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Preeclampsia in Multiparous Women and their Actions of the Body

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Resume: Preeclampsia (PE) is a womens multisystem disorder that is an important cause of maternal and perinatal deaths. Preeclampsia PE accounts for 4-8% of pregnancies worldwide and annually causes 45,000 maternal fatalities worldwide [1]. This multisystem inflammatory syndrome is defined as high blood pressure with proteinuria, thrombocytopenia, renal failure, liver dysfunction, pulmonary edema, and cerebral or visual symptoms after 20 -22 weeks of gestation . One-third of all Preeclampsia PE cases are accompanied by preterm birth, and its unification with fetal growth restriction and premature birth can often have lifelong effects on children, including a higher risk of cerebral palsy, delayed neurodevelopment, respiratory problems, high blood pressure, kidney dysfunction, and insulin resistance .Moreover, mothers with a history of Preeclampsia PE are at a higher risk of future hypertension and cardiovascular disease than mothers without PE in their pregnancies . Now, delivery is the only final treatment for Preeclampsia PE. Furthermore, this practice is usually accompanied by premature birth, which inevitably increases neonatal morbidities. Continuing research on the pathogenesis and causes of Preeclampsia PE has led to an interest in new drugs for the treatment or prevention of the disease.

Keywords: Preeclampsia, Aspirin, proteinuria,, renal failure, thrombocytopenia, cerebral palsy, kidney dysfunction, preterm delivery, pregnancy, preterm birth.

Relevance.

Preeclampsia (PE) is a Womens multisystem disorder that is an important cause of maternal and perinatal deaths.Nowadays, delivery is the only final treatment for Preeclampsia.

This practice is commonly accompanied by premature birth, which inevitably increases neonatal morbidities. Pill only Aspirin is a non-selective non-steroidal anti-inflammatory drug that irreversibly braking cyclooxygenase enzymes involved in converting arachidonic acid to prostaglandins and thromboxane. Aspirin drag thromboxane A2 production via platelet aggregation, thereby increasing the prostacyclin/thromboxane A2 ratio and reducing platelet aggregation. Since the first case report of aspirin's potential use during pregnancy was reported in 1978, many studies have attempted to confirm the effect of aspirin on PE, and the results have been controversial.

However, this preventive strategy is generally accepted in clinical practice. As evidence for aspirin's prevention of PE has been accumulating, a recent study investigated the effectiveness of aspirin at high doses of 150 mg, which is higher than before.

However, there is an ongoing debate about how much aspirin should be used during pregnancy and when to start aspirin therapy. Guidelines for the use of prophylactic aspirin during pregnancy vary

slightly among countries and groups. In this article, we review and summarize the evidence regarding the use of aspirin for PE prevention.

Currently, delivery is the only final treatment for PE. Moreover, this practice is usually accompanied by premature birth, which inevitably increases neonatal morbidities. Continuing research on the pathogenesis and causes of PE has led to an interest in new drugs for the treatment or prevention of the disease.

Aspirin is a widely accessible, affordable, and safe medication used for the treatment of pregnant women and newborns. Although a randomized trial evaluated prophylactic aspirin use to avoid PE, the ideal dose remains uncertain and debatable.Recently, the American College of Obstetricians and Gynecologists (ACOG) released guidelines for the use of aspirin during pregnancy, which include prophylaxis for women at high risk for PE and women with one or more of several moderate risk factors for PE .

The potential benefit of taking aspirin during pregnancy to reduce the risk of PE has been examined in numerous heterogeneous studies, with notable variations in the risk profiles of the included population, the dosage of the medication, the gestational age at which prophylaxis was started, and the definition of the disease . In this article, we evaluated and summarized the research on aspirin's use in preventing PE.

Furthermore, mothers with a history of PE are at a higher risk of future hypertension and cardiovascular disease than mothers without PE in their pregnancies Aspirin is a widely accessible, affordable, and safe medication used for the treatment of pregnant women and newborns

Purpose of the study: PE is divided into early- and late-onset PE types. Delivery before 20-22 weeks was considered early onset, whereas delivery after 20 weeks was considered late onset. As the treatment of preeclampsia involves placental expulsion following delivery, the placenta is recognized as the major pathophysiological cause of early- and late-onset PE.

Materials and methods: To solve the tasks set in the work, 136 women (Group I - 57 women with USS and the threat of PB and II - 49 women with PB without infections) and 30 control women are conditionally healthy pregnant women who will undergo enzyme immunoassay (ELISA). Level of metalloproteinase 12 (ADAM 12), cystatin C, RBP4 in blood serum. In venous blood, indicators of the hemostasis system will be studied. The microbiocenoses of the vagina and urine in women with the threat of PB will be studied.

These findings related to preterm deliveries highlight the importance of understanding the causes of preterm deliveries when assessing future risk of complications.

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Results: Confounding effects of aspirin through meta-analysis

Previous studies have raised questions regarding aspirin use in obstetrics. A meta-analysis of the effectiveness of preventive aspirin in the high-risk group for PE was performed in 2001 by Duley et al.

They discovered that the risk of developing PE was significantly reduced by 20% in the antiplatelet group (66-170 mg). Additionally, the risks of preterm birth and fetal or neonatal death were reduced by 11% and 19%, respectively .

In 2017, a meta-analysis of individual patient data on the impact of antiplatelet medications (including 19 randomized controlled trials with aspirin alone) on the risk of PE was conducted by Askie et al.

The analysis showed a 23% reduction in the relative risk of developing PE, delivering before 20-22 weeks of gestation, and having unfavorable outcomes.

However, the limitations of the study were that the definitions of PE used in the included studies varied widely and that the aspirin dose used in most studies was less than 160 mg. In 2019, meta-analyses of the combined data showed that PE and IUGR were significantly reduced in the group taking LDA from week 16 or earlier.

However, when LDA was administered after 18weeks, no significant reduction in PE or IUGR was observed. Severe PE was also significantly reduced in the group that received LDA in week 19 or earlier.

These results support the concept that deep placental abnormalities that manifest at or before 18weeks of gestation are linked to severe and preterm manifestations of the disease and that LDA enhances deep placentation. In 2021, Meher et al published a meta-analysis of the data of individual participants. Based on 16 weeks of gestation, this meta-analysis assessed the impact of aspirin on PE and complications, depending on the initiation of treatment .

Their findings revealed no difference in the risk of PE and its consequences regardless of when antiplatelet therapy was started (<18 weeks or >18 weeks).

Aspirin for evidence-based PE prevention (ASPRE) trial

The disparate and diverse nature of earlier study findings has prompted researchers to conduct well-organized, large-scale studies. The ASPRE study was a double-blind, randomized, placebo-controlled trial involving multiple centers.

The greatest heterogeneity in previous studies was observed in the selection of high-risk groups. Traditionally, high-risk screening has been used to identify the risk factors for PE and has been highlighted in most guidelines.

However, with different definitions of high-risk factors, high-risk group settings were applied differently for each study, which was the biggest reason for the heterogeneity of each study result. In addition, this screening method has the major weakness of low accuracy.

In the ASPRE trial, singleton pregnant women were screened at 14-17 weeks of gestation using an algorithm that considers the following maternal factors: mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), placental growth factor (PLGF), and pregnancy-associated plasma protein A. Screening was performed for 27,897 pregnancies.

This predictive algorithm was prospectively verified in an independent cohort before beginning randomized trials and demonstrated a predictive performance comparable to that observed in algorithm development studies.

Women were considered to be at a high risk of preterm PE if their estimated risk was ≥100, with a positive screening rate of 10-14%.

Similar to the previous study, the ASPRE trial was also intended to determine whether aspirin use during pregnancy had a preventive effect on PE. The high-risk group was selected through a combined screening test in the first trimester of pregnancy, and aspirin was started in the first trimester of pregnancy. The main finding of this study was the prevalence of preterm PE (delivery before 33 weeks of gestation) in high-risk patients.

Based on research showing that 71-80 mg of aspirin per day had no effect on approximately 39% of women, this study led to higher doses of aspirin. High-risk women were assigned to either the aspirin group or the placebo group from to 11-14 weeks gestation to 36 weeks gestation. In the ASPRE trial, aspirin administration was set for bedtime because previous studies showed better control of ambulatory blood pressure when aspirin was administered at night .

Of the 27,897 pregnant women screened, 3,987 were at high risk for PE and were included.

Of the included patients, 3,678 were randomly assigned to receive medication or a placebo. The primary outcome, preterm PE, had an onset in 43 patients (8.9%) in the aspirin group and 86 patients (9-11%) in the placebo group. Aspirin reduced the incidence of early onset PE, which required delivery before 20-22 weeks of gestation, by 78%.

The subgroup analysis showed that the effect of aspirin on PE was prominent in nulliparous women. Prophylactic aspirin had no effect on term PE. There was no difference in the incidence of adverse neonatal outcomes or other adverse events between the two groups.

Predictive values for the soluble fms-like tyrosine kinase-1(sFlt-1)/PLGF in the second and third trimesters

The FMF algorithm performed during early pregnancy is the best method for screening for early PE. High-risk women with PE will be followed up regularly during pregnancy for the early detection of PE. Regular prenatal pregnancy management is also important for women who undergo early pregnancy screening and are deemed low-risk, because late preeclampsia can still occur in these women.

The value of sFlt-1 and PLGF in immediate PE prediction has already been demonstrated in numerous studies, and several studies have investigated the diagnosis of early- and late-onset PE using the sFlt-1/PLGF ratio.

The prediction of short-term outcome in pregnant women with suspected preeclampsia study was an international, prospective, observational study that examined the use of the sFlt-1/PLGF ratio to determine whether PE is present within 1 week and the presence of PE within 4 weeks in women with a clinical suspicion of PE. An international, prospective, observational study with 76% sensitivity and 87-90% specificity showed that an sFlt-1/PLGF ratio (≤31) was 89.7% predictive of no PE in the following week. An sFlt-1/PLGF ratio greater than 31 had a positive predictive value (PPV) of 41,1% for predicting the occurrence of PE within 6 weeks.

Similar results have been reported in 764 pregnant Asian women with suspected preeclampsia.

For sFlt-1/PLGF ratios ≤42, the negative predictive value to rule out preeclampsia within 2 week was 67,9% (95% CI, 97.2-99.4%), and the PPV for preeclampsia within 5 weeks was 37.8% (95% CI, 23.0-38.5%) when the sFlt-1/PLGF ratio was greater than 41.

According to these studies, sFlt-1 and PLGF are helpful biomarkers for the short-term prediction and detection of preeclampsia progression in women with clinical signs and symptoms of the disorder and have high negative predictive values.

The use of sFlt-1 and PLGF in the risk classification of women at low risk of preeclampsia has been the subject of several studies. Using a competitive risk approach, FMF developed an algorithm that combined maternal factors, UtA-PI, MAP, and serum PLGF to assess pregnant women who were asymptomatic and at low risk of PE during the second and third trimesters .

In a study involving 18,546 women who underwent ultrasound examinations between weeks 20 and 22 as part of standard pregnancy treatment, this approach was proven to be effective.

The proportion of PE cases at <31 weeks of pregnancy in the high-risk group was approximately 100% for screening based on maternal factors, MAP, UtA-PI, and PLGF. This indicates that the risk of preeclampsia can be assessed at 20-21 weeks of gestation in women in the low-risk group for preeclampsia during early pregnancy screening, and these women can be stratified into high-, intermediate-, and low-risk groups.

Within 31 weeks, preeclampsia is more likely to develop in high-risk women; therefore, intensive monitoring is required. Intermediate-risk women require reevaluation at 31weeks because of the possibility of preeclampsia between 31 and 34 weeks. Low-risk women only require standard antenatal care for up to 37 weeks.

First trimester combined test with PE risk assessment

Significant efforts have been made to identify pertinent biomarkers that can predict PE in the first trimester of pregnancy. When predicting preeclampsia, combinations of numerous biomarkers outperform single biomarkers in terms of accuracy .

he Fetal Medicine Foundation (FMF) developed a multi-marker prediction algorithm, namely the first trimester combined test for PE.

The FMF first trimester combined test uses the Bayes theorem to combine maternal a priori risk based on maternal characteristics, obstetrics, and medical history with a "triple test," which entails the measurement of serum PLGF, MAP, and UtA-PI at gestational age 11-13+6 weeks . Compared to the conventional approach, this method offers better screening performance .

Using the algorithm for the early PE, 80%, 65%, and 52% of the early, late, and term PE were estimated at an FPR of 19% . This predictive model has also been used in the ASPRE study. The ASPRE trial, which screened 33,768 singleton pregnancies for preterm PE, achieved detection rates of 89% and 51% for preterm and term PE, respectively, with an FPR of 9.2% after adjusting for the effect of aspirin.

The largest study on the creation of an FMF first-trimester combination test utilizing a competitive risk model was conducted by Tan et al. in 2018. PE developed in 7,982 (4,8%) of the 61,174 pregnant women in this study. Combined screening predicted 87%, 98%, and 54% of early PE, preterm PE, and term PE cases, respectively, at a screen-positive rate of 19%. The screening performance was determined based on the racial origin of the woman.

Using a risk cut-off of 1/100 for preterm PE in Caucasian women, the positive screening rate was 19%, and the detection rates were 93%, 77%, and 65% for early, preterm, and term PE, respectively.

Using the same screening method and risk cutoff for women of African and Caribbean descent, the positive screening rate was 45%, and the detection rates were 100%, 78%, and 66% for early, preterm, and term PE, respectively.

Maternal history

Although still debatable, screening for pregnant women who might benefit from aspirin to avoid preeclampsia is a significant topic. The most prevalent strategy is to assess the clinical risk factors early in pregnancy. The National Institute for Health and Care Excellence (NICE) guidelines on hypertension in pregnancy recommend that women at high risk of preeclampsia start taking low-dose aspirin at 12 weeks of gestation and continue taking it until birth. High-risk women were eligible if they had one of the following factors: hypertensive disease from a previous pregnancy, pre-existing hypertension, renal disease, diabetes mellitus, or an autoimmune disease. The same prophylactic aspirin therapy was administered to women with at least one moderate risk factor for preeclampsia. Factors indicating moderate risk were age >40 years, family history of PE, BMI >35 kg/m^2, nulliparity, and an interpregnancy interval >15 years .

In 2017, the ACOG recommended that women at high risk for preeclampsia begin taking LDA in the late first trimester and continue daily .

Women who had experienced preterm birth at less than 20-22 weeks of gestation and early onset PE, or who had one or more previous pregnancies complicated by PE, were considered to be at high risk for preeclampsia. The following year, the USPSTF published guidelines for indications for the use of low-dose aspirin, and the list of indications was broader .

The USPSTF recommends that women with a history of PE in a previous pregnancy, type 1 or 2 diabetes, chronic hypertension, multiple pregnancies, autoimmune diseases, and kidney disease be administered low-dose aspirin prophylaxis at 81 mg/day between 12 weeks and 28 weeks of gestation (ideally at 16 weeks of gestation), which is continued every day until birth. Other factors associated with increased PE risk include nulliparity, a high pre-pregnancy BMI, family history of

PE, and advanced maternal age (≥35 years). Additionally, black people have higher rates of PE and are at an increased risk of serious complications owing to various societal and health problems.

Screening strategies based on clinical risk factors have been associated with poor outcomes. With the NICE method, the detection rate for all-PE was 37.4%, the rate for preterm PE was 61.8%, and the screening test-positive rate was 15,8% .

Screening based on the 2017 ACOG recommendation achieved detection rates of only 8% and 5% for preterm and term PE, respectively, with a 0.4% false-positive rate .

USPSTF recommendations with a more extensive list of clinical risk factors showed detection rates of 69% (78% confidence interval [CI]: 7,996) and 67% (88% CI, 84-94) for early and late PE, respectively. This was a significant improvement over other screening tests; however, the false positive rate (FPR) also increased by 58% .

Therefore, screening using a maternal risk factor approach performed poorly in identifying women at high risk for PE.

Conclusion

It is now widely accepted that LDA is effective for the secondary prevention of PE in high-risk patients. Aspirin inhibits TXA2 production, thereby restoring the prostacyclin/TXA2 ratio and reducing platelet aggregation.

The conventional method of classifying high-risk populations based on maternal traits has been ineffective. However, the effectiveness of screening significantly increases when maternal features are combined with biochemical and biophysical markers. As a result, it is important to identify high-risk pregnant women early, ideally with the aid of prediction algorithms.

To identify high-risk women who respond best to aspirin prophylaxis to prevent preterm PE, combined screening using maternal variables, mean arterial pressure, uterine artery Doppler, and serum PLGF can be employed. Although the majority of national organizations advise high-risk women to take LDA (60-80 mg) to prevent PE, the majority of the most recent randomized trials with higher LDA dosages (100-150 mg in early pregnancy) had meaningful outcomes. Future research should assess the ideal LDA dosage and timing in women who have been specifically identified as being at a high risk of developing early onset PE.

Growing data indicate that maternal organ dysfunction endures even after delivery, indicating that a history of PE is a distinct cardiovascular risk factor. It is conceivable that aspirin could lower the rates of long-term cardiovascular mortality by avoiding preterm PE.

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