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Review Article

The Pharmacology of Preventing Preeclampsia

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Preeclampsia is a syndrome that is characterized by heterogeneous clinical and laboratory findings. The clinical features and manifestations are generally in the mother. However, sometimes the fetal syndrome may dominate the clinical picture.[1] The current understanding of preeclampsia has not given us an exact etiological factor or a precise pathophysiologic mechanism. However, it is becoming clear that it is much more than hypertension, proteinuria and edema in pregnancy. Despite extensive research in the pathogenesis of preeclampsia, the etiology remains a mystery. A number of mechanisms postulating the development of preeclampsia have been put forward. Some of these mechanisms have included impaired trophoblast differentiation and invasion, placental and endothelial dysfunction, immune maladaptation to paternal antigens, and exaggerated systemic inflammatory response.[1] Because the disorder is heterogeneous, the pathogenesis can differ in women with various risk factors. The mechanisms underlying preeclampsia in a healthy primigravida may be quite different from those through which occur in a 40-year old chronic hypertensive woman or a woman with a previous pregnancy affected by preeclampsia.[2]

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From the public health perspective, the condition complicates 2–8% of pregnancies. [3] Worldwide, 10–15% of the half million maternal deaths that occur every year are associated with hypertensive disorders of pregnancy. 99% of these occur in low-resource countries. [4] Preeclampsia also takes a massive toll on perinatal health and is responsible for a significant proportion of preterm births (iatrogenic and spontaneous), growth restriction and mortality. Preventing preeclampsia would therefore be a highly desirable goal.

Who is at risk?

Preventing preeclampsia would be possible if we can identify the underlying pathophysiological mechanisms. This would also allow us to predict preeclampsia more successfully and target the high risk population. As things stand today, strategies to predict preeclampsia are based on epidemiological data, biochemical and sonographic markers. These seem to be either the consequence of the disease or its epiphenomena. When the biological markers become apparent, it is likely that the disease process is already underway in the body and measures taken at this stage would be more to do with preventing the consequence rather than the occurrence of the disease. Table 1 gives a comprehensive list of risk factors that are associated with a higher risk of preeclampsia. [5] In clinical practice, the following are encountered most commonly:

- Age over 40 years
- Chronic hypertension, obesity and diabetes

- Previous pregnancy complicated by severe preeclampsia (especially early onset), IUGR or abruption
- Multiple pregnancy
- False positive results for trisomy screening
- Abnormal uterine artery Doppler waveform (high S/D ratio or notching).

Some of these factors are known before the index pregnancy begins and are amenable to correction. Women should attempt to bear children in their best possible condition. Potential measures to ensure an optimal health status would include achieving a normal body weight and BMI, control of preexisting medical disorders and achieving optimal organ function for renal disease patients. The drugs used for control of hypertension and diabetes should be suitable for pregnancy and doses and class of agents may have to be changed keeping this in mind. It would be ideal if this control could be achieved for a few months before conception occurs. Though there are no randomized trials to prove these benefits, these measures are supported by widely available epidemiological data.[6, 7]

Table 1. Prediction of Preeclampsia.

Preexisting or Preconceptional risk factors	Pregnancy-related risk factors	Biochemical and Biophysical markers
Chronic hypertension	Hydrops/hydropic degeneration of placenta (triploidy, trisomy 13)	Unexplained second-trimester elevations of serum alpha-fetoprotein, human chorionic
Renal disease	Multifetal gestation (depends on number of fetuses and maternal age)	gonadotropin, inhibin A, activin A Abnormal uterine artery Doppler
Pregestational diabetes mellitus	Unexplained fetal growth restriction	velocimetry in first and second trimesters
Autoimmune disease (SLE, rheumatoid arthritis)	Gestational hypertension	Decreased placental growth factor in the second trimester
Primary antiphospholipid antibody syndrome and other thrmobophilias	Urinary tract and periodontal infections	Elevated soluble fms-like tyrosine kinase-1 in second trimester
Obesity, insulin resistance		Elevated soluble endoglin in second trimester
Age > 40 years		Elevated asymmetric dimethylarginine in second trimester
Previous pregnancy with severe preeclampsia especially of early onset, IUGR, abruption or fetal death		Reduced serum placental protein-13 in the first trimester
Family history of preeclampsia in mother		Reduced pregnancy associated plasma protein A in first trimester
Partner who has a fathered a pregnancy affected by preelampsia in another woman		
Limited sperm exposure (donor insemination)		

Table 2.

Drugs that have been studied for preventing preeclampsia.

Antithrombotic agents	Aspirin Heparin Dipyridamole
Antioxidants	Vitamin C Vitamin E Calcium (high dose) Magnesium (high dose) Selenium Zinc
Nitric oxide donors	Arginine Nitroglycerin patches Sildenafil
Fish oil supplementation	
Progesterone	
Traditional medications	Ayurvedic medications Traditional Chinese medications

Pharmacological agents for preventing preeclampsia

Since the exact pathophysiology of preeclampsia is not known, drug therapy to prevent the disease is based in empiricism. Physicians may start using a drug based on anecdotal records, past experience or protocols adopted during training. These drugs are seldom subjected to the rigors of a randomized trial. Pharmacological therapy to prevent preeclampsia is usually empirical, of unproven value and often speculative. A number of candidate drugs have been proposed to prevent preeclampsia. Aspirin is the most widely studied and used drug in this category. A list of the drugs is presented in Table 2.

Aspirin

Rationale

Increased platelet activation is one of the established component of preeclampsia pathophysiology. This may lead to platelet consumption and subsequent activation of the coagulation system in the microvasculature. [8] This in turn results in endothelial injury, vasospasm and end organ damage as evidenced by the classic lesions associated with preeclampsia such as glomerular endotheliosis. [9] Biochemical studies suggest a pathological imbalance between vasodilator and vasoconstrictor eicosanoid products of the cyclooxygenase pathway. With regards to preeclampsia, prostacyclin (PGI2) and thromboxane A2 (TXA2) are the two most relevant vasoactive compounds. The imbalance favors increased TXA2 and this causes abnormal activation of the rennin-angiotensin system (RAS). This results in more angiotensin II and norepinephrine production which worsens the vasospasm. The increased TXA2 – to – PGI2 ratio is therefore a central feature of preelampsia biochemistry. [10]

Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase enzyme. Cyclooxygenase is required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the enzyme. This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors. Aspirin has been shown to have additional modes of action in preeclampsia prevention as well. These include uncoupling oxidative phosphorylation in mitochondria, inducing NO-radicals formation and signal modulation of proinflammatory kinins and transcription factors. [11] The optimal dose of aspirin to achieve these effects remains unknown. Doses as low 20 mg/day and as high as 3.5 g/day have been utilized for the antithrombotic effects of aspirin. [12] In most studies, aspirin is used in a dose of 75 to 150 mg. This is the commonly accepted range for "low dose" aspirin therapy. To achieve the maximum benefit, it seems logical to start aspirin therapy early in pregnancy. The common practice is to initiate aspirin in the first trimester after confirming fetal cardiac activity.

One of the early concerns about the use of antiplatelet agents during pregnancy was the possibility of an increase in bleeding problems for either the woman or her child. This concern has been allayed by results from trials one of which even found no evidence of risk in children born at preterm gestations. The results of a case-control study indicate that aspirin use in early pregnancy does not result in an increased risk of congenital abnormalities in infants. [14] There is no increased risk of postpartum or antepartum hemorrhage between women who received antiplatelet agents and

Table 3.

Aspirin efficacy and number needed to treat (NNT) for varying baseline rates. [15]

Preeclampsia	Sample baseline event rate	PARIS relative risk (95%CI)	Number needed-to-treat (95% CI)
Pregnancy with serious	18% 6% 2%	0.90 (0.84–0.97)	56 (35–185) 167 (104–556) 500 (313–1667)
adverse outcome*	25% 15% 7%	0.90 (0.85–0.96)	40 (27–100) 67 (44–167) 143 (95–357)

* Preeclampsia, preterm delivery < 34 weeks, small for gestational age fetus, perinatal death

Table 4.

Randomized trials of Vitamin C and E for the prevention of preeclampsia.

	Population	**Enrollment gestational age (week)**	**No. of Patients**		**Number of patients Incidence of preeclampsia (%)**	
			Vitamin C and E	Placebo	Vitamin C and E	Placebo
Roberts et al [22]	Low risk nulliparous women	9 - 16	5087	5065	6.1	5.7
Villar et al [23]	Lower nutritional strata	14 – 20	207	205	26	28
McCance et al [24]	Insulin dependent diabetes	8 – 22	375	374	15	19
Poston et al [25]	Previous preeclampsia, HELLP or eclampsia	14 – 21	1199	1205	15	16

those who did not, nor was there an effect on infant bleeding. [15]

Evidence

Recently, the Perinatal Antiplatelet Review of International Studies (PARIS) Collaborate Group performed a metaanalysis of the effectiveness and safety of antiplatelet agents (predominantly aspirin) for the prevention of preeclampsia. [15] Thirty-one randomized trials involving 32,217 women are included in this review. For women assigned to antiplatelet agents, the RR of developing preeclampsia was 0.90 (95% CI 0.84–0.96). For women with a previous history of hypertension or preeclampsia (n = 6,107) who were assigned to antiplatelet agents, the RR for developing preeclampsia was 0.86 (95% CI 0.77–0.97). The effectiveness of aspirin in preventing preeclampsia and its adverse pregnancy outcomes can be best understood by ascertaining the NNT (number needed to treat) to prevent a particular outcome. A low NNT would suggest high effectiveness and vice-versa. The NNT and therefore the efficacy of low dose aspirin would therefore depend on the baseline risk in a particular population as shown in Table 3. The inference from this is that for aspirin to be effective, it should be used in a high risk population. For example, if it is used in a population of women who had developed severe proteinuric preeclampsia early in the second trimester in a previous pregnancy (baseline risk of preeclampsia in current pregnancy is 65%), the NNT is as low as 14 to prevent one case of preeclampsia. On the other hand, in an unselected population with a baseline risk of preeclampsia of 2%, the NNT would be 500 to prevent one case of preeclampsia. Even though the metaanalysis is methodologically strong and involves a large number of women, the limitation is that it is based on subgroup analysis. Also, the timing of starting aspirin was not uniform and there was some heterogeneity in the populations taken for analysis.

Antioxidants

Rationale

There is strong evidence of a central role for oxidative stress in the production preeclampsia. [16] There is an imbalance of oxidant and antioxidant activity involving placental and maternal lipid peroxidation and the multiorgan endothelial dysfunction observed among preeclamptic patients appears to be related to damage caused by unregulated free radical production. Uterine and intrauterine tissues are potential sources of lipoxygenase products during pregnancy and parturition and aberrant lipoxygenase activities may contribute to the complications of preeclampsia. [17]

Antioxidants are molecules, which scavenge free radicals and block the chain reaction of unregulated oxidation before damage occurs. There are several enzyme systems within the body that scavenge free radicals, including superoxide dismutase (SOD), catalase, glutathione peroxidase (GSHPx), and glutathione reductase. The principle micronutrient (vitamin) antioxidants are vitamins C and E as well as carotenoids such as beta-carotene. Additionally, calcium, magnesium, selenium, zinc, coenzyme Q, melatonin and other trace elements may also be important. Together these vitamins, enzymes, and cofactors provide protection from the potentially damaging consequences of reactive oxygen species to endothelial cells. [18]

Evidence about calcium

A recent updated Cochrane review assessed the supplementation of at least 1 gram of calcium daily versus placebo or no supplementation. [19] Thirteen studies of good quality (involving 15,730 women) were included. There was a reduction in the average risk of preeclampsia associated with calcium supplementation (13 trials, 15,730 women: RR 0.45, 95% CI 0.31 to 0.65). The effect was greatest for high-risk women (five trials, 587 women: RR 0.22, 95% CI 0.12 to 0.42), and those with low baseline calcium intake (eight trials, 10,678 women: RR 0.36, 95% CI 0.20 to 0.65). There was no overall effect on the risk of stillbirth or infant death before discharge from hospital (11 trials 15,665 babies; RR 0.90, 95% CI 0.74 to 1.09). There was no difference in maternal mortality. The Cochrane data is supportive of calcium use in pregnancy. However, these trials involved calcium deficient women. There was no segregation of women with previous preeclampsia and no subgroup analysis. A contrary point of view has been presented by the U.S. Food and Drug Administration which concluded that "the relationship between calcium and risk of hypertension in pregnancy is inconsistent and inconclusive, and the relationship between calcium and the risk of pregnancy induced hypertension and preeclampsia is highly unlikely." [20] Evidence about Vitamin C and E Vitamin C and E supplementation has been proposed as a method of improving the oxidative capability of women at risk for preeclampsia. A pilot study performed with a limited sample size suggested a beneficial effect from pharmacologic doses of vitamins E and C in women

identified as being at risk for preeclampsia because of abnormal uterine Doppler flow velocimetry. [21] Since then, a number of larger randomized trials have been published evaluating the use of vitamin C (1,000 mg/d) plus vitamin E (400 international units/d) supplementation during pregnancy for the prevention preeclampsia. The main results of these trials are summarized in Table 4.

There is now overwhelming evidence to state that the supplementation of Vitamins C and E is of no use in preventing preeclampsia. This has been shown in unselected populations [22], women thought to poorly nourished 23, those with a medical disorder placing them at risk of preeclampsia [24] and those with preeclampsia or its variants in previous pregnancies. [25] There is concern about safety of these agents in regards to adverse pregnancy outcomes. Spinnato et al [25] had shown the incidence of preeclampsia was similar in the vitamin C and E treatment and placebo groups (15% compared with 16%). Among those with preeclampsia, the mean gestational age at diagnosis of preeclampsia and the mean gestational age at delivery were significantly earlier in the antioxidant group. Of note, there were significantly more low birth weight babies born to mothers in the supplemented group.

Heparin +/- Aspirin

There are no published randomized trials evaluating thromboprophylaxis with low-dose aspirin and heparin for prevention of recurrent adverse perinatal outcome in women with previous severe preeclampsia though numerous observational studies evaluating this treatment have been published. Considering the unproven value, cost and potential for side effects (thrombocytopenia, osteoporosis, maternal hemorrhage), heparin cannot be recommended as a prophylactic agent in women at low risk or even those with a past history of preeclampsia. A very small proportion of women who are at risk for preeclampsia due to a proven, established primary antiphospholipid antibody syndrome (PAPS) or those who have a diagnosed autoimmune disorder such as systemic lupus erythomatosus may benefit from low dose low molecular heparin use. [26]

Fish Oil Supplementation

The beneficial effects of fish oil on the incidence of preeclampsia are supported by observational studies. The effect is postulated due to the beneficial fatty acid concentration in fish oil and its antioxidant properties. There is one multicenter randomized trial evaluating fish oil supplementation for the prevention of preeclampsia in high-risk women. [27] This trial included 350 women with previous preeclampsia. For women assigned to treatment with fish oil, the odds ratio of developing preeclampsia was 0.98 (95% CI 0.63–1.53). In addition, an observational prospective study evaluated the relationship between high consumption of marine fatty acids in early pregnancy and hypertensive disorders in pregnancy. The authors found that consumption of high doses of fish oil in early pregnancy may increase the risk of developing hypertensive disorders of pregnancy. [28] Thus, fish oil supplementation is not recommended for the prevention recurrent preeclampsia.

Other Agents

The other agents which have been studied to some extent in randomized or case controlled trials in pregnant women are nitric oxide and nitric oxide donors and progesterone. None of these have been found to be effective in preventing preeclampsia and are not recommended for this purpose. [29, 30] A number of other agents purported to have a beneficial effect on reducing preeclampsia risk such as traditional medicines (Chinese herbal medications, Ayurvedic preparations) remain poorly studied and published.

Conclusions

Based on the presently available evidence, we do not recommend the supplementation of calcium, vitamin C and E, fish oil, or heparin for the prevention of preeclampsia. Because the results of the recent meta-analysis of low dose aspirin use in such women found a reduction in preeclampsia and given the safety and economy of this agent, aspirin is the drug of choice in preventing preeclampsia. It is not to be used routinely for unselected populations. Aspirin is likely to benefit high risk women and the efficacy will depend on the baseline risk a particular woman faces in that pregnancy. At the present time, our tools to identify women at risk for preeclampsia are limited to preexisting medical risk factors, past obstetric history and some biochemical and biophysical risk factors of doubtful value

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