Proton Pump Inhibitors and Preeclampsia Risk Among 157 720 Women

A Swedish Population Register–Based Cohort Study

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Abstract—Preeclampsia is a hypertensive disorder of pregnancy with a high rate of maternal and neonatal morbidity and mortality. The only definite treatment is delivery. Preclinical investigations have identified proton pump inhibitors (PPIs), which are commonly used to treat reflux during pregnancy, as a potential treatment for preeclampsia. The aim of this study was to determine the association between PPI use during pregnancy and preeclampsia risk in a population-based register cohort. Using the Swedish Pregnancy Register, we conducted a cohort study of nulliparous pregnant women delivering from January 2013 to July 2017. Associations between PPI use and preeclampsia were investigated using logistic regression analyses with risk estimates presented as crude and adjusted odds ratios (aOR) with 95% CI. Of 157 720 nulliparous pregnant women, 6051 (3.8%) reported PPI use during pregnancy. PPI use during any point of pregnancy was associated with an increased risk of overall preeclampsia (aOR of 1.17; 95% CI, 1.04–1.32) and preeclampsia at term (aOR of 1.20; 95% CI, 1.04–1.39). However, PPI use recorded after 28 gestational weeks was associated with a reduced risk of preterm (delivery <37 weeks) preeclampsia (aOR of 0.63; 95% CI, 0.41–0.96) and early (delivery <34 weeks) preeclampsia (aOR of 0.41; 95% CI, 0.20–0.82). These findings highlight the heterogeneity of this disease, with a potential role PPIs for preventing preterm preeclampsia when used in close proximity to disease onset. Targeting PPI use to women at greatest risk of preterm preeclampsia may help prevent this severe form of disease. **(*Hypertension*. 2019;73:1097-1103. DOI: 10.1161/HYPERTENSIONAHA.118.12547.)** • **Online Data Supplement**

Key Words: preeclampsia ■ pregnancy ■ prevention ■ proton pump inhibitors ■ risk

Preeclampsia is a common pregnancy complication and a leading cause of global maternal morbidity and mortality.[1,2] There is no treatment apart from delivery, which can inflict significant neonatal morbidity and mortality at preterm gestations.[1]

The preeclamptic placenta releases high levels of antiangiogenic factors sFlt-1 (soluble fms-like tyrosine kinase 1) and sEng (soluble endoglin) into the maternal circulation. It is strongly hypothesized that these antiangiogenic factors drive the pathogenies of preeclampsia[3] by inducing widespread vascular endothelial dysfunction, hypertension, and multiorgan injury.[4] Thus, given the effects of sFlt-1 and sEng, quenching their excess release has been suggested as a therapeutic strategy to prevent and treat preeclampsia.

Preclinical investigations have identified proton pump inhibitors (PPIs), which are used to treat gastroesophageal reflux symptoms, as potential therapeutics for preeclampsia.[5,6] PPIs are used throughout pregnancy and are considered safe[7–9]; however, they have been associated with a possible increased risk of asthma in offspring.[10] The preclinical evidence for PPIs as treatment for preeclampsia is strong; PPIs reduce the secretion of sFlt-1 from primary placental cells, placental tissue, and primary endothelial cells from both normotensive and preeclamptic patient samples. PPIs have also been shown to induce whole blood vessel dilation ex vivo after treating with a vasoconstrictor, reduce vascular endothelial dysfunction in vitro, and lastly, reduce elevated blood pressure in a mouse[5] and rat model of preeclampsia.[11] To date, few studies have investigated PPI use and preeclampsia in humans. In a cross-sectional study, PPI use was associated with decreased circulating sFlt-1 levels and no change in the proangiogenic molecule, PlGF (placental-like growth factor), when compared with a cohort of gestation-matched controls with no PPI use.[12] This effect on sFlt-1 and not PlGF is also seen in vitro.[5] A randomized double-blinded placebo control trial investigating the PPI, esomeprazole, in women with preterm preeclampsia found esomeprazole did not prolong gestation nor reduce circulating levels of antiangiogenic

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factors compared to placebo controls.[13] Despite this negative finding, PPIs may still hold therapeutic benefit for preventing preeclampsia. No studies to date have assessed the potential of PPIs for the prevention of preeclampsia. The aim of this study was therefore to investigate the potential of PPIs for preventing preeclampsia in a population-based setting.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Population

This was a Swedish population register–based study using data retrieved from the Swedish Pregnancy Register. The Swedish Pregnancy Register was launched in 2013 and prospectively combines data from the Swedish Maternal Health Care Register, the Swedish National Quality Register for Prenatal Diagnosis,[14] and obstetric data from electronic birth records.[15] The Swedish Pregnancy Register now covers over 90% of all deliveries within Sweden, from first antenatal visit to delivery.

We included deliveries (including multiple pregnancies) from January 2013 to July 2017. We excluded pregnancies with missing maternal health records (n=116) and restricted our analysis to nulliparous women.

Maternal characteristics included: age at delivery (categorized into <18, 18–34 and ≥35 years), body mass index calculated from measured weight, and self-reported height registered at first antenatal visit and further categorized into <30 and ≥30 g/m^2. Country of birth was classified into Sweden, other Nordic countries, other western countries (Europe, North America, Australia, and New Zealand), and nonwestern countries. Socioeconomic factors included: level of education set to ≤9 years, 10–12 years and >12 years, occupation was defined as employed or government assistance (sick leave, student, unemployed). Housing situation was defined as living with farther or living in another situation (such as same-sex partner, living alone, or with extended family). Daily smoking at first antenatal visit was recorded as yes regardless of quantity, alcohol use before conception was screened using the Alcohol Use Disorders Identification Test,[16] where scores ≥6 indicate hazardous use of alcohol or alcohol dependency.

Pregnancy characteristics included: multiple pregnancy (twins, triplets, quadruples), in vitro fertilization, pregestational, and gestational disorders recorded using predefined checkboxes in the electronic birth records by the midwife or using diagnosis codes according to the *International Classification of Diseases, Tenth Revision*[17]: pregestational hypertension (I10, O10), pregestational diabetes (O24.0–1, E10–14).

Exposure

PPI Use

Within the Swedish Pregnancy Register, maternal medication use is routinely collected from the time of registration for antenatal care, which occurs before 15 weeks in 95% of the pregnancies, up until delivery. Information on ongoing medication is collected by midwives, with women reporting both prescribed and over the counter medications. PPI use during pregnancy was defined as women reporting the use of any PPI, including omeprazole, esomeprazole, pantoprazole, rabeprazole, or lansoprazole at any point across gestation. PPI use was categorized by use ever during pregnancy, first trimester (0–12 weeks of gestation), second trimester (13–27 weeks), and third trimester (from 28 weeks of gestation onward).

Main Outcome

Preeclampsia was identified by the diagnosis codes O14 or O15 according to *International Classification of Diseases, Tenth Revision* coding. During the study period, preeclampsia was defined as the new onset of hypertension combined with proteinuria occurring after 20 weeks of gestation. Preeclampsia was further classified by disease severity, stratifying on gestational age at delivery, including women with preeclampsia and term delivery (greater than or equal to 37 weeks), preeclampsia, and preterm delivery categorized as less than 37 weeks or less than 34 weeks. Additionally, pregnancies complicated with preeclampsia and a concomitant diagnosis of small for gestational age (SGA) fetus, based on a birth weight of >2 SDs below the mean weight for gestational age according to a Swedish sex-specific fetal growth curve,[18] were also identified.

Fetal outcomes included gestational age at delivery, fetal weight, SGA, spontaneous preterm birth, nonreassuring fetal heart rate on admission, which was assessed by the attending midwife at labor ward. Stillbirth was defined as both antenatal and intrapartal death occurring at or over 22 gestational weeks.

Statistical Analysis

Characteristics of the population were described according to PPI use during pregnancy and preeclampsia status using means with SD or counts with percentages. Groups were compared via bivariate analysis using Pearson $\chi 2$ test for categorical data and Student *t* test for continuous variables.

Associations between PPI use during pregnancy and diagnosis of preeclampsia were estimated by means of logistic regression analysis, presented as odds ratios (OR) with 95% CI. To adjust for baseline differences between PPI users and nonusers, a propensity scoring was performed by logistic regression setting PPI use as the outcome. Propensity scoring aims to summarize the risk of exposure (PPI use) into a single measure, which, however, does not imply that all included factors are confounders. An important advantage is that variables describing and predicting an individual's probability of using PPIs can be included without concern of overfitting and collinearity. This methodology is an effective technique for reducing the effects of confounding in observational studies where random assignment is not possible.[19]

Maternal and socioeconomic factors present at first antenatal visit were used to create a propensity score for each participant including maternal age, body mass index, year of delivery, country of birth, smoking status, educational level, occupation, use of assisted reproduction, and the presence of pregestational disorders (hypertension, diabetes mellitus, and inflammatory diseases; inflammatory bowel disease and systemic lupus erythematosus). The distribution of the final propensity score was checked and balanced across PPI users and

nonusers and covariates balanced across PPI users and nonusers within blocks of the propensity score.

The propensity score was included in a multiple logistic regression along with multiple births as a covariate, to estimate the association between PPI use during pregnancy and diagnosis of preeclampsia. Analyses were repeated using the outcomes of preeclampsia with delivery ≥37 weeks, <37 weeks, <34 weeks and preeclampsia with SGA and using the exposures of PPI use from 0 to 12 weeks, 13 to 27 weeks, and ≥28 weeks.

Propensity scores were initially calculated with missing values included as an additional category, allowing all participants to be included in the analysis. To assess the impact of missing values on our analyses, we repeated propensity score calculations and logistic regression analyses with missing values excluded from the analysis. Estimates are presented as adjusted ORs (aOR) with 95% CIs. All analyses were performed using StatSE version 15.1.

Ethical approval for this study was obtained by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2018/287).

Results

Study Characteristics

Of 157 720 nulliparous women included in this study, 6051 (3.8%) reported using PPIs at any time during pregnancy (Table 1). Women reporting PPI use during pregnancy were more obese, more likely to be smokers, more often had multiple pregnancies, pregestational hypertension, and inflammatory diseases compared with nonusers. Education and employment levels were lower among PPI users compared with nonusers (Table 1). The incidence of preeclampsia within this population was 4.6% (n=7258; (Table S1 in the online-only Data Supplement).

PPIs and the Risk of Developing Preeclampsia

Table 2 presents rates and aORs, with the propensity scores and multiple births included in as covariates, for preeclampsia by any reported PPI use during pregnancy. Both crude ORs and aORs with missing values excluded in the analysis are presented in Tables S2 and S3. Compared with non-PPI users, women reporting any PPI use during pregnancy was associated with a higher risk of developing preeclampsia, with an aOR of 1.17 and 95% CI of 1.04 to 1.32. On subgroup analyses of forms of preeclampsia, PPI use ever during pregnancy was also associated with a higher risk of preeclampsia with delivery after 37 weeks (aOR, 1.20; 95% CI, 1.04–1.39). However, this effect was not found for preterm preeclampsia with delivery before 37 weeks (aOR, 0.89; 95% CI, 0.68–1.16), delivery before 34 weeks (aOR, 0.78; 95% CI, 0.48–1.27) nor for women with preeclampsia and a SGA fetus (aOR 0.92; 95% CI, 0.66–1.28).

Effect of Gestational Age at the Time of PPI Use and the Risk of Preeclampsia

Next, using data on recorded gestation of PPI use, we investigated whether the risk of preeclampsia was dependent on the gestational age at which PPI use was reported (Table 3). PPI use recorded from either early (0–12 weeks) or middle (13–27 weeks) gestation was not associated with an altered risk of preeclampsia (all forms) nor any subtype of preeclampsia (Table 3). However, PPI recorded from 28 weeks of gestation was associated with increased risk preeclampsia (all forms) and preeclampsia with delivery after 37 weeks, with an aOR of 1.15 (95% CI, 1.01–1.32) and 1.29 (95% CI, 1.09–1.51), respectively. Conversely, women reporting PPI use from 28 weeks had a reduced risk of developing preeclampsia with SGA compared with non-PPI users (aOR, 0.63; 95% CI, 0.41–0.96). Additionally, the risk of preterm preeclampsia with delivery before 37 weeks was also reduced among these women, with an aOR of 0.68 (95% CI, 0.49–0.96), which was further reduced for preterm preeclampsia with delivery before 34 weeks: aOR of 0.41 (95% CI, 0.20–0.82). These results were similar across unadjusted ORs and aORs when missing values were excluded (Tables S2 and S3).

PPI Use and Fetal Outcomes

Given fetal safety is a significant concern for all therapeutics used during pregnancy, we also compared unadjusted fetal outcomes by PPI use (Table S4). Compared with non-PPI users, women reporting PPI use during pregnancy had no difference in mean gestational length at delivery (39.7 weeks versus 39.6 weeks), mean fetal weight, incidence of SGA, spontaneous preterm birth, nonreassuring fetal heart rate on admission, or stillbirth.

Discussion

To our knowledge, this is the first study to evaluate the association between PPIs and the risk of preeclampsia. In this large population-based cohort of nulliparous women, we found that any PPI use during pregnancy was associated with an increased risk of preeclampsia at term. However, this association was not found for preeclampsia with SGA or preterm delivery. In contrast, the risk of preeclampsia complicated by SGA or and preterm delivery was in fact reduced among women reporting PPI use after 28 weeks of gestation, with the greatest reduction seen for early preeclampsia (delivery before 34 weeks). Thus, PPIs may have potential to prevent preterm preeclampsia, a disease subtype that disproportionately contributes to the morbidity and mortality arising from this disease.

Concordant with previous findings,[7] we did not find PPI use to be associated with adverse fetal outcomes. Together, our data suggest a variable effect of PPI use for the prevention of preeclampsia based on preeclampsia subtype and the gestational age at use.

There is a growing body of evidence suggesting distinct disease pathophysiology between preterm and term preeclampsia.[20–22] Preterm preeclampsia commonly represents a more severe and complicated form of disease compared with preeclampsia occurring at term, with lower mean birth weight centiles and higher neonatal morbidity and mortality. Poor placental implantation and placental pathology are thought to be central to preterm preeclampsia, an effect that is less pronounced in term cases, with minimal histopathologic placental features present in term preeclampsia compared to preterm, regardless of disease severity.[21,22] Given these placental

Table 1. Maternal Characteristics by PPIs Use During Pregnancy

Maternal Characteristic	Total Births (n=157 720)	Non-PPI User (n=151 669)	PPI User (n=6051)	*P* Value
Age, y, mean±SD	29.2±5.0	29.2±5.0	29.1±5.0	0.230
<18	802 (0.5)	777 (0.5)	25 (0.4)	
18–34	136 525(86.6)	131 256 (86.6)	5271(87.1)	
≥35	20 353 (12.9)	19 599 (12.9)	754 (12.5)	
Missing	38	37	1	
BMI, kg/m^2, mean (SD)	24.3±4.4	24.2±4.4	25.2±5.0	<0.001
BMI ≥30, n (%)	15 997 (10.1)	15 078(9.9)	919 (15.2)	
Missing	6959 (4.4)	6703 (4.4)	256 (4.2)	
Country of birth, n (%)				<0.001
Sweden	108 262 (68.6)	104 183 (68.7)	4079 (67.4)	
Other Nordic	1351 (0.9)	1326 (0.9)	25 (0.4)	
Other western	7811 (5.0)	7575 (5.0)	239 (3.9)	
Nonwestern	23 305 (14.8)	22 169 (14.6)	1136 (18.8)	
Missing	16 991 (10.8)	16 416 (10.8)	575 (9.5)	
Education, y, n (%)				
≤9	8139 (5.2)	7734 (5.1)	405 (6.7)	<0.001
10–12	49 447 (31.4)	47 384 (31.2)	2063 (34.1)	
>12	70 834 (44.9)	68 308 (45.0)	2526 (41.8)	
Missing	29 300 (18.6)	28 243 (18.6)	1057 (17.5)	
Occupation, n (%)				
Employed	108 777 (69.0)	104 819 (69.1)	3958 (65.4)	<0.001
Government assistance (sick leave, student, unemployed)	31 468 (19.9)	29 980 (19.8)	1488 (24.6)	
Missing	17 473 (11.1)	16 868 (11.1)	605 (10.0)	
Housing situation, n (%)				<0.001
Living with partner	138 576 (87.9)	133 332 (87.9)	5244 (86.7)	
Other situation	13 617 (8.6)	13 010 (8.6)	607 (10.0)	
Missing	5527 (3.5)	5327 (3.5)	200 (3.3)	
Smoking first antenatal visit, n (%)				
Yes	6952 (4.40)	6601 (4.4)	351 (5.8)	<0.001
Missing	17 360 (11.0)	16 513(10.9)	847 (14.0)	
Alcohol use before pregnancy				
AUDIT >6	10 677 (6.8)	10 270 (6.8)	407 (6.7)	0.498
Missing	35 877 (22.8)	34 619 (22.8)	1258 (20.8)	
Multiple pregnancies, n (%)				
2–4 fetus	2259 (1.4)	2153 (1.4)	106 (1.8)	0.033
IVF, n (%)				
Yes	10 896 (6.9)	10 492 (6.9)	404 (6.7)	0.461
Missing	295 (0.2)	287 (0.2)	8 (0.1)	
Pregestational disorders, n (%)				
Hypertension	1137 (0.7)	1079 (0.7)	58 (1.0)	0.026
Diabetes mellitus	1035 (0.7)	1994 (0.7)	41 (0.7)	0.834
Inflammatory diseases (IBD, SLE)	1455 (0.9)	1343 (0.9)	112 (1.9)	<0.001

Comparison between groups with Pearson χ^2 test and Student *t* test expressed in *P* values. AUDIT indicates Alcohol Use Disorders Identification Test; BMI, body mass index; IBD, inflammatory bowel disease; IVF, in vitro fertilization; PPI, proton pump inhibitor; and SLE, systemic lupus erythematosus.

Table 2. Rates and ORs of Preeclampsia by PPI Use

Outcome	Non-PPI User (N=151 669) Reference	PPI Use Ever During Pregnancy (N=6051)		
	N (%)	N (%)	OR (95% CI)	Adjusted OR (95% CI)
Preeclampsia, all N= 7258	6929 (4.57)	329 (5.44)	1.20 (1.07–1.35)	1.17 (1.04–1.32)
Preeclampsia ≥37 gestational weeks N=4658	4443 (2.93)	215 (3.55)	1.22 (1.06–1.40)	1.20 (1.04–1.39)
Preeclampsia with SGA* N=1037	999 (0.68)	38 (0.65)	0.96 (0.69–1.33)	0.92 (0.66–1.28)
Preeclampsia with delivery <37 gestational weeks n=1605	1547 (1.02)	58 (0.96)	0.94 (0.72–1.22)	0.89 (0.68–1.16)
Preeclampsia with delivery <34 gestational weeks N=597	579 (0.38)	18 (0.30)	0.78 (0.49–1.25)	0.78 (0.48–1.27)

ORs and 95% CIs were retrieved by means of logistic regression using nonexposed as the reference category. Adjusted OR with 95% CIs were retrieved from logistic regression with calculated PS on baseline characteristics and multiple births as covariates. OR indicates odds ratio; PPI, proton pump inhibitor; PS, propensity scores; and SGA, small for gestational age.

*N=153 418 included in analysis. For all other outcomes, N=157 720 included in analysis.

abnormalities, it is not surprising that preterm preeclampsia is more commonly associated with higher circulating concentrations of the antiangiogenic factor sFlt-1[23]. sFlt-1 is placentally secreted and central to disease pathophysiology, with concentrations increasing across gestations as well as with disease severity.[3,4] It is perhaps this heterogeneity in disease pathophysiology between preterm and term preeclampsia that has resulted in the differing effects of PPI use and the risk of preeclampsia within the present study.

Members of our team and others have previously reported PPIs can quench excess sFlt-1 secretion in vitro, in vivo, and ex vivo,[5] as well as reducing maternal sFlt-1 levels among women with suspected preeclampsia.[12] Therefore, it is mechanistically plausible that that PPI use (from 28 weeks) quenches excessive secretion of sFlt-1 levels, preventing the development of preterm preeclampsia. This effect may be less pronounced among term cases, where the relative difference in sFlt-1 levels between those affected and those who are not, are lower compared to cases of preterm preeclampsia.[23] Additionally, PPI use (from 28 weeks) may play roles in reducing the risk of preterm preeclampsia, however, possibly shifting the gestational age of onset since a higher incidence of preeclampsia was found with delivery after 37 weeks among PPI users.

We also found a differing effect of PPI use on preeclampsia risk based on gestational age at use, with significant differences only found for use reported after 28 weeks, with no change in preeclampsia risk among women reporting use during the first or second trimester. This gestational age-dependent effect may again be because of increasing circulating sFlt-1 concentrations across gestation, where PPI use might be able to reduce these increased concentrations when used in close proximity to the rise is sFlt-1 levels and the onset of disease. This effect may also be because of compliance of PPI use given gastroesophageal reflux is more common in the third trimester, and the efficient relief of symptoms with PPI's is coupled to greater compliance.[24] Additionally, PPI use during early pregnancy was reported less compared to late gestation, and thus, these strata may be underpowered to detect a significant effect.

Our interpretations are limited by the reliance on maternal self-reported PPI use during pregnancy, which may be affected by recall bias and underreporting. Additionally, self-reporting is heavily reliant on the individual healthcare provider's focus on capturing such data, which again may have resulted in underreporting of PPI use.

We also lack compliance data, with women simply reporting therapeutics currently in use, with no data on neither dosage nor frequency. Given PPIs are often used symptomatically because of episodic gastroesophageal reflux symptoms (the primary indication for PPI use during

Table 3. Rates and ORs by Gestational Range of Proton Pump Inhibitor Use During Pregnancy

Outcome	Non-PPI User	PPI User Recorded 0–12 wk; N=1371		PPI User Recorded 13–27 wk; N=2678		PPI User Recorded From 28 wk; N=4927	
	N (%)	N (%)	Adjusted OR (95% CI)	N (%)	Adjusted OR (95% CI)	N (%)	Adjusted OR (95% CI)
Preeclampsia, all N=7258	6929 (4.6)	75 (5.5)	1.11 (0.87–1.42)	140 (5.2)	1.04 (0.86–1.25)	270 (5.5)	1.15 (1.01–1.32)
Preeclampsia ≥37 wk N=4658	4443 (2.9)	51 (3.0)	1.19 (0.88–1.60)	86 (3.2)	0.99 (0.79–1.26)	185 (3.8)	1.29 (1.09–1.51)
Preeclampsia with SGA* N=1037	999 (0.7)	7 (0.5)	0.65 (0.30–1.39)	18 (0.7)	0.95 (0.58–1.57)	25 (0.5)	0.63 (0.41–0.96)
Preeclampsia with delivery <37 wk n=1605	1547 (1.0)	13 (0.9)	0.89 (0.50–1.61)	32 (1.2)	1.13 (0.77–1.66)	40 (0.8)	0.68 (0.49–0.96)
Preeclampsia with delivery <34 wk N=597	579 (0.4)	5 (0.4)	1.09 (0.42–2.77)	10 (0.4)	1.06 (0.54–2.06)	9 (0.2)	0.41 (0.20–0.82)

Adjusted OR with 95% CI were retrieved from logistic regression using PS on baseline characteristics and multiple birth as a covariate. OR indicates odds ratio; PPI, proton pump inhibitor; PS, propensity scores; and SGA, small for gestational age.

*N=153 413 included in analysis. For all other outcomes, N=157 720 included in analysis.

pregnancy), it is likely that although reported, PPIs were not used daily and as outlined previously, the frequency of individual use may have increased across gestation as gastroesophageal reflux symptoms increased.[24] Although maternal self-reporting does limit our study, because of the availability of PPIs without prescription, it is not possible to perform a linkage study with the national prescribing database. Performing such a study would result in gross underreporting and unreliable estimates of the association between PPI use and the risk of preeclampsia.

Here, we have identified a potential association between PPI use and a reduced risk of preeclampsia subtypes, specifically early preeclampsia with delivery before 34 weeks. However, PPIs may be associated with an increased risk of term preeclampsia (without SGA), which may be attributed to residual confounders. Although subgroup analyses were determined a priori because of the inherent risks associated with multiple and subgroup analyses and the potential of unmeasured confounding factors, caution is still required in interpreting these findings. Thus, further observational- and register-based cohort studies in other populations are required to verify our findings. In a second step, a well-designed randomized placebo-controlled prevention trial is warranted, which would be strengthened by including interim analysis and long-term follow up of childhood outcomes. Such a trial would overcome the limitations of an epidemiological approach and further elucidate the role of PPIs in the prevention of preeclampsia and any adverse maternal and long-term childhood outcomes associated with PPI use during pregnancy.

Conclusions

Our findings highlight the heterogeneity of preeclampsia, with a potential role for PPIs in preventing preterm preeclampsia when used in close proximity to disease onset. To fully elucidate the role of PPIs in the prevention of preeclampsia, further trials are required. Targeting PPI use to women at greatest risk of preterm preeclampsia may help prevent this severe form of disease and reduce neonatal morbidity and mortality related to being born too early.

Perspectives

PPIs have a potential role in preventing preterm preeclampsia, but further clinical trials are required.

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Disclosures

None.

References

1. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol*. 2012;36:56–59. doi: 10.1053/j.semperi.2011.09.011
2. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33:130–137. doi: 10.1053/j.semperi.2009.02.010
3. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111:649–658. doi: 10.1172/JCI17189
4. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. *Annu Rev Pathol*. 2010;5:173–192. doi: 10.1146/annurev-pathol-121808-102149
5. 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;69:457–468. doi: 10.1161/HYPERTENSIONAHA.116.08408
6. Kaitu'u-Lino TJ, Brownfoot FC, Beard S, Cannon P, Hastie R, Nguyen TV, Binder NK, Tong S, Hannan NJ. Combining metformin and esomeprazole is additive in reducing sFlt-1 secretion and decreasing endothelial dysfunction - implications for treating preeclampsia. *PLoS One*. 2018;13:e0188845. doi: 10.1371/journal.pone.0188845
7. Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol*. 2009;104:1541–1545; quiz 1540, 1546. doi: 10.1038/ajg.2009.122
8. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. *N Engl J Med*. 2010;363:2114–2123. doi: 10.1056/NEJMoa1002689
9. Matok I, Levy A, Wiznitzer A, Uziel E, Koren G, Gorodischer R. The safety of fetal exposure to proton-pump inhibitors during pregnancy. *Dig Dis Sci*. 2012;57:699–705. doi: 10.1007/s10620-011-1940-3
10. Lai T, Wu M, Liu J, Luo M, He L, Wang X, Wu B, Ying S, Chen Z, Li W, Shen H. Acid-suppressive drug use during pregnancy and the risk of childhood asthma: a meta-analysis. *Pediatrics*. 2018;141:e20170889. doi: 10.1542/peds.2017-0889
11. Shafik AN, Khattab MA, Osman AH. Magnesium sulfate versus esomeprazole impact on the neonates of preeclamptic rats. *Eur J Obstet Gynecol Reprod Biol*. 2018;225:236–242. doi: 10.1016/j.ejogrb.2018.05.004
12. 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;70:594–600. doi: 10.1161/HYPERTENSIONAHA.117.09741
13. Cluver CA, Hannan NJ, van Papendorp E, Hiscock R, Beard S, Mol BW, Theron GB, Hall DR, Decloedt EH, Stander M, Adams KT, Rensburg M, Schubert P, Walker SP, Tong S. Esomeprazole to treat women with preterm preeclampsia: a randomized placebo controlled trial. *Am J Obstet Gynecol*. 2018;219:388.e1–388.e17. doi: 10.1016/j.ajog.2018.07.019
14. Petersson K, Lindkvist M, Persson M, Conner P, Åhman A, Mogren I. Prenatal diagnosis in Sweden 2011 to 2013-a register-based study. *BMC Pregnancy Childbirth*. 2016;16:365. doi: 10.1186/s12884-016-1165-8
15. Stephansson O, Petersson K, Björk C, Conner P, Wikström AK. The Swedish Pregnancy Register - for quality of care improvement and research. *Acta Obstet Gynecol Scand*. 2018;97:466–476. doi: 10.1111/aogs.13266
16. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. *Addiction*. 1993;88:791–804.
17. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th revision, fifth edition, 2016.* (Swedish version.) Stockholm, Sweden: National Board of Health and Welfare; 2015.
18. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85:843–848.
19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424. doi: 10.1080/00273171.2011.568786
20. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013;209:544.e1–544.e12. doi: 10.1016/j.ajog.2013.08.019
21. Phillips JK, Janowiak M, Badger GJ, Bernstein IM. Evidence for distinct preterm and term phenotypes of preeclampsia. *J Matern Fetal Neonatal Med*. 2010;23:622–626. doi: 10.3109/14767050903258746
22. Sebire NJ, Goldin RD, Regan L. Term preeclampsia is associated with minimal histopathological placental features regardless of clinical severity. *J Obstet Gynaecol*. 2005;25:117–118. doi: 10.1080/01443610540004139 6
23. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, Calda P, Holzgreve W, Galindo A, Engels T, Denk B, Stepan H.

The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol*. 2012;206:58.e1–58.e8. doi: 10.1016/j.ajog.2011.07.037

24. Rey E, Rodriguez-Artalejo F, Herraiz MA, Sanchez P, Alvarez-Sanchez A, Escudero M, Diaz-Rubio M. Gastroesophageal reflux symptoms during and after pregnancy: a longitudinal study. *Am J Gastroenterol*. 2007;102:2395–2400. doi: 10.1111/j.1572-0241.2007.01452.x

Novelty and Significance

What Is New?

- Proton pump inhibitors have a variable effect on preeclampsia subtypes.
- When used in close proximity to disease onset, proton pump inhibitors may have a potential role in preventing preterm preeclampsia.

What Is Relevant?

- Preeclampsia is a serious complication of pregnancy, with delivery as the only definite treatment.
- Through preclinical investigation, proton pump inhibitors have been identified as candidate drugs to prevent or treat preeclampsia.
- This is the first study to examine the therapeutic potential of proton pump inhibitors for the prevention of preeclampsia in a register-based cohort study.