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Mini Review

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Low-Dose Aspirin in High-Risk Pregnancy: Implications for Preeclampsia and Fetal Growth Restriction

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Abstract

Preeclampsia and fetal growth restriction continue to be leading causes of maternal and perinatal morbidity worldwide and are predominantly associated with placental dysfunction. The abnormal placental development, defective trophoblastic invasion and endothelial dysfunction constitute key mechanisms underlying these disorders. Over the past several decades low-dose aspirin has been increasingly recognized as an effective prophylactic measure, aimed at enhancing uteroplacental blood flow and minimizing adverse pregnancy outcomes in women at elevated risk. This mini review provides an overview of the current clinical evidence supporting the prophylactic use of low-dose aspirin prior to 16 weeks of gestation, for the prevention of preeclampsia and fetal growth restriction, based on findings from randomized controlled trials and meta-analyses. Additionally, available data suggests a positive impact on fetal growth, especially in high-risk pregnancies.

However, current evidence indicates that this benefit is primarily mediated through prevention of placental dysfunction rather than direct stimulation of fetal growth. Key aspects regarding optimal dosing, patient selection and timing of initiation have been discussed. Overall, low-dose aspirin demonstrates a favorable safety profile, with minimal maternal or fetal adverse effects when appropriately prescribed. In conclusion, while prophylactic low-dose aspirin has been increasingly implemented as it represents a simple, cost-effective, and evidence-based intervention for reducing the risk of preeclampsia and fetal growth restriction in high-risk pregnancies, early initiation of therapy and accurate identification of the eligible patients remain critical to maximizing its clinical effectiveness.

Keywords: Low-dose Aspirin; Placental Dysfunction; Preeclampsia; Fetal growth restriction; High-risk pregnancies; Platelet aggregation.

Abbreviations: Abbreviations: FGR - fetal growth restriction; PE - preeclampsia; IUGR - intrauterine growth restriction NICU - neonatal intensive care unit; sFlt-1 - soluble fms-like tyrosine-kinase-1 IL-6 - interleukin-6; TNFα - tumoral necrosis factor-alpha VEGF - vascular endothelial growth factor PlGF - placental growth factor; COX-1- cyclooxygenase-1 BMI - body-mass index; SGA - small for gestational age LE2, LE3 - level of evidence 2,3

Introduction

Preeclampsia and fetal growth restriction (FGR) are major causes of maternal and perinatal morbidity and mortality, largely driven by abnormal placentation and uteroplacental insufficiency. Together, these conditions account for a substantial proportion of

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indicated preterm births and are major contributors to long-term cardiovascular and metabolic risk in both mother and offspring. Impaired spiral artery remodeling in early pregnancy leads to placental ischemia, oxidative stress, and the imbalance in vasoactive and angiogenic factors resulting in endothelial dysfunction ultimately manifests as maternal hypertension and compromised fetal growth. The rationale preventive strategy of initiating low-dose aspirin during early pregnancy is based on its effect as an antiplatelet agent. By reducing the synthesis of thromboxane A2, aspirin decreases platelet aggregation, reduces microthrombus formation and improves blood flow, including in the uteroplacental circulation [1]. Beyond reducing the incidence of preeclampsia-especially preterm and severe forms-low-dose aspirin has also been associated with a lower risk of FGR and small- for-gestational-age neonates.

This review aims to explore the shared pathophysiological mechanisms linking preeclampsia and fetal growth restriction and to critically appraise current evidence regarding the role of low-dose aspirin in their prevention.

Discussion

Preeclampsia (PE) and intrauterine growth restriction (IUGR) are distinct clinical conditions, but which are often described as having a common underlying pathogenesis - impaired angiogenesis and widespread endothelial dysfunction accompanied by inflammation. This spectrum of placental disorders is characterized by high levels of circulating endothelial damage markers, the main difference between them being that PE is defined by severe maternal systemic inflammation and endothelial dysfunction, leading to hypertension and proteinuria, while IUGR is portrayed as restricted fetal growth due to inadequate placental blood flow [2]. Insufficient remodeling of the uterine spiral arteries arises from abnormal placentation early in gestation. In PE and IUGR, the trophoblastic invasion into the maternal decidua and myometrium is shallow and incomplete and the arteries retain their muscular and vasoreactive structure. A high level of oxidative stress within the placenta and pro-inflammatory cytokines (IL-6, TNFα), the imbalance between pro- angiogenic (VEGF, PlGF) and anti-angiogenic factors (sFlt-1) and maladaptive maternal–fetal immune interactions finally result in placental ischemia and endothelial dysfunction [3].

Preeclampsia affects between 2% and 5% of pregnancies and is a major cause of maternal and perinatal morbidity and mortality globally. It is associated with preterm birth and a higher risk of other complications such as abruptio placentae, HELLP syndrome, disseminated intravascular coagulation, IUGR and stillbirth in severe cases, with increased rate of cesarean delivery and higher risk of NICU admission [4]. The disorder is defined by new-onset gestational hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) occurring after 20 weeks of gestation, in association with proteinuria ≥0.3 g/24 hours or a proteinuria/creatininuria ratio ≥30 mg/mmol [5].

Pre-eclampsia is characterized by persistent high-resistance uteroplacental circulation due to inadequate spiral artery remodeling. In addition, the oxidative stress and placental ischemia trigger the release of antiangiogenic and inflammatory factors (sFlt-1) into the maternal circulation, antagonizing proangiogenic molecules (VEGF, PlGF) and leading to widespread maternal endothelial dysfunction. Furthermore, this endothelial injury promotes vasoconstriction, activation of the coagulation system, increased vascular permeability and end-organ damage - liver, kidneys, brain and placenta [6].

A case report published in 1978 was the first potential association between Aspirin use and the prevention of preeclampsia. The mechanism involved was based on the fact that low-dose aspirin (below 300mg), selectively and irreversibly inhibits cyclooxygenase-1 (COX-1), leading to reduced synthesis of thromboxane and prostaglandins, with anti-inflammatory and antiplatelet effects [7]. Subsequently, NICE and FIGO recommend low-dose aspirin (75-150 mg of aspirin daily) if the patient has one or more high- risk factors (history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease or an autoimmune disease) or more than one moderate-risk factors (nulliparity, BMI >35, maternal age over 40 years), initiated optimally before 16 weeks of gestation and continued until delivery [8].

Intrauterine growth restriction (IUGR) refers to a fetus that fails to achieve its genetically determined growth potential due to intrinsic or extrinsic factors, frequently resulting in clinical features of in-utero malnutrition or impaired development. Fetal growth restriction (FGR) is commonly used synonymously and denotes failure to follow the expected growth trajectory during gestation. In contrast, small-for- gestational-age (SGA) describes neonates with a birth weight below the 10th percentile for gestational age, sex, and race. SGA represents a cross-sectional, weight-based classification and does not necessarily imply pathological growth restriction, as some infants are constitutionally small yet healthy. Thus, IUGR/FGR reflects abnormal fetal growth secondary to underlying pathology, whereas SGA includes both growth- restricted and constitutionally small infants [9]. The pathophysiology of IUGR is multifactorial; nonetheless, in the context of PE, placental insufficiency represents the dominant mechanism. Abnormal spiral artery remodeling results in reduced uteroplacental perfusion, chronic fetal hypoxia, and nutrient deprivation. Compensatory fetal adaptations, including preferential redistribution of blood flow to vital organs (brain-sparing effect), can be detected by Doppler assessment of the middle cerebral artery and cerebroplacental ratio [9]. Given this shared placental origin, strategies that improve uteroplacental perfusion may influence both conditions.

The clinical significance of growth restriction is underscored by the substantially increased morbidity and mortality associated with SGA neonates. Compared with infants of appropriate weight for gestational age, SGA newborns exhibit markedly higher rates of adverse neonatal outcomes (LE3), with neonatal mortality reported to be two to four times higher than in non-SGA preterm and term infants (LE2) [10]. Because preterm preeclampsia is a major contributor to severe placental insufficiency and secondary

SGA, preventive interventions targeting early placental dysfunction are of particular importance.

The well-known ASPRE trial demonstrated that low-dose aspirin (150 mg/day from 11-14 weeks' gestation, determined by fetal crown-rump length) in high-risk pregnancies reduced the incidence of preterm preeclampsia by 62%, potentially preventing severe placental dysfunction and associated fetal growth restriction, while having no significant effect on term preeclampsia [11]. According to the Journal of the Fetal Medicine Foundation, primary prevention of fetal growth restriction remains challenging. However, in women at high risk for placental insufficiency, low-dose aspirin can be prescribed to delay the onset of preterm preeclampsia and reduce the severity of associated fetal growth restriction, thereby prolonging gestation and improving birth outcomes. The estimated number needed to treat is 38 for preterm preeclampsia (<37 weeks) and 16 for birth weight below the 10th percentile, supporting the routine use of aspirin in high-risk pregnancies in line with national guidelines [12]. It is also demonstrated that low-dose aspirin initiation after 16 weeks showed no significant benefit [13].

Nevertheless, evidence indicates that the beneficial effect of aspirin is primarily mediated through prevention of placental dysfunction rather than direct stimulation of fetal growth [14]. Furthermore, recent cohort studies suggest that low-dose aspirin does not significantly reduce recurrence of SGA in women with a prior SGA infant in the absence of preeclampsia [15]. Similarly, meta-analytic data in twin pregnancies demonstrate a significant reduction in preeclampsia, particularly at doses exceeding 100 mg/day, without a consistent impact on neonatal birth weight or overall fetal growth parameters [16]. These findings reinforce the concept that aspirin acts mainly by modifying the placental disease process, rather than directly enhancing fetal growth potential.

Low-dose aspirin is generally well tolerated. The most common adverse effects of low-dose aspirin include mild gastrointestinal discomfort, dyspepsia, and nausea. In addition to its antiplatelet action, it may slightly increase the risk of minor bleedings (epistaxis, easy bruising). Overall, low-dose aspirin is considered to have a high-safety profile with minimal risk to both mother and fetus. Regarding major adverse outcomes, it has been linked to a possible higher risk of postpartum hemorrhage, which may be avoided by discontinuing the treatment around 36 weeks of pregnancy [17].

In October 2020, the U.S. Food and Drug Administration issued a warning regarding the use of nonsteroidal anti-inflammatory drugs beyond 20 weeks of gestation due to the rare risk of fetal renal impairment and oligohydramnios; Even so, low-dose aspirin (81 mg) prescribed for specific obstetric indications remains an approved exception under medical supervision [18].

Conclusion

In conclusion, low-dose aspirin is an evidence-based and generally safe strategy for the prevention of preeclampsia and, to a lesser extent, fetal growth restriction in high-risk pregnancies. It targets the key mechanisms of placental dysfunction including impaired uteroplacental perfusion and platelet activation, particularly when initiated early in gestation. Nevertheless, aspirin prophylaxis should not be administered universally. Careful first-trimester risk stratification and individualized assessment are essential to identify women who are most likely to benefit, thereby optimizing maternal and perinatal outcomes while avoiding unnecessary treatment in low-risk pregnancies. In this context, low-dose aspirin remains a simple, cost- effective, and clinically meaningful intervention in contemporary obstetric practice.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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