Aspirin for the Prevention of Preeclampsia and Intrauterine Growth Restriction

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KEYWORDS

• Pregnancy • Preeclampsia • Intrauterine growth restriction • Aspirin • Placenta

KEY POINTS

- Low-dose aspirin (LDA) (80–160 mg) reduces the risk of preeclampsia (PE) and intrauterine growth restriction by approximately half when started in early pregnancy.
- LDA reduces mainly the preterm and severe forms of PE when started in early pregnancy.
- Women with chronic hypertension and those with prior PE should begin taking LDA in early pregnancy.
- First-trimester screening programs should be implemented to identify women at high-risk for preterm or severe PE.
- Further studies should evaluate the optimal dosage of aspirin and the benefit of adding low molecular weight heparin in women at very-high risk, such as those with prior early onset PE.

INTRODUCTION

Preeclampsia (PE) is a hypertensive disorder of pregnancy characterized by high blood pressure and proteinuria that affects 2% to 5% of pregnant women in developed countries and up to 8% of pregnant women in developing countries.[1,2] It is a major contributor to maternal and fetal morbidity and mortality worldwide, with more than 100,000 maternal deaths every year.[3]

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The origins of PE are multifactorial, but it is well accepted that abnormal invasion of the placenta and systemic endothelial dysfunction play key roles in the development of the disease. Transformation of uterine spiral arteries by the cytotrophoblasts, which occur mainly in the first-trimester of pregnancy, is typically missing in PE, particularly in preterm PE.[4–8] Such a deep placentation disorder leads to the production of angiogenic factors by the placenta, systemic endothelial cell dysfunction, maternal underperfusion, and ultimately the signs and symptoms of PE.[5,9] Endothelial dysfunction is worsened by other factors such as advanced maternal age, high blood pressure, and obesity. In severe PE, placental disorders are also associated with intrauterine growth restriction (IUGR), preterm birth, and in the worst cases, fetal death, and/or eclampsia.

Numerous therapies have been used to prevent PE, including low-dose aspirin (LDA), calcium, unfractionated heparin, low molecular weight heparin (LMWH), progesterone, antioxidants, and physical activity with inconsistent results.[10–19] Recently, there has been a renewed interest in LDA when meta-analyses showed that PE and other adverse placenta-mediated outcomes of pregnancy could be significantly reduced with LDA started before 16 weeks' gestation.[13,20] The authors reviewed the literature regarding prevention of hypertensive disorders and related perinatal outcomes with LDA started in early pregnancy.

Preeclampsia

According to the American College of Obstetricians and Gynecologists (ACOG), PE is defined by the combination of a high blood pressure (140 mm Hg systolic or higher or 90 mm Hg diastolic or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure) and proteinuria (urinary excretion of 0.3 g protein or higher in a 24 hour urine specimen or 2 + protein on dipstick) but the definition can vary between countries.[10,21] PE is associated with placental disease in most cases, with the severity of the disease being more important with early gestational age at delivery.[22] Data from placental bed biopsies showed that most cases of PE are associated with incomplete transformation of uterine spiral arteries.[4] However, deep placentation disorders are also observed mainly in the preterm and severe forms of the disease and are not necessarily specific to the disease.[6,23,24]

Low-Dose Aspirin for the Prevention of Preeclampsia

In 1978, Goodlin and colleagues[25] suggested that recurrent PE can be prevented using LDA and unfractionated heparin. A year later, Crandon and Isherwood reported that primigravidae who were taking LDA during pregnancy were less likely to develop PE than those who did not.[26] The same year, Masotti and colleagues[27] reported that 2 to 5 mg of aspirin per kilogram were associated with a differential inhibition of platelets and vessel-wall cyclooxygenase that could potentially explain the impact of LDA on placentation and PE. Following those studies, Beaufils and colleagues[28] evaluated the benefits of 150 mg of aspirin combined with 300 mg of dipyridamole from 12 weeks of gestation in women at high risk for PE or intrauterine growth restriction (IUGR) on the basis of the obstetric history. In this randomized trial, PE (12%) and major complications (18%, including severe IUGR and fetal death) occurred more frequently in the control group than in the LDA + dipyridamole group, in which no case of PE or major complications was observed. Following that publication, more than 60 randomized trials were published with controversial results.

In 2007, Askie and colleagues[29] reported that LDA could prevent 10% of PE cases. However, they showed high heterogeneity between the studies. In 2010, another meta-analysis from Bujold and colleagues,[13] looking specifically at the time of initiation of LDA, demonstrated that randomized trials that initiated LDA before 16 weeks'