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REVIEW ARTICLE

The pathophysiology of pre-eclampsia

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ABSTRACT

The etiology of pre-eclampsia, a disorder specific to pregnancy, has not yet been clearly established. Generalized endothelial dysfunction is thought to occur. Inadequate trophoblast invasion at the feto-maternal junction has also been postulated as the cause. However, recent findings are more suggestive of an inappropriate maternal inflammatory response within the framework of placentation, the innate immune system being primarily involved. This exaggerated maternal intravascular inflammatory reaction to the invading trophoblast leads to the manifestations of pre-eclampsia in the mother and feto-placental unit. The extent of the inflammatory reaction, which is also present in normal pregnancy, is probably determined by genetic factors and any pre-existing disorder affecting the mother or fetus. The process is very complex and cannot be attributed to any one single cause.

Keywords: Placenta, pre-eclampsia, trophoblast, etiology, immune.

INTRODUCTION

In 1694, Mauriceu recognised that convulsions of pregnancy often ceased when the baby was delivered. Hence he postulated that they were probably due to malignant vapours arising from the decomposition of the fetus which was often dead in utero in this condition[1]. Over the next three centuries attempts have been made to identify the aetiology and understand the pathogenesis of this condition. During the 18th and 19th centuries the links with oedema, hypertension and proteinuria were recognised. Many toxins of maternal, fetal or environmental origin were thought to be responsible[2]. Several theories were postulated to explain its pathogenesis prompting it to be called the disease of theories[3].

All patients with pregnancy induced hypertension were initially grouped together and it was only during the last two decades that it was appreciated that pre-eclampsia was probably a distinct entity in itself and quite different from gestational hypertension[4,5,6]. The most recent theory is that pre-eclampsia is due to vascular endothelial dysfunction resulting from vasoactive substance/s secreted into the maternal circulation by an ischaemic placenta[7,8,9].

The aetiology of pre-eclampsia remains obscure at present. Inadequate invasion of the trophoblast into the spiral arteries and endothelial dysfunction have been identified as important signs of this syndrome, but not its cause.

Placentation and pre-eclampsia

In humans, the invasion of trophoblast cells into the decidualized endometrium and the inner third of the myometrium is of vital importance for both the anchoring of the placenta and connection with the maternal vascular system. The placenta becomes anchored by extensive invasion of the decidua by cytotrophoblast cells, this process being limited physically and restricted to the first 18 weeks of pregnancy. During this process the trophoblast comes into contact with the spiral arteries, and the trophoblast cells flood into the lumen and replace the endothelial cells. Immunohistochemical investigations revealed that the cytotrophoblast takes on an adhesion-receptor profile similar to that of the endothelial cells[65], thereby replacing them by means of a kind of mimicry. These physiological changes lead to reduced vascular resistance and a considerable increase in blood supply to the fetus. This trophoblast invasion appears to occur in two phases up to about the 18th week of pregnancy. In pre-eclampsia and some cases of intra-uterine growth retardation, the physiological changes in the

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spiral arteries are confined to their decidual segments. A third to a half of the length of the spiral arteries in the placental bed is not affected by the endovascular trophoblast invasion so that the myometrial segments remain intact. The reason for the incomplete trophoblast invasion of the myometrial segments of the spiral arteries associated with pre-eclampsia is unclear. The main problem in research into this condition is the lack of material for morphological investigation from the first trimester, the stage at which the disease arises. Invasion by the trophoblast is a process that is finely balanced between the invasive potential of the cytotrophoblast and the maternal defense mechanisms.

Utero Placental Ischaemia

In a normal pregnancy, migratory extravillous trophoblasts invade the wall of the spiral arteries of the uterine wall, destroy the muscular elastic layer of the media of these vessels and replace it with a trophoblast and amorphous matrix containing fibrin. These arteries which supply the interavillous spaces are thus converted into low-pressure high flow utero placental vessels. The decidual and myometrial segments of these spiral arterioles undergo these changes. Increased permeability of the endothelial cell wall leads to extravasation of fluid, hypovolaemia, oedema, proteinuria and decreased cardiac output (CO). Another factor in the aetiology of placental ischaemia is abnormal placentation which is believed to be immunologically mediated.

Consumptive Coagulopathy

Activation of the coagulation system and hypercoagulability is a normal physiological adaptation to pregnancy. This leads to an increase of both Factor VIII activity as well as Factor VIII antigen keeping the ratio between them constant[32]. In pre-eclampsia this hypercoagulable state is accentuated. The excess thrombin destroys Factor VIII activity and the final levels of Factor VIII activity are low. The difference between Factor VIII antigen and the Factor VIII activity will reflect the extent of Factor VIII consumption and this difference is not only detected early in pre-eclampsia it also reflects its severity[33,34]. Fibrinopeptides A & B that are formed as a result of thrombosis are also increased [35,36]. The levels of the regulating proteins Antithrombin III[37], Protein C[38] and Protein S[39] too are decreased as a result of consumption by thrombin binding and these changes too precede the clinical onset of pre-eclampsia.

Pre-eclampsia is also associated with thrombocytopenia probably caused by immunologically mediated platelet activation and consumption in the microcirculation of the kidneys, liver and placenta[40,41]. This may result in an increased mean platelet volume due to younger and larger platelets in the peripheral circulation[42]. This ultimately leads to a diminished platelet responsiveness to aggregating agents[41].

A mutation (R506 Q) in the coagulation Factor V which leads to resistance to activated Protein C may cause the HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome[43].

Fibrinolysis

In pre-ecalmpsia there is evidence of increased fibrinolysis such as reduced levels of plasminogen and fibrinogen. However, there is conflicting evidence of both increased and decreased plasminogen activators as well as fibrin-fibrinogen degredation products. Whether these changes are causative or whether they occur, as a result of the disease condition is not clear[44].

Kidney

Initially there is an impairment of tubular function, which results in reduced clearance of uric acid and increased serum uric acid[45]. Later glomerular endotheliosis (subendothelial fibrinoid deposition, swelling of glomerular epithelium and occlusion of capillary lumen) results in a selective proteinuria of intermediate weight molecules viz. albumin, transferrin and δ globulin. This leads to hypoproteinaemia, reduced oncotic pressure and oedema[46,47].

Although proteinuria especially if it occurs early is known to have a poor prognosis especially for the fetus, it is suggested that neither its severity nor its rate of increase is a good predictor of maternal or neonatal outcome[48].

Liver

It is thought that in pre-eclampsia segmental vasospasm of the hepatic arterial bed leads to a localised coagulopathy, which results in peri portal haemorrhage and liver cell necrosis[49,50]. This probably leads to elevation of liver enzymes[51].

Liver dysfunction (eg. acute fatty liver of pregnancy) occurs in the absence of pre-eclampsia. Hence there is no consensus as to what hepatic changes may be considered as being primarily due to pre-eclampsia[52,53].

The HELLP syndrome is a well-recognised complication of pre-eclampsia[43,54,55] and carries a poor fetal and maternal prognosis. It may be due to severe

hepatic vasospasm or genetic factors[43]. Either frank or subclinical Disseminated Intravascular Coagulation is often associated with it[56,57]. Severe hepatic vasospasm may also rarely result in hepatic infarction and rupture which are often fatal[58].

Haemodynamic Effects

The haemodynamic changes in pre-eclampsia are not fully understood as yet. The majority appear to have a reduced plasma volume, decreased cardiac output (CO), vasoconstriction and hypoperfusion of placenta and kidneys[15–18].

A hyperdynamic model with increased CO and compensatory vasodilatation has been described recently[19]. The authors proposed that the elevated levels of atria natriuretric factor[20], increased clearance of dehydroepiandrosterone sulphate[21] and the increased sensitivity to pressor agents[22], all supported this hypothesis. They postulated that as these women had already compensated to the increased CO by vasodilatation, they were unable to respond to any additional increase in blood pressure and thus they were more susceptive to pressor agents. However it is also possible that this hyperdynamic model is due to the effects of treatment[23].

Cerebral Effects

Eclamptic convulsions are the most dangerous clinical sequelae. This is most likely due to intense vasoconstriction of the cerebral arteries which results in ischaemia and oedema especially of the parietal and occipital lobes which leads to abnormal electrical activity resulting in the triggering of convulsions[59].

Retinal[60] or cortical[61] blindness are rare complications of eclampsia. The commonest cause of death in women with eclampsia is cerebral haemorrhage[47].

An alternative theory is that the hypertension results in a breakthrough in cerebral autoregulation, which results in a forced overdistention of intracranial arteries leading to endothelial damage, which results in extravasation of fluid and cerebral oedema. However this vasodilatation could also be explained as being due to treatment[44].

Two stages at 10 – 12 weeks and 14 – 16 weeks gestation respectively[7,9,10].

In pre-eclampsia, the above pathophysiological changes are either absent or are limited to the decidual segments only[7,10,11]. This presumably leads to placental hypoperfusion and ischaemia. However, it has been found that the absence of these changes does not necessarily lead to either uteroplacental ischaemia or pre-eclampsia. On the other hand normotensive pregnancies associated with intra uterine growth restriction too have been found to have a significant proportion where these changes were absent[12]. The role of vasoactive substances such as plasminogen activator, metalloproteinases, cytokines (Tumor Necrosis Factor α – TNF α, Interleukin 1-β, Transforming Growth Factor β)[13], and the molecules integrin, cadherin and certain immunoglobulins[14] in regulating trophoblastic migration is not clear.

Predisposing Factors

Pre-eclampsia is more common in conditions where placental oxygen demand is increased. eg. multiple pregnancy, trophoblastic tumours and hydropic placenta (Table I). It is also common in conditions where placental transfer is decreased. eg. primigravidae, abnormal placentation and pre existing vascular disease (chronic hypertension, collagen vascular disease, Diabetes mellitus etc). These features support the role of placental ischaemia in the pathogenesis of this condition. Genetic predisposition and environmental factors may also modify the threshold for the clinical manifestations of the condition.

TABLE I

Factors predisposing to pre-eclampsia

Increased oxygen demand
Multiple pregnancies
Hydatidiform mole
Hydropic placenta
Decreased oxygen transfer
Primigravida
Microvascular disease (hypertension, diabetes, collagen disease)
Abnormal placentation

ENDOTHELIAL CELL DYSFUNCTION IN PRE-ECLAMPSIA

Normal endothelium function

The endothelium, a monolayer of epithelial cells, is in direct contact with the blood and constitutes a physical and metabolic barrier. Among other known functions, it regulates capillary transport, controls plasma lipid content and- modulates vascular smooth muscle reactivity in response to various stimuli. To maintain

vascular function, endothelial cells synthesize several substances, including large molecules such as fibronectin, heparan sulphate and growth-promoting factors and smaller molecules such as prostacyclin (PGI_2), nitric oxide (NO), platelet-activating factor and endothelin. PGI_2 and NO are considered to be the most important mediators of vasodilation and normally inhibit human platelet adhesion to vascular endothelium and play a synergistic role in the homeostatic regulation of platelet-vessel wall interactions[66]. In addition, the endothelium plays an active role in preventing blood clot formation in vivo and in fibrinolysis, through release of plasminogen activators. Conversely, the endothelium can become thrombogenic by secreting von Willebrand's factor, which acts as a cofactor for platelet adhesion, and by secreting platelet-activating factor. According to the wide range of functions displayed by endothelial cells, it is an attractive hypothesis that endothelial cell dysfunction plays an important role in the pathophysiology of pre-eclampsia.

Endothelial cell damage

Regardless of its causes (increased consumption or decreased oxygen availability) placental hypoperfusion is proposed to lead to the production of circulating factors that modify endothelial cell function (for review see Ness and Roberts[67].) Damage to the endothelial cells will have several consequences, including activation of the coagulation cascade, fluid extravasation due to loss of integrity of the endothelial barrier and increased pressor effects of vasoactive substances, all of which correspond to clinical features of the pre-eclamptic syndrome. In addition, endothelial synthesis of PGI_2 and NO is reduced in women with pre-eclampsia. Their deficit would have a role in the reversal of the pregnancy-induced refractoriness to vasopressor agents and increased thrombosis. Moreover, dysfunctional endothelium would activate platelets that subsequently release thromboxane. The resulting increase in the thromboxane: prostacyclin ratio would favour relative or absolute vasoconstriction[66].

Recent experiments have demonstrated that the NO synthase pathway is activated in normal pregnancy as assessed by the increased plasma concentration, urinary excretion and metabolic production rate of cyclic guanosine 3', 5'-monophosphate (cGMP), the second messenger of NO, in gravid rats. In addition, urinary excretion of nitrate, the stable metabolite of NO, increases in parallel to the rise in cGMP. There is convincing evidence indicating that expression and activity of different NO synthases are increased in pregnant animals. Acute blockade of NO synthase causes a dose-response increase in blood pressure and reverses the blunted vasopressor response to vasoconstrictor agents, whereas long-term NO synthase inhibition produces a pre-eclampsia-like syndrome characterized by maternal hypertension, proteinuria, thrombocytopenia, plasma volume contraction, reduced plasma renin activity, renal morphological abnormalities and fetal growth restriction. In addition, in vitro studies have demonstrated that endothelial-derived relaxing factor released by endothelial cells of human umbilical vessels is impaired in pregnancy-induced hypertension. This finding is compatible with an alteration of endothelial cell number or an alteration of the enzymatic pathway due to cytotoxic factors. Taken together, these data suggest that a disturbance in NO release, either primarily or secondarily to endothelial cell dysfunction, may play an important role in the pathogenesis of pre-eclampsia.

In addition to the loss of protective functions, damaged endothelial cells express new functions. Results from prospective studies revealed increased circulating levels of factor VIII antigen, growth factor activity and cellular fibronectin levels several weeks before the clinical onset of the disease. These substances are considered markers of endothelial cell activation, thus indicating that endothelial cell dysfunction may be the cause rather than the consequence of the increased blood pressure observed in pre-eclampsia. In addition to the biochemical evidence of endothelial cell injury, the characteristic glomerular endotheliosis and ultrastructural changes in the placental bed provide morphological evidence of this damage[66].

As a consequence of endothelial cell damage, the clinical syndrome of pre-eclampsia will develop, leading to vasospasm and increased blood pressure, abnomal coagulation and thrombosis, increased permeability and the corresponding oedema, proteinuria and hypovolaemia.

It is postulated therefore that in pre-eclampsia the ischaemic placenta secretes vasoactive substances, which circulate in the maternal circulation and cause endothelial, cell activation and/or dysfunction[7,8,9]. The vascular endothelium is ubiquitous and this could explain the multi organ/multi system involvement in pre-eclampsia.

Pre-eclampsia: a maternal systemic inflammatory reaction?

There is no doubt that the placenta itself represents the starting point for the development of pre-eclampsia. In the rare case of an extrauterine pregnancy that

continued into the third trimester and in which the placenta could not be removed after delivery of the child, the condition was found to persist. It is also interesting to note that the importance of the placenta is not expressed in full-blown pre-eclampsia until the second half of pregnancy. Recent reports suggest that the clinical features of pre-eclampsia could best be explained as the result of an excessive maternal inflammatory response[68], there being inflammatory changes even in normal pregnancy. Pre-eclampsia can therefore be thought of as an exaggerated maternal inflammatory response to the inflammatory agent placenta/pregnancy.

If one regards the interaction between mother and fetus as a genetic conflict because the genes of the mother and fetus do not necessarily share the same interests, it is easy to come to the conclusion that pre-eclampsia could be a maternal defense mechanism[69]. The active genes of the fetus (trophoblast) represent a mixture of the mother's own genes and foreign (paternal) genes and their function is to promote fetal development. The active maternal genes selectively protect the interests of the mother. If the fetal/trophoblast genes are prevalent and their effects are not kept within reasonable limits by a maternal counter-reaction, there is excessive trophoblast invasion, leading ultimately to uterine rupture and the death of both mother and child. The maternal genes therefore have to counteract this trophoblast penetration, either by the output of signals to the trophoblast itself or by a pronounced defence response. In the course of evolution of placentation, a corresponding and over-emphasis on these maternal "defense" genes had to develop because excessive trophoblast invasion occurring in the majority of cases could have led to extinction of the species. On the other hand, over-reaction of the maternal defense mechanisms leads to occasional loss of the fetus, but does not prevent further pregnancies. Thus the maternal "defense" genes were able to prevail in a population during the course of evolution and every feto-maternal relationship is characterized by a "genetic conflict". To avoid escalation of this conflict, it is necessary for mother and fetus to interact, that is, exchange appropriate signals. However, this communication does not always function perfectly: there are several conditions in which the "fine tuning" between maternal and fetal interests appears to be faulty, for example in the case of abortion and pre-eclampsia. They represent an inappropriate response of the mother to the fetus/trophoblast. The maternal inflammatory response to pregnancy appears to have been necessary from an evolutionary point of view for the rejection of abnormal conceptuses[69]. Inadequate placentation in pre-eclampsia could be a result of the maternal inflammatory attack on the conceptus.

Although inadequate trophoblast invasion is often cited as the cause of pre-eclampsia there is as yet no proof of this as the findings are purely descriptive and lack functional substantiation. For example, intrauterine growth retardation and small placental size are not always associated with pre-eclampsia. Fetal growth retardation is found with viral infections, genetic aberrations, maternal malnutrition and smoking. In many cases, no cause is found. Hypertension is typical of pre-eclampsia, but acute generalized inflammation such as sepsis is accompanied by a fall in blood pressure or even shock. This discrepancy may be related to the quantity of inflammatory stimuli and the duration of exposure to them[10]. The reduced trophoblast invasion in pre-eclampsia appears to be a part of the condition and not its cause. Although there are many smilarities between pre-eclampsia and inflammatory events various questions remain to be answered. What is the agent that triggers this inflammory reaction? If it is to be found in cytotoxic or pathogenic trophoblastic elements, why is the condition more common in first pregnancies. The first partner (primipaternity) appears to play an important role. Vaginal exposure to paternal antigens resulting from prolonged sexual cohabitation with the same partner before conception would seem to have a protective effect[71]. Pre-eclampsia is more common in molar pregnancies in which the conceptus contains only paternal genes.

Animal experiments have also produced evidence for infection as a possible cause of pre-eclampsia. In rats, it was found that a single intravenous microdose of endotoxin on day 14 of pregnancy induced hypertension, proteinuria, and DIC that persisted until the end of pregnancy (day 21). This effect was observed only in pregnant animals. An increase in polymorphonuclear leukocytes and macrophages, indicative of a marked inflammatory reaction, was also present in various organs, including the kidney, until the end of pregnancy. The fact that this sensitivity to endotoxin was confined exclusively to pregnancy suggests that the monocytes are in a "primed" state during pregnancy. This reaction, which is attributed to the innate immune system, probably occurs mainly in species with hemochorial placentation (e.g., in humans, the rat and the mouse) because there is direct contact between the trophoblast and maternal blood (Fig. 1) The innate immune system is older from the evolutionary point of view and less specific than the adaptive immune system, and appears to be responsible for the extent of

the inflammatory reaction in pre-eclampsia. The complement system is also part of the innate immune system; it is activated by foreign antigens, and this activation leads to an inflammatory response. Complement activation at the feto-maternal interface leads to a strong inflammatory reaction in the mouse placenta and loss of the embryo[72]. It is possible that such phenomena may play a role in pre-eclampsia, but more research needs to be done in this area.

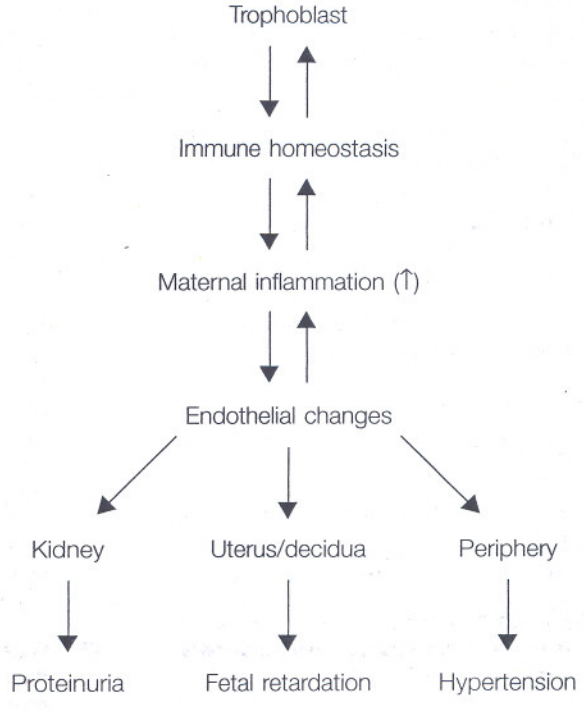


Fig. 1. The fetal trophoblast induces an inflammatory response in the mother. In normal pregnancy, the signals produced by the trophoblast and the maternal response (e.g. "cytokine crosstalk") are in equilibrium (immune homeostasis). The maternal inflammation leads to endothelial changes, which, in normal pregnancy, often manifest themselves as edema. The extent of the inflammatory reaction and the endothelial changes are in equilibrium. In pre-eclampsia (↑), a more exaggerated maternal inflammatory response, which shares similarities with the features of sepsis, leads, via enzymes, cytokines, etc, to a state of imbalance with endothelial damage. This, in turn, causes damage to various organ systems, the extent of which determines the clinical manifestations of pre-eclampsia.

CONCLUSION

It is important to differentiate pre-eclampsia from non-proteinuric gestational hypertension. The exact aetiology and pathogenesis of the condition is still an enigma. In 1694, Mauriceu suggested that it was probably due to a 'toxin' produced by a dead fetus. The knowledge today is not much different.

Current evidence suggests that the initiating factor is probably placental ischaemia due to failure of the endovascular trophoblastic invasion. This leads to the release of a vasoactive substance/s (similar to the TNF α produced by macrophages) into the maternal circulation which in turn activates/damages endothelial cells throughout the body (in all organs) thus resulting in multi organ dysfunction and the primary features of hypertension, coagulopathy, and proteinuria. The associated imbalance of vasoconstrictor and vasodilator substances in the circulation may be a cause or an effect of the endothelial activation/damage. Maternal immune maladaptation to the pregnancy and genetic factors may also have a role in its pathogenesis.

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