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Editorial

Prevention of Pre-eclampsia

Preeclampsia refers to a syndrome of new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation in a previously normotensive woman. The syndrome is called superimposed preeclampsia when accelerating hypertension and either proteinuria or end-organ dysfunction develop after 20 weeks in a woman with preexisting hypertension[1].Signs of end-organ dysfunction (platelet count <100,000/microliter, serum creatinine >1/1 mg/dL or doubling of the serum creatinine, elevated serum transaminases to twice normal concentration) [2].

Prevention of a disease is possible if the cause is understood and if it is feasible to avoid or manipulate those causes. The pathogenesis of preeclampsia is incompletely understood. Shallow endovascular cytotrophoblast invasion in the spiral arteries, an exaggerated inflammatory response, and inappropriate endothelial-cell activation are key features in the pathogenesis of pre-eclampsia[3].

Different strategies to prevent preeclampsia have been studied extensively over the past 20 years. To date prevention has focused on mechanisms thought to be behind the pathophysiology of the disease process. No intervention has been proved unequiv-ocally effective. Current strategies for prevention focus on antenatal surveillance, modification of lifestyle, nutritional supplementation, and pharmacological therapy.

Role of Calcium: Several studies have examined the effectiveness of cal-cium supplementation to prevent preeclampsia. Some epidemiological studies have suggested that the frequency of pre-eclampsia/ eclampsia is inversely proportional to nutritional calcium intake[4]. However, a large U.S. cohort of healthy primiparous women, calci-um supplementation did not reduce incidence of pre-eclampsia[1].

Calcium supplementation might be expected to be of greater benefit in women who have a nutritional deficiency of calcium. A meta-analysis of 13 trials that involved 15,730 women reported a significant reduction in preeclampsia risk with calcium supplementation, with the greatest effect among women with low baseline calcium intake [5]. Thus, calcium supplementation may be considered in pregnant women from pop-ulations with low baseline calcium intake (less than 600mg/day) In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/ day) is strongly recommended by WHO for the prevention of pre-eclampsia in all women, but especially those at high risk of developing pre-eclampsia[6].

Ante platelet Agents

It has been hypothesized that alterations in systemic prostacyclin–thromboxane balance contribute to pre-eclampsia. Low-dose aspirin (81 mg or less), an anti-inflammatory agent that blocks the production of thromboxanes, has been studied in dozens of trials for the prevention of preeclampsia, both in high-risk groups and in healthy nulliparous women. A Cochrane review (2007) containing 59 trials (37560 women) reported a 17% reduction in the risk of PE associated with the use of antiplatelet agents (46 trials, 32,891 women). Antiplatelet agents were associated with an 8% reduction in the relative risk of preterm birth (29 trials, 31,151 women), a 14% reduction in fetal or neonatal deaths (40 trials, 33,098 women), and a 10% reduction in small-for-gestational age babies (36 trials, 23,638 women). It was concluded that antiplatelet agents, largely low-dose aspirin, have moderate benefits when used for prevention of PE and its consequences[7].

The U.S. preventive task force reviewed the evidence of the effectiveness of low-dose aspirin in preventing preeclampsia in women at increased risk and in decreasing adverse maternal and perinatal health outcomes, and assessed the maternal and fetal harms of low-dose aspirin during pregnancy. The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia[8].

The American College of Obstetricians and Gynecologists also recommends initiating use of low-dose aspirin (60to 80 mg/d) during the late first

trimester to prevent preeclampsia in women with a medical history of early onset preeclampsia and preterm delivery (<34 weeks) or history of preeclampsia in more than 1 previous pregnancy.(1) The World Health Organization also recommends the use of low-dose aspirin (75 mg/d) starting as early as 12 to 20 weeks of gestation for high-risk women (i.e., those with a history of preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multifetal pregnancies[6]. The National Institute for Health and Care Excellence recommends that women at high risk for preeclampsia (i.e., those with a history of hypertension in a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or 2 diabetes, or chronic hypertension) should take 75 mg/d of aspirin from 12 weeks until delivery[9].

Antioxidant Supplementation with Vitamin C and Vitamin E

Because oxidative stress appears to contribute to the pathogenesis of preeclampsia, it has been suggested that antioxidants may prevent preeclampsia. Despite initial enthusiasm for using a combination of the anti-oxidants vitamin C and vitamin E for this purpose, large randomized, placebo-controlled trials conducted during pregnancy found that supplementation with vitamin C and vitamin E did not reduce the risk of pre-eclampsia or improve maternal and fetal outcomes in various populations[10-12]. A recent Cochrane systematic review of 15 randomized controlled trials (20,748 women) that used vitamin C and vitamin E for the prevention of preeclampsia also found no benefit [13]. Administration of vitamin C or vitamin E to prevent preeclampsia is not recommended by the USPTF[8].

Vitamin D deficiency has been suggested as a factor contributing to preeclampsia[14]; however, whether supplementation with vitamin D is helpful is unknown. Evidence is insufficient for reliable conclusions with regard to other nutritional interventions, such as fish oil or garlic, which have been used to prevent pre-eclampsia. Protein and calorie restriction for obese pregnant women shows no reduction in the risk of pre-eclampsia or gestational hypertension and may increase the risk of intrauterine growth restriction and should be avoided[1].

Reduced Dietary Salt

The advice of reducing salt during pregnancy is a common practice among clinicians, probably because this is a valid recommendation for hypertensive patients in general. A Cochrane review published in 2010 compared restricted dietary salt with a normal diet in pregnancy. It included 2 trials, with 603 women as participants of the study. However, there was no significant correlation observed (RR 1.11, 95% CI 0.46 to 2.66) to advice reduced salt intake during pregnancy[15].

Lifestyle Modifications

Although bed rest has been suggested as a preventive strategy, the evidence for this is scarce. Only two studies evaluated bed rest as a pre-ventive strategy, both were small (32 participants and 72 participants) and did not evaluate perinatal and maternal morbidity and mortality and adverse effects of bed rest. However, regular exercise has been hypoth-esized to prevent preeclampsia by improving vascular function [16, 17]. Moderate exercise has been hypothesized to stimulate pla-cental angiogenesis and improve maternal endothelial dysfunction. Several small clinical trials have evaluated the utility of modest exercise for the prevention of preeclampsia, but the confidence intervals were too wide to make any reliable conclusions about the efficacy[18.]

Conclusions Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. In an attempt to prevent preeclampsia, many strategies based on antenatal care, change in lifestyle, nutritional supplementation, and drugs have been studied.

Interventions such as rest, exercise, reduced salt intake, antioxidants showed insufficient evidence to be recommended as preventive measurements. On the other hand, low-dose aspirin especially when initiated before 16 weeks in high-risk groups and calcium especially in low-intake populations show promise in the prevention of pre eclampsia.

Prof. Firoza Begum
Professor, Fetomaternal Medicine wing, Deaprtment of Obstetrics & Gynaecology
Banga Bandhu Sheikh Mujib Medical University.

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