PRE-ECLAMPSIA—Pathogenesis, prediction and prevention

PRE-ECLAMPSIA – PATHOGENESIS, PREDICTION AND PREVENTION

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Abstract

Pre-eclampsia is an entity whose pathogenesis and predictive factors are not clearly understood. There are multiple etiological factors and the complex interplay between these leads to the cascade of events that leads to clinical manifestations of pre-eclampsia. It is for this very reason that prediction and prevention of pre-eclampsia is proving to be extremely difficult. Several predictive factors have been proposed but only a few are of clinical significance. Maternal history, the mean arterial blood pressure, the uterine artery Doppler and biochemical markers have not found to be ideal for screening for pre-eclampsia when used in isolation. Combining these factors, however has improved the detection rates of pre-eclampsia significantly.

Introduction

Pre-eclampsia is a disease of pregnancy that is difficult to predict and whose pathogenesis is unclear. An understanding the pathogenesis and using this knowledge to try and find ways to predict or even prevent the disease is essential for effective management of pre-eclampsia. Pre-eclampsia can develop before 34 weeks (early onset), between 34 and 37 weeks (intermediate onset) and after 37 weeks (late onset). The maximum impact on the health system and economics of healthcare is with the early onset and so this at the forefront of the screening process.

Pathogenesis of pre-eclampsia

The pathogenesis of pre-eclampsia is the source of extensive research worldwide. The reasons for this are the various hypotheses regarding the origins and progression of the disease. The basic final pathway is the abnormal placentation, which is critical to pre-eclampsia. The evidence linking the placenta to pre-eclampsia is based on two main findings from studies.

1. The presence of the placenta is essential to the development of pre-eclampsia and not the foetus – as in a vesicular mole
2. The delivery of the placenta is the only definitive treatment for pre-eclampsia

The components of the abnormal placentation that leads to pre-eclampsia are

1. Abnormal trophoblastic invasion
2. Abnormal modelling of the spiral arterioles

Normally, the cytotrophoblasts which form the outer layer of the tertiary villi, extend beyond the villi and invade the maternal spiral arterioles. This allows converts the spiral arterioles from high resistance vessels to low resistance vessels with significantly more blood supply to the foetus. This ensures that adequate nutrients reach the foetus and also makes sure that the maternal vessels are no longer controlling the amount of blood reaching the foetus. This is an adaptive mechanism of the foetus in order to increase its chances of survival and growth.

This process takes place in two stages (or waves). The primary wave of trophoblastic invasion
takes place at the end of the first trimester when they invade the decidual portion of the spiral arterioles. The secondary wave of invasion takes place at around 16-18 weeks gestation when they invade the myometrial portion.\(^{(1)}\) In pre-eclampsia this secondary wave of invasion does not take place and so the spiral arterioles remain as narrow, high resistance vessels.\(^{(2,3)}\)

The hypoperfusion and ischemia that results from the narrow vessels sets off a cascade of events that eventually lead to clinical manifestations and complications of pre-eclampsia.

**Etiological factors**

The etiological factors predisposing to abnormal placentation are many and no single hypothesis has been able to tick all the boxes. In reality, predisposition to pre-eclampsia is a result of a combination of these factors and not one single factor acting in isolation. The factors studied thus far are:

1. **Immunological:** The immune maladaptation theory presumed to be due to incompatibility between maternal and paternal immunological systems has been studied extensively and continues to be the subject of research. The evidence lies in higher rate of pre-eclampsia in women who conceive after limited exposure to their partner’s sperm and among those who have changed their partner since their last pregnancy. Also, low rates of pre-eclampsia are seen in women having repeated pregnancies with the same partner where there was no pre-eclampsia in an earlier pregnancy.

2. **Genetic:** The incidence of pre-eclampsia is higher in women with history of pre-eclampsia in their first degree relatives. Scientists continue to look for the exact gene responsible for pre-eclampsia.

3. **Endothelial dysfunction:** Studies have shown that endothelial damage is essential to the cascade of events leading to clinical manifestations of pre-eclampsia. Factors like free radicals; hypoxia, etc. damage the endothelium releasing cytokines and chemotactic agents that then propagate the disease process.

4. **Inflammation/Infection:** Histopathological evaluation of placentas from women with pre-eclampsia has shown extensive inflammatory changes. Recently the link between infections like urinary tract infections, periodontal infections, etc. has been studied and small studies have shown positive correlations.

The complex interplay between multiple factors leads to the cascade of events that leads to clinical manifestations of pre-eclampsia. It is for this very reason that prediction and prevention of pre-eclampsia is proving to be extremely difficult.\(^{(4)}\)

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**Pre-eclampsia**

<table>
<thead>
<tr>
<th>Etiological Factors:</th>
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<tbody>
<tr>
<td>Immunological</td>
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<tr>
<td>Genetic</td>
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<tr>
<td>Endothelial dysfunction</td>
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<tr>
<td>Inflammation/Infection</td>
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</table>

**Predictive factors:**

1. Maternal history related factors
2. Biophysical markers
   - Maternal mean arterial pressure
   - Uterine artery Pulsatility Index
3. Biochemical markers
   - Pregnancy associated plasma protein A
   - Placental growth factor

**Predictors of pre-eclampsia**

Predictors of pre-eclampsia are broadly divided into

1. Maternal history related factors
2. Biophysical markers
3. Biochemical markers

**Maternal history** when used in isolation has a poor detection rate for pre-eclampsia. However, when used in conjunction with other factors, its value increases considerably. History which increases the risk of pre-eclampsia in this pregnancy...
are listed in Table 1.

**Biophysical markers** that have been proven to be useful include measurement of maternal mean arterial blood pressure (MAP) and ultrasound to measure the pulsatility index (PI) in the uterine artery. Measurement of blood pressure – as early as the first trimester may show that the woman is at high risk for pre-eclampsia. The MAP has been shown to be superior to the systolic and diastolic blood pressure, measured individually.

Ideally, multiple readings must be taken till there is no fluctuation between readings but since this is not practical, at least two readings must be taken in each arm and the mean is calculated. The patient should be sitting or lying comfortably with the blood pressure apparatus at the level of her heart and the cuff size should be appropriate (the inflatable part of the cuff should cover 80% of her arm). The other argument seems to be between the mercury sphygmomanometer and automated blood pressure measuring devices. The argument against the mercury device seems to be the potential operator error involved in auscultating for the Korotkoff sounds and visualising the drop in mercury in addition to the potential for hazards due to mercury spill.

The MAP is calculated using the formula

\[
MAP = \text{diastolic pressure} + \frac{1}{3} \text{rd} (\text{systolic-diastolic pressure})^* 
\]

*This difference between the systolic and diastolic pressures is referred to as the pulse pressure.

The uterine artery Doppler study has been the subject of interest for researchers and clinicians keen on predicting adverse outcomes in pregnancy. Since the uterine artery is the main maternal vessel supplying the pregnant uterus, assessment of its blood flow would likely reflect any possible compromise in the same, before clinical signs are evident. There was, however, no consensus regarding the timing of this test and also which value of the test was the most useful.

Just as they pioneered the aneuploidy screening by advocating measuring the nuchal translucency

**Table 1: Maternal risk factors for pre-eclampsia**

(i) Previous preeclampsia (PE)  
(ii) Previous early onset PE and preterm delivery at <34 weeks’ gestation  
(iii) PE in more than one prior pregnancy  
(iv) Chronic kidney disease  
(v) Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome  
(vi) Heritable thrombophilias  
(vii) Type 1 or type 2 diabetes  
(viii) Chronic hypertension  
(ix) First pregnancy  
(x) Pregnancy interval of more than 10 years  
(xi) New partner  
(xii) Reproductive technologies  
(xiii) Family history of PE (mother or sister)  
(xiv) Excessive weight gain in pregnancy  
(xv) Infection during pregnancy  
(xvi) Gestational trophoblastic disease  
(xvii) Multiple pregnancies  
(xviii) Age 40 years or older  
(xix) Ethnicity: Nordic, Black, South Asian, or Pacific Island  
(xx) Body mass index of 35 kg/m2 or more at first visit  
(xxi) Booking systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg  
(xxii) Increased prepregnancy triglycerides  
(xxiii) Family history of early onset cardiovascular disease  
(xxiv) Lower socioeconomic status  
(xxv) Cocaine and methamphetamine use  
(xxvi) Nonsmoking
and combining it with other biophysical and biochemical markers to improve efficiency, the Foetal Medicine Foundation has once again shown the way. They advocate doing the uterine artery Doppler at 11-14 weeks gestation at the same time when aneuploidy screening is being done. They have also described, in detail the technique to be employed and which values we should assess from the test. The technique for measurement of uterine artery Doppler wave forms at 11-14 weeks is as given below:  

- Sagittal section of the uterus - cervical canal and internal cervical os are identified.
- Transducer tilted from side to side with colour flow to identify each uterine artery along the side of the cervix and uterus at the level of the internal os.
- Pulsed wave Doppler with the sampling gate set at 2 mm to cover the whole vessel and ensuring that the angle of insonation is less than 30º.
- Three similar consecutive waveforms obtained, the PI measured and mean PI of the left and right arteries calculated
- The amplitude of the wave must be > 60cm/s to ensure that it is indeed the uterine artery and not the arcuate artery being sampled.
Although it was believed that the presence or absence of the notch in the uterine artery during pregnancy was the important determinant of the impaired blood supply to the uterus, we now know that this is not entirely true. Although it may be an adjunct to the screening process, the main determinant is actually the pulsatility index (PI) of the uterine artery. The other issue was whether the side ipsilateral or contralateral to the placental insertion was the stronger determinant of the uterine artery function (Figures 2, 3). This has been solved by using the mean value of the two sides. Therefore, the timing, technique and interpretation of the uterine artery Doppler study have now been streamlined mainly due to the efforts of the Foetal Medicine Foundation, UK.

Biochemical markers

Biochemical markers have been studied more than any of the other markers mentioned in this article. Of these, only the pregnancy associated plasma protein - A (PAPP-A) and Placental growth factor (Pl.GF) have shown some promise. The fact that PAPP-A is also used for aneuploidy screening at 11-14 weeks makes it a key marker for first trimester screening for both purposes. Both PAPP-A and Pl.GF are useful only when used in conjunction with other markers and offer little benefit when used in isolation. Low levels of PAPP-A and Pl.GF are seen to be associated with a higher incidence of pre-eclampsia, especially early onset pre-eclampsia, which occurs before 34 weeks gestation.

Each of the above described factors – maternal history, the mean arterial blood pressure, the uterine artery Doppler and biochemical markers have not found to be ideal for screening for pre-eclampsia when used in isolation. Combining these factors, however has improved the detection rates of pre-eclampsia significantly (Table 3 next page).

Prevention of pre-eclampsia

Prevention of pre-eclampsia is an imperfect science, mainly because the pathogenesis is so complex and there are several deficiencies in the attempts to explain the complications with any one particular hypothesis. Of the factors that prevent pre-eclampsia, only low dose aspirin and high dose calcium have been of some benefit. Cochrane reviews done regarding the use of low-dose aspirin showed evidence that there was a significant reduction in pre-eclampsia (17%), preterm labour (8%), foetal growth restriction (10%) and foetal and neonatal deaths (14%) without any significant adverse effects to the mother or foetus. They advocate 75-100mg of aspirin, to be started ideally before 16 weeks gestation and continued until at least 34-36 weeks gestation. The use of high-dose calcium (1-2 g/day) has been found to be useful in preventing pre-eclampsia in a population with low dietary calcium intake but is of little use in populations with adequate dietary calcium intake. Other factors studied in relation to the prevention of pre-eclampsia are garlic, fish oil, rest, exercise, vitamins C,D and E, nitric oxide donors. These have not proven to be beneficial in preventing pre-eclampsia. The search goes on for an ideal theory that explains all the effects of pre-eclampsia with the hope that predicting and preventing the same will become a reality in the near future.
Table 3: Estimated detection rates of pre-eclampsia (PE) before 34, 37 AND 42 weeks’ gestation, at false positive rates (FPR) of 5% and 10%

<table>
<thead>
<tr>
<th>Screening test</th>
<th>FPR (%)</th>
<th>PE &lt;34 weeks</th>
<th>PE &lt;37 weeks</th>
<th>PE &lt;42 weeks</th>
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<tbody>
<tr>
<td>Maternal characteristics</td>
<td>5.0</td>
<td>36</td>
<td>33</td>
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<td></td>
<td>10.0</td>
<td>51</td>
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<tr>
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<td></td>
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<td></td>
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<td>Pregnancy associated plasma protein-A (PAPP-A)</td>
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<td></td>
<td>10.0</td>
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<tr>
<td>Placental growth factor (PIGF)</td>
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<td></td>
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<tr>
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<td></td>
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References:

There are two types of rewards—an extrinsic reward is the one we obtain through others’ adulation for what we possess or for what we have achieved while an intrinsic reward is the enjoyment of the reward itself. It is the difference between the enjoyment of the applause from the audience due to a musical masterpiece and the pleasure from the music itself.

C.S. Lewis