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Review Article

Update on Immunology, Pathogenesis and Management of Precalmpsia-Revisted

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Abstract

Immunological response during pregnancy is essential to maintain a successful pregnancy. There seems a dysruption in immunological tolerance to foetus by maternal immune system during pregnancy which results in pregnancy-related complications, such as recurrent spontaneous abortions. Among 8% of pregnancies preeclampsia stands out as a leading cause of maternal and perinatal mortality and morbidity. This presents as pregnancy-specific disease characterized by the development of both hypertension and proteinuria yet at times it may progress into a multiorgan involvement with varying clinical manifestations. Although the precise etiology of the disorder is still unknown, deficient early placentation is particularly associated with early onset preeclampsia which is thought to be immunologically mediated. Despite various biomarkers available, prevention and prediction of preeclampsia are still not possible, symptomatic clinical management must focus on preventing maternal morbidity (e.g., generalized seizures of eclampsia) and mortality.

INTRODUCTION

Hypertensive disorders of pregnancy occur in 10%of 1st pregnancy and 6-8% of all pregnancies [1]. Preeclampsia complicates up to 10% of pregnancies in developing countries, in India maternal mortality rate due to preeclampsia is around 8.3% [2]. Despite being the leading cause of maternal and neonatal death worldwide yet there is no effective strategies available in prevention and treatment.

Hypertension during pregnancy has clinical relevance especially its timing in differentiating gestational versus chronic undiagnosed hypertension or preeclampsia. At times its occurrence during second half of pregnancy without other signs of pre-eclampsia may pose difficulties in diagnosis and management.

DEFINITION

Preeclampsia is defined as a multisystem disorder of pregnancy which is characterized by new onset hypertension (>-140/90 mm Hg on 2 occasions at least 6 hours apart and proteinuria >-300mg /24 hours that has developed after 20 weeks of gestation in a previously normtensive women. It can be early onset if it appears before 34 weeks or late when it happens after 34 weeks of gestation. A widely applicable and affordable test is required to permit presysmptomatic diagnosis in order to identify and monitor patient at risk and provide the best prenatal care for women and their child.

Evidence based guidelines submitted by International society of Hypertension in pregnancy categorized 4 situation, Gestational hypertension, chronic hypertension, preeclampsia, and white coat hypertension.

Antepartum diagnosis of mild, moderate, and severe preeclampsia is based on series of defined criteria occurring after 20 weeks of gestation .Severe PE is defined as a blood pressure greater than 160 mm Hg (systolic) or 110 mm Hg (diastolic) associated with proteinuria greater than or equal to 5 grams per day. Furthermore, PE is regarded as severe in the presence of multiorgan involvement including thrombocytopenia (platelet count less than 100,000/uL), pulmonary edema, or oliguria (less than 500 mL per day). In contrast, mild PE is characterized by an elevated blood pressure less than 160 mm Hg (systolic) or 120 mm Hg (diastolic) with proteinuria greater than 300 mg, but less than 5 gr. per day.

The care of women at risk for preeclampsia should start from preconception counseling; prevention, treatment and post partum follow up. It is recommended to assess for preconceptional counseling among high risk pregnancy for development of preeclampsia.

RISK FACTORS TO PREECLAMPSIA

Disorder associated with autoimmune disorders, metabolic, vascular or renal disease has increased potential for development of preeclampsia.

Non invasive markers to predict preeclampsia

Till date no therapeutic approaches are available for treatment or prevention .Regardless of lack of existing prophylaxis and therapeutics against preeclampsia search for noninvasive biomarkers and sonological markers could predict the development or assist in prediction. A combination of series of biophysical and biochemical markers that can change from as early as 1st trimester of pregnancy can help in predicting subsequent development of PE [3-5]. Studied biophysical markers like mean arterial blood pressure [11]. Uterine artery doppler (Poon et al) [13] maternal cardiac output [12] while biochemical markers include products of fetal and placental origin markers of renal or endothelial damage angiogenic and antiangiogenic factors and markers of oxidative stress [7-9].

Pathogenesis is yet not clear but there seems the central role of maternal endothelial dysfunction activating inflammatory response and accumulation of antiangiogenic factors in its causation. Elevated levels of soluble fms-like tyrosine kinase 1 (sFlt-1; an inhibitor of vascular endothelial growth factor), reduced levels of placental growth factor (PlGF), and an increased sFlt-1: PlGF ratios have been associated with occurrence of preeclampsia as well as in established cases also [7]. Prediction of preeclampsia early in pregnancy with the help of these angiogenic factors have not successfully reciprocated in outcomes however its usefulness as a diagnostic tool in late pregnancy may be useful as a diagnostic aid for triaging women with singleton pregnancies and suspected preeclampsia [6,8]. There has been increasing evidences to suggest that women affected by Preeclampsia will be at higher risk to cardiovascular disease in life [8,9]. Hence WHO has recognized the importance of Preeclampsia by launching a programmed dedicated to study and treats this problem [10].

Immunological aspects

Literature evidences suggests that for a successful pregnancy it requires a immune tolerance by the maternal immune system which is mediated through the prevalent cytokine milieu producing Th2 cells at the maternal foetal interface inhibiting Th1 response whereby helping in accepting the human foetus [14,15]. Pregnancy related complications like recurrent abortions have been associated with a tendency towards Th1 response .Th2 preponderance in normal pregnancy shifts to Th1 predominance in preeclampsia by an increase in the IL2/IL4 and IFNg/IL4 ratios along with proinflammatory cytokines IL-6 and TNF-alpha, chemokines IL-8, IP-10, and MCP-1, and adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) as compared to normal pregnancy [16]. Surprisingly, the increased IP-10, MCP-1, ICAM-1, and VCAM-1 concentrations in preeclamptic patients correlate significantly with blood pressure values and liver and renal function parameters In line with this, the peripheral blood mononuclear cell production of IL-12, which induces Th1 responses, diminishes in normal pregnant women but increases in preeclamptic patients [17].

A close association has been found between unexplained recurrent spontaneous abortions and defective maternofetal tolerance in which Treg cells play a key role. As Foxp3 is a crucial regulatory factor for the development and function of Treg cells is found to in such pregnancies especially in patients with preeclampsia who display low levels of Tregs in both their own blood as well as in placenta. These preeclamptic patients demonstrate a lower percentage of cells in the CD4+ T cell population in peripheral blood mononuclear cells as compared to normal pregnancies and non pregnant healthy controls. Moreover, placental samples from preeclamptic patients show a low percentage of FoxP3+ cells in CD3+ T-cells as compared to those reported in normal pregnancy subjects. There seems some suggestion that cytotoxic T-cells is increased at the decidua basalis in preeclampsia since the CD8+ T/CD3+ T-cells ratio in placental preeclamptic samples was much higher than in the samples taken from healthy pregnancies. The frequency of conventional CD4+ CD25high FoxP3+ Tregs and that of nonconventional CD4+ CD25– FoxP3+ Tregs diminish in peripheral blood in preeclamptic patients as compared to healthy pregnant women. In addition, the prevalence of Th17 cells and the Th17/Treg ratio increases in peripheral blood in preeclampsia as compared with normal pregnancy [18-20].

With this background, the cytokine mileue in the serum, placental tissue and the cord blood together needs assessment regarding the pathophysiology of preeclampsia before a definite treatment can be directed against the triggering factor.

TREATMENT

The only treatment for preeclampsia during pregnancy is to deliver the foetus. Decisions regarding delivery largely depend on the severity of the conditions in terms of potential risk to maternal as well foetal outcomes. The obstetricians in majority give the foetus as much time to mature before delivery with minimum risk to the mother.

If the fetus is at 37 weeks or later, it is ideal time to deliver the baby to avoid further complications. If the fetus is younger than 37 weeks, however, the obstetricians may consider options in giving the fetus more time to develop, depending on severity of the condition is.

Conventionally the obstetricians consider following treatment options:

1. If the preeclampsia is mild, they could possibly wait to deliver the infant. To prevent further complications, mother may be offered to go on bed rest (to try to lower blood pressure and increase the blood flow to the placenta).

-Careful monitoring of the mother and foetus needs to be done. Tests for the mother might include blood and urine tests to see f the preeclampsia is progressing (such as tests to assess platelet counts, liver enzymes, kidney function, and urinary protein levels). Tests for the fetus might include ultrasound, heart rate monitoring, assessment of fetal growth, and amniotic fluid assessment.

-Anticonvulsive medication, such as magnesium sulfate, might be used to prevent a seizure.

-In some cases, such as with severe preeclampsia, the woman would be required to be admitted in the hospital for closer monitoring .Treatment in the hospital might include intravenous medication to control blood pressure and prevent seizures or other complications as well as steroid injections to help speed up the development of the fetus's lungs.

2. When the woman has severe preeclampsia, the obstetricians deliver the fetus as soon as possible especially if the pregnancy has lasted more than 34 weeks. If the fetus is less than 34 weeks, then probably prescribing corticosteroids may be used to speed up the maturation of the lungs [20].

3. In some cases, obstetricians may deliver the fetus prematurely; even if that means likely complications for the infant because of the risk of severe maternal complications the symptoms of preeclampsia usually go away within 6 weeks of delivery [21,22].

CONCLUSION

A defective maternofetal immune response may contribute to the development of pregnancy-related complications, such as bleeding complications during the first trimester, pregnancy-induced hypertension, preeclampsia, or preterm birth. Therefore, suitable knowledge of the maternal immune response during pregnancy will enable us to understand the etiopathogenesis to elucidate prevention and to improve the treatment of these pathologies.

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