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Review Article

Preeclampsia: A review of the pathogenesis and possible management strategies based on its pathophysiological derangements

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ABSTRACT

This review is divided into three parts. The first part briefly describes the pathogenesis of preeclampsia. This is followed by reviewing previously reported management strategies of the disease based on its pathophysiological derangements. Finally, the author defines the safe and acceptable methods/medications that may be used to 'prevent' preeclampsia (in high risk patients) and those that may be used to 'treat' preeclampsia (meant to prolong the pregnancy in patients with established preeclampsia). The review concludes that multi-center trials are required to include multiple drugs in the same management protocol.

Introduction

Preeclampsia is a disorder of pregnancy characterized by hypertension and proteinuria of ≥300 mg/day. It is a serious disorder which may lead to maternal and fetal morbidity and mortality. The aim of this paper is to review the pathogenesis of preeclampsia and possible management strategies based on these pathophysiological derangements.

Methods

We carried out a literature review using electronic databases of PubMed [MEDLINE], and ScienceDirect; accessing published work on the pathogenesis of preeclampsia and management from 2000 to 2017. We aimed: to highlight possible management strategies based on the pathophysiological derangements of preeclampsia. We used the following search terms: "preeclampsia", "pathogenesis", and "management".

Results

Pathogenesis of preeclampsia

A) Placental ischemia and the increased levels of soluble fms-like tyrosine kinase 1(sFlt-1) and soluble endoglin (sEng):

In normal pregnancy, the cytotrophoblasts of the placenta invade the uterine wall and replace the highly resistant uterine spiral arteries and arterioles with a low-resistance vascular system. This remodeling is defective in preeclampsia (probably secondary to altered immunological response at the fetal–maternal interphase) leading to placental ischemia [1]. This leads to excessive production of sFlt-1 [2]. sFlt-1 binds in the blood to both the vascular endothelial growth factor (VEGF) and the placental growth factor (PLGF). The status of high sFlt-1 and low VEGF/PLGF contributes to the development of hypertension [2,3].

Placental ischemia is also known to induce placental secretion of endoglin; increasing the levels of sEng in the maternal blood. sEng participates in the transforming growth factor Beta pathway. Once again, the status of high sEng contributes to the development of hypertension and proteinuria [4].

B) The generalized multi-system vasoconstrictive state, oxidative stress, micro-emboli, and endothelial cell dysfunction:

Endothelial nitric oxide synthase (e-NOS) induces the synthesis of nitric oxide (NO) which acts to vasodilate the arteriolar bed. In preeclampsia, there is deficiency of e-NOS leading to vasoconstriction of the placental bed, the renal vasculature and the vascular bed of other organs [5].

Placental ischemia in preeclampsia is also associated with diminished expression of the anti-oxidant heme oxygenase-2 (HO-2) [6]; and this contributes to the increased oxidative stress of ischemia and the formation of micro-emboli [7].

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The multi-organ ischemia induces the production of hypoxia-inducible factor 1-alpha (HIF-1α); and this contributes to the abnormal placental function as well as the induction of elevated levels of sFlt-1 [8].

Preeclampsia is also associated with an increased sensitivity to the vasoconstrictive actions of angiotensin II; and this leads to renal dysfunction [9]. Endothelin 1 released from the placenta is another potent vasoconstrictor which is increased in preeclampsia [10]. Another reason for the vasoconstrictive state in preeclampsia is the imbalance between the vasoconstrictive thromboxane A2 and the vasodilator prostacyclin [11,12].

A controversial theory of pathogenesis is the genetic predisposition to preeclampsia secondary to apolipoprotein E (Apo E) polymorphism [13,14]. Certain Apo E alleles are associated with dyslipidemia which may contribute to endothelial cell dysfunction [14]. Furthermore, the Apo E-knockout homozygous mice model is a well-known animal model of preeclampsia featuring hypertension, proteinuria and increased expression of sFlt-1 [15].

C) The systemic inflammatory response:

Toll-like receptor 4 (TLR4 receptors) are most abundant in the placenta, leukocytes, and renal podocytes. These receptors are responsible for the induction of inflammatory cytokines. Preeclampsia is associated with over-expression of placental and renal TLR4 leading to an increase in inflammatory cytokines and placental/renal dysfunction [15,16]. Furthermore, very high levels of TLR4 receptors are associated with early onset preeclampsia and HELP (Hemolysis, Elevated Liver enzyme, and low Platelets) syndrome of preeclampsia [17].

In cytomegalovirus (CMV)-seropositive mothers, the monocyte is the major cell type harboring the virus in a latent state. These mothers are at high risk of CMV reactivation during pregnancy and this contributes to the over-expression of TLR4 [17].

The risk of eclampsia is higher in mothers with low level of Vitamin D. Vitamin D deficiency is known to induce pro-inflammatory cytokines and the over expression of TLR4 receptors; participating in the pathogenesis of preeclampsia [18,19].

Preeclampsia is not only associated with an increase in pro-inflammatory cytokines, but is also associated with a decrease in anti-inflammatory cytokines [20,21]. The most important pro-inflammatory cytokines are interferon-γ (IFN-γ), tumor necrosis factor—α (TNF-α), and the pro-inflammatory interleukins (IL): IL-1, -2, -6, -8, -15, -16, and -18 [22]. In fact, preeclamptic patients may have a genetic polymorphism of TNF-α and IL-1 resulting in increased levels of these cytokines [23]. Furthermore, acute phase reactants (such as the C-reactive protein) are higher in preeclampsia compared to normal pregnancy [20]. Finally, preeclampsia is associated with higher levels of serum heat shock protein 70 (Hsp 70) and the degree of elevation of Hsp 70 correlates with the degree of elevation of circulating pro-inflammatory cytokines in preeclampsia [24]. The end result is a state of systemic inflammatory response reaction leading to edema and extravasation; compounding the insults to the placental, renal, and other organ vascular beds.

D) Structural changes of the glycocalyx and hyaluronic acid leading to feto-maternal interface dysfunction:

Glycocalyx is expressed in the feto-maternal interface and mediate interactions between fetal and maternal cells. Placentas of women with preeclampsia show alterations of glycocalyx composition coating the endothelium and is thought to play an important role in the pathogenesis of intra-uterine growth retardation [25]. The reason for these alterations in composition of glycocalyx is unknown but they may be related to the systemic inflammatory response of preeclampsia [26].

Hyaluronic acid (HA) is a main component of the extracellular matrix. Normally, high molecular weight HA is predominant. In preeclampsia, there is predominance of low molecular weight HA. This alteration is also thought to participate in placental endothelial cell dysfunction of preeclampsia [26].

Syndecan-1 (Sdc1, also known as CD138) is a component of glycocalyx [27]. In preeclampsia, both the soluble and placental sdc1 are significantly lower when compared to controls [27].

Heparan sulfate is also a component of the glycocalyx; and it is interesting to note that the 3-0 sulfating enzyme of heparan sulfate is decreased in the placenta of preeclamptic women [28].

Management of preeclampsia in the current practice

Although preeclampsia is defined as hypertension with proteinuria, clinicians are aware that preeclampsia is a systemic disease. The blood flow to every maternal organ is reduced with vasoconstriction and microthrombi formation ending in multi-organ dysfunction. Simultaneously, fetal complications and growth retardation occur secondary to placental hypo-perfusion. The current management strategies of preeclampsia is based on the diagnosis of the disease, the assessment of its severity, anti-hypertensive therapy, and finally deciding on the timing of delivery. Intrapartum treatment includes seizure prophylaxis (usually by magnesium sulfate), control of blood pressure (usually by hydralazine) and appropriate intravenous fluid management [29,30]. In other words, preeclampsia has defeated clinicians; forcing them to deliver these mothers to abort further fetal and maternal complications.

New management strategies in the current review are directed to reverse or arrest the pathological processes of preeclampsia or to prevent its occurrence in high risk patients; and hence defeating the disease.

Management strategies based on the pathological derangements in preeclampsia

Patients at high risk for preeclampsia should attend high-risk antenatal clinics and are usually given daily aspirin [31]. However, there is no clear evidence that these measures are effective in the prevention of preeclampsia. Dietary measures (such as chocolate and fish oil) have also been tired and proved ineffective in the prevention of the disease [32,33].

A. Management directed against the oxidative stress

Oxidative factors are involved in the pathogenesis of preeclampsia and the thrombocytopenia [34]. In a double-blind clinical trial, silymarin (a drug which has an antioxidant effect) did not have a positive effect in improving the abnormal parameters in patients with preeclampsia [34].

B. Management directed against the formation of micro-emboli

Several studies studied the effect of adding low-molecular-weight heparins to aspirin on the prevention of preeclampsia and demonstrated no positive effect [31,35]. However, a recent systematic review and meta-analysis found a modest beneficial effect and recommended further studies on the topic [36].

In patients with severe preeclampsia, antithrombin infusions may have a potential maternal benefit, but a recent trial did not support its use in patients with early/severe preeclampsia [37].

C. Management directed against the vasoconstrictive state in preeclampsia

Vasodilators have been tried clinically both to prolong pregnancy in women with preeclampsia and to prevent preeclampsia in patients with high risk factors for preeclampsia. Trapani et al. [38] conducted a randomized controlled trial to evaluate therapy with the vasodilator sildenafil citrate in preeclamptic women. Compared to controls (receiving a placebo), therapy with sildenafil was associated with pregnancy prolongation of 4 days.

The vasoconstrictive state of preeclampsia is associated with deficiency of endothelial nitric oxide with is a vasodilator to the arteriolar system [39]. Hence, the use of nitric oxide donors (such as glycerol trinitrate and isosorbid mononitrate) or nitric oxide precursors (such as L-arginine) is thought to be an attractive option for preventing preeclampsia in high risk patients. The Cochrane database systematic review of 2007 [39] could not find good quality trials to draw reliable conclusions on the effectiveness of nitric oxide donors/precursors to prevent preeclampsia. However, more recent studies clearly demonstrated that both nitric oxide donors (isosorbid mononitrate) and precursors (L-arginine) are effective in the prevention of preeclampsia [40,41]. Not only there was significantly lower incidence of preeclampsia in the treatment groups, but there was also a significant reduction in intrauterine growth restriction and neonatal admissions to the intensive care unit [40,41].

D. Management directed against the excessive production of sFlt-1 and sEng:

As mentioned earlier in the pathogenesis, the increased levels of sFlt-1 and sEng are the most prominent feature of preeclampsia. sFlt-1 is normally produced in the syncytiotrophoblast extracellular vesicles and is then released into the maternal blood. This process is greatly accelerated in preeclampsia [42]. Hence, the reduction of sFlt-1/sEng is an attractive method for the prevention and treatment of preeclampsia. This area has been extensively studied in the literature. In experimental preeclampsia mice models, the drug GYY4137 was effective in decreasing circulating sFlt-1 and sEng [43].

The author of the current review has classified methods used clinically to reduce the level of sFlt-1/sEng into four categories: Induction of the heme-oxygenase (HO) pathway, inhibition of syncytiotrophoblast extracellular vesicle shedding and secretion of sFlt-1/sEng, inhibition of hypoxic inducible factor 1α (HIF-1α) and removal of circulating sFlt-1 by dextran sulfate apheresis.

The HO pathway is known to inhibit sFlt-1/sEng [44]. Statins (drugs commonly used to lower cholesterol levels) induce the HO and hence suppress sFlt-1 and sEng [44]. In a recent review of the literature, Marrs and Costantine [45] stated that there is enough encouraging data from preclinical and pilot clinical studies to recommend statins (such as pravastatin) in clinical practice of preeclampsia and recommended the conduction of randomized–controlled trials.

sFlt-1 is secreted into the maternal circulation from shedding of the syncytiotrophoblast extracellular vesicles. Recombinant human gelsolin supplementation has been shown to inhibit this shedding process; and hence reducing the levels of sFlt-1 [42]. Another drug (esomeprazole) was found to be a potent inhibitor of the secretion of both sFlt-1 and sEng from the placenta. Cluver et al. [46] announced the start of the PIE trial which is a double blind, randomized placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset preeclampsia.

sFlt-1 is excessively produced from the placenta secondary to hypoxia. There is sufficient evidence that HIF-1α (which is induced by hypoxia) is a main factor leading to the excessive production of sFlt-1 [47]. Hence, small molecule inhibitors of HIF-1α are known to reduce sFlt-1. However, the safety of these small molecules in pregnancy is unknown [47]. Metformin is safe in pregnancy and is a potent inhibitor of HIF-1α and has excellent potential to prevent and treat preeclampsia [47].

Finally, removal of circulating sFlt-1 is possible by dextran sulfate apheresis. Thadhani et al. [48] conducted an open pilot study to evaluate the efficacy of dextran sulfate apheresis in 11 women with early-onset preeclampsia. Compared to controls, treated women had reduced circulating sFlT-1 and reduced proteinuria. Furthermore, treated women had prolongation of their pregnancies by an average of 15 days (range 11–21 days) compared to controls.

E. Management directed to replace the deficiency of circulating VEGF and PLGF.

As mentioned in the pathogenesis, the elevated sFlt-1 binds in the circulation to both VEGF and LPGF resulting in endothelial dysfunction of the placenta and the systemic maternal vasculature. Several experimental studies in animal models of preeclampsia have shown the efficacy of intravenous VEGF and PLGF in reducing the elevated blood pressure and proteinuria [49,50]. Clinically, the use of VEGF causes edema because of its high affinity to VEGF-receptor 2 [51]. However, PLGF is specific for sFlt-1 and does not have adverse effects on the mother or fetus [51]. Hence recombinant human PLGF has a strong therapeutic potential in preeclampsia [51].

F. Management directed against the increased systemic inflammatory response in preeclampsia.

As mentioned earlier, the increased systemic inflammatory response plays a major role in the pathogenesis of preeclampsia. This inflammatory response is manifested by increased levels of pro-inflammatory cytokines (such as TNF-α), over expression of TLR4 receptors, elevated heat shock proteins, and the structural changes of placental glycocalyx (these structural changes are thought to be induced by the inflammatory response).

TNF-α antagonists are relatively safe in pregnancy and have potential to treat severe cases of preeclampsia [52]. Aspirin prevents TNF-α induced endothelial dysfunction [53]. Hydroxy-chloroquine (an anti-malarial drug) not only reduces the production of TNF-α, but it also reduces the levels of endothelin-1 in preeclampsia experimentally [54]. Hence, the use of hydroxychloroquine as an adjuvant therapy in preeclampsia requires an investigation in the clinical setting. Experimentally, the administration of apolipoprotein (a constituent of high density lipids and also acts as an anti-inflammatory agent) protects against the effects of TNF-α in human in-vitro models of trophoblast invasion in preeclampsia [55].

Another way to reduce the systemic inflammatory response of preeclampsia is to suppress or alter the TLR-4 receptor overexpression. Curcumin is extracted from plants and is commonly used as a herbal supplement and a food coloring additive. Chemically, curcumin is a phenol [56]. Curcumin is known to inhibit the TLR-4 signaling pathway [57]. In a rat preeclampsia model, Gong et al. showed the efficacy of curcumin in reducing placental TLR4 expression, reducing the blood pressure and normalizing the urinary protein levels in treated animals compared to the controls [57].

Another inhibitor of TLR4 is vitamin D [19]. Hence, vitamin D supplements are associated with significant reduction of proinflammatory cytokines [22,58]. High-dose supplementation (up to 35,000 IU/week) is relatively safe in pregnancy [59]. The trial of Mirzakhani et al. showed several important findings on the topic [60]. High dose vitamin D supplementation (4400 IU/day) initiated in weeks 10–18 of pregnancy did not reduce the incidence of

preeclampsia in the intention-to-treat paradigm. However, maternal vitamin D levels ≥30 ng/mL at trial entry and in late pregnancy were associated with a lower risk of preeclampsia [60].

Discussion

The current review highlights the various management strategies in preeclampsia based in its pathological derangements; and these strategies are summarized in Table 1.

Despite all advances, the review demonstrates that preeclampsia is still difficult to 'defeat'. The clinician should differentiate between methods used to 'prevent' preeclampsia (in high risk patients) and methods used to 'treat' preeclampsia (meant to prolong the pregnancy in patients with preeclampsia). Table 2 shows these modalities and demonstrates that some of the medications are suitable for both prevention and treatment.

A) Preventive methods:

A classic example to demonstrate prevention is a patient with a history of preeclampsia and IUCD in place. The patient decides to remove the IUCD to conceive. All previous studies attempted to study the effect of a single method or drug to prevent the disease in such high risk patients and the results have been modest at best. The author of the current review recommends a protocol that combines multiple safe preventive methods in a multi-center trial.

It is well known that the risk of preeclampsia is higher in women with pre-existing obesity [61], dyslipidemia (particularly hypertriglyceridemia and hypercholesterolemia) [62], poorly controlled diabetes mellitus [63], obstructive sleep apnea (chronic hypoxemia) [64]. Hence, weight reduction, correction of the abnormal lipid profile, strict control of blood sugar and surgical treatment of sleep apnea should be implemented in high risk patients.

Adding a low molecular weight heparin to aspirin showed a modest beneficial preventive effect [36]; but it may prove more effective if combined with other preventive methods.

Recent studies [40,41] showed that L-arginine or isosorbid mononitrate (both enhance the production endothelial nitric oxide) will not only lower the incidence of preeclampsia, but will also improve intrauterine growth and fetal outcome. Hence, enhancement of nitric oxide production should be part of the preventive protocol.

Even in patients with no pre-existing dyslipidemia, statins should be included in the preventive protocol because of their known positive effects in inducing the HO pathway and in reducing the risk of preeclampsia [45].

Furthermore, metformin (as an inhibitor of HIF-1α) and curcumin (as an anti TLR4 receptor) proved effective and are worth including in preventive protocols [47,57].

Finally, the author believes that vitamin D should be included in the multi-agent preventive protocol as stressed by Mirzakhani et al. [60]. Vitamin D levels should be ≥30 ng/ml prior to and throughout pregnancy [60]. If the levels of vitamin D are low after conception, vitamin D replacement is not effective in preventing preeclampsia [60].

B) Treatment of established preeclampsia:

Treatment of preeclampsia is more difficult than its prevention. Our literature review showed that the pathology of an established preeclampsia cannot be completely reversed or arrested. Hence, current 'treatment' methods are meant to slow down the pathological process in order to prolong pregnancy. Besides the standard treatment methods of treating hypertension, aspirin and control of blood sugar and renal function; a multi-center treatment protocol is needed to include several new treatment modalities in the same protocol.

From the current review, the following medications have proven safe and effective in prolonging the pregnancy: Sildenafil as a vasodilator [32], esomeprazole as an inhibitor of vesicle shedding [46], metformin as an inhibitor of HIF-1α [47], hydroxy-chloroquine as an antagonist of TNF-α [54], and curcumin as an anti-TLR4 receptors [57], It should be noted that all these medications have been tried individually in preeclampsia and showed their ability to prolong the pregnancy for 2–4 days only (enough for the steroid therapy for fetal lung maturity). However, the effectiveness of using multiple medications is unknown and may prove more effective in pregnancy prolongation.

More invasive treatment methods have also proven effective in pregnancy prolongation such as recombinant placental growth factor injections [51] and dextran sulfate apheresis to remove circulating sFlt-1 [48]. These more invasive methods may be indicated in early-onset/severe cases. The most impressive period of pregnancy prolongation in preeclampsia was a mean of 15 days with apheresis [48].

Table 1
Management strategies in preeclampsia based on its pathological derangements.

Pathology	Management strategies
1) Oxidative stress	Antioxidants (such as silymarin)
2) Formation of micro-emboli in the small vascular bed	Aspirin, low molecular weight heparin, antithrombin infusion
3) Vasoconstriction	Vasodilators (sildenafil citrate), Nitric oxide donors (glycerol trinitrate, isosorbid mononitrate), nitric oxide precursors (L-arginine)
4) Excessive production of placental sFlt-1 and endoglin	A. Induction of the heme-oxygenase pathway (statins) B. Inhibition of syncytiotrophoblast vesicle shedding (gelsolin, esomeprazole) C. Inhibition of HIF-1α (metformin) D. Removal of circulating sFlt-1 (dextran sulfate apheresis)
5) Deficiency of circulating VEGF/PLGF	Replacing PLGF or VGEF; but the latter has side effects
6) Systemic inflammatory response (excessive TNF-α, TLR4 receptors)	A) Anti-TNF-α: TNF-α antagonists, aspirin hydroxy-chloroquine, apolipoprotein. B) Anti-TLR4 receptors: Curcumin, Vitamin D

sFlt-1 = Soluble fms-like tyrosine kinase 1; HIF1α = hypoxic inducible factor-1α; VGEF = Vascular endothelial growth factor; PLGF = Placental growth factor; TNF-α = Tumor necrosis factor-α; TLR4 = Toll-like receptor 4.

Table 2
Preventive and treatments methods in preeclampsia.

Preventive methods	Treatment methods
Weight loss/correct abnormal lipid profile/strict control of blood sugar in diabetics/treat any pre-existing sleep apnea	Strict control of blood sugar in diabetics, Hydralazine
Aspirin	Aspirin
Low molecular weight heparin	Low molecular weight heparin
L-arginine/Isosorbid mononitrate	Sildenafil
Statins	Esomeprazole
Metformin	Hydroxy-chloroquine
Curcumin	Curcumin
Vitamin D	Recombinant placental growth factor Dextran sulfate apheresis

Conflicts of interest

There is no conflict of interest.

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