral Ofloxacin vs unexposed	OR: 1.60 (0.10, 18.05)	Misclassification of person-time
Zhang, 2016	Cohort	Time-fixed	Pennicilin vs adequately treated	OR: 1.50 (1.20, 2.10)	Misclassification of person-time
Small for gestational age:					
Mission, 2018	Cohort	Time-fixed	Any antibiotics vs unexposed	OR: 1.00 (0.88, 1.15)	Misclassification of person-time
Large for gestational age:					
Mission, 2018	Cohort	Time-fixed	Any antibiotics vs unexposed	OR: 1.00 (0.86, 1.17)	Misclassification of person-time
Gestational diabetes:					
Mission, 2018	Cohort	Time-fixed	Any antibiotics vs unexposed	OR: 0.90 (0.72, 1.13)	Misclassification of person-time

Author, year	Study design	Time-fixed vs time-varying analyses	Specific drug(s) vs comparator	Measure of Association (95% CIs) or proportion	Time-related bias
Preterm premature rupture of membranes (PPROM), ≤30 weeks:					
Kim, 2019	Case–control	Time-varying	Azithromycin treatment for maternal ureaplasma spp. colonization vs no colonization and no treatment	54% vs 29.1%	None
Pre-eclampsia:					
Minassian, 2013	Nested case-control	Time-varying	Any antibiotics vs unexposed	OR: 1.28 (1.14, 1.44)	None

Abbreviations: OR- Odds ratios, HR- Hazard ratios.

FIGURE LEGENDS

Figure 1. Description of (A) Immortal time bias and (B) Time-window bias. Figure 1A: Women 1, 2, and 3 enter the cohort at the same time. Using binary, time-fixed grouping for exposure (ever/never exposed during pregnancy), rather than considering person-time of exposure, results in any woman (e.g., Woman 2) who is exposed to the medication of interest being grouped as 'exposed', regardless of the timing of exposure. Consequently, this leads to misclassification of unexposed, event-free person-time as exposed for Woman 2 as the time-zero or follow-up period for the two groups (Woman 1 and Woman 2) are different, and this could result in an inflation of the denominator of the exposed group (number of women in exposed group will be higher), resulting in an underestimated risk of the outcome in the exposed group. This misclassification is particularly apparent when comparing Women 2 to Woman 3, who experienced an early event; the use of a time-fixed exposure definition considers the former 'exposed' and the latter 'unexposed' even though both are identical between cohort entry and the time at which Woman 3 experiences an event. The longer the pregnancy is, the greater opportunity the woman will have to be exposed, as preterm birth is inherently a time related. For instance, a preterm delivery can only be exposed up to 36 weeks, while there is a longer period for possible drug exposure for term pregnancies (37-40 weeks). Similarly, the exclusion of the immortal time prior to exposure results in immortal time bias. Figure 1B: If

the cases and controls are not matched on follow-up time (typically gestational age in pregnancy studies), cases will typically have a shorter follow-up time and opportunity for exposure than controls, resulting in a downward bias.

Figure 2. Flow diagram describing systematic literature search for studies of antiemetic, antibiotic, and antifungal medications among pregnant women.

Figure 3. Forest plot of studies of antibiotic medication use during pregnancy, with and without time-related bias. Stillbirth analyses in the study by Shin *et al* has a zero cell and so is not included in the plot. Abbreviations: GDM: Gestational diabetes mellitus, LGA: Large-for-gestational age, NCC: Nested case control, PTB: Preterm birth, SA: Spontaneous abortion, SGA: Small-for-gestational age. *Other is Ceftriaxone, clarithromycin and metronidazole.