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EFFICACY OF LOW-DOSE ASPIRIN IN THE PREVENTION OF HYPERTENSIVE COMPLICATIONS IN PREGNANCY

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ABSTRACT: **Objective:** To evaluate the efficacy and safety of low-dose aspirin in preventing complications related to hypertension during pregnancy. **Methods:** This study is a simple literature review. Articles were selected based on searches in the PubMED database using predetermined keywords and inclusion and exclusion criteria. **Results:** The analyzed articles presented discrepancies regarding the timing of treatment initiation and the recommended optimal dose. In this context, it is possible to conclude that aspirin in higher doses (≥ 100 mg/day), started before the 16th week of gestation, demonstrates efficacy in preventing preeclampsia. **Conclusions:** This study reinforces the importance of an individualized approach to the pharmacological prevention of hypertensive complications in pregnancy using low-dose aspirin, given the discrepancies found in the analyzed studies regarding dosage, timing of treatment initiation, and its effects.

Keywords: Hypertension. Aspirin. Pregnancy. Pre-eclampsia. Narrative review.

RESUMO: **Objetivo:** Avaliar a eficácia e a segurança da aspirina em baixa dosagem na prevenção de complicações relacionadas à hipertensão durante a gravidez. **Métodos:** Este estudo é uma simples revisão da literatura. Os artigos foram selecionados com base em pesquisas na base de dados PubMED, utilizando palavras-chave pré-determinadas e critérios de inclusão e exclusão. **Resultados:** Os artigos analisados apresentaram discrepâncias quanto ao momento de início do tratamento e à dose ideal recomendada. Nesse contexto, é possível concluir que a aspirina em doses mais altas (≥ 100 mg/dia), iniciada antes da 16ª semana de gestação, demonstra eficácia na prevenção da pré-eclâmpsia. **Conclusões:** Este estudo reforça a importância de uma abordagem individualizada para a prevenção farmacológica de complicações hipertensivas na gravidez com aspirina em baixa dosagem, dadas as discrepâncias encontradas nos estudos analisados em relação à dosagem, momento de início do tratamento e seus efeitos.

Palavras-chave: Hipertensão. Aspirina. Gravidez. Pré-eclâmpsia. Revisão narrativa.

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INTRODUCTION

Hypertensive disorders have a high incidence during pregnancy and are a major cause of maternal and perinatal morbidity and mortality. They affect about 3-5% of all pregnancies in Brazil, with a maternal mortality rate of 0.8% in more developed regions, while in less favored areas, the prevalence reaches 8%, and the maternal mortality ratio is 22%. Among hypertensive disorders during pregnancy, Preeclampsia (PE), eclampsia, gestational hypertension, chronic hypertension, and chronic hypertension superimposed on preeclampsia stand out. PE is defined by the onset of hypertension after 20 weeks of gestation in a previously normotensive pregnant woman, combined with proteinuria (>300 mg/day) or other target organ dysfunctions, such as renal or hepatic dysfunction, neurological complications, or Intrauterine Growth Restriction (IUGR).[1]

The reason why a pregnancy develops or complicates with a hypertensive disorder is still not well defined. It is believed that in preeclampsia, the second wave of migration occurs incompletely, causing inadequate reduction in arterial resistance, and the vessels remain narrow, leading to placental ischemia. This ischemia results in vascular endothelial injury, culminating in vasospasm and increased peripheral vascular resistance, as well as promoting arterial hypertension. This phenomenon can also be aggravated by other factors, such as the activation of the coagulation cascade, leading to a hypercoagulable state. This last aspect may be related to a relative deficiency in prostacyclin production, a potent vasodilator, and excessive thromboxane production, a vasoconstrictor prostaglandin synthesized during platelet aggregation. Other theories regarding the etiology of this disease have also been accepted, such as poor immune adaptation and genetic susceptibility. During a normal pregnancy, the formation and structuring of the placenta is carried out by the migration of trophoblastic cells, occurring in two waves in the first and second trimesters.[2]

These abnormalities lead to numerous complications, both maternal and fetal, posing a major challenge in medicine. The decision to maintain the pregnancy longer until fetal maturation increases the risk of progression to eclampsia, placental abruption, and Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP) Syndrome, resulting in severe maternal outcomes, as well as the development of late complications such as renal failure and cerebrovascular events. On the fetal side, there is a risk of low birth weight and prematurity, contributing to increased infant morbidity and mortality and a higher risk of various chronic diseases during adulthood, such as diabetes mellitus, cardiovascular diseases, and obesity.[3]

Various studies have been conducted to optimize the prevention of hypertensive disorders during pregnancy. As discussed, preeclampsia is associated with insufficient prostacyclin production and excessive thromboxane production. In this context, platelet aggregation inhibitors, such as Acetylsalicylic Acid (ASA), have been shown to be beneficial in reducing the risk of preeclampsia and its complications, as they act as modulators of platelet function and the inflammatory response, reducing thromboxane levels without significantly affecting prostacyclin levels. It has become evident that this therapy prevents the risk of preeclampsia, especially in its early form, which is the most concerning. Additionally, it also helps reduce complications such as preterm labor, fetal growth restriction, and perinatal mortality in high-risk pregnancies.(4)

Although there is still no consensus on the appropriate dose for aspirin prophylaxis, the risk criteria for the development of the disease in pregnant women, and the optimal timing for initiation, the administration of low-dose ASA (60-150 mg/day) is recommended only for high-risk patients for preeclampsia. High-risk patients include those who are chronically hypertensive, diabetic, or have a family or obstetric history of preeclampsia. This effect has not been confirmed when comparing it with low-risk pregnant women. Gestational age is an important factor, as this measure has shown better results when initiated between 12 and 16 weeks of gestation, with inferior results when started after this period. This is because placental development is already completed around 18 weeks of gestation, making the benefit of aspirin absent from additional advantages.(5)

Moreover, the incidence of antepartum and postpartum hemorrhage and premature placental abruption were potential risks associated with ASA use, raising significant concerns. Therefore, the importance of individualized treatment becomes evident.

METHODS

The study is a simple literature review. It was developed in the following phases: formulation of the guiding research question, followed by the establishment of inclusion and exclusion criteria and the literature search; in the third phase, data from the articles were collected, and the included studies were thoroughly analyzed; in the fifth phase, the data obtained from the analysis were discussed, and in the final phase, the synthesis of the addressed topic was performed.

The literature search was conducted in the PubMed database, using the combination of keywords and the Boolean operator "(Pre-Eclampsia OR pregnancy toxemia) AND (Aspirin OR ASA OR acetylsalicylic acid)". The inclusion criteria were as follows: full-text articles (randomized and non-randomized clinical trials) published in Portuguese or English between 2014 and 2024, addressing the efficacy of low-dose aspirin in preventing hypertensive complications in pregnancy, as well as complication rates and improvements in quality of life. The exclusion criteria included: letters to the editor, case studies, systematic reviews without meta-analysis, incomplete studies and/or studies with low methodological quality, and those presenting outcomes different from the inclusion criteria. Subsequently, a second screening was performed, in which articles with similar content were excluded, resulting in the inclusion of 32 out of the 71 articles initially selected.

OBJECTIVES

The main goal of this article is to analyze, through a simple literature review, the use of low doses of aspirin in the prevention of gestational complications resulting from hypertension, as well as to evaluate the efficacy and safety of using low-dose aspirin in this context.

RESULTS

After analyzing the selected articles, a wide range of studies with different analyses regarding the use of aspirin in preventing hypertensive complications during pregnancy were identified, varying in dosage and the specific groups studied. A Pakistani meta-analysis from 2023 revealed that the use of aspirin compared to placebo did not significantly reduce the incidence of preeclampsia (p=0.06), with moderate heterogeneity between the studies (59%).[6] Another systematic review with more than 25 million participants clarified the main risk factors associated with the high incidence of preeclampsia, including antiphospholipid antibody syndrome, a history of preeclampsia, chronic hypertension, pre-gestational diabetes, and Body Mass Index (BMI) greater than 30.[7]

Additionally, an American study analyzing low-dose aspirin in multiple pregnancies indicated a significant reduction in the risk of overall preeclampsia (Risk Ratio (RR), 0.67; 95% Confidence Interval [CI], 0.48–0.94) and mild preeclampsia (RR, 0.44; 95% CI, 0.24–0.82) with the use of the medication in low doses, but there was no significant impact on severe

preeclampsia (RR, 1.02; 95% CI, 0.61–1.72).[8] Studies involving twin pregnancies indicated that aspirin significantly reduced the risk of preeclampsia (Odds Ratio [OR], 0.64; 95% CI, 0.48–0.85; P=0.003), although no significant difference was found in the risk of gestational hypertension (P=0.987), fetal growth restriction (P=0.9), or other maternal and perinatal adverse events.[9]

The reduction in the risk of preeclampsia did not differ between women who started aspirin before or after 16 weeks of gestation (p=0.50). In multiple pregnancies, low-dose aspirin showed low evidence for preventing preeclampsia and small for gestational age neonates. In a comparative analysis between two groups, women who began aspirin administration before 16 weeks had a greater reduction in the severity of preeclampsia, while the group starting after this period had more controversial results.[10] The administration of low doses of aspirin before 11 weeks of gestation showed no impact on reducing the risk of gestational hypertension, hypertensive disorders in pregnancy, or fetal growth restriction but was associated with a reduced risk of preterm birth and increased birth weight.[11]

There was no significant difference in gestational age at birth (P=0.2) or neonatal weight (P=0.06) between women who received aspirin and those who did not. When the aspirin dose was greater than 100 mg/day, the risk of preeclampsia was significantly lower (OR, 0.45; 95% CI, 0.23–0.86; P=0.02), although the risk of gestational hypertension and fetal growth restriction remained unchanged.[12]

In a meta-analysis involving 46 studies and 24,028 participants, starting aspirin treatment (<100 mg/day) before 16 weeks of gestation was associated with a significant reduction in the incidence of preeclampsia (RR, 0.75; 95% CI, 0.58–0.98; P=0.03). At doses ≥100 mg/day, the reduction was even greater (RR, 0.71; 95% CI, 0.53–0.95; P=0.02). However, when treatment was started after 16 weeks, the preventive effect was reduced (RR, 0.80; 95% CI, 0.64–1.00; P=0.05), and at higher doses, no statistical significance was found (RR, 0.76; 95% CI, 0.45–1.31; P=0.32).[13] Aspirin showed a protective effect in reducing preterm births, but there was an increased risk of postpartum hemorrhage.

Further analyses indicated that doses of 75 to 81 mg of aspirin, compared to placebo, were not associated with a significant reduction in the risk of early preeclampsia (RR, 0.66; 95% CI, 0.27–1.62; P=0.36). However, doses of 150 to 162 mg, when started in the first trimester, were associated with a more significant reduction in the risk of early preeclampsia compared to lower doses.[14]

DISCUSSION

The analysis of the selected articles revealed a wide variety of approaches regarding the use of aspirin to prevent hypertensive complications in pregnancy, considering different dosages, gestational ages, and specific groups. This reduction is primarily due to aspirin's anti-inflammatory and anti-aggregatory action, which inhibits the enzyme cyclooxygenase-1 (COX-1) responsible for the production of thromboxane A2, consequently reducing vasoconstriction and platelet aggregation.[15] By blocking this cascade, aspirin causes vasodilation and reduces platelet aggregation, improving placental perfusion, a critical factor in cases of preeclampsia, which is characterized by endothelial dysfunction and excessive vasoconstriction.[16] In this context, aspirin has also been associated with a reduction in preterm births, as the placenta is properly perfused, preventing fetal distress.

However, the use of aspirin, like any medication, carries risks. In addition to potential issues related to drug effects on the body, such as allergies, hypersensitivities (types I and II), and other side effects, aspirin increases the risk of postpartum hemorrhage.[17] Given this, the importance of an individualized approach in medical indication, dosage selection, and the timing of therapy initiation is reinforced.

Among the studies analyzed, meta-analyses and systematic reviews showed greater robustness due to the large number of participants and lower variability in the results, while studies with smaller sample sizes presented more specific and less generalizable results. A systematic review including over 25 million participants highlighted the main risk factors associated with the high incidence of preeclampsia, such as antiphospholipid antibody syndrome, a history of preeclampsia, chronic hypertension, pre-gestational diabetes, and an BMI above 30.[7] The high incidence of these factors in the population underscores the importance of investigating the efficacy of aspirin, especially in high-risk populations.

In the present study, several articles with mostly positive results were used, especially those with larger and more comprehensive populations. Nevertheless, there were discrepancies regarding the appropriate dosage, as shown by a study that reported that doses between 75 and 81 mg of aspirin, when compared to a placebo, did not show a significant association with a reduction in the risk of early preeclampsia (RR, 0.66; 95% CI, 0.27-1.62; P=0.36).[18] On the other hand, higher doses, between 150 and 162 mg, when initiated in the first trimester, were associated with a more significant reduction in the risk of early preeclampsia compared to lower doses.[14] An American study focused on multiple pregnancies showed that the use of

low-dose aspirin significantly reduced the risk of general preeclampsia (RR, 0.67; 95% CI, 0.48-0.94) and mild preeclampsia (RR, 0.44; 95% CI, 0.24-0.82). However, in this same study, no significant impact was observed on severe preeclampsia (RR, 1.02; 95% CI, 0.61-1.72), which may suggest that the observed discrepancy was not related to dosages but rather the classification of preeclampsia severity.[8] The divergences between studies, as seen in the Pakistani meta-analysis and the American study on multiple pregnancies mentioned earlier, can be attributed to the heterogeneity of populations, different inclusion criteria, and variations in aspirin dosages used. These methodological variations make it difficult to generalize the results.

There were also disagreements regarding the best period to begin aspirin administration to prevent gestational hypertensive disorders. A meta-analysis involving 46 studies and 24,028 participants showed that the use of aspirin in doses less than 100 mg/day, when started before 16 weeks, significantly reduced the incidence of preeclampsia (RR, 0.75; 95% CI, 0.58-0.98; P=0.03). The reduction was even more pronounced in doses greater than or equal to 100 mg/day (RR, 0.71; 95% CI, 0.53-0.95; P=0.02).[13] However, when treatment was started after 16 weeks, the preventive effect was less significant (RR, 0.80; 95% CI, 0.64-1.00; P=0.05), and higher doses did not show statistical significance (RR, 0.76; 95% CI, 0.45-1.31; P=0.32). On the other hand, another study indicated that there was no significant difference in the reduction of preeclampsia risk between women who started aspirin use before or after 16 weeks of gestation (P=0.50). Initiating administration before 16 weeks showed a greater reduction in preeclampsia severity compared to starting after that period, suggesting that the timing of initiation may influence the treatment's effectiveness.[10] Additionally, it was observed that administering aspirin in doses greater than 100 mg/day significantly reduced the risk of preeclampsia (OR, 0.45; 95% CI, 0.23-0.86; P=0.02), corroborating the previous studies mentioned, although the risk of gestational hypertension and fetal growth restriction remained unchanged.[12]

These absence of risk changes were also observed in a study with twin pregnancies, where the use of aspirin showed a significant reduction in the risk of preeclampsia (OR, 0.64; 95% CI, 0.48-0.85; P=0.003).[9] A 2023 Pakistani meta-analysis did not find a significant reduction in preeclampsia manifestation with aspirin use compared to a placebo (P=0.06), indicating that the clinical trials addressed in this study diverge considerably in terms of populations or methodologies.[6]

CONCLUSION

The systematic review conducted in this study highlighted that the effectiveness of low doses of aspirin as a prophylactic measure for hypertensive complications in pregnancy in patients with previous cardiovascular conditions remains controversial. Some studies suggest that the medication does not have a significant impact on reducing the chances of preeclampsia and its complications, while others report a decrease in the risks of mild preeclampsia, but without relevant effects in severe cases.

Furthermore, when there are positive impacts from the medication therapy, they are primarily due to its dosage and the timing of its administration during pregnancy. It was evident that there is no consensus regarding the ideal gestational age and the appropriate dose. However, in general, when administered in higher doses ≥100 mg/day and before 16 weeks of gestation, aspirin appears to be effective in preventing preeclampsia and other outcomes, such as gestational hypertension and fetal growth restriction. Thus, the importance of screening in the first trimester of pregnancy and the individualization of therapy becomes evident, as it allows for early and appropriate screening of patients at high risk for preeclampsia and the implementation of prophylactic treatment that minimizes risks and maximizes benefits.

In light of this, aspirin can be very effective in guiding health policies and preventing maternal-fetal health complications, potentially reducing maternal mortality rates. There is a need for the selection of a population with risk factors associated with preeclampsia so that investigations are directed toward high-risk patients. The discrepancies found between the results may be due to the heterogeneity of the populations, different inclusion criteria, and various dosages used.

Therefore, the conclusion is that the efficacy of administering platelet aggregation inhibitors during pregnancy still requires further studies to be fully established as consolidated scientific evidence. However, the available data already indicates significant prophylactic potential, suggesting the possibility of integrating this approach into treatment protocols for pregnant women at high risk of developing preeclampsia.

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