Early Predictors of Pre-eclampsia

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Abstract

Pre-eclampsia is defined by the International Society for the Study of Hypertension in Pregnancy as, "Gestational hypertension of at least 140/90 mm Hg on two separate occasions 4-6 h apart accompanied by significant proteinuria of at least 300 mg in a 24 h collection of urine. It arises de novo after the 20th week of gestation in a previously normotensive woman and resolves completely by the 12th postpartum week." Pre-eclampsia is a major reason for maternal and perinatal mortality and morbidity worldwide inflicting 15% of all direct maternal deaths and a multiple increase in perinatal mortality with induced prematurity being the most perpetrators.

Keywords: Hypertension; Pre-eclampsia; Perinatal mortality

Pathophysiology of Pre-eclampsia

Preeclampsia is characterized by a complex pathophysiology which incorporates vascular remodeling of maternal–fetal interface, excessive immunologic response to paternal antigens, general inflammatory response and dysfunctional placental or endothelial response. There is evolving proof that both the degree of impaired placentation and also the incidence of adverse foetal and maternal short-term and long-term consequences of pre-eclampsia are reciprocally associated with the gestational age at onset of the disease [1]. Placental spiral arteries underlying placental infarcts were studied in a hysterectomy specimen with the placenta in situ and in placental biopsies from multiple cases of severe pre-eclampsia. The spiral arteries supplying infarcted placentae differed from normal spiral arteries in two important features. The differences were, in the failure of trophoblast infiltration along with concomitant physiological changes of the myometrial segment of the spiral artery and in the appearance in this segment of hypertensive, occlusive vascular lesions [2]. Underlying reason for pathophysiologic mechanism that is thought to be chargeable for disease process appear to occur much earlier in gestation between 9-13.6 weeks. Thus early diagnosis and intensive management of pre-eclampsia is of utmost necessity.

Tests to Predict Pre-eclampsia

Several tests have been proposed to identify women at risk of developing pre-eclampsia however none of these tests have been proven as an ideal test for prediction. A number of these tests like the cold pressure test, the isometric hand grip exercise and also the roll-over test rely upon the pathophysiologic changes that occur in pre-eclampsia. The degree of sensitivity to angiotensin 2 could also be used as a screening test to identify the patient at risk but has a high incidence of false positive and false negative results. Likewise, an elevation in blood pressure of 20 mm Hg or additional once the patient rolls over from the lateral posture to the supine position is taken into account as positive in roll-over test. However, this test too has poor sensitivity and specificity. Mean arterial pressure in first trimester is a better predictor of pre-eclampsia than SBP/DBP or a rise in blood pressure. Once first trimester mean arterial pressure is ≥ 90 mm Hg, there’s a major increase in frequency of albuminuria, high blood pressure and diagnosed pre-eclampsia in the third trimester as well as still birth rate and IUGR [3]. Mean arterial pressure is calculated as diastolic BP+1/3 (systolic BP- diastolic BP). The detection rate of pre-eclampsia by log multiple of the median mean arterial pressure was 62.5% [4]. Other tests like urinary Calcium or plasma fibronectin are based on the presence of biochemical alterations peculiar to the disease. A urinary Calcium concentration up to or less than twelve mg/dl 24 h collection has positive and negative prognostic values of 85% and 91%, respectively, for the identification of pre-eclampsia. Pre-eclamptic patients have elevated level of plasma fibronectin –a glycoprotein that has a crucial role in all cellular adhesions and is a component of connective tissue and basement membranes. There is evolving evidence that both the degree of impaired placentation and the incidence of adverse fetal and maternal short-term and long-term consequences of PE are inversely related to the gestational age at onset of the disease [1].

Pre-eclampsia Newer Peptide Markers

In 2004, after performing a scientific review of screening tests for pre-eclampsia, WHO reaffirmed that "there is not any clinically helpful screening tests to predict the event of pre-eclampsia in either low risk or high risk populations. Further prospective, longitudinal studies are required." Since this assertion, several groups have identified potential biochemical and/or biophysical markers based on physiological mechanisms. Two of the angiogenic growth factors, vascular endothelial growth factor (VEGF) and placental induced growth factor (PIGF) are thought to contribute to normal trophoblastic proliferation and implantation, and it's been hypothesized that an imbalance in levels of these growth factors features a crucial role in pre-eclampsia [5].

Two of the foremost extensively studied peptides, which are released by the placenta, are soluble FMS-like tyrosine kinase (sFLT-1) and soluble endoglin. The mRNA of sFLT-1 is up-regulated in the placenta of women with pre-eclampsia, resulting in raised general levels [6]. In normal pregnancy, levels of soluble endoglin fall between the first and

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second trimesters, however in women who go on to develop pre-eclampsia this reduction is blunted [7]. Uric acid could be a marker of oxidative stress, tissue injury and renal pathology, and several other studies have reported a direct correlation between elevated maternal serum uric acid levels and adverse pregnancy outcomes in women with pre-eclampsia [8]. During normal pregnancy levels of Placental Protein-13 gradually increase, however abnormally low levels of PP-13 are reported at gestational weeks 11-13 and weeks 9-12 in women who went on to develop pre-eclampsia and fetal growth restriction [9].

Women with pre-eclampsia have an abnormal lipid profile, with elevated concentrations of triglyceride-rich lipoproteins, which can contribute to endothelial dysfunction. It has been postulated that Apolipoprotein E levels and polymorphisms of its gene are related to an exaggerated risk of pre-eclampsia. Given the role of insulin resistance in the pathologic process of pre-eclampsia it’ve been hypothesized that visceral fat accumulation throughout pregnancy might induce dysregulation of adipocytokines, contributing to the development of the condition [10].

Second trimester levels of Inhibin A have been reported to be elevated in both serum and amniotic fluid in women who went on to develop severe pre-eclampsia and once measured at term, serum levels have been shown to correlate with pre-eclampsia severity. Additionally, urinary Activin A and Inhibin A levels have jointly been found to be elevated in women with pre-eclampsia. Elevated levels of E-selectin, P-selectin and ICAM-1 and lower levels of L-selectin and VCAM-1 were documented in women who later developed pre-eclampsia [11].

During recent years a lot of attention has been given to relationship between low maternal serum pregnancy associated plasma protein-A at 9-13.6 weeks and resultant development of pre-eclampsia. Pregnancy-Associated plasma protein A, (PAPP-A) is a large and highly glycosylated protein complex produced by the developing trophoblast, which is used in several centers as a marker for Down’s syndrome. It’s been shown to be accountable for the cleavage of insulin-like growth factor (IGF) binding proteins, which are inhibitors of IGF action, in many biological fluids. PAPP-A was 1st reported to be altered in the plasma of pre-eclamptic women nearly thirty years ago. More recent studies have shown that reduced first trimester serum levels of PAPP-A are related to pre-eclampsia, the levels also are reduced in women with other pregnancy-related complications like ante-partum hemorrhage and still-birth [12].

The free beta subunit of human chorionic gonadotropin (β-hcg) is secreted by the syncytiotrophoblast cells. Many studies have investigated the potential of β-hcg to predict these disorders. Low β-hcg levels in pregnant women between 9-13.6 weeks were found to be associated with future development of pre-eclampsia.

**Mean Arterial Pressure**

Mean arterial pressure in the first trimester is found to be a stronger predictor of pre-eclampsia than systolic blood pressure, diastolic blood pressure or a rise of blood pressure. Poon et al. [12] found in their study that detection rate of pre-eclampsia by log multiples of median of mean arterial pressure is 62.5% with a false positive rate of 10% (p value=0.001) Cnossen et al. [13] in their study that areas under summary receiver operating characteristics curves for blood pressure. Kucmail et al. [14] found measurement in the first trimester was 0.76 (0.70 to 0.82) which was much higher than areas for systolic or diastolic blood pressure [14] found in their study that the detection rate of pre-eclampsia by log multiples of median of mean arterial pressure is 65.0% with a false positive rate of 100 p c (p value=0.016). The mom for mean arterial pressure in women developing pre-eclampsia was 1.08 with a 95th confidence interval of 1.02-1.17 and in women who remained normotensive it was 0.99 with a confidence interval of 0.93-1.05.

On contrary Miller et al. [15] found in their study that first-trimester MAP did not strongly predict future pre-eclampsia (area under the receiver operative curve, 0.71). A MAP>=88 mm hg predicted pre-eclampsia with a sensitivity of 0.78 and a specificity of 0.63.They concluded that though first-trimester MAP is strongly related to risk of pre-eclampsia, it poorly discriminates between women who can and will not develop the disease.

**β-Human Chorionic Gonadotrophin Levels**

β-HCG has role in invasion of trophoblasts and angiogenesis and so in pregnancies complicated by pre-eclampsia and other disorders due to placental dysfunction are found to be insufficient (Table 1).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Median β HCG levels (MoM)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer et al. [21]</td>
<td>2005</td>
<td>0.923</td>
<td>0.933</td>
</tr>
<tr>
<td>Katherine et al. [22]</td>
<td>2010</td>
<td>0.91</td>
<td>1.01</td>
</tr>
<tr>
<td>Scazzocchio et al. [17]</td>
<td>2013</td>
<td>0.92</td>
<td>1</td>
</tr>
<tr>
<td>Saxena et al. [18]</td>
<td>2013</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ozdamar et al. [19]</td>
<td>2014</td>
<td>0.985</td>
<td>1.018</td>
</tr>
</tbody>
</table>

Table 1: Comparative figures of β HCG levels in different studies.

The above studies showed that reduced concentration of beta human chorionic gonadotropin in first trimester although associated with an enhanced risk, however is not a good predictor of pre-eclampsia. Maternal serum-free β-HCG concentration at 9-13.6 weeks, as distinct from the findings in the second trimester, was not significantly different between normotensive women and those that later on develop pre-eclampsia. Kucmail et al. [14] additionally concluded that in the first trimester of pregnancy human chorionic gonadotropin isn’t valuable for prediction of pre-eclampsia.
Pregnancy Associated Plasma Protein – A Levels

PAPP-A is a large protein complex that has been shown to reduce in maternal serum at gestational weeks 11+0 to 13+6 in pregnancies afterwards developing pre-eclampsia. As PAPP-A is a protease for IGF binding proteins (IGFBP), low PAPP-A is associated with high levels of IGFBP. This consequently leads to a lowering of free IGF, resulting in impaired invasion of the trophoblasts into the maternal decidua. This hypothesis provides biologic plausibility for the association of low first trimester PAPP-A and the development of pre-eclampsia later in gestation (Table 2).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Median PAPP-A Levels in MoM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poon et al. [12]</td>
<td>2010</td>
<td>0.555</td>
<td>1.002</td>
</tr>
<tr>
<td>Bestwick et al. [20]</td>
<td>2012</td>
<td>0.970</td>
<td>1.000</td>
</tr>
<tr>
<td>Saxena et al. [18]</td>
<td>2013</td>
<td>0.900</td>
<td>1.110</td>
</tr>
<tr>
<td>Kucmail et al. [14]</td>
<td>2013</td>
<td>0.890</td>
<td>1.010</td>
</tr>
<tr>
<td>Scuzzocchio et al. [17]</td>
<td>2013</td>
<td>0.870</td>
<td>1.060</td>
</tr>
<tr>
<td>Ozdamar et al. [19]</td>
<td>2014</td>
<td>0.792</td>
<td>1.184</td>
</tr>
</tbody>
</table>

Table 2: Comparative figures of PAPP-A levels in different studies.

Thus maximum studies above showed low PAPP-A to be significantly associated with a future risk of pre-eclampsia.

Assessment of Pre-eclampsia by Uterine Artery Resistance Index

In pre-eclampsia the remodeling of the spiral arteries is impaired; the spiral arteries maintain their muscular elastic coating, and impedance to blood flow persists. This pathological resistance to placental flow is detected by Doppler studies of the maternal uterine vessels. Thus the etiology of pre-eclampsia is thought to lie in failure of placenta to establish an adequate circulation within the uterus in the first half of pregnancy which might be detected by Doppler examination of uterine artery at 11-13.6 weeks of gestation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Median Levels Of RI in MoM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrington et al. [16]</td>
<td>1997</td>
<td>0.80</td>
<td>0.695</td>
</tr>
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</table>

Table 3: Comparative figures of uterine artery resistance index in a study.

Assessment of Preeclampsia by Uterine Artery Pulsatility Index

The median level for Pulsatility Index of Uterine Artery in multiples of median in women who developed preeclampsia was 2.31 MoM with an interquartile range of 1.75-3 MoM. Mean was 2.35 MoM with standard deviation of 0.75. The median level for Pulsatility Index of Uterine Artery in multiples of median in women who remained normotensive was 1.47 MoM with an interquartile range of 0.95-1.85 MoM. Mean was 1.5 MoM with standard deviation of 0.55. Thus, Pulsatility Index of Uterine Artery was significantly increased in cases that developed pre-eclampsia compared to those that remain normotensive (Table 4).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Median value of Pulsatility Index (MoM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrington et al. [16]</td>
<td>1997</td>
<td>2.01</td>
<td>1.43</td>
</tr>
<tr>
<td>Scuzzocchio et al. [17]</td>
<td>2013</td>
<td>2.23</td>
<td>1.67</td>
</tr>
</tbody>
</table>

Table 4: Comparative figures of uterine artery pulsatility index in a study.
Integrated first trimester screening shows a high performance for detection of pre-eclampsia maternal serum free β-hCG and PAPP-A levels vary between normal pregnancies and those that later on develop pre-eclampsia. Though serum free β-hCG showed no significant difference, PAPP-A levels were significantly reduced in the pre-eclampsia group compared to normotensive group. Hence measuring PAPP-A in the first trimester may be useful in the prediction of preeclampsia. Combinations of biochemical and Doppler markers improved the performance of early prediction of preeclampsia. A large population based study evaluating algorithms combining multiple markers are required, if screening approaches are to be eventually implemented.

References