The Use of Proton Pump Inhibitors in Managing Preeclampsia: A Systematic Review

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Abstract

Background: Maternal mortality remains a major global challenge, with preeclampsia (PE) as a leading cause after hemorrhage and infection. PE, a hypertensive disorder after 20 weeks of gestation, affects over. 4 million pregnancies annually, causing 50,000–70,000 maternal deaths. If untreated, it can lead to severe complications like eclampsia, HELLP syndrome, organ failure, and death. It also increases risks for the fetus, including low birth weight, preterm birth, and perinatal mortality. Early and effective management is crucial. Research suggests proton pump inhibitors (PPIs) may help by reducing sFlt-1 secretion, offering potential treatment options.

Methods: A literature search was conducted in PubMed, ScienceDirect, Directory of Open Access Journals, and Cochrane Library, yielding 354 studies. Two studies meeting inclusion and exclusion criteria were included in this review.

Result: Omeprazole and esomeprazole reduced sFlt-1 levels and increased PlGF levels in PE pregnancies, although the changes were not statistically significant. Esomeprazole increased sFlt-1 levels specifically in placental tissue. No adverse effects were reported with PPI use in the included studies.

Conclusions: PPIs (omeprazole or esomeprazole 40 mg) show potential as safe therapies for managing preeclampsia, with minimal side effects, by reducing sFlt-1 levels and increasing PlGF levels. Further research is needed to confirm these findings.

Introduction

Maternal mortality rate (MMR) is a key indicator of maternal well-being and remains a global concern. According to data from the World Health Organization (WHO), 287,000 women worldwide died during and after pregnancy, as well as during childbirth, in 2020.[1] One of the targets of the Sustainable Development Goals (SDGs) is to reduce MMR to 70 per 100,000 live births by 2030. However, in Indonesia, MMR was still at 305 per 100,000 live births in 2019. Among the leading causes of MMR, after severe hemorrhage and infections, is preeclampsia (PE). PE is a hypertensive condition occurring in pregnancies beyond 20 weeks of gestation, accompanied by organ dysfunction.[2] Annually, more than 4 million pregnant women are affected by PE,

with approximately 50,000–70,000 deaths attributed to it.[3]

Untreated PE can lead to severe complications for both mother and fetus. Maternal complications include eclampsia, hemolysis syndrome (HELLP), pulmonary edema, disseminated intravascular coagulation (DIC), kidney dysfunction, placental abruption, and even maternal death. Fetal complications include low birth weight (LBW), preterm birth, asphyxia, and perinatal death.[4] These complications pose significant risks to both maternal and fetal survival, necessitating effective therapies to manage PE and prevent eclampsia.[5]

The wide clinical variability and complexity of PE have posed challenges to fully understanding its pathogenesis and establishing appropriate therapeutic strategies. However, studies have shown that PE is caused by the placenta releasing large amounts of sFlt-1 (soluble fms-like tyrosine kinase-1) into maternal circulation. This binds to and reduces free placental growth factor (PIGF) and vascular endothelial growth factor, increasing antiangiogenic factors and triggering the release of vasoconstrictor endothelin-1 (ET-1). This, in turn, induces systemic endothelial dysfunction in the mother, leading to PE. Therefore, reducing sFlt-1 and increasing PlGF levels can restore the antiangiogenic balance in PE cases.[6,7]

Recent research has revealed that PPIs can reduce sFlt-1 release in a dose-dependent manner in placental explants or trophoblast cells. PPIs, commonly prescribed for acid reflux treatment, are considered safe for use during pregnancy.[8] This literature review analyzes the effects of PPI use in managing PE and preventing eclampsia, aiming to establish clinically relevant evidence-based medicine.

Material And Methods

The study search was conducted across various databases, including PubMed, ScienceDirect, Directory of Open Access Journals, and the Cochrane Library on 31 December 2024. The search utilized keywords such as “proton-pump inhibitor” and “preeclampsia.” Studies retrieved were filtered based on inclusion and exclusion criteria. The inclusion criteria for this review were:

- The study subjects were patients with preeclampsia or pregnant women.
- The intervention involved the administration of proton-pump inhibitors.
- The comparator included conventional therapy or placebo.
- Outcomes included levels of sFlt-1, PlGF, angiogenic factors, antiangiogenic factors, or other maternofetal factors.

The exclusion criterion was studies published more than ten years ago. Studies meeting the inclusion and exclusion criteria were accessed in full text to evaluate their availability. Articles that could not be accessed in full were excluded. Ultimately, studies meeting all criteria were included in this literature review. Study selection process was performed by all authors independently.

The search initially identified a total of 354 studies. However, only two studies fulfilled the inclusion and exclusion criteria and were subsequently analyzed in this review.

Result

Work should be reported in SI units. Undue repetition in text and tables should be avoided. Comment on validity and significance of results is appropriate but broader discussion of their implication is restricted to the next section. Subheadings that aid clarity of presentation within this and the previous section are encouraged.

The effects of PPI administration on various outcomes in preeclampsia patients can be comprehensively seen in **Table 1**.

Discussion

The Mechanism of Action of PPIs in Preeclampsia

The mechanisms by which PPIs work in preeclampsia have been extensively studied in human tissues (in vitro) and animal models (in vivo), revealing several therapeutic pathways. PPIs reduce the secretion of sFlt-1 and soluble endoglin, which are derived from trophoblasts, placental explants, and endothelial cells. They also improve endothelial function by mitigating tumor necrosis factor-induced dysfunction, inhibiting the expression of endothelial vascular cell adhesion molecule-1, reducing leukocyte adhesion to the endothelium, and preventing disruption of endothelial tube formation. Additionally, PPIs lower endothelin-1 secretion and enhance endothelial cell migration, contributing to vascular health. Notably, esomeprazole, a specific PPI, has been shown to reduce blood pressure in transgenic rat models with excessive placental expression of sFlt-1. Furthermore, PPIs exhibit antioxidant and anti-inflammatory effects by increasing endogenous antioxidant levels and reducing cytokine secretion from placental tissues and endothelial cells. These diverse mechanisms suggest that PPIs can address preeclampsia through antiangiogenic, endothelial, and anti-inflammatory pathways, offering promising therapeutic benefits.[9–11]

Effects of PPI Administration on sFlt-1 and PlGF Biomarkers in Pregnant Women with Preeclampsia

The impact of PPI administration on maternofetal biomarkers in preeclampsia has been explored in various studies.

Neuman et al. conducted a study involving 20 pregnant women diagnosed with preeclampsia between 20 and 34 weeks of gestation. Participants were over 18 years old, carrying singleton pregnancies, and diagnosed according to the International Society for the Study of Hypertension in Pregnancy 2018 criteria, which requires new-onset hypertension accompanied by proteinuria or maternal/uteroplacental dysfunction after 20 weeks of gestation. Women who had previously used PPIs, had contraindications or hypersensitivity to PPIs, or were taking medications interacting with PPIs were excluded. The participants were divided into two groups: one received 40 mg/day of omeprazole, and the other received no intervention, both observed over four days.[12]

Participants in the omeprazole group were given oral doses without specific storage conditions, instructed to take the medication in the morning before meals, and monitored for compliance. Women in the non-omeprazole group did not receive PPIs, and those experiencing acid reflux were advised to use alternative medications. Persistent reflux requiring PPIs led to their exclusion from the study.[12]

Results showed that preeclamptic women receiving omeprazole had a reduction in sFlt-1 levels compared to the non-omeprazole group, but the difference was not statistically significant (8364 vs. 13,017 pg/mL, p = 0.14). Similarly, PlGF levels were higher in the omeprazole group but not significantly so (90 vs. 55 pg/mL, p = 0.14). These findings suggest that omeprazole administration did not significantly affect sFlt-1 and PlGF levels in preeclampsia.[12]

Additionally, the study examined the effects of omeprazole and esomeprazole on placental tissue. Perfusion of the placenta with esomeprazole significantly reduced sFlt-1 levels compared to control placentas, whereas omeprazole did not show a significant effect on sFlt-1 levels.[12] Another study by Cluver et al. involved 120 pregnant women with singleton pregnancies between 26 and 31 weeks of gestation. Preeclampsia was diagnosed based on hypertension and proteinuria. Women with indications for immediate delivery, contraindications or hypersensitivity to PPIs, or those taking medications that could interact with PPIs were excluded. Participants were randomly assigned to receive either 40 mg of esomeprazole or a control treatment. The results showed that esomeprazole administration reduced sFlt-1 levels, but the difference was not statistically significant compared to the control group. Similarly, esomeprazole increased PlGF levels, but this was also not significant compared to the control group. Additionally, another preeclampsia biomarker, endothelin, showed no significant differences between the two groups.[13]

In both studies (Neuman et al. and Cluver et al.), PPI administration generally resulted in a reduction of sFlt-1 levels and an increase in PlGF levels, although the results were not statistically significant. This suggests that higher doses of PPIs (greater than 40 mg) may be necessary to achieve significant reductions in sFlt-1 and increases in PlGF levels in pregnant women with preeclampsia. The administration of esomeprazole to the placenta demonstrated a significant reduction in sFlt-1 levels, which is important as sFlt-1 plays a critical role in endothelial dysfunction in preeclampsia. A more pronounced decrease in sFlt-1 levels indicates a better therapeutic outcome in preeclampsia. Furthermore, a greater increase in PlGF levels also indicates a more favorable therapeutic outcome. Although a 40 mg dose of PPI may reduce sFlt-1 and increase PlGF, these changes are not significant at this dose.

Side Effects of PPI Use in Managing Preeclampsia

In all the included studies, the side effects of using PPIs in preeclampsia therapy, measured by circulating various maternofetal factors, did not show any adverse effects. This suggests that the use of PPIs in managing preeclampsia is relatively safe, with better effectiveness compared to control therapy with a placebo.

Table 1. The Effect of PPI Administration on Various Outcomes in Preeclampsia

Author (Year)	Population	Intervention	Outcome	Side Effects
Neuman et al. (2022)	20 pregnant women with preeclampsia (GA: 20 – 34 weeks)	Omeprazole 40mg/day vs no intervention (4 days)	No significant difference in sFlt-1, PlGF levels between the groups	No side effects reported
Cluver et al. (2018)	120 pregnant women with singleton pregnancy (GA: 26 – 31 weeks)	Esomeprazole 40mg vs placebo	No significant difference in sFlt-1, PlGF, and endothelin levels between the groups	No side effects reported

Conclusion

In this literature review, the administration of PPIs to pregnant women with preeclampsia can lower sFlt-1 levels (a factor contributing to preeclampsia) and increase PlGF levels (a protective factor for preeclampsia), but this effect was not significant at a 40mg dose. However, in placental tissue treated with the PPI omeprazole, there was a significant reduction in sFlt-1 levels. Additionally, no side effects were reported in any of the included studies. Therefore, it can be concluded that PPI therapy has the potential to address preeclampsia by lowering sFlt-1 levels and increasing PlGF levels. However, further investigation is required to determine the optimal dosage and type of PPI that can be used in pregnant women to effectively manage preeclampsia.

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