Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 593–598

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

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

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ARTICLE INFO

Article history:
Accepted 21 July 2017

Keywords:
Preeclampsia
Pathogenesis
Management

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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http://dx.doi.org/10.1016/j.tjog.2017.08.004

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].