Updates in the Prevention of Preeclampsia, What's Beyond Aspirin?

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Abstract

Hypertensive disorders of pregnancy are among the most common medical problems during pregnancy and they are associated with significant mortality and morbidity rate. Low dose Aspirin is already approved by many societies like ACOG and WHO to be used as prophylaxis for preeclampsia in high-risk patients. Recent studies showed a possible reduction in the incidence of preeclampsia and intrauterine growth restriction for high-risk mothers who taking LMWH during pregnancy. Although, the published evidence supporting LMWH is characterized by profound heterogeneity and inconsistency in terms of selection criteria and treatment regimens. Antepartum treatment with a combination of LMWH with low-dose ASA is endorsed by the American College of Chest Physicians and The American College of Obstetricians and Gynecologists for treatment of Antiphospholipid syndrome during pregnancy. WHO recommends Calcium as the first nutritional supplementation to prevent preeclampsia among population with low calcium in the diet. Folic acid and statins showed possible reduction in incidence of preeclampsia in high-risk patients but there is a need for further studies to confirm that. Dietary and lifestyle interventions have the potential to reduce the risk of preeclampsia. Both Metformin and vascular endothelial growth factors has promising preventive role that has been found through recent studies.

Keywords: Preeclampsia; Prevention; Hypertensive disorders of pregnancy

Introduction

Hypertensive disorders of pregnancy are among the most common medical problems during pregnancy and they are associated with significant mortality and morbidity rate [1]. They affect 4 % of pregnant women and may cause serious complications like stroke, heart failure, and renal failure [2]. Those diseases are among the top 6 causes of maternal mortality in the USA being responsible for 10% of maternal deaths [3]. They should be considered as a syndrome rather than a single disease entity [4]. Highest mortality rates were found to be related to eclampsia, HELLP syndrome, hemorrhage, delayed diagnosis [5]. The incidence may be affected by parity, socioeconomic level, race, and environmental factors [6]. African Americans have a high incidence of preeclampsia, eclampsia, related maternal mortality [5]. Their incidence has been dramatically increased recently with significant health burden in terms of affection of both mother and fetus health [3]. Having standardized health care for those patients is associated with a significant reduction in both mortality and morbidity [7,8].

Many societies contribute to Classifying hypertensive disorders of pregnancy in order to determine proper management lines and timelines for each category.

Chronic hypertension is defined as systolic BP of 140 or greater Or diastolic BP of 90 or greater Or both on 2 separate occasions at least 4 hours apart, This condition is diagnosed at or before 20 gestational weeks or already documented before pregnancy [9]. However, ACOG suggests that gestational hypertension or early-onset preeclampsia should be considered if 1st trimester BP measures are within normal range [10]. Gestational hypertension

is defined as elevated BP above 140/90 mmHg after 20 weeks at two separate occasions 6 hours apart in the absence of features of severe preeclampsia [11]. Severe gestational hypertension is defined by sustained elevated BP at more than or equal 160/110mmHg [12]. SOMANZ defines preeclampsia with severe features as a unique condition of pregnancy with multisystem effects involving liver, kidney and hematological parameters [13]. ACOG criteria for diagnosis include new-onset hypertension after 20 weeks associated with new-onset proteinuria (>300 mg/24 hours urine collection) [14]. In absence of proteinuria, diagnosis can be made upon presence of gestational hypertension plus any of the following: low platelet count less than 100.000/cc, creatinine level more than 1.1 (double the baseline creatinine level in absence of other renal problem), raised liver enzymes (double baseline), pulmonary edema, visual or cerebral symptoms [15].

Low dose Aspirin is already approved by many societies like ACOG and WHO to be used as prophylaxis for preeclampsia in high-risk patients. In this article, we are going beyond Aspirin to know more updates about other possible prophylactic measures of preeclampsia including Low molecular weight heparin, Calcium, vitamin D, Arginine, statins, and Folic acid.

Pathogenesis

The pathogenesis of preeclampsia is not completely understood despite extensive researches focused on it [16,17]. Placental ischemia remains the most accepted theory that was postulated to explain the pathogenesis of preeclampsia because delivery of the fetoplacental unit remains the main curative line of treatment [17,18]. In addition to that, placental ischemia also explains other complications e.g. IUGR and oligohydramnios. Also, it explains a higher incidence of disease in patients with chronic hypertension, DM and autoimmune diseases. Placental ischemia may explain the effectiveness of both low dose Aspirin and Low molecular weight heparin [19,20]. In normal pregnancy, invasion of uterine arteries to cytotrophoblast causes their transformation from epithelial to endothelial cells with low resistance pressure allowing enough blood supply to fetus through a process called ''pseudo-vasculogenesis'' [18]. Cytotrophoblast cells initiate migration of extra villous trophoblast to decidua of uterus and invade partially myometrium inducing remodeling of spiral arteries [16]. 2-stage theory has been hypothesized recently to understand this pathology [17,21]. The first stage is abnormal events during embryogenesis of trophoblast which contribute to fetoplacental oxidative distress and abnormal release of antiangiogenetic factors in maternal circulation and subsequent multisystem endothelial dysfunction [17,22]. Abnormal remodeling of spiral arteries and early immunologically mediated events are considered major causes of those events [18]. Moreover, trophoblast fails to adequately invade uterine wall and spiral arteries so subsequently vascular resistance in this area could not be decreased to allow adequate placental transfusion [23]. Also, the failure of obliteration of tunica media of myometrium vessels contributes to inability of placenta to accommodate enough

blood supply due to lack of thinning of those vessels [17]. This leads to excessive secretion of sFlt-1 (soluble-fms like tyrosine kinase-1) and soluble endoglin [24]. sFlt-1 binds in the blood to both the vascular endothelial growth factor (VEGF) and the placental growth factor (PLGF). Both sFlt-1 and low VEGF/PLGF play a major role in the development of systematic hypertension [21,24]. Later on, maternal syndrome may occur in terms of vascular endothelial dysfunction, intravascular hypercoagulability, and vasospasm leading to multiple systems dysfunctions [21]. Abnormal vascular changes in placenta are confirmed by histopathological examination of postpartum specimens of placenta which showed vascular infarcts and sclerosis of arterioles [17]. Immunological maternal reaction towards fetal and paternal derived Antigens may also contribute, which is considered a certain type of immunological intolerance [25]. Immunological theory is supported by high serum level of cell-free fetal DNA. This theory has been also postulated to understand pathogenesis of hyperemesis gravidarum [26,27]. Recently genetic factors were found to contribute to preeclampsia; Angiotensinogen gene T235 and Leiden factor deficiency were found to be associated with disease [28]. Also, the higher incidence of preeclampsia was found in trisomy 13 pregnancy than pregnancy with normal karyotyping [29,30]. Interestingly, the gene for sFlt-1 which is known for contributing to preeclampsia is also encoded in chromosome 13q [31].

Low molecular weight Heparin (LMWH)

Recent studies have shown potential reduction in the incidence of preeclampsia and IUGR for high-risk mothers who take LMWH during pregnancy [32]. Since preeclampsia has been hypothesized to be linked to thrombotic and vasoconstrictive events in placenta, It is proposed that LMWH has beneficial effects on certain patients [33]. Examination of the placenta of patients with preeclampsia or restriction of fetal growth after delivery revealed ischemic thrombotic lesions (33). Another research investigated the impact of LMWH on both in vitro and in vivo endothelial functions and reported that pregnant women at high risk of preeclampsia had major cardiovascular abnormalities relative to low-risk women at 24 weeks of gestation, validated by in vivo and in vitro tests [34]. They also reported with proof that LMWH affects the endothelial function and serum level of angiogenic proteins in pregnant women at elevated risk of preeclampsia. In parallel, LMWH also influenced the in vitro endothelial cell function, with significant pro-angiogenic reactions [34]. Researchers also investigate the effects of low molecular weight heparins (LMWHs) on the invasiveness of extra villous trophoblast and its expression of heparin binding-EGF and cysteine-rich angiogenic inducer 61 (Cyr61) related to the trophoblast invasion process [35], They found that LMWHs are capable of promoting trophoblast development and invasion because they are capable of stimulating the invasive extra villous trophoblast properties that provide a possible biological rationale for the clinical use of LMWH for placental-mediated complications of pregnancy not related to thrombophilia [35]. In addition, low-

molecular heparin (LMWH) may control invasiveness and placental development of matrix metalloproteinase's (MMPs) and other tissue inhibitors in vitro trophoblast (36). Heparin greatly improved pro-MMPs and active forms, as well as the invasiveness of extra villous trophoblast and choriocarcinoma cells [37]. Heparin also blocked apoptosis caused by other agents including Staurosporin, kinase inhibitor of broad range, and Thrombin. In addition, Heparin decreased caspase-3 function, a hallmark of apoptosis in first trimester villous and extra villous trophoblast cell lines in human studies [37].

Another systematic study and meta-analysis of randomized controlled trials (RCTs) was undertaken, pregnant women were randomized to receive LMWH or non-fractionated heparin in addition to low-dose aspirin (LDA) and were contrasted with those receiving low-dose aspirin alone [38]. They concluded that the introduction of LMWH to low-dose aspirin in high-risk patients could decrease the prevalence of preeclampsia and small for gestational-age disease. Though they noted that these findings are focused on minimal data and require additional studies to validate this correlation [38]. The advantages of applying LMWH to Low dose Aspirin may be restricted to early onset of Preeclampsia, which is primarily attributed to an abnormal placentation [39]. Nearly all studies examined the relationship between preeclampsia and small-for-gestational-age infants as secondary outcomes so that evidence contained in such studies should be carefully considered [33].

In the other side, there is insufficient data based upon LMWH as a solo preventive tool. pregnant women with thrombophilia at an increased risk of venous thromboembolism or with previous placenta-mediated pregnancy complication, were registered in an open label randomized trial conducted in 36 tertiary care centers in five countries. Eligible participants obtained either Dalteparin Antepartum prophylactic dose once daily up to 20 weeks gestation, and twice daily up to at least 37 weeks gestation afterwards, or to no Dalteparin Antepartum (control group) [40]. Results revealed that Antepartum prophylactic Dalteparin does not prevent venous thromboembolism, pregnancy loss or placenta-mediated complications in women with thrombophilia, and is correlated with an increased risk of mild bleeding [40].

The published evidence supporting LMWH is characterized by a deep heterogeneity and inconsistency with regard to selection criteria and treatment regimens [38]. Obstetric or medical history in such preventive trials is usually the only entry criteria [38]. Most of the studies carried out have several limitations [41]. Several are underpowered or have a rather sluggish recruiting rate; some have taken patients with heterogeneous medical records into account [41]. Although for Anti-phospholipids syndrome, Antepartum treatment with a combination of LMWH with low-dose ASA is endorsed by the American College of Chest Physicians and The American College of Obstetricians and Gynecologists [41].

Calcium supplements and vitamin D

WHO recommends calcium as the first dietary supplement to avoid preeclampsia in low-calcium diet communities [42]. Other professional societies state recommend that as well [43,44]. This strong recommendation is focused on moderate-quality data from meta-analysis of randomized clinical trials, which show that calcium supplementation prevents around half of cases of preeclampsia [45]. The guideline recommends routine administration of 1,5–2,0 g of supplementary calcium beginning at 20 wk gestation, and points out that separating calcium and iron supplementation by many hours is preferred in order to reduce the potential adverse effects of calcium on iron absorption [45].

The recommended calcium dosage recommended by the WHO, 1.5–2.0 g elemental calcium / day, is higher than both the current average requirement in the US and the recommended dietary dose for pregnant women (800 and 1000 mg, respectively) [45,46]. Dose of calcium determines the amount absorbed; as the dose's calcium concentration rises, the calcium 's fractional absorption reduces. Doses of 500 mg are indicated per administration [46]. So, the WHO recommendations will involve 3 pill-taking events daily which may be inconvenient for patients [45]. Several calcium formulations are currently available in a variety of doses [47]. Compared with calcium gluconate, both calcium citrate and calcium carbonate are extremely bioavailable sources [47].

Iron and folic acid supplementation as part of routine antenatal treatment has been advised, for example to improve maternal and neonatal outcomes, to improve pregnancy anemia and to prevent neural tube defects especially in high-risk patients [14]. Calcium has been documented to interfere with iron absorption in vitro and short-term studies, but the clinical consequences of the interaction are limited over longer periods, since adaptive responses in iron regulatory mechanisms may resolve short-term interactions [45]. If held up to 500 mg of elemental calcium / dose, the WHO recommended 3 daily doses. Separation of calcium and iron supplements will involve at least four different doses a day; this may lead to growing complexity of medicine intake with a possible negative effect on patient adherence [45]. Trials do nnot support the value of removing calcium from iron, because it is also speculative. In addition, the impact of the complexity of dosing would likely outweigh it to improve patient adherence. Therefore, It is recommended that women will take iron with one of the calcium doses, either in the morning or in the evening [42]. The WHO recommends that calcium supplementation be initiated at a gestational age of 20 weeks, based on the reference timing used in the meta-analyses on which the guidelines are based [45]. Although, further research is warranted to clarify research issues related to minimum effective dose, timing of initiation, mode of administration of prenatal calcium supplements and possible side effects [42].

Arginine

Pathogenesis of preeclampsia could be explained by endothelial dysfunction, platelet aggregation, and systemic vasoconstriction [17,23]. Nitric oxide is considered to be a potent inhibitor of platelet aggregation and vasoconstriction that participates in hemodynamic changes in preeclampsia patients [17]. Biochemical reactions involving L-Arginine as a producer of that substance produce nitric oxide. In preeclampsia patients, there is an increase in the synthesis of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS), and as a result, NO synthesis is reduced [48]. So researchers postulate that L- Arginine could antagonize ADMA to produce more Nitric oxide which enhances its positive effects on circulation [49].

A randomized trial, examined the effect of low dose L Arginine on fetoplacental circulation and subsequently on fetal growth in preeclampsia patients vs control patients, shows improved fetal gain and placental circulation in terms of Doppler indices of the middle cerebral umbilical arteries [50]. Another systematic review of randomized trials assessing its effectiveness in both prevention of preeclampsia in hypertensive pregnant patients besides preventing complication of preeclampsia, this study shows that it may be effective for both purposes [51]. Another randomized trial showed the effectiveness of L Arginine in preventing preeclampsia in high risk patients as well as decreasing IUGR and Preterm labor ratios compared to placebo controlled group [52]. Exciting results were found when a study assessed its effectiveness in preventing preeclampsia and its complications in high risk teenage pregnancies, the results have showed its positive physiological effects on both maternal and fetal circulations [53].

Folic acid

Folic acid is recommended by ACOG and other professional societies during preconception care and prenatal care to prevent neonatal neural tube defects [54]. Recent studies showed a debate around the possible role of folic acid in the prevention of preeclampsia in high-risk patients [55–57]. A large study using the UK regional database showed that supplementation with folic acid significantly reduces the risk of Small for Gestational Age at birth but only when started before pregnancy, regardless of other risk factors [57]. Although further research is needed to define the dose and onset of starting therapy [57]. Another analysis of 215 pregnant women who were enrolled in a pilot study showed that the concentration of folic acid in maternal blood was significantly higher following folic acid supplementation (24.6ng/mL vs.11.8ng/mL). Besides, the rates of both preeclampsia (odds ratio [OR] = 0.27, 95% confidence interval [CI]=0.09–0.76) and small for gestational age (SGA: 9.2% vs. 20.0%; OR= 0.42, 95% CI=0.18–0.99) were lower in the folic acid supplementation group than those in the control group [58]. Another longitudinal study of women who obtained routine oral folic acid supplementation (15mg) as a prophylactic therapy for persistent preeclampsia after the first trimester with those who did not obtain it [59]. Tests found that women with previous preeclampsia who obtained routine supplementation of folic acid have a substantially decreased occurrence of overall preeclampsia, severe preeclampsia and early preeclampsia [59]. Another broad cohort study that involved a total of 10,041 pregnant women without recurrent hypertension or gestational hypertension was performed in 2010–2012 at the Gansu Provincial Maternity & Child Care Hospital in Lanzhou, China. Researchers observed that consumers with folic acid supplementation have lower preeclampsia incidence relative to non-user groups (OR= 0.61, 95 % CI= 0.43–0.87). The reduced risk associated with Folic acid supplement was similar for mild or severe preeclampsia and early or late preeclampsia, although statistically significant associations were only observed for mild preeclampsia (OR = 0.50, 95 % CI = 0.30–0.81) and late onset (OR = 0.60, 95%CI = 0.42–0.86). The decreased risk correlated with dietary consumption of folate during pregnancy was shown only with severe preeclampsia (OR = 0.52, 95 % CI = 0.31–0.87) [60]. Most studies agreed that further studies are needed to confirm this relationship and explain possible pathogenesis and mechanism of this preventive effect [59–62].

Statins

As preeclampsia bears pathogenic similarities with adult cardiovascular disorders such as endothelial dysfunction and inflammation that are central to both atherosclerosis and preeclampsia initiation and progression [63]. Moreover, they share common basis of risk factors like hypertension, diabetes, and obesity [64]. In preclinical animal trials, evidence supports the potential involvement of Statins in reversing the endothelial and cardiovascular impairment triggered by preeclampsia and reverses the angiogenesis imbalance induced by preeclampsia, contributing to a decrease in the risk of pregnancy loss and fetal growth restriction [65,66]. During the first phase of the clinical trial, Statins did not show any notable side effects in patients at high risk of developing preeclampsia with potential beneficial effects in terms of preeclampsia incidence reduction, premature labor, admission to neonatal care and improvement of the angiogenesis profile [63].

A review of 4 preterm preeclampsia patients who presented at <30 weeks of gestation and obtained Pravastatin every day. Pravastatin tended to regulate blood pressure, proteinuria and amounts of uric acid in the serum. In comparison, amounts of serum soluble forms such as tyrosine kinase -1 (sFlt-1) drop. They also collected the placenta at delivery and found that sFlt-1 secretion decreased by Pravastatin. These results show that Pravastatin reduced sFlt-1 and the production of soluble endoglin and decreased endothelial dysfunction in primary human tissues(67). Another study examined 21 pregnant women with an Antiphospholipid syndrome who experienced preeclampsia and/or restriction of intrauterine growth (IUGR) during low-dose aspirin (LDA) and low molecular weight heparin care. Low dose Aspirin and LMWH were given to the control group of 10 patients. 11 patients received Pravastatin (20mg/d), in addition to LDA+LMWH. Hemodynamic of uteroplacental plasma, development of preeclampsia (hypertension

and proteinuria), and fetal / neonatal outcomes is evaluated. Patients receiving Pravastatin and LDA+LMWH showed increased placental blood flow and improved preeclampsia features [68].

Other lines of prevention

Interventions in diet and lifestyles have the potential to reduce the risk of preeclampsia. While, the impact of additional therapeutic treatments on preeclampsia is uncertain in women with gestational diabetes mellitus [69]. Additionally, there was a decreased chance of preeclampsia with higher rates of physical activity before and during pregnancy [70]. Recombinant endothelial growth factor injection was found to be beneficial in preventing restriction of fetal development in animal models [71]. Metformin reduced sFlt-1 and sENG secretion from primary human tissues by potentially inhibiting the chain of transportation of mitochondrial electrons. In preterm preeclampsia placenta, the activity of the mitochondrial electron transport chain increased. Metformin decreased endothelial damage, increased omental vasodilatation and angiogenesis [72]. Methylprednisolone was not effective in maintaining platelet counts above 100,000 in preeclampsia patients with platelet count around 150,000 [73].

Summary

Hypertensive disorders of pregnancy are among the most common medical problems during pregnancy and they are associated with significant mortality and morbidity rate. Low dose Aspirin is already approved by many societies like ACOG and WHO to be used as prophylaxis for preeclampsia in high-risk patients. Recent studies showed a possible reduction in the incidence of preeclampsia and intrauterine growth restriction for high-risk mothers who taking LMWH during pregnancy. Although, the published evidence supporting LMWH is characterized by profound heterogeneity and inconsistency in terms of selection criteria and treatment regimens. Antepartum treatment with a combination of LMWH with low-dose ASA is endorsed by the American College of Chest Physicians and The American College of Obstetricians and Gynecologists for treatment of Antiphospholipid syndrome during pregnancy. WHO recommends Calcium as the first nutritional supplementation to prevent preeclampsia among population with low calcium in the diet? Folic acid, statins, and Arginine showed a possible reduction in incidence of preeclampsia in high-risk patients but there is a need for further studies to confirm that. Dietary and lifestyle interventions have the potential to reduce the risk of preeclampsia. Both Metformin and vascular endothelial growth factors has promising preventive role that has been found through recent studies.

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Conflict of Interest

Authors declare no conflict of interest.

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