Pre-eclampsia trio

Pathogenesis and genetics of pre-eclampsia

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After more than a century of intensive research, pre-eclampsia and eclampsia remain an enigmatic set of conditions. Aberration of the interaction between placental and maternal tissue is probably the primary cause, but the exact nature of the differences from normal pregnancy remain elusive. In this review attempts to understand the sequence of physiological changes have concentrated on vascular endothelium and oxidative stress issues. There are genetic components to susceptibility, but the relative contributions of maternal and fetal genotypes are still unclear. Whole-genome mapping could ultimately define the causative genes.

Pre-eclampsia is a pregnancy-specific syndrome, recognised from antiquity as a leading cause of maternal and perinatal mortality,[1] diagnosed by the accompanying increased blood pressure and proteinuria, which affects 3–5% of pregnancies. It has been termed the "disease of theories", reflecting the confusion that surrounds the causes and pathophysiology of pre-eclampsia. Recent insights, however, may be clarifying this enigmatic condition.[2]

The pathophysiology of pre-eclampsia is much more than the increased blood pressure and altered renal function that facilitate diagnosis. Perfusion is decreased to virtually all organs, which is secondary to intense vasospasm due to an increased sensitivity of the vasculature to any pressor agent. Perfusion is proposed to be further compromised by activation of the coagulation cascade, especially platelets, with attendant microthrombi formation. Additionally, plasma volume is decreased by loss of fluid from the intravascular space, further compromising organ blood flow. The search for proximate pathophysiological changes requires identification of early alterations present before the profoundly disordered state that occurs with overt disease. With this proviso, increased platelet activation and markers of endothelial activation antedate clinically evident pre-eclampsia by weeks to months in groups of women destined to develop the disorder. This finding has led to the unifying notion that vascular endothelium could be an early target for pathophysiological modification in pre-eclampsia.[2] This hypothesis is supported by the well-established morphological alteration of glomerular capillary endothelium that accompanies the disorder, the presence of increased circulating concentrations of numerous markers of endothelial activation, and by alterations of endothelial function in vessels obtained from women with pre-eclampsia and examined in vitro.

Lancet 2001; **357:** 53–56

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Pre-eclampsia only occurs in the presence of a placenta and its resolution begins with the removal of the placenta. More than 50 years ago, E W Page suggested that the feature that characterised the pre-eclamptic placenta was its exposure to decreased perfusion.[3] This low perfusion in many cases is secondary to abnormal placentation. Whereas pregnancy is associated with striking modifications of the spiral arteries that provide the blood supply to the placenta, these changes do not take place normally in pre-eclampsia.[4] In normal pregnancy, the luminal diameter of the spiral arteries is very enlarged and the walls are remodelled such that they contain very little smooth muscle. These changes extend into the vessels to the inner third of the myometrium to provide a large bore, flaccid, low-resistance circuit for perfusion of the intervillous space. These modifications are associated with endovascular invasion of fetal trophoblast into these maternal vessels. Endovascular invasion and spiral artery remodelling occur either very superficially or not at all in pre-eclampsia. It seems likely that this abnormal implantation may be immunologically mediated. Pre-eclampsia occurs mainly in first pregnancies suggesting that exposure to paternal antigen is protective. This idea is supported by the increased risk of those who carry a pregnancy by a new father.[5] (Data indicating increased risk in women using barrier contraception have not been confirmed in another study.[6])

The maternal fetal tolerance that allows the intimate interaction of genotypically disparate cells in the intervillous space does not happen normally in pre-eclampsia, compromising appropriate endovascular invasion. Other conditions can also decrease placental blood supply and increase pre-eclampsia risk. Pre-existing maternal conditions that are associated with microvascular disease, such as hypertension or diabetes, or that are thrombophillic (eg, anticardiolipin antibody syndrome), increase the risk of pre-eclampsia. In addition, obstetric conditions that increase placental mass, such as hydatidiform moles or multiple gestations increase the risk of pre-eclampsia, apparently by a "relative" decrease of placental blood flow.

Predisposing factors

Pre-eclampsia, however, requires more than lowered placental perfusion. Other conditions such as intrauterine growth restriction[7] and the fact that approximately a third

of preterm births[9] manifest abnormal modification of the spiral arteries identical to that present in pre-eclampsia, suggest that pre-eclampsia is a two-stage disorder. Numerous maternal factors can predispose to the disorder; these may be genetic, behavioural, or environmental. The list of predisposing factors includes hypertension, diabetes, increased insulin resistance, increased testosterone, black race, and increased blood homocysteine concentration. Interestingly, these are also risk factors for other endothelial diseases, particularly atherosclerosis and the late complications of diabetes mellitus.[8] Pre-eclampsia, atherosclerosis, and diabetes also share a common dyslipidaemia. Increased triglycerides, decreased HDL, and an increased concentration of small dense LDL are characteristic of these disorders. In addition, although the classic work of Leon Chesley showed that pre-eclampsia does not cause cardiovascular disease,[9] the work of Fisher and associates indicates that women who have a pregnancy without pre-eclampsia have less risk of cardiovascular disease in later life.[10] This finding supports common risk factors for pre-eclampsia and atherosclerosis, with normal pregnancy a screening test indicating the absence of these factors.

Oxidative stress

A current hypothesis explaining the endothelial alterations in atherosclerosis invokes oxidative stress as pathogenically important.[11] The small dense LDLs which are part of the atherogenic dyslipidaemia are proposed to have preferential access to the subendothelial space, where they bind to proteoglycans and reside longer than other LDLs. Small dense LDL are inherently more easily oxidisable. Protected from circulating antioxidants in the subendothelial space, they form oxidised LDL. Oxidised LDL are quite reactive and alter membrane protein and phospholipids, and increase the expression of signalling molecules which recruit monocytes. The membrane damage by oxidised LDL alters endothelial function while monocytes take up oxidised LDL to form foam cells and eventually the fatty streak characteristic of atherosclerosis. It has been proposed that, as with atherosclerosis and diabetic vasculopathy, oxidative stress is a component of pre-eclampsia which could provide the linkage between decreased placental perfusion and the maternal syndrome.[12] Maternal predispositions could interact with the poorly perfused intervillous space to generate reactive oxygen species. Markers of oxidative stress have been detected in the blood of women with pre-eclampsia for over 40 years. Although morphological changes reminiscent of the atherosclerotic lesion are seen only in decidual vessels, the alterations of endothelial function present in pre-eclampsia, including lower endothelial-mediated relaxation, are similar to that of atherosclerosis. Several suggestions, have been advanced to explain the transfer of oxidative stress from the intervillous space to the systemic circulation. Activated neutrophils and monocytes are present in pre-eclampsia. These cells could be activated by oxidative stress in the intervillous space and then generate free radicals on contact with endothelium. Again, the consequences of this interaction are defined by maternal factors (decreased antioxidants, sensitised endothelium, lipoproteins especially sensitive to oxidation). Transfer of oxidative stress could also be secondary to the formation of stable products of lipid peroxidation (eg, malondialdehyde) or by oxidised fragments of syncytiotrophoblast entering the systemic circulation. Finally the hypoxic placenta might produce cytokines with the potential to generate oxidative stress. Administration of antioxidants to women in early pregnancy decreased oxidative stress, endothelial activation, and the frequency of pre-eclampsia, which lends support to the potential role of oxidative stress in pre-eclampsia.[13] Larger studies are now underway to reproduce this finding and assess safety for the fetus.

Pre-eclampsia is proposed to be a disorder secondary to decreased placental perfusion interacting with maternal constitutional factors to result in oxidative stress, endothelial activation, and a multisystemic maternal disease. Perhaps the alterations in maternal physiology and metabolism in pre-eclampsia which lead to oxidative stress could be appropriate fetal/placental directed responses to increase substrate delivery across the poorly perfused placenta. Pre-eclampsia occurs in a subset of women unable to tolerate these modifications.

The genetic constitution of mother and baby might potentially affect maternal fetal interactions at several levels. Thus, the genetically defined immunological relationship between mother and baby could be an important determinant of successful implantation. However, maternal factors that might increase sensitivity to fetal/placental signals of decreased perfusion could also be important. For example, in the model that posits oxidative stress as the linkage between lowered placental perfusion and the maternal syndrome, genetically mediated deficiencies in antioxidant activity, metabolic variants, which increase sensitivity to free-radical challenge, including dyslipidaemias, or that may themselves induce oxidative stress such as hyperhomocysteinaemia, could all contribute. Similarly, the relation between pre-eclampsia and atherosclerosis suggests that the study of genes associated with increased cardiovascular risk including those that modulate the renin angiotensin system, the haemostasis cascade, and especially lipid metabolism, could be important in understanding the link between the abnormal placenta and the maternal syndrome.

Genetic factors

The hypothesis that the cause of eclampsia and pre-eclampsia is at least partly genetic is broadly suggested by its occurrence in time and space. The earliest record of eclampsia was in the Kahun papyrus from Egypt of 3000 years ago.[14] Data on its occurrence per confinement in 18th century and 19th century Europe, principally in Germany and France, have been summarised by Chesley.[1] Davies[15] has listed the 741 papers on the geographical distribution of occurrence of pre-eclampsia published up until 1971. These two massive compilations of information suggest that eclampsia and pre-eclampsia can occur under all environmental conditions—thus purely environmental hypotheses are implausible.

Early attempts to interpret genetic data on susceptibility[1] illustrate a recurring theme in all eclampsia and pre-eclampsia research over more than a century. As fundamental advances in understanding biological systems are made, the new knowledge is used to attempt to find the cause(s) of these conditions. In genetic terms, the most recent hypothesis to be advanced is genetic imprinting.[16]

Genetic analysis is made very difficult by the nature of the conditions which occur only in women who have reproduced. It is not clear whether the maternal genotype, the fetal genotype, or some combination of both is responsible. The greatly decreased incidence in second and later pregnancies makes analysis of the fetal contribution very difficult. Additionally, as serious collection of family genetic data was initiated in the last few decades, the increase in the quality of care caused the incidence of eclampsia to fall in the populations under

study, which were mostly western European. Eclampsia is an unambiguous phenotype but pre-eclampsia is easily confused with other hypertensive disorders of pregnancy.[2] Lack of data in men and uncertainty of diagnosis has blunted the admittedly not very great power of conventional genetic analysis to reveal the mode of inheritance.

Nonetheless, such data suggest that genetic factors play a major part. Collection of genetic data was initiated by Chesley[17] and has been continued by other groups.[18–23] Most of the family data suggest that the maternal genotype is responsible for susceptibility, with only a minor part being played by the fetal genotype.[24] However, a Norwegian study has ascribed an influence to the fetus.[23] There is a striking lack of concordance between monozygous twins.[25–27] Changed paternity is a significant risk factor for eclampsia and pre-eclampsia in multiparous women.[6,28] Together with discordant twins this is best explained by a fetal genotypic influence. Further support for a fetal contribution is indirectly suggested by data showing that a period of cohabitation[29] or a period of exposure to paternal antigens[5] affects susceptibility.[29] The relative contributions of the two genotypes will probably only be apparent once the fundamental biological classification of these conditions is established, which could quite possibly vary between populations.

Modern attempts at genetic modelling of these conditions were by Cooper and Liston.[18] They proposed a single recessive gene, which is clearly incompatible with subsequently collected data. Arngrimsson and colleagues[22] suggested that a single dominant gene with incomplete penetrance could be acting in the mother. Broughton-Pipkin[30] supports the current majority view that pre-eclampsia is under multifactorial control; the evidence for this is weak if the condition is strictly defined. Eclampsia and pre-eclampsia-like symptoms occur in several other conditions, such as multiple pregnancy, hydatidiform mole, fetal chromosomal abnormalities, and placental hydrops. In genetic terms these are phenocopies. The extent to which they would contribute to the population incidence of the disorder, if its definition were to be widened to include them is small, and the pathways through which they each produce symptoms are probably different. One of us (DWC) believes that the hypothesis of a single gene whose expression is pregnancy-specific and which is alone responsible for the progression from pre-eclampsia to eclampsia should still be seriously investigated. If the single gene hypothesis is correct, a DNA-based test could allow identification and specific management of putative eclampsia-susceptible patients. Such tests will be more expensive and probably of less predictive value if several genes are involved.

Another kind of genetic study involves a mix of population association and candidate gene approaches. The possibility that the dependence of incidence on parity might have an immunological basis has led to many studies on the HLA system, with suggestions of weak and diverse influences. Linkage studies decisively rule out any direct influence of HLA genes, at least for western European populations.[31,32] A later suggestion that HLA-G might be involved was also discounted.[33] Genes that affect blood pressure have come under investigation and work on angiotensin has produced both positive and negative results.[34–37] Associations with other genetic markers have been studied; examples are lipoprotein lipase;[38] methylenetetrahydrofolate reductase;[39] factor V Leiden;[40] and apolipoprotein E.[41] There have been many studies on the population association/candidate gene approach but there are no clear conclusions.

In principle, a whole-genome linkage study is the most powerful way of identifying disease-susceptibility genes wherever there is a strong genetic component. In practice, the uncertainties of diagnosis combined with the huge effort needed to assemble the family and medical records information make this a slow and expensive effort. Linkage studies fall into two categories, exclusion maps that eliminate candidate genes, and whole-genome searches that positively identify portions of the genome where susceptibility loci might lie. If positive evidence is found, fine mapping can be carried out followed by positional cloning. So far, a number of regions have been excluded eg, HLA.[31,32] Whole-genome searches have so far been inconclusive. Unless the lod scores are very high, results from single investigations should be regarded as hypothesis-generating rather than definite evidence of the presence of susceptibility loci. Suggestive positive lod scores have been found for a candidate region on 4q in one study,[42] but not in another.[43] Similarly a region of 7q36, which contains the eNOS locus involved in blood-pressure regulation has been identified in two studies,[44,45] but not in later work by these investigators,[43] or in another independent study.[46] The eNOS locus itself is probably not a candidate for eclampsia and pre-eclampsia susceptibility.[47] Arngrimsson and colleagues[43] have reported the highest lod score for a region on 2p13 without any obvious candidate genes, which has been confirmed.[48]

Where should genetic studies of pre-eclampsia and eclampsia be directed? The candidate gene approach is probably best directed towards genes involved in the maternal fetal interaction as described above. Especially pertinent to the single-gene hypothesis are genes expressed in pregnancy, in either the placenta or the decidua, preferably genes expressed exclusively in pregnancy. Linkage studies require investigation of many more families under study than now available. A major gap in attempts to understand the mode of inheritance and to find linkage is the absence of any large-scale study on non-European populations. Both the pathology and the genetics give more precise insights into the nature of pre-eclampsia and eclampsia, but the goal of obtaining an understanding of their fundamental causes remains tantalisingly elusive.

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