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Introduction

Preeclampsia is defined as being a pregnancy specific syndrome of elevated blood pressure (>140/90 mmHg) and proteinuria of >100 mg/dl by urine analysis or >300mg in a 24-hour urine collection, after 20 weeks of gestation.[1]

The disorder, almost 2000 years ago, was called eclampsia reflecting the description given by Celsus as pregnant women with seizures, that abated with delivery and thus, for 2000 years this disorder was considered a pregnancy-specific seizure disorder.[2] In the late 1800s, the association of initial proteinuria and later increased blood pressure with eclampsia was noted. Additionally, the fact that increased blood pressure and urinary protein antedated the seizures[2], the term preeclampsia was introduced.

Preeclampsia is one of the major causes of maternal and fetal morbidity and mortality[3] and accounts for the majority of referrals to obstetric day care units[4] and hospital admissions.[5] It has been reported that the greatest impact is seen in developing countries where it accounts for 20-80% of the strikingly increased maternal mortality.[6] However, even in developed countries the impact is heavy, primarily on the fetus, where perinatal mortality is increased 5-fold and indicated preterm deliveries for preeclampsia account for 15% of preterm births.[6] The incidence of preeclampsia is about 5-7% of all pregnancies.[1] Preeclampsia is more common in a primigravida; the risk reducing to >50% in the subsequent pregnancies.[7] The established risk factors for preeclampsia are obesity, black race, chronic hypertension, diabetes or insulin resistance, collagen vascular disease, thrombophilias, increased circulating testosterone, multiple gestations and previous preeclampsia.[8] Most researches have focused on maternal contribution to the disease however, little is known about the paternal contribution to this disease. A study conducted to assess the paternal role in particular, provided evidence of both paternal and maternal components of the predisposition to preeclampsia, supporting the theory that genetic contributions from both parents are important in the development of the disorder.[9]

The purpose of this review article is to discuss the means by which preeclampsia can be potentially predicted even before the disease can become clinically diagnosable. Prior knowledge about the preeclampsia and the application of appropriate prenatal care and management before the disease progresses to become life threatening can largely eliminate maternal mortality.[6]

Pathophysiology of Preeclampsia

Preeclampsia has long been a disease with an unknown etiology. Various studies have been conducted to decipher the factors involved and this has lead to the development of a few theories. From history, it comes that uterine distension and even fetus have been thought to be the probable contributors. Since it was found that preeclampsia can occur with abdominal ectopic pregnancies without increased uterine size and is more common in pregnancies without a fetus [hydatidiform mole][10], this eliminated these two possibilities. The placenta is necessary for preeclampsia but all pregnant women have placentas and only 5% become preeclamptic.[11]

The trend of thought changed when Page E.W. many years ago suggested that the important placental feature in preeclampsia was poor perfusion.[12] It was presumed that with the large placenta the normal vasculature of the placental site is inadequate to perfuse the very large organ and relative placental hypoperfusion is present.[13]

Preeclampsia now is thought to be a 2-stage disease.[8] Stage 1 is characterized by a reduction in perfusion. Stage 2 is the maternal syndrome. A predominant pathophysiological feature is reduced perfusion of virtually all organs that is due to vasoconstriction, micro thrombi formation and reduced circulating plasma volume.[3] The endovascular trophoblastic invasion that occurs in normal pregnancies is absent in the placenta of preeclamptic women and therefore the blood flow is reduced, leaving the placenta ischemic.[8] The vasoconstriction is secondary to an increased sensitivity of the vasculature to any pressor agent.[3] Activation of the coagulation cascade produces micro thrombi.[3] The reduced plasma volume, reflecting an endothelial leak with fluid loss from the intravascular compartment, further compromises perfusion.[3] These abnormalities precede clinically evident disease by weeks to months and have led to the suggestion that a primary target in preeclampsia is the vascular endothelium.

The role of various circulating factors including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), fms-like tyrosine kinase 1 (Flt1), agonistic

agonistic antibodies against angiotensin 1 receptors and asymmetric dimethylarginine has also been studied. These factors might interfere with angiogenesis, engage angiotensin II signaling, and directly impair endothelial function.[14]

Need to discover methods for predicting Preeclampsia

Preeclampsia being a substantial cause of maternal and fetal morbidity and mortality has drawn the attention of researchers since long. There have been several attempts to discover methods that may help in early diagnosis of the disease. The need of the discovery of such screening methods has also been emphasized by the discovery of various other facts, one of which is that children born to preeclamptic mothers may suffer from various diseases like diabetes type 1.[15] Clinical screening may fail to detect the disease before severe complications have developed.[16] The requirements for an effective screening test are that it needs to identify women at risk early in pregnancy so that care and outcome can be modified.

Biochemical markers for Preeclampsia

The objective in most of the researches conducted in various parts of the world has been the discovery of biochemical markers because these new plasma/serum biochemical markers might be helpful in identifying subjects at increased risk for developing preeclampsia. A couple of these attempts have been fruitful however; many queries need to be answered yet.

Inhibin A and Activin A levels

Inhibins and activins are glycoprotein hormones belonging to the transforming growth factor βsuper family[17] produced by the feto-placental unit in pregnancy.[18] Concentrations of circulating dimeric inhibin A rise in early pregnancy, fall after 12 weeks of gestation, and remain low until 24 weeks.[19] Thereafter, concentrations increase gradually but with a marked rise in the third trimester.[19] Circulating concentrations of activin A are similar during the first and second trimester and rise progressively in the third trimester with a steep increase at term.[20] It has been shown that maternal serum concentrations of inhibin A and activin A are 10-fold higher in women with severe preeclampsia compared to gestational age-matched controls.[21] A study conducted to investigate the time course of the changes in relation to the onset of the maternal syndrome and if their measurement could be useful for clinical prediction particularly in relation to early onset disease, showed that serum inhibin A and activin A concentrations increase before the onset of preeclampsia at gestational ages that depend on when preeclampsia develops.[17] It is not known why inhibin A and activin A are increased and whether they contribute to the etiology or the compensatory

mechanism of the disease. A probable explanation for the concomitant increases in activin A and inhibin A may be that activin A stimulates production of human chorionic gonadotrophin (HCG) by first-trimester trophoblast[22] and HCG increases secretion of inhibin A production by cultured placental cells.[23] However, activin A may be produced by circulating inflammatory cells rather than or as well as, from trophoblast.[24]

Leptin levels

Leptin, the product of the ob gene, is a hormone that is produced mostly in adipose cells.[25] It is also produced in the placenta and may affect a number of processes in this organ, including angiogenesis, growth and immunomodulation.[26] It has been suggested that leptin may be involved in the pathogenesis of preeclampsia.[26] Many studies have reported high maternal leptin concentrations in the second trimester of pregnancy in women with preeclampsia.[27] However, serum leptin concentrations in the early part of pregnancy did not differ between the preeclamptic and non-preeclamptic women.[28] This finding undermines the predictive value of leptin levels in the early stages of pregnancy.

Insulin-like growth factor-1 Levels

Insulin-like growth factor-1 (IGF-1) is a hormone that may be involved in both normal and abnormal fetal growth.[29] During circulation it is bound to 6 proteins, the IGFBPs that regulate IGF-1 action by inhibiting or enhancing its effects.[30] Seventy-five percent of IGF-1 is a high molecular mass ternary complex formed by IGF-1, IGFBP-3, and an acid-labile subunit; 24% is bound to IGFBP-3 and remaining 1% circulates as free IGF-1.[31]

This hormone stimulates the renal and placental 1,25-dihydroxyvitamin D synthesis.[32] During normal pregnancy birth weight is positively correlated with maternal and fetal IGF-1 and IGFBP-3A, and negatively correlated with maternal and fetal IGFBP-1concentrations.[33] It has been found that during preeclampsia the maternal IGF concentrations are lower compared with those in normal pregnancy.[34]

Maternal Plasma Fetal DNA Levels

It has been shown that there is a 5-fold increase in circulating fetal DNA concentrations in the plasma of women with established preeclampsia compared with control pregnant subjects.[35] A further study aimed at testing that whether the abnormal increase in circulating fetal DNA concentrations can be detected in susceptible subjects before the onset of the clinical disease resulted in affirmative evidence.[36] In that study, plasma samples were assayed for circulating fetal DNA, using the SRY gene on the Y chromosome as a marker. Circulating fetal DNA was detected in all subjects carrying male fetuses in both the

detected in all subjects carrying male fetuses in both the preeclamptic and control groups. The possible pathway for maternal plasma fetal DNA increase in preeclampsia is likely to be increased liberation of fetal DNA into the maternal circulation.[36] This increase could be secondary to an increased entry of fetal cells, such as trophoblasts[37] and erythroblasts[38], into the maternal circulation or the fetal DNA could liberate directly from dying cells in the placenta and a confirmation to this comes from the demonstration of widespread apoptosis in cytotrophoblasts obtained from the placental beds of preeclamptic pregnancies.[39] Nevertheless, this is a new marker that may help in predicting preeclampsia.

Comments

As discussed, since preeclampsia is associated with significant morbidity and mortality for both mother and fetus, it is a desirable objective that the disorder should be diagnosed as early as possible, preferably before the onset of complications. The aim of the early diagnosis is that the therapeutic interventions can be modified and tailor-made accordingly. However, the effective means of prediction of the disease are still lacking. In the context of the pathophysiology of preeclampsia, the levels of biochemical markers are considered as the potential candidates for predicting the development of disease at later stages. The requirements of an ideal marker for the prediction of preeclampsia would be that it should be highly sensitive and specific. Besides it should be able to identify the women at risk very early in the pregnancy.

As far as various biochemical markers with a potentially predictive value for preeclampsia are concerned, none has shown to be universally acceptable and reliable. For example, it has been seen that there is an overlap in the fetal DNA concentrations between the preeclamptic and control groups.[36] This implies that a relatively low sensitivity and specificity would result if maternal plasma fetal DNA measurement is used as the sole predictor for preeclampsia. However, the statistical analysis revealed that the best discrimination between the preeclamptic and control groups was obtained at a fetal DNA concentration of 33.5 genome-equivalents/mL.[36] Work needs to be done to explore the use of fetal DNA markers outside the Y chromosome so that this type of analysis can be extended to pregnant women carrying female fetuses.

Similarly, serum leptin levels have been observed to be raised in preeclamptic women, albeit in the second trimester of pregnancy.[27] In the early stages, no difference in the concentration of this hormone was noted between the normal and would be preeclamptic women.[28] These results eclipse the predictive value of leptin for high risk groups.

However, inhibin A, which has already proved to be useful in screening for fetal karyotype abnormalities, has been shown to be a potentially promising predictive biochemical marker for the diagnosis of early placental abnormality. This hormone has been shown to be raised in a significant number but not all of cases of preeclampsia before the onset of complications.[21] However, it remains to be seen whether inhibin A concentrations that are measured prospectively in early pregnancy are useful predictors of preeclampsia. Further studies need to be conducted to confirm the results and to evaluate the predictive value of serum inhibin A concentration early in pregnancy, and the efficiency of prediction may be increased by the consideration of other risk markers, such as pregnancy-associated plasma protein levels,[40] or first-trimester Doppler studies of the uterine arteries.[41] It would be important to assess whether the measurement of other indices combined with inhibin A can produce a test with greater sensitivity for preeclampsia as occurs with triple or quadruple blood tests for Down's syndrome. This would open up new possibilities for the testing of preventive methods and the trials of treatments for this pregnancy-specific syndrome.

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