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ORIGINAL RESEARCH

Associations Between Late-Onset Preeclampsia and the Use of Calcium-Based Antacids and Proton Pump Inhibitors During Pregnancy: A Prospective Cohort Study

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Purpose: Preeclampsia is a leading cause of maternal morbidity and mortality. Calcium-based antacids and proton pump inhibitors (PPIs) are commonly used during pregnancy to treat symptoms of gastroesophageal reflux disease. Both have been hypothesized to reduce the risk of preeclampsia. We determined associations of calcium-based antacid and PPI use during pregnancy with late-onset preeclampsia (≥34 weeks of gestation), taking into account dosage and timing of use.

Patients and Methods: We included 9058 pregnant women participating in the PRIDE Study (2012–2019) or The Dutch Pregnancy Drug Register (2014–2019), two prospective cohorts in The Netherlands. Data were collected through web-based questionnaires and obstetric records. We estimated risk ratios (RRs) for late-onset preeclampsia for any use and trajectories of calcium-based antacid and PPI use before gestational day 238, and hazard ratios (HRs) for time-varying exposures after gestational day 237.

Results: Late-onset preeclampsia was diagnosed in 2.6% of pregnancies. Any use of calcium-based antacids (RR 1.2 [95% CI 0.9–1.6]) or PPIs (RR 1.4 [95% CI 0.8–2.4]) before gestational day 238 was not associated with late-onset preeclampsia. Use of low-dose calcium-based antacids in gestational weeks 0–16 (<1 g/day; RR 1.8 [95% CI 1.1–2.9]) and any use of PPIs in gestational weeks 17–33 (RR 1.6 [95% CI 1.0–2.8]) seemed to increase risks of late-onset preeclampsia. We did not observe associations between late-onset preeclampsia and use of calcium-based antacids (HR 1.0 [95% CI 0.6–1.5]) and PPIs (HR 1.4 [95% CI 0.7–2.9]) after gestational day 237.

Conclusion: In this prospective cohort study, use of calcium-based antacids and PPIs during pregnancy was not found to reduce the risk of late-onset preeclampsia.

Keywords: extended Cox models, gestational hypertension, gastroesophageal reflux disease, longitudinal clustering methods, PRIDE study, The Dutch Pregnancy Drug Register

Introduction

Preeclampsia is a common pregnancy complication, affecting approximately 4.6% of pregnancies worldwide, with a wide variation across different regions.[1] It is characterized by the new onset of hypertension after 20 weeks' gestation, accompanied by proteinuria, other maternal organ dysfunction (ie liver, kidney, neurological) or haematological involvement (haemolysis or thrombocytopenia), and/or foetal growth restriction,[2] and is one of the leading causes of maternal and perinatal morbidity and mortality.[3–6] Based on their distinct aetiology and prognosis, two subtypes have been described: early-onset preeclampsia, occurring before or at gestational week 33, and late-onset preeclampsia, occurring at gestational week 34 or later.[4,7,8] The only curative treatment is delivery, which emphasizes the need for preventive measures. A promising intervention seems to be

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calcium supplementation: in a meta-analysis, the risk of preeclampsia was decreased by more than 50% after both low-dose calcium supplementation (<1 g/day, risk ratio [RR] 0.38, 95% confidence interval [CI] 0.28–0.52; 9 trials) and high-dose calcium supplementation (≥1 g/day, RR 0.45, 95% CI 0.31–0.65; 13 trials) compared to placebo.[9] In addition to calcium supplements, multivitamin-multimineral supplements, and nutritional intake, many over-the-counter antacids represent a substantial source of calcium with up to 680 mg of calcium carbonate per tablet. Antacids are used to treat symptoms of gastroesophageal reflux and are among the most commonly used medications during pregnancy, with prevalence estimates up to 37%.[10,11] Whether using calcium-based antacids during pregnancy is associated with a decreased risk of preeclampsia, however, has not been studied yet.

If symptoms of gastroesophageal reflux persist, second-line treatment options include histamine-2 receptor antagonists (H_2RA) and proton pump inhibitors (PPI). The latter are also hypothesized to have the potential for preventing preeclampsia by reducing the secretion of soluble fms-like tyrosine kinase 1 (sFlt-1) from primary placental cells, placental tissue, and primary endothelial cells.[12,13] The few epidemiologic studies on the association between PPIs and preeclampsia generally showed no decreased risks,[14–16] with the exception of PPI use recorded after gestational week 28 in a study using data from the Swedish Pregnancy Register.[14]

Potential beneficial effects of gastroesophageal reflux medication during pregnancy on the risk of preeclampsia may influence the choice of treatment. However, the current level of knowledge is insufficient to make a fair benefit-risk assessment. Therefore, we aimed to determine the potential beneficial side effects of using calcium-based antacids and PPIs during pregnancy in the prevention of late-onset preeclampsia, taking dosage and timing of use into account.

Materials and Methods

Study Population

For this study, we used data from 2 ongoing prospective cohorts among pregnant women in The Netherlands. The PRegnancy and Infant DEvelopment (PRIDE) Study aims to identify factors that affect maternal and child health during or after pregnancy.[17,18] The Dutch Pregnancy Drug Register is a national registry for medication use during pregnancy and lactation at the Netherlands Pharmacovigilance Centre Lareb aiming to provide information on the safety of medication use and modelled after the PRIDE Study.[19] For both cohorts, women aged ≥18 years were invited for participation as early in pregnancy as possible by participating midwives and gynaecologists, as well as through the 'Moeders voor Moeders' initiative and online advertisements in the PRIDE Study. In the Netherlands, the data collection for the International Registry of Antiepileptic Drugs and Pregnancy EURAP[20] is embedded in The Dutch Pregnancy Drug Register, so women with epilepsy were oversampled. In both cohorts, participating women were asked to complete Web-based questionnaires at baseline, in gestational weeks 17 and 34, and at multiple time points postpartum, starting 2 months after the estimated date of delivery. Through these questionnaires, we gathered data on demographic characteristics, obstetric history, maternal health including medication use, lifestyle factors, pregnancy complications, and infant health. Furthermore, PRIDE Study participants were asked consent for obtaining records from prenatal care providers. Approval for the PRIDE Study was granted by the Regional Committee on Research Involving Human Subjects Arnhem-Nijmegen (CMO 2009/305). The Regional Committee on Research Involving Human Subjects Arnhem-Nijmegen has confirmed that no ethical approval is required for The Dutch Pregnancy Drug Register. All participants provided informed consent digitally.

Outcomes

The primary outcome was late-onset preeclampsia, defined as new-onset hypertension accompanied by proteinuria after gestational week 34 (gestational day 237) irrespective of severity.[7,8] Details on the diagnostic criteria for hypertensive disorders of pregnancy in The Netherlands are outlined in Supplementary Table 1.[21] Data on the diagnosis of preeclampsia were obtained from previously validated questionnaires (sensitivity 88%, specificity 100%).[22] In case of loss to follow-up, outcome data were extracted from obstetric records whenever possible.

Exposures

Data on medication exposures were obtained from the three prenatal questionnaires and the first postpartum questionnaire. For a wide range of indications, including heartburn and acid reflux, women reported the name of the medication taken, time period of use, frequency of use, and quantity taken. Missing data on the duration of treatment, frequency, or quantity were replaced with the median cohort value for that variable specific for the medication of interest. Medications were coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.[23] Exposure to calcium-based antacids was defined as reported use of antacids (ATC code A02) containing any amount of calcium carbonate. The dose of calcium on each day was calculated by multiplying the amount of calcium carbonate in mg per medication unit by the number of units taken per day. The doses for multiple calcium-based antacids per day were summed. PPI exposure was defined as report of medication belonging to ATC group A02BC. Dosage was converted to Defined Daily Dose (DDD) per day. Following, daily doses were expressed as the average daily dose (milligrams per day for calcium-based antacids and DDDs per day for PPIs) per week. For calcium-based antacids, we considered a daily dose of ≥1 g calcium as high,[9] while a high dose for PPIs was >1 DDD. The sensitivity of the questionnaires was 0.89 (95% CI 0.86–0.93) for gastroesophageal reflux medication.[24]

We adhered to a recently published guidance on longitudinal methods for modelling medication exposures in pregnancy.[25] We evaluated exposure binarily (any versus none) in the first 237 days of pregnancy, further subdivided into early pregnancy (gestational weeks 0–16) and mid-pregnancy (gestational weeks 17–33), reflecting the temporality of data collection in both sources (in weeks 17 and 34). Furthermore, we clustered women with similar individual trajectories of calcium dose or DDDs of PPIs in gestational weeks 0–33 using *k*-means clustering with the R statistical software package "kml".[26] This unsupervised learning approach makes no a priori assumptions about trajectory shape or membership.[27] We considered daily and cumulative dose in each gestational week allowing for $k = 2$ to $k = 8$ clusters. We selected the number of clusters based on (a) optimization of three statistical quality criteria,[27] (b) clinical relevance of the clusters, and (c) at least 100 pregnancies per cluster.

K-means clustering requires all pregnancies to have the same gestational length to avoid including exposure after the diagnosis of preeclampsia and on postpartum days.[28] Moreover, immortal time bias could be introduced if we would apply the binary exposure categories after gestational day 237, as pregnancies without preeclampsia and pregnancies with longer gestations have more opportunity for exposure.[29,30] Therefore, we modelled time-dependent changes in dose on each gestational day between 238 and the end of follow-up, defined as diagnosis of preeclampsia or delivery, allowing for daily changes in use (none/any) and dose (none/low/high). We determined exposure time by dividing the average number of person-weeks in each exposure category by the number of women with any exposure to each level after day 237. Women could contribute person-weeks to multiple dose levels.[31]

Covariates

For each exposure-outcome association, we identified a minimally sufficient set of confounders using directed acyclic graphs (Supplementary Figure 1).[32,33] These included maternal age (continuous), parity (0 vs ≥1 previous delivery), pre-pregnancy Body Mass Index (BMI; continuous), maternal asthma (yes vs no), maternal depression (yes vs no), and smoking (yes vs no), alcohol consumption (yes vs no), and any use of calcium-containing supplements (yes vs no) during pregnancy. All confounder data were obtained from the prenatal questionnaires.

Inclusion and Exclusion Criteria

We selected all PRIDE Study participants with an estimated date of delivery in 2012–2019 (N = 9054) and participants in The Dutch Pregnancy Drug Register with an estimated date of delivery in 2014–2019 (N = 3911). Participants included in both cohorts were included only once, retaining the record with most complete information. Participants who were diagnosed with early-onset preeclampsia (pathophysiology differs from late-onset preeclampsia)[7] or who delivered before gestational week 34 (not at risk for the outcome of interest) were excluded.

Statistical Analysis

We used modified Poisson regression to estimate RRs with 95% CIs between exposure groups before gestational day 238 and late-onset preeclampsia.[34] Cox proportional hazard models with time since gestational day 238 were used to estimate

hazard ratios (HR) for exposure after gestational day 237. We used robust standard errors to account for correlation within women who participated with >1 pregnancy in the PRIDE Study.[35,36]

The models were weighted using inverse probability of censoring weights and adjusted for a sufficient set of confounders. We used inverse probability of censoring weights to account for potential selection bias resulting from differential loss-to-follow-up,[37] by fitting logistic regression models to predict not being lost-to-follow up using determinants of attrition. We used the models' predicted probabilities to calculate inverse weights for loss-to-follow-up. Under the assumption that data were missing at random, we imputed missing data on confounders through multiple imputation (25 imputations; Supplementary Table 1).

We conducted a number of sensitivity analyses to assess the robustness of the primary analysis. Firstly, we selected gestational hypertension as secondary outcome measure, distinguishing between exposure in gestational weeks 0–19 and after gestational week 20, as some studies indicate a protective effect of calcium supplements on this outcome as well.[9] Women with chronic hypertension (N=85) were excluded from these analyses. Secondly, we used an externally validated prediction model to select women at high risk of developing preeclampsia, with a risk threshold of 3%,[38,39] and replicated the main analyses in this population. Finally, we restricted the analyses to women who did not use calcium-containing supplements during pregnancy. All statistical analyses were performed using Stata/SE 16.0.

Results

Cohort and Trajectory Group Characteristics

A total of 9058 pregnancies were included in this study (Figure 1). The characteristics of the pregnancies included and those lost-to-follow-up are shown in Supplementary Table 2, and the characteristics of participants stratified by cohort are

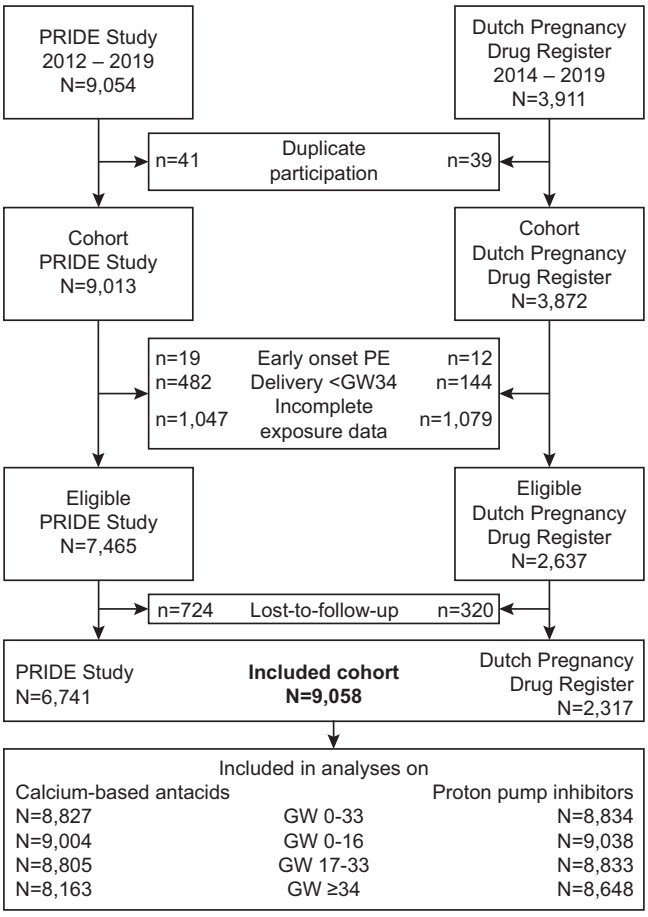

Figure 1 Flow chart of participation. GW, gestational week; PE, preeclampsia.

shown in Supplementary Table 3. Calcium-based antacid use in gestational weeks 0–33 was reported in 21.1% of pregnancies. Women who used calcium-based antacids in gestational weeks 0–33 seemed to be more likely to have a high level of education, to have asthma, to be primiparous, and to have used calcium-containing supplements compared to non-users (Table 1). In 3.8% of pregnancies, PPI use in gestational weeks 0–33 was reported. Omeprazole was most commonly reported (92.5%), followed by pantoprazole (6.6%) and esomeprazole (6.0%). PPI exposed women were more likely to have a low/intermediate level of education, asthma, depression, and a higher BMI, while more exposed women smoked in pregnancy, but fewer used alcohol. Late-onset preeclampsia was diagnosed in 2.6% of pregnancies at a mean gestational age of 37^{+6} weeks.

Two trajectories best described intake of calcium from antacids in the first 33 weeks of gestation (Figure 2). The low use trajectory is characterized by negligible use in the first 15 weeks of pregnancy, with moderate intake thereafter, whereas the high use trajectory showed a steep increase in dose after the first trimester up to 2500–3250 mg/day after gestational week 17. Maternal and pregnancy characteristics of the trajectory groups are shown in Supplementary Table 4. In the longitudinal cluster analyses, we did not identify trajectories describing intake of calcium from antacids in gestational weeks 0–16 and 17–33 separately or trajectories that described PPI use that fulfilled the selection criteria.

Table 1 Cohort Characteristics by Use of Calcium-Based Antacids and Proton Pump Inhibitors in Gestational Weeks 0–33. Data from the PRIDE Study (2012–2019) and the Dutch Pregnancy Drug Register (2014–2019)

Characteristic	Calcium-Based Antacid Use[a]				Proton Pump Inhibitor Use[a]			
	No (N=6964)		Yes (N=1863)		No (N=8502)		Yes (N=332)	
Maternal age, mean (SD)	31.4	(3.7)	31.4	(3.7)	31.4	(3.7)	31.6	(3.8)
Maternal country of birth, n (%)								
The Netherlands	6629	(95.2)	1781	(95.6)	8096	(95.2)	319	(96.1)
Other	264	(3.8)	66	(3.5)	321	(3.8)	11	(3.3)
Level of education, n (%)								
Low/intermediate	1629	(23.4)	383	(20.6)	1920	(22.6)	90	(27.1)
High	5278	(75.8)	1465	(78.6)	6510	(76.6)	241	(72.6)
Chronic conditions, n (%)								
Asthma	398	(5.7)	149	(8.0)	509	(6.0)	34	(10.2)
Chronic hypertension	19	(0.3)	9	(0.5)	26	(0.3)	2	(0.6)
Depression	113	(1.6)	24	(1.3)	125	(1.5)	12	(3.6)
Pre-existing diabetes	16	(0.2)	6	(0.3)	21	(0.2)	1	(0.3)
Pre-pregnancy BMI, mean (SD)	23.6	(4.0)	24.2	(4.5)	23.6	(4.1)	25.6	(5.4)
Parity, n (%)								
0 previous deliveries	3764	(54.0)	1059	(56.8)	4658	(54.8)	176	(53.0)
≥1 previous delivery	3179	(45.6)	797	(42.8)	3818	(44.9)	154	(46.4)
History of preeclampsia, n (%)								
Yes	131	(1.9)	36	(1.9)	160	(1.9)	8	(2.4)
No	6746	(96.9)	1813	(97.3)	8243	(97.0)	323	(97.3)
Smoking during pregnancy, n (%)								
Yes	330	(4.7)	114	(6.1)	415	(4.9)	28	(8.4)
No	6470	(92.9)	1709	(91.7)	7898	(92.9)	299	(90.1)
Alcohol during pregnancy, n (%)								
Yes	1095	(15.7)	292	(15.7)	1351	(15.9)	37	(11.1)
No	5722	(82.2)	1536	(82.4)	6981	(82.1)	291	(87.7)
Calcium-containing supplements, n (%)								
Yes	4073	(58.5)	1143	(61.4)	5025	(59.1)	194	(58.4)
No	1211	(17.4)	266	(14.3)	1433	(16.9)	48	(14.5)

Notes: [a]Numbers may not add up to totals due to missing values, ranging from 0.3% to 0.9% (level of education, chronic hypertension, pre-existing diabetes, pre-pregnancy BMI, and parity), 1.0% to 1.4% (country of birth, asthma, depression, and history of preeclampsia), and 2.1% to 2.3% (smoking and alcohol during pregnancy). For calcium-containing supplement use, the percentage of missing values was 24.2%, because details on multivitamin use were unavailable in The Dutch Pregnancy Drug Register.

Abbreviations: BMI, Body Mass Index; SD, standard deviation.

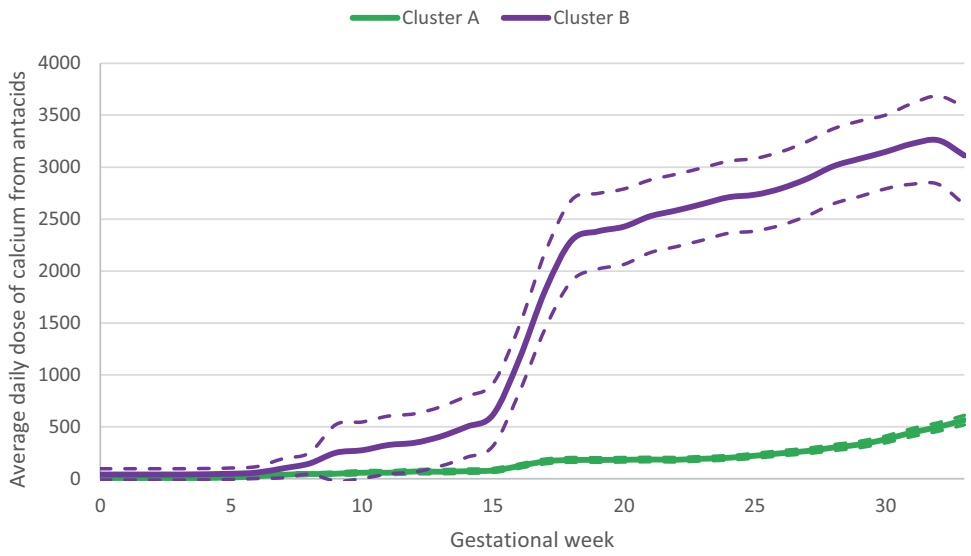

Figure 2 Mean trajectories (solid lines) with 95% confidence intervals (hashed lines) for 33-weeks calcium-based antacid use among 1115 pregnancies with exposure between LMP and gestational week 33. The average daily calcium intake from antacids was 161 mg (standard deviation 187) for the low use trajectory (Cluster A, N= 992) and 1502 mg (standard deviation 891) for the high use trajectory (Cluster B, N = 123).

Exposure in Early and Mid-Pregnancy and Late-Onset Preeclampsia

Any use of calcium-based antacids in gestational weeks 0–33 was not associated with the risk of late-onset preeclampsia (adjusted RR 1.2 [95% CI 0.9–1.6]; Table 2). The results did not differ substantially in the analyses on dosage or using the trajectories. An increased risk of late-onset preeclampsia was observed for women who used a low dose of calcium-based antacids (<1g/day) in gestational weeks 0–16 (adjusted RR 1.8 [95% CI 1.1–2.9]) compared to women who did not use calcium-based antacids in gestational weeks 0–16. An excess risk was not observed among women who used calcium-based antacids in gestational weeks 17–33.

We did not observe clear associations between PPI use in gestational weeks 0–33 and the risk of late-onset preeclampsia either. However, late-onset preeclampsia seemed to occur more often among women who used PPIs in gestational weeks 17–33 (4.8%) than among women who did not use PPIs in these gestational weeks (2.5%; adjusted RR 1.6 [95% CI 1.0–2.8]).

Exposure in Late Pregnancy and Late-Onset Preeclampsia

Table 3 shows the results for the use of calcium-based antacids and PPIs after gestational week 33. No associations were observed between any calcium-based antacid use (adjusted HR 1.0 [95% CI 0.6–1.5]) or PPI use (adjusted HR 1.4 [95% CI 0.7–2.9]) and late-onset preeclampsia. Using a high dose of PPIs after gestational week 33 seemed to increase the risk of late-onset preeclampsia (crude HR 2.7 [95% CI 0.9–8.5]), but this observation was based on a small number of exposed pregnancies (N=55).

Sensitivity Analyses

The prevalence of gestational hypertension was 7.7% with a median gestational age at diagnosis of 37^{+0} weeks (interquartile range 34^{+2} to 38^{+6} weeks). A high dose of calcium-based antacids (≥1 g/day) in gestational weeks 0–19 was associated with an increased risk of gestational hypertension (adjusted RR 1.6 [95% CI 1.2–2.1], Supplementary Table 5). Use of calcium-based antacids after gestational week 19 and use of PPIs in early and late pregnancy was not associated with the risk of gestational hypertension (Supplementary Tables 5 and 6).

Within the PRIDE Study, 38.4% of women (N = 2078) were at high risk of developing preeclampsia based on the externally validated prediction model.[38,39] Among these women, excess risks of exposure in early and mid-pregnancy

Table 2 Associations Between Calcium-Based Antacid and Proton Pump Inhibitor Use in Gestational Weeks 0–33 and Late-Onset Preeclampsia. Data from the PRIDE Study (2012–2019) and the Dutch Pregnancy Drug Register (2014–2019)

Exposure Group	Total	N (%) With PE		Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Calcium-based antacids in GW 0–33					
No use	6964	171	(2.5)	Reference	Reference
Any use	1863	60	(3.2)	1.3 (1.0–1.7)	1.2 (0.9–1.6)
Low dose (<1 g/day)	959	31	(3.2)	1.3 (0.9–1.9)	1.3 (0.9–1.8)
High dose (≥1 g/day)	893	29	(3.3)	1.3 (0.9–1.9)	1.2 (0.8–1.8)
Low use trajectory	992	30	(3.0)	1.2 (0.8–1.8)	1.2 (0.8–1.7)
High use trajectory	123	3	(2.4)	1.0 (0.3–3.1)	N/A
Calcium-based antacids in GW 0–16					
No use	8276	206	(2.5)	Reference	Reference
Any use	728	26	(3.6)	1.4 (1.0–2.1)	1.3 (0.9–1.9)
Low dose (<1 g/day)	314	16	(5.1)	2.0 (1.2–3.4)	1.8 (1.1–2.9)
High dose (≥1 g/day)	235	7	(3.0)	1.2 (0.6–2.5)	1.1 (0.5–2.4)
Calcium-based antacids in GW 17–33					
No use	7201	185	(2.6)	Reference	Reference
Any use	1604	45	(2.8)	1.1 (0.8–1.5)	1.0 (0.7–1.4)
Low dose (<1 g/day)	847	20	(2.4)	0.9 (0.6–1.4)	0.9 (0.6–1.4)
High dose (≥1 g/day)	690	22	(3.2)	1.2 (0.8–1.9)	1.2 (0.8–1.8)
Proton pump inhibitors in GW 0–33					
No use	8502	217	(2.6)	Reference	Reference
Any use	332	14	(4.2)	1.7 (1.0–2.8)	1.4 (0.8–2.4)
Low dose (≤1 DDD/day)	242	11	(4.6)	1.8 (1.0–3.2)	1.5 (0.8–2.8)
High dose (>1 DDD per day)	85	3	(3.5)	1.4 (0.5–4.2)	N/A
Proton pump inhibitors in GW 0–16					
No use	8868	229	(2.6)	Reference	Reference
Any use	170	6	(3.5)	1.4 (0.6–3.0)	1.1 (0.5–2.6)
Low dose (≤1 DDD/day)	91	4	(4.4)	1.7 (0.6–4.5)	N/A
High dose (>1 DDD/day)	53	0	(0.0)	N/A	N/A
Proton pump inhibitors in GW 17–33					
No use	8544	217	(2.5)	Reference	Reference
Any use	289	14	(4.8)	1.9 (1.1–3.2)	1.6 (1.0–2.8)
Low dose (≤1 DDD/day)	210	9	(4.3)	1.7 (0.9–3.2)	1.5 (0.8–3.0)
High dose (>1 DDD/day)	57	3	(5.3)	2.1 (0.7–6.3)	N/A

Notes: [a]Inverse probability of censoring weights; all models were adjusted for maternal age, asthma, pre-pregnancy BMI, parity, smoking during pregnancy, alcohol use during pregnancy, and use of calcium-containing supplements. Models for proton pump inhibitors were additionally adjusted for depression.

Abbreviations: CI, confidence interval; DDD, Defined Daily Dose; GW, gestational weeks; PE, preeclampsia; RR, risk ratio.

were more evident compared to the total population with an adjusted RR of 2.3 (95% CI 1.2–4.4) for low-dose calcium-based antacids in gestational weeks 0–16 and 2.2 (95% CI 1.2–4.3) for any PPI use in gestational weeks 0–33 (Supplementary Table 7). The latter was attributable to PPI use in gestational weeks 17–33, as no increased risk was observed for PPI use in gestational weeks 0–16 (adjusted RR 1.4 [95% CI 0.5–4.3]). We did not observe associations between late-onset preeclampsia and any calcium-based antacid use (adjusted HR 0.7 [95% CI 0.3–1.3]) or PPI use (adjusted HR 2.1 [95% CI 0.8–5.2]) after gestational week 33 among women at high risk of developing preeclampsia (Supplementary Table 8). Restricting the analyses to women who did not use calcium-containing supplements during pregnancy (N=1482) did not materially change the results, although these analyses were hampered by small numbers (Supplementary Tables 9 and 10).

Table 3 Associations Between Calcium-Based Antacid and Proton Pump Inhibitor Use After Gestational Week 33 and Late-Onset Preeclampsia. Data from the PRIDE Study (2012–2019) and the Dutch Pregnancy Drug Register (2014–2019)

Time-Dependent Exposure After GW33	N	PE	Person Weeks	Rate (Per 1000/Week)	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Calcium-based antacids						
No use	7897	187	41,539	4.5	Reference	Reference
Any use	1170	21	5078	4.1	0.9 (0.6–1.4)	1.0 (0.6–1.5)
Low dose (<1 g/day)	589	8	2252	3.6	0.8 (0.4–1.6)	0.8 (0.4–1.6)
High dose (≥1 g/day)	630	13	2826	4.6	1.0 (0.6–1.8)	1.1 (0.6–1.9)
Proton pump inhibitors						
No use	9008	216	48,594	4.4	Reference	Reference
Any use	267	8	1168	6.8	1.6 (0.8–3.2)	1.4 (0.7–2.9)
Low dose (≤1 DDD/day)	217	5	918	5.4	1.3 (0.5–3.0)	1.2 (0.5–2.9)
High dose (>1 DDD/day)	55	3	250	12.0	2.7 (0.9–8.5)	N/A

Notes: [a]Inverse probability of censoring weights; all models were adjusted for maternal age, asthma, pre-pregnancy BMI, parity, smoking during pregnancy, alcohol use during pregnancy, and use of calcium-containing supplements. Models for proton pump inhibitors were additionally adjusted for depression.
Abbreviations: CI, confidence interval; DDD, Defined Daily Dose; GW, gestational week; HR, hazard ratio; PE, preeclampsia.

Discussion

In this prospective cohort study, we did not observe decreased risks of late-onset preeclampsia after use of calcium-based antacids or PPIs during pregnancy, irrespective of the timing of use. In contrast, low dose calcium-based antacid use in gestational weeks 0–16 and any PPI use in gestational weeks 17–33 were associated with a modestly increased risk of late-onset preeclampsia.

This is the first study to evaluate the potential of calcium-based antacids to reduce the risk of preeclampsia. Several mechanisms through which calcium intake could prevent preeclampsia have been proposed. Calcium may protect endothelial cells from endothelial activation by multiple activators, including necrotic trophoblast debris and inflammatory cytokines, and prevent hypertension by increasing the production of nitric oxide, which is a potent vasodilator.[40] Additionally, low serum calcium could increase blood pressure by inducing parathyroid release, which stimulates renin release, resulting in increased intracellular calcium leading to vasoconstriction.[41,42] Indeed, hypocalciuria seems to be a marker of preeclampsia severity,[43] and calcium supplementation has been shown to substantially decrease the risk of preeclampsia based on data from randomized controlled trials, although publication bias cannot be excluded.[9] Only a few observational studies on the association between calcium supplementation and hypertensive disorders of pregnancy have been conducted, indicating that beneficial effects may only apply to women with a diet low in calcium or observing no effect at all.[44–46] In exploratory analyses in the current study, we did not observe a decreased risk of late-onset preeclampsia associated with calcium-based antacid use among women at high risk of developing preeclampsia or among women who did not use calcium supplementation either. Alternatively, intestinal absorption of calcium may differ between intake from supplements and antacids.

In line with previous studies,[14–16] we did not find the risk of late-onset preeclampsia to be reduced after use of PPIs, neither in early or mid-pregnancy or in late pregnancy. The latter, however, is in contrast with the results from Hastie et al,[14] who observed a reduced risk of preterm preeclampsia (delivery <37 weeks of gestation; adjusted odds ratio 0.63 [95% CI 0.41–0.96]) and early preeclampsia (delivery <34 weeks of gestation; adjusted odds ratio 0.41 [95% CI 0.20–0.82]) associated with PPI use after gestational week 28. In addition to a different outcome definition applied in our study (ie late-onset preeclampsia: any preeclampsia diagnosed after 33^{+6} weeks of gestation), this difference in results could be explained by the analytical approach. The extended Cox model applied in our study accounts for PPI use to be a function of time, whereas the standard time-independent model used by Hastie et al[14] may be biased by immortal time,[29,47,48] leading to overestimation of the protective effects of PPI use.

Mechanistically, PPIs may be more likely to prevent preterm preeclampsia than term preeclampsia, in which the relative difference in sFlt-1 levels between those affected and those who are not is smaller than in preterm preeclampsia.[49] Therefore, PPI use may prevent the development of early-onset preeclampsia in particular. We excluded

cases with this subtype, however, due to etiologic and prognostic heterogeneity,[7,8] as small numbers prevented us from including these cases as a separate outcome group.

Instead of the hypothesized decreased risk, we actually observed an increased risk of late-onset preeclampsia associated with use of low-dose calcium-based antacids in gestational weeks 0–16 or use of PPIs in gestational weeks 17–33, in particular among women at high risk of developing preeclampsia. As the World Health Organisation recommends calcium supplementation as part of prenatal care to prevent preeclampsia among women in populations in which calcium intake is low,[50] future studies on this topic are warranted. We did not identify other studies with similar results on calcium in early pregnancy, but slightly increased risks of overall preeclampsia associated with PPI use in pregnancy were also observed in other studies,[14–16] as summarized in a recent meta-analysis (RR 1.27, 95% CI 1.23–1.31).[51] Animal and in vitro studies showed that PPIs, particularly pantoprazole, have a negative impact on vascular endothelium and renal tissue,[52] aggravate ischaemia-induced arrhythmias,[53] and may be responsible for a depression of cardiac contractility,[54] providing a possible biological mechanism for the association observed. However, these results may also be biased by confounding by indication, as illustrated by the attenuated RR in comparisons with an H_2RA-exposed group in a nationwide cohort study in South Korea.[16] Furthermore, reverse causation cannot be excluded, since epigastric pain is one of the symptoms consistent with preeclampsia.[55]

A major strength of this study is the availability of detailed, validated self-reported data on the use of calcium-based antacids and PPIs, enabling us to take dosage and timing of exposure into account, despite actual use being slightly underreported.[24] Studies relying on administrative databases, however, are prone to exposure misclassification due to the wide and uncaptured over-the-counter availability of the medications of interest (underestimation) and non-adherence to prescribed medications (overestimation),[56] making them unsuitable to assess the associations of interest. Other strengths include the application of advanced methods to deal with time-varying exposures and the availability of a wide range of confounders, although residual confounding cannot be ruled out completely.

This study also has some limitations. Participants in the PRIDE Study and The Dutch Pregnancy Drug Register differ from the general Dutch population of pregnant women in terms of level of education, but selection into the study has been reported not to bias exposure-outcome associations in comparable cohort studies.[57–59] Differential loss-to-follow up, however, may affect the effect estimates. Therefore, we applied IPCW, which is a robust method to handle bias resulting from this type of selection.[60] Although we included a relatively large study population, study power was insufficient for some secondary analyses and to use an active comparator. The validity of self-reported data on the secondary outcome gestational hypertension is considerably lower compared to that of the primary outcome preeclampsia, mainly due to relatively high numbers of false-positive reports.[22] Due to a partial lack of data, we could not take dietary calcium intake and the dose of supplementation into account in our confounder definition. Of note, the calcium content in supplementation is usually low (120–200 mg).

Conclusion

This study adds to the growing body of evidence that PPIs do not prevent preeclampsia, despite their ability to reduce the secretion of sFlt-1. Furthermore, calcium-based antacids did not reduce the risk of preeclampsia in this population of pregnant women, even in high doses. Based on these results, choice of treatment of symptoms of gastroesophageal reflux does not need to be influenced by potential beneficial side effects with regard to the risk of preeclampsia. Nevertheless, benefit-risk assessment should also include other relevant outcomes for maternal and child health, which slightly favour the choice of calcium-based antacids.[61] Future research may focus on identifying specific groups of women for whom calcium-based antacids or PPIs might reduce the risk of preeclampsia, in particular early-onset preeclampsia.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(1):1–7. doi:10.1016/j.ejogrb.2013.05.005
2. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Hypertension*. 2018;72:24–43. doi:10.1161/HYPERTENSIONAHA.117.10803
3. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011;25(4):391–403. doi:10.1016/j.bpobgyn.2011.01.006
4. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013;209(6):544.e1–544.e12. doi:10.1016/j.ajog.2013.08.019
5. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010;376(9741):631–644. doi:10.1016/S0140-6736(10)60279-6
6. Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. *Lancet*. 2021;398(10297):341–354. doi:10.1016/S0140-6736(20)32335-7
7. Von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. *Hypertens Pregnancy*. 2003;22(2):143–148. doi:10.1081/PRG-120021060
8. Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Pregnancy Hypertens*. 2013;3(1):44–47. doi:10.1016/j.preghy.2012.11.001
9. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev*. 2018;10:CD001059. doi:10.1002/14651858.CD001059.pub5
10. Ceulemans M, Van Calsteren K, Allegaert K, Foulon V. Health products' and substance use among pregnant women visiting a tertiary hospital in Belgium: a cross-sectional study. *Pharmacoepidemiol Drug Saf*. 2019;28(9):1231–1238. doi:10.1002/pds.4862
11. Meyer A, Fermaut M, Drouin J, Carbonnel F, Weill A. Drug use for gastrointestinal symptoms during pregnancy: a French nationwide study 2010–2018. *PLoS One*. 2021;16(1):e0245854. doi:10.1371/journal.pone.0245854
12. Onda K, Tong S, Beard S, et al. Proton pump inhibitors decrease soluble fms-like tyrosine kinase-1 and soluble endoglin secretion, decrease hypertension, and rescue endothelial dysfunction. *Hypertension*. 2017;69(3):457–468. doi:10.1161/HYPERTENSIONAHA.116.08408
13. Saleh L, Samantar R, Garrelds IM, van den Meiracker AH, Visser W, Danser AHJ. Low soluble fms-like tyrosine kinase-1, endoglin, and endothelin-1 levels in women with confirmed or suspected preeclampsia using proton pump inhibitors. *Hypertension*. 2017;70(3):594–600. doi:10.1161/HYPERTENSIONAHA.117.09741
14. Hastie R, Bergman L, Cluver CA, et al. Proton pump inhibitors and preeclampsia risk among 157 720 women. *Hypertension*. 2019;73(5):1097–1103. doi:10.1161/HYPERTENSIONAHA.118.12547
15. Bello NA, Huang Y, Syeda SK, Wright JD, D'Alton ME, Friedman AM. Receipt of proton-pump inhibitors during pregnancy and risk for preeclampsia. *Am J Perinatol*. 2021;38(14):1519–1525. doi:10.1055/s-0040-1713864
16. Choi A, Noh Y, Park SH, Choe SA, Shin JY. Exploration of proton pump inhibitors use during pregnancy and preeclampsia. *JAMA Netw Open*. 2021;4(9):e2124339. doi:10.1001/jamanetworkopen.2021.24339
17. Van Gelder MMHJ, Bretveld RW, Roukema J, et al. Rationale and design of the PRegnancy and Infant DEvelopment (PRIDE) Study. *Paediatr Perinat Epidemiol*. 2013;27(1):34–43. doi:10.1111/ppe.12023
18. Van Gelder MMHJ, Merkus PJFM, van Drongelen J, Swarts JW, van de Belt TH, Roeleveld N. The PRIDE Study: evaluation of online methods of data collection. *Paediatr Perinat Epidemiol*. 2020;34(5):484–494. doi:10.1111/ppe.12618
19. Vorstenbosch S, te Winkel B, van Gelder MMHJ, Kant A, Roeleveld N, van Puijenbroek E. AIM and design of pREGnant, the Dutch Pregnancy Drug Register. *Drug Saf*. 2019;42(1):1–12. doi:10.1007/s40264-018-0722-7
20. Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol*. 2018;17(6):530–538. doi:10.1016/S1474-4422(18)30107-8
21. De Boer J, Zeeman K, Verhoeven C. KNOV-standaard: hypertensieve aandoeningen tijdens de zwangerschap, bevalling en kwaamperiode [homepage on the internet]. Utrecht: Koninklijke Nederlandse Organisatie van Verloskundigen; 2011. Available from: https://assets.knov.nl/p/557056/none/PDF%20Vakkennis/KNOV_Standaard_Hypertensie_versie2012.pdf. Accessed September 7, 2022.
22. Beekers P, Jamaladin H, van Drongelen J, Roeleveld N, van Gelder MMHJ. Data from web-based questionnaires were valid for gestational diabetes and preeclampsia, but not gestational hypertension. *J Clin Epidemiol*. 2020;125:84–90. doi:10.1016/j.jclinepi.2020.05.023
23. ATC/DDD Index 2022 [homepage on the Internet]. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2021. Available from: https://www.whocc.no/atc_ddd_index/. Accessed September 7, 2022.
24. Van Gelder MMHJ, Vorstenbosch S, te Winkel B, van Puijenbroek EP, Roeleveld N. Using web-based questionnaires to assess medication use during pregnancy: a validation study in 2 prospectively enrolled cohorts. *Am J Epidemiol*. 2018;187(2):326–336. doi:10.1093/aje/kwx239
25. Wood ME, Lupattelli A, Palmsten K, et al. Longitudinal methods for modeling exposures in pharmacoepidemiologic studies in pregnancy. *Epidemiol Rev*. 2021;43(1):130–146. doi:10.1093/epirev/mxab002
26. Genolini C, Falissard B. KmL: a package to cluster longitudinal data. *Comput Methods Programs Biomed*. 2011;104(3):e112–e121. doi:10.1016/j.cmpb.2011.05.008
27. Genolini C, Alacoque X, Sentenac M, Arnaud C. Kml and kml3d: r packages to cluster longitudinal data. *J Stat Softw*. 2015;65(4):1–34. doi:10.18637/jss.v065.i04

28. Palmsten K, Rolland M, Hebert MF, et al. Patterns of prednisone use during pregnancy in women with rheumatoid arthritis: daily and cumulative dose. *Pharmacoepidemiol Drug Saf*. 2018;27(4):430–438. doi:10.1002/pds.4410
29. Matok I, Azoulay L, Yin H, Suissa S. Immortal time bias in observational studies of drug effects in pregnancy. *Birth Defects Res a Clin Mol Teratol*. 2014;100(9):658–662. doi:10.1002/bdra.23271
30. Platt RW, Hutcheon JA, Suissa S. Immortal time bias in epidemiology. *Curr Epidemiol Rep*. 2019;6:23–27. doi:10.1007/s40471-019-0180-5
31. Palmsten K, Bandoli G, Watkins J, Vazquez-Benitez G, Gilmer TP, Chambers CD. Oral corticosteroids and risk of preterm birth in the California medicaid program. *J Allergy Clin Immunol Pract*. 2021;9(1):375–384.e5. doi:10.1016/j.jaip.2020.07.047
32. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology*. 2011;22(5):745. doi:10.1097/EDE.0b013e318225c2be
33. Bandoli G, Palmsten K, Flores KF, Chambers CD. Constructing causal diagrams for common perinatal outcomes: benefits, limitations and motivating examples with maternal antidepressant use in pregnancy. *Paediatr Perinat Epidemiol*. 2016;30(5):521–528. doi:10.1111/ppe.12302
34. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702–706. doi:10.1093/aje/kwh090
35. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc*. 1989;84(408):1074–1078. doi:10.1080/01621459.1989.10478874
36. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res*. 2013;22(6):661–670. doi:10.1177/0962280211427759
37. Howe CJ, Cole SR, Lau B, Napravnik S, Eron JJ Jr. Selection bias due to loss to follow up in cohort studies. *Epidemiology*. 2016;27(1):91–97. doi:10.1097/EDE.0000000000000409
38. Syngelaki A, Bredaki FE, Vaikousi E, Maiz N, Nicolaides KH. Body mass index at 11–13 weeks' gestation and pregnancy complications. *Fetal Diagn Ther*. 2011;30(4):250–265. doi:10.1159/000328083
39. Meertens LJE, Scheepers HCJ, van Kuijk SMJ, et al. External validation and clinical usefulness of first trimester prediction models for the risk of preeclampsia: a prospective cohort study. *Fetal Diagn Ther*. 2019;45(6):381–393. doi:10.1159/000490385
40. Chen Q, Zhang Y, Tong M, et al. Pre-treatment with calcium prevents endothelial cell activation induced by multiple activators, necrotic trophoblastic debris or IL-6 or preeclamptic sera: possible relevance to the pathogenesis of preeclampsia. *Placenta*. 2013;34(12):1196–1201. doi:10.1016/j.placenta.2013.09.014
41. Sukonpan K, Phupong V. Serum calcium and serum magnesium in normal and preeclamptic pregnancy. *Arch Gynecol Obstet*. 2005;273:12–16. doi:10.1007/s00404-004-0672-4
42. Jain S, Sharma P, Kulshreshtha S, Mohan G, Singh S. The role of calcium, magnesium, and zinc in pre-eclampsia. *Biol Trace Elem Res*. 2010;133:162–170. doi:10.1007/s12011-009-8423-9
43. Gasnier R, Valério EG, Vettorazzi J, Barros EG, Martins-Costa SH, Ramos JGL. Calciuria and preeclampsia: a case-control study. *J Obstet Gynaecol Res*. 2012;38(4):674–680. doi:10.1111/j.1447-0756.2011.01774.x
44. Mackillop L. Pre-eclampsia: reducing the risk with calcium supplements. *BMJ Clin Evid*. 2015;2015:1402.
45. Santorelli G, Whitelaw D, Farrar D, West J, Lawlor DA. Associations of maternal vitamin D, PTH and calcium with hypertensive disorders of pregnancy and associated adverse perinatal outcomes: findings from the Born in Bradford cohort study. *Sci Rep*. 2019;9:1205. doi:10.1038/s41598-018-37600-9
46. Forde H, Crowley RK, McKenna MJ, et al. No effect of calcium and vitamin D intake on maternal blood pressure in a healthy pregnant population. *Eur J Obstet Gynecol Reprod Biol*. 2021;264:8–14. doi:10.1016/j.ejogrb.2021.07.005
47. Xu R, Luo Y, Chambers C. Assessing the effect of vaccine on spontaneous abortion using time-dependent covariates Cox models. *Pharmacoepidemiol Drug Saf*. 2012;21(8):844–850. doi:10.1002/pds.3301
48. Daniel S, Koren G, Lunenfeld E, Levy A. Immortal time bias in drug safety cohort studies: spontaneous abortion following nonsteroidal antiinflammatory drug exposure. *Am J Obstet Gynecol*. 2015;212(3):307.e1–307.e6. doi:10.1016/j.ajog.2014.09.028
49. Verlohren S, Herraiz I, Lapaire O, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol*. 2012;206(1):58.e1–58.e8. doi:10.1016/j.ajog.2011.07.037
50. World Health Organization. Guideline: calcium supplementation in pregnant women [homepage on the Internet]. Geneva: World Health Organization; 2013. Available from: http://apps.who.int/iris/bitstream/handle/10665/85120/9789241505376_eng.pdf. Accessed September 7, 2022.
51. Hussain S, Singh A, Antony B, et al. Proton pump inhibitors use and risk of preeclampsia: a meta-analysis. *J Clin Med*. 2022;11(16):4675. doi:10.3390/jcm11164675
52. Taneja G, Thanikachalam PV, Rajput SK. Dose and time-dependent toxicological impact of pantoprazole on vascular endothelium and renal tissue. *Toxicol Lett*. 2020;333:97–104. doi:10.1016/j.toxlet.2020.07.031
53. Abdel-Kawy HS. Chronic pantoprazole administration and ischemia-Reperfusion arrhythmias in vivo in rats-antiarrhythmic or arrhythmogenic? *Cardiovasc Ther*. 2015;33(2):27–34. doi:10.1111/1755-5922.12107
54. Schillinger W, Teucher N, Sossalla S, et al. Negative inotropy of the gastric proton pump inhibitor pantoprazole in myocardium from humans and rabbits: evaluation of mechanisms. *Circulation*. 2007;116(1):57–66. doi:10.1161/CIRCULATIONAHA.106.666008
55. Sibai BM, Stella CL. Diagnosis and management of atypical preeclampsia-eclampsia. *Am J Obstet Gynecol*. 2009;200(5):481.e1–481.e7. doi:10.1016/j.ajog.2008.07.048
56. Andrade SE, Bérard A, Nordeng HME, Wood ME, van Gelder MMHJ, Toh S. Administrative claims data versus augmented pregnancy data for the study of pharmaceutical treatments in pregnancy. *Curr Epidemiol Rep*. 2017;4:106–116. doi:10.1007/s40471-017-0104-1
57. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology*. 2006;17(4):413–418. doi:10.1097/01.ede.0000220549.14177.60
58. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009;23(6):597–608. doi:10.1111/j.1365-3016.2009.01062.x
59. Hatch EE, Hahn KA, Wise LA, et al. Evaluation of selection bias in an internet-based study of pregnancy planners. *Epidemiology*. 2016;27(1):98–104. doi:10.1097/EDE.0000000000000400
60. Biele G, Gustavson K, Czajkowski NO, et al. Bias from self selection and loss to follow-up in prospective cohort studies. *Eur J Epidemiol*. 2019;34:927–938. doi:10.1007/s10654-019-00550-1
61. Thélin CS, Richter JE. Review article: the management of heartburn during pregnancy and lactation. *Aliment Pharmacol Ther*. 2020;51(4):421–434. doi:10.1111/apt.15611