The disease of theories: unravelling the mechanisms of pre-eclampsia

Perhaps no disease of pregnancy has been more thoroughly studied than pre-eclampsia (PE), and yet despite all of our efforts we are only beginning to understand the molecular mechanisms which underpin the disease. Many people are surprised by the frequency of PE in the population, as it is believed to occur in approximately one pregnancy out of 20 in the United States, with similar rates throughout the developed world. In severe cases the disorder can progress to eclampsia, which is characterized by maternal seizures and can lead to death. PE can only be treated by ending the pregnancy, often by inducing labour prior to term, making PE a leading cause of premature birth and all of the associated health complications which accompany it. All in all, PE is one of the leading causes of maternal and fetal morbidity and mortality. It is now also becoming apparent that PE disposes both the mother and the baby to increased risk of cardiovascular disease throughout life, meaning that we still don’t fully understand the long-term implications of the disease.
Historical perspective

PE is one of the oldest documented obstetrical disorders, arguably being mentioned in a wide variety of texts coming down to us from antiquity in a variety of cultures. These early scientists recognized a common constellation of symptoms which have been used as the basis of diagnosis until very recent times: hypertension, protein in the urine (proteinuria) and oedema, (swelling due to fluid retention, especially in the extremities). In recent years, we have recognized that PE is a spectrum disorder, and that while new-onset hypertension is almost always present, sometimes proteinuria and oedema are not. However, if new-onset hypertension is associated with cerebrovascular and visual disturbances or organ damage, among other symptoms, a diagnosis of pre-eclampsia is indicated.

While the existence of the disorder has long been appreciated, it is only in the last 40 odd years that we have begun to understand the underlying problem, and in the process understand a fundamental process of pregnancy. To briefly summarize a large volume of research, it was found that during healthy pregnancy, cells (invasive cytotrophoblasts) from the placenta (and by extension from the developing fetus) invade the arteries of the uterus (termed spiral arteries). These blood vessels are normally small diameter, low-flow vessels. The invading cells displace the endothelial lining of the vessels, as well as part of the smooth muscle around them and increase the size of the vessels to increase the amount of blood that can flow to the placenta and nourish the fetus. The most common finding in PE is that these cells are unable to invade the maternal vessels. As a result, the placenta doesn’t receive enough blood and is deprived of oxygen. In the short term this is termed hypoxia, and the long-term deprivation of oxygen to a tissue is termed ischaemia. It is now commonly recognized that placental ischaemia is the central causative factor of PE.

The big question: what causes pre-eclampsia?

Although it is generally (though not universally) accepted that placental abnormalities are the central cause of the maternal symptoms, there is no commonly accepted initiating cause of the disorder and it remains one of the great unsolved questions in obstetrics. Tellingly, though pre-eclampsia normally resolves after delivery of the baby and placenta, several case reports found that if portions of the placenta remained undelivered, the disease remained. This led to the hypothesis that hypoxia was causing the placenta to secrete factors which caused the maternal symptoms of the disorder. While there is much debate, it is believed that the underlying cause could be partially through immune mechanisms.

While the placental (and fetal) cells get half of their genetic information from the mother, they

This micrograph of placental tissue shows syncrretial knotting, a bunching of cytoplasm and nuclei resulting from preeclampsia, a serious complication of late pregnancy. Magnification 400x (Jubal Harshaw - Shutterstock)
also get half from the father. As such, the mother’s body has to tolerate an entirely new organ (the placenta), these invasive cells and the developing fetus which the immune system could recognize as being foreign. Could it be then, that the invasive cells which normally remodel the maternal blood vessels are being recognized by the immune system as foreign invaders? The epidemiology suggests that this may be the case, specifically prior exposure to paternal antigens. For women who have normal first pregnancies, their risk of developing PE in second pregnancies is lower if the subsequent pregnancy is from the same father. This suggests a build-up in immune tolerance to the father’s antigens. There are also studies suggesting that prolonged exposure to paternal antigens lessens the risk of pre-eclampsia generally. While there is still a significant amount of work to do in this area, it is likely that immune intolerance between the mother and father could be a significant contributing factor to the development of the disease.

**From placental dysfunction to maternal hypertension**

The question remains, how does placental ischaemia lead to all of the symptoms seen in the mother? The first clue came from studies which found elevated production of a protein called soluble Fms-Like Tyrosine Kinase-1 (sFlt-1). sFlt-1 as it turned out, was a splice variant of a receptor for the cytokine Vascular Endothelial Growth Factor (VEGF). VEGF-A (one of a complex family of signalling proteins) is often associated with growth of new blood vessels in response to increased oxygen demand due to prolonged hypoxia or ischaemia. Many don’t recognize that it is also important for maintenance of vascular endothelial health in arteries. The full length Flt-1 protein recognizes VEGF and has signalling activity in the cell. However, this spliced variant was secreted from the cell and bound VEGF, preventing VEGF activating its receptors as normal. As a consequence, the maternal vasculature, in particular the renal arteries, constricts; causing an increase in vascular resistance and a reduction in renal perfusion. This latter constriction would then lead to reduced sodium excretion and increased blood pressure. Besides supporting studies looking at the effect of sFlt-1 excess in animals, we have strong supporting evidence for the effects of VEGF loss in cancer patients who receive antibodies to VEGF for their treatment. These antibodies bind and sequester VEGF similarly to sFlt-1, and tellingly, these patients often present with hypertension and proteinuria, suspiciously like pre-eclampsia patients.

This wasn’t the only mechanism that emerged, however. It became clear over time that women that had PE were exhibiting signs of increased inflammation. Interestingly, the earliest theories about the disorder focused on a belief that toxins were eliciting the maternal response, and for this reason pre-eclampsia was originally described as ‘toxaemia of pregnancy.’ Studies from both human patient populations and animal models of the disorder have repeatedly suggested that there is an increased activation of the maternal inflammatory response during PE. This takes the form of complement activation, inflammatory cell recruitment and activation, and production of inflammatory mediators known as inflammatory cytokines. Chief among these are the protein Tumour Necrosis Factor-α (TNF-α) and Interlukin-6 (IL-6). Animal models of pregnancy have reproducibly shown that infusion of inflammatory cytokines like TNF-α during pregnancy cause a hypertensive response which mimics that seen in PE, though they do not fully explain the range of symptoms. It has also become more and more apparent that inflammation can play a major role in cardiovascular disease and
hypertension by acting directly on the vasculature and altering its function. It is now commonly accepted that the maternal symptoms of pre-eclampsia are at least partially dependent on excess production of inflammatory factors, though their origin and exact composition are still an active area of research.

**Where do we go from here?**

Despite the intense body of research targeting pre-eclampsia in recent years, we are still far from understanding the disorder, and little in the way of new treatments have been forthcoming. The single biggest question is the nature of the (possibly immune-mediated?) underlying cause. This question has remained elusive, as suitable spontaneous animal models of pre-eclampsia have been unavailable, and studying human pregnancy in the earliest stages is difficult to impossible. Likewise, though we understand the importance of pathogenic proteins like sFlt-1 and inflammatory factors, we still don’t fully understand the molecular mechanisms which regulate these molecules, or ways that we could try to target them with drugs to help pre-eclampsia patients. And, while several potential therapies (PDE5 inhibitors, various anti-inflammatories, statins, etc.) have been suggested by animal research, a great deal of research remains to be done on their safety and efficacy during pregnancy and in both experimental models of pre-eclampsia and in the patient population. For all of our efforts, pre-eclampsia remains one of the great obstetrical complications without adequate treatment options. However, the inroads that we have made into understanding the disorder give us hope that new innovations are forthcoming in the near future. Regardless, a great deal of work remains before us if we’re to fully understand and treat this complex disorder.

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**Recommended Reading**