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PREECLAMPSIA DISORDER, PATHOGENESIS, PRESENTATION, AND MANAGEMENT

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Abstract:

Introduction:

Preeclampsia is considered a disorder of pregnancy defined as hypertension and proteinuria of more than 300 mg/day. It is considered a highly serious disorder which could potentially lead to maternal and fetal morbidity and mortality. The aim of this review article is to summarize the pathogenesis of preeclampsia and potential management plans according to these pathophysiological changes. Preeclampsia remains to elude doctors and researchers as an enigma or a "disease of theories". Recently, there has been advancement made in the last fifteen years that helped us understand the pathogenesis, which gives great hope to recognize and rational treatment. Though the pathogenesis of the disorder has not yet been fully understood, recent data suggest that there's imbalance in angiogenic factors responsible for the clinical symptoms of the disorder and could possibly explain why specific populations are at higher risk than the others.

Aim of work: *In this review, we will discuss preeclampsia disorder, pathogenesis, presentation, and management.*

Methodology: *We did a systematic search for preeclampsia disorder, pathogenesis, presentation, and management. using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.*

Conclusions: *Recently, there has been great advancement in the management of preeclampsia, if not transformed, our understanding of pathogenesis of preeclampsia to the extent that new management and predictive markers are in sight. But, research studies must be translated to the clinical world, which should be prioritized, particularly in terms of funding. Concern for hypertension disorders of pregnancy are gaining more attention as potential mothers delay their childbearing years which elevate their risks for these disorders. Prevention and management measures continue to be very limited. With the more epidemiologic data of the persistent vascular effects of preeclampsia after delivery, both patients and doctors need to be aware so that proper surveillance and treatment can commence.*

Key words: *preeclampsia disorder, pathogenesis, presentation, and management.*

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INTRODUCTION:

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METHODOLOGY:

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The terms used in the search were: preeclampsia disorder, pathogenesis, presentation, and management.

PATHOGENESIS:

The pathogenesis although not fully understood, is generally speaking believed to be started by placental ischemia then by placental release of antiangiogenic factors into the circulation. In pregnancy, invasion of uterine arteries changes cytotrophoblasts from an epithelial to an endothelial phenotype normally, a process called pseudovasculogenesis. [1] This process of remodeling aims at increasing the supply of oxygen and nutrients to the fetus. [2] So, the cytotrophobasts upregulate expression of molecules that are important to uterine invasion such as those from the vascular endothelial growth factor (VEGF) family. [3] But in preecplampsia the pseudovasculogenesis is considered incomplete, so it results in placental ischemia and the triggering of hypoxia inducible factors and other placenta-derived factors. Likewise, expression of the highly important VEGF family of molecules is downregulated, while its inhibitor is upregulated. [4]

Some of these placenta-derived factors have been known in the last decade. Several groups have showed that the soluble fms-like tyrosine kinase 1 (sFlt-1) is upregulated in placentae of preeclamptic women. [5] sFlt-1 is a circulating decoy receptor that binds to PlGF, preventing their interaction with cell surface receptors on endothelial cells and leading to endothelial dysfunction. [6]

EPIDEMIOLOGIC STUDIES:

The risk factors for preeclampsia have been very well studied. Altered angiogenic factors could explain the mechanism behind these risk factors. sFlt-1 levels were found to be two times higher in the maternal serum of nonpreeclamptic twin pregnancies than in singleton pregnancies, which correlated well with placental mass. [7] similarly, sFlt-1 was concluded to be significantly upregulated in molar pregnancies as compared with normal controls. [8] Other risk factors such as mulitparous women, [9] smoking, Black women, and diabetes have all shown altered angiogenic profiles. of noteworthy, trisomy 13 pregnancies, usually plagued by a disproportionate high incidence of preeclampsia, have showed higher sFlt-1 staining in their placentae and higher plasma levels in early pregnancy. [10]

ANGIOGENIC FACTORS AS BIOMARKERS:

One huge boon that has been thought to be resulted from the discovery of angiogenic factors is their usage as either predictive or diagnostic biomarkers of preeclampsia. Many studies have been conducted that highlighted the association of preeclampsia with an abnormal pattern of circulating maternal proangiogenic and antiangiogenic factors that has interrupted the proper angiogenic balance at various points of gestation [11] Using stored serum specimen derived from the landmark CPEP trial, Levine et al [12] found that the mean sEng levels of females with preterm and term preeclampsia were both markedly higher than in healthy control pregnancies. case-control studies have concluded higher levels of sFlt-1 and lower levels PlGF, and in some situation's higher levels of sFlt-1/PlGF ratios weeks after manifestation of the disease versus levels in normal pregnant controls. [13]

FETAL COMPLICATIONS:

More evidence has now been gleaned from the effect of preeclampsia on fetal complications. Bronchopulmonary dysplasia (BPD), is a well-recognized complication of prematurity. Due to an appropriate angiogenic state is necessary for normal pulmonary vascular development and airway branching, an antiangiogenic state like preeclampsia

could additionally predispose infants to BPD. In fact, infants who were born to women with preeclampsia and fetal growth restriction have a markedly higher odds ratio of having BPD. [14]

Likewise, the incidence of BPD in preterm infants born to preeclamptic females was markedly higher than in preterm infants born to normotensive women. [15] To show pathogenicity, sFlt-1-injected Sprague-Dawley rats at twenty days of gestation produced newborn pups with decreased alveolar number and pulmonary vessel density.53 This further led to right and left ventricular hypertrophy and increased apoptosis in endothelial and mesenchymal cells in the newborn lungs. [16] Preeclampsia could also predispose the offspring of affected women to cardiovascular disease in adulthood. kids who were born to a preeclamptic mother demonstrated an about thirty percent higher pulmonary arterial pressure as compared with children born to mothers without preeclampsia. [17] So, preeclampsia seems to leave a permanent defect in the systemic and pulmonary circulation of the offspring, which, could result in cardiovascular disease later in life.

THERAPEUTIC STRATEGIES:

Based on the information of angiogenic disturbance in preeclampsia, many techniques to either promote angiogenic factors or block antiangiogenic factors could be feasible. Studies on animals have demonstrated beneficial results of replenishing with VEGF or PlGF, which are naturally occurring ligands for sFlt-1. Administration of VEGF 121 has alleviated symptoms of preeclampsia and reversed many of genes are that up- or downregulated by sFlt-1 in a pregnant rat model of preeclampsia. [18] Similar findings were reported in another pregnant rat model of reduced uterine perfusion pressure (RUPP) in which blood pressure, glomerular filtrate rate, and endothelial function were all improved. [19] The coadministration of adenovirus and VEGF in an sFlt-1– induced model of preeclampsia can reduce free sFlt-1 in the plasma by more than 70% and rescue endothelial dysfunction. A recent ressearch using PlGF to rescue the RUPP mouse model of preeclampsia demonstrated that it abolished the derangements of decreased glomerular filtration rate and increased blood pressure, though there was no mention of proteinuria.58 Because PlGF demonstrates specific affinity to Flt-1 (VEGF receptor 1 [VEGFR-1]) opposite to VEGF, which binds to both Flt-1 (VEGFR-1) and Flk-1 (VEGFR-2) and could lead to unwanted adverse effects like edema, the authors conclude that PlGF is the preferred rescue agent. [20]

Another approach would be to use molecules that upregulate proangiogenic factors. As statins have been demonstrated to prevent the signs of preeclampsia in a mouse model by inducing PlGF expression, both its safety and effectiveness are currently being tested in humans. The Pravastatin for Prevention of Preeclampsia trial is being tested by the Eunice Kennedy Shriver National Institute of Child Health and Human Development to evaluate the pharmacokinetics and safety profile of statins in pregnancy (NCT01717586). The StAmP trial, a double-blind, randomized, placebocontrolled trial, is underway in the United Kingdom to establish whether pravastatin reduces antiangiogenic factors in preeclampsia.

In another new approach is to inhibit sFlt-1 upstream. Ouabain, which is a cardiac glycoside, was reported to be effective by inhibiting hypoxia-inducible factors (hypoxia inducible factor 1-alpha) protein expression in the placenta and was able to decrease the mean arterial pressure in the RUPP rat model of placental ischemia.62 There are likely more candidates that have to be discovered and tested for safety in human pregnancy. The idea of removing antiangiogenic factors has led to two pilot studies of extracorporeal removal. The first one utilized a negatively charged dextran sulfate cellulose column to adsorb sFlt-1 and was tested in a total of five women who experienced severe, early preeclampsia.

PREVENTION OF PREECLAMPSIA:

Many preventive methods such as calcium and antioxidants have been tested and studied in large, randomized designed trials; but, many of the trials have been largely disappointing.

Low-Salt Diet/Diuretic Use Though the concept of using a low-salt diet with or without diuretics is tempting due to the presence of hypertension and edema in preeclampsia, the evidence from the studies is against it. A large review found no convincing evidence that salt restriction helps to prevent preeclampsia, another randomized control trial of a low-salt diet (r 50 mmol sodium/d) vs normal diet also not showing a difference in diastolic blood pressure, admissions for hypertension, or obstetric results. In terms of diuretic use, a meta-analysis of nine randomized trials revealed that giving of diuretics, though lowered incidence of edema and hypertension, did not lower the incidence of preeclampsia. Thus, salt restriction and diuretic use are not suggested. Calcium Supplementation The idea behind calcium supplementation stemmed from epidemiologic data that revealed an inverse relationship between calcium intake and maternal blood pressure as well as preeclampsia. [21] This led to promising animal studies followed by ten

randomized human trials. The biggest one that exceeded one thousand healthy nulliparous females essentially showed that there was no significant difference in the incidence of preeclampsia in women who received calcium or placebo; only the subgroup of women with possible calcium deficiency appeared to benefit. One large randomized control trial that did show a reduction in hypertensive disorders in patients who received two g of elemental calcium versus placebo was conducted in countries with low calcium intake. So, it is highly important follow-up study the CPEP trial ensued in the United States.

CONCLUSIONS:

Recently, there has been great advancement in the management of preeclampsia, if not transformed, our understanding of pathogenesis of preeclampsia to the extent that new management and predictive markers are in sight. But, research studies must be translated to the clinical world, which should be prioritized, particularly in terms of funding. Concern for hypertension disorders of pregnancy are gaining more attention as potential mothers delay their childbearing years which elevate their risks for these disorders. Prevention and management measures continue to be very limited. With the more epidemiologic data of the persistent vascular effects of preeclampsia after delivery, both patients and doctors need to be aware so that proper surveillance and treatment can commence.

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