Pre-eclampsia: pathophysiology and clinical implications

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ABSTRACT

Pre-eclampsia is a common disorder that particularly affects first pregnancies. The clinical presentation is highly variable but hypertension and proteinuria are usually seen. These systemic signs arise from soluble factors released from the placenta as a result of a response to stress of syncytiotrophoblast. There are two sub-types: early and late onset pre-eclampsia, with others almost certainly yet to be identified. Early onset pre-eclampsia arises owing to defective placentation, whilst late onset pre-eclampsia may center around interactions between normal senescence of the placenta and a maternal genetic predisposition to cardiovascular and metabolic disease. The causes, placental and maternal, vary among individuals. Recent research has focused on placental-uterine interactions in early pregnancy. The aim now is to translate these findings into new ways to predict, prevent, and treat pre-eclampsia..

Introduction

Eclampsia has been documented for more than 2400 years, and features of the prodromal syndrome pre-eclampsia (previously referred to as toxaemia of pregnancy) have been documented for almost 200 years. The pathophysiology of these conditions, however, remains poorly understood, limiting therapeutic interventions. It has long been established that a placenta, but not a fetus, is required, and that the syndrome eventually resolves once the placenta is removed. Hence, in terms of pathogenesis it is primarily a placental disorder. Although commonly portrayed as a distinct entity, pre-eclampsia, at least its early onset variety, is just one in a spectrum of complications of pregnancy that share a common pathophysiology centered upon disordered placentation. That spectrum, referred to as "disorders of placentation" or the "great obstetrical syndromes," includes late spontaneous miscarriage, abruptio placentae, fetal growth restriction (FGR), pre-term rupture of the membranes, and premature delivery.[1] The lack of spontaneous pre-clinical animal models for these conditions has limited our understanding, but the recent advances in "omics technologies"[2] and the derivation of organoid cultures of the endometrium[3] and placental trophoblast[4 5] create new opportunities for systematic research.

This review considers modifications to the definition of pre-eclampsia, and the epidemiology, prediction, treatment, and long term consequences of the syndrome. In terms of the pathophysiology, the review summarises emerging evidence that there are at least two sub-types: early and late onset pre-eclampsia, with others almost certainly yet to be identified.[6] Early onset pre-eclampsia is widely acknowledged to have primarily a placental cause, while late onset pre-eclampsia may center around interactions between senescence of the placenta and a maternal genetic predisposition to cardiovascular and metabolic disease. While often presented as distinct sub-types, in reality the balance between the placental and maternal causations most likely varies among individuals across the spectrum of gestational age at clinical presentation. We discuss the pathophysiology in the light of recent advances of our understanding of the maternal-fetal interactions that take place in the first weeks following implantation, and emphasize the importance of the endometrium during the pre- and peri-conceptional periods for pregnancy success.

Sources and selection criteria

A PubMed search (pre-eclampsia OR preeclampsia) AND (placenta OR placental)] at the end of 2018 with no date restrictions yielded 10 611 citations. About 10% of our references date from the last century, the earliest to 1953. The rest were published in this millennium, the most recent in 2019, and more than one third in the last five years. We considered only articles published in English. Additional articles and references were obtained by searching the bibliography of published papers. Most of the chosen references are exclusively data based. Trivial, repetitive, or inconsistent research reports were rejected. In this way, we summarized what is known about the pathophysiology and clinical aspects of pre-eclampsia.

Definition

Defining pre-eclampsia is difficult because it is a syndrome characterized by a group of clinical features that, when they occur together, lead to diagnosis and treatment. There is no gold standard, and all the features

are, in isolation, non-specific. Numerical features such as arterial blood pressure or proteinuria are defined by thresholds, which themselves are arbitrary. Hence, while the definitions seem precise, they are not securely based and leave important uncertainties. Only a definition based on unique pathogenic feature(s) will resolve this unsatisfactory situation.

Until recently, the accepted definition of pre-eclampsia was new onset hypertension and proteinuria developing in the second half of pregnancy and resolving after delivery. The more common and less dangerous new onset hypertension without proteinuria was called gestational hypertension.[7] Subsequently, refinements have been proposed, but new onset hypertension remains common to all versions. Currently, the diagnosis endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) embraces new onset hypertension (systolic >140 mmHg and diastolic >90 mmHg) accompanied by one or more other features: proteinuria, other maternal organ dysfunction (including liver, kidney, neurological), or hematological involvement, and/or uteroplacental dysfunction, such as fetal growth restriction and/or abnormal Doppler ultrasound findings of uteroplacental blood flow.[8] The categories of hypertension in pregnancy recognised by the ISSHP are shown in fig 1.

As the pathophysiology becomes clearer, assays of biochemical markers, such as maternal concentrations of angiogenic or anti-angiogenic factors, are being developed to improve diagnosis and prediction.[9 10] These assays may eventually be incorporated into more precise definitions of pre-eclampsia, and of related placental syndromes. Consequently, hypertension itself is not a necessary part of the syndrome.[11]

Both the ISSHP and the American College of Obstetricians and Gynaecologists recommend that the terms "severe" and "mild" pre-eclampsia should no longer be used, as all cases are potentially threatening clinically.[8] By contrast, the distinction between the early and late onset forms of the syndrome is increasingly recognized, with a watershed of 34 weeks' gestational age·6

Epidemiology

The complexities of defining pre-eclampsia affect the accuracy of determining its incidence, especially across different countries. Ascertainment is incomplete in low and/or middle income countries (LMIC), and standardization of diagnostic accuracy is almost impossible. Rates based on institutions will be biased by referral of cases, especially in tertiary centers where most research is con-

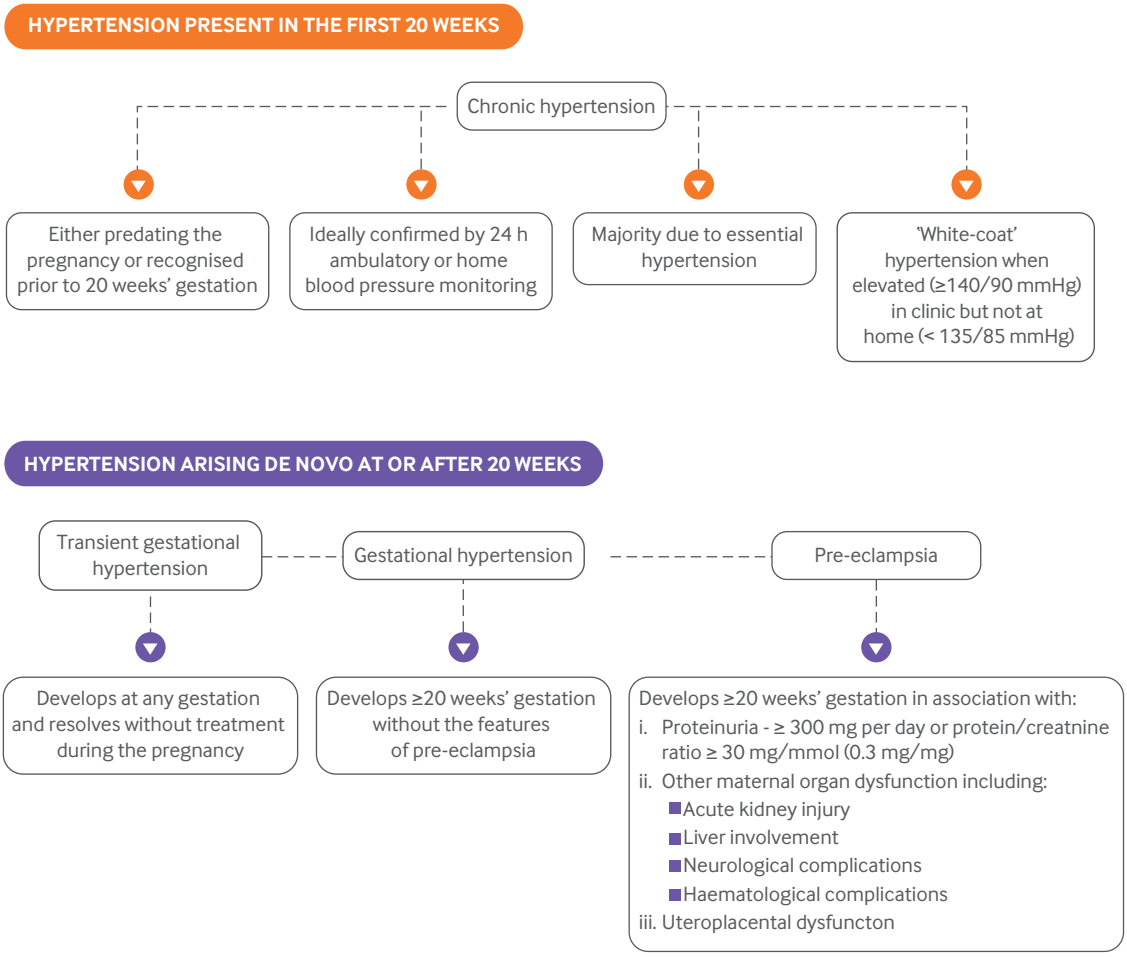

Fig 1 | Categories of hypertension in pregnancy recognised by the ISSHP[8]

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ducted. A global estimate derived from data of nearly 39 million pregnancies suggests an incidence of 4.6%.[12] Wide regional differences are found, with a reported incidence as low as 0.4% in Vietnam.[13] The condition is especially common in women indigenous to, or with ancestry from, sub-Saharan Africa.[14] The incidence of eclampsia is lower but quite variable, ranging from 0.015% in Finland[15] to an estimated 2.9% in some parts of Africa,[12] illustrating that the rate depends in part on access to obstetric care.[16]

Maternal mortality from pre-eclampsia/eclampsia is highest in LMIC, and worldwide accounts for at least 63 000 maternal deaths per annum. In high income countries, most progress in reducing the maternal toll was made during the period 1940-1970.[201] Over the same time, major breakthroughs in clinical management were few, and the substantial improvements in maternal death rates from pre-eclampsia/eclampsia were achieved by empirical advances in care, professional education, higher clinical competence, and, more recently, consistent application of national guidelines such as in the UK from the National Institute for Health and Care Excellence (NICE).[17] In LMIC, which lack equivalent resources, pre-eclampsia accounts for nearly 30% of all maternal deaths in 29 countries (20 per 100 000), a mortality rate of 0.8% for affected women.[202] This is more than 200 times higher than the mortality specific rate of 0.03% in the UK, assuming that the national incidence of pre-eclampsia is about 3%.[203]

Risk factors listed in box 1 represent data from three systematic reviews.[13 18 19] However, as there are likely multiple pathophysiological sub-types, it cannot be expected that all risk factors will be shared. The risk of pre-eclampsia is higher in a first pregnancy (~4%), and there is a protective effect of a normal first pregnancy with lower risk (~2%) in subsequent pregnancies. The risk of recurrence is high; ~15% after one pre-eclamptic pregnancy and ~32% after two pregnancies in a cohort of nearly 800 000 pregnancies in Sweden, with some confounding effect from a longer interbirth interval.[20]

Fetal sex is increasingly recognised as an important risk feature. A meta-analysis based on 219 575 singleton pregnancies, of which 9033 developed pre-eclampsia, found that when the pregnancy delivered at term (≥37 weeks) there was no difference in the sex ratio.[21] However, a predominance of female fetuses was found in those pregnancies delivering before 34 weeks (odds ratio 1.36, 95% confidence interval 1.17-1.59). Analyses of sex differences in placental gene expression indicate that almost half are X linked and arise from escape of X inactivation.[22 23] Thus, the male fetus may be more susceptible to suboptimal placentation, or less adaptable to adverse conditions.[24 25] This may reflect sex differences in uteroplacental malperfusion. The uterine artery pulsatility index is higher, and notching of the Doppler waveform more common in women carrying a male compared with a female fetus, indicating greater vascular resistance.[26] Hence, early loss of more severely impaired pregnancies carrying male fetuses could explain the female sex bias of early onset pre-eclampsi[a].[21]

The primary role of the placenta

Factors emanating from the placenta into the systemic circulation are considered to result in the maternal syndrome of pre-eclampsia.[27] Oxidative stress of the syncytiotrophoblast, the cell type that forms the epithelial covering of the placental villi in contact with maternal blood, is one of the hallmarks, particularly in the early onset form.[28 29] When stressed, the syncytiotrophoblast releases a complex mix of factors, including pro-inflammatory cytokines, exosomes, anti-angiogenic agents, and cell-free fetal DNA, into the maternal circulation. These disrupt maternal endothelial function resulting in a systemic inflammatory response, the clinical syndrome of pre-eclampsia (fig 2).[27 30] Different stressors can perturb the syncytiotrophoblast, but the main one in early onset pre-eclampsia is uteroplacental malperfusion secondary to defective remodeling of the uterine spiral arteries.[1] By contrast, in late onset cases the cause is more likely an increasing mismatch between normal maternal perfusion and the metabolic demands of the placenta and fetus, coupled with a maternal predisposition to inflammation, a high BMI, and/or a high arterial pressure.[31] To understand the primary underlying defect in the spectrum of placentally related complications of pregnancy, it is necessary to focus on early events in the development of the placenta.

Placental development, spiral artery remodeling, and early onset pre-eclampsia

Placental development is precocious. By the end of the third week post-fertilization a shell of trophoblast cells encapsulates the conceptus and forms the interface with the maternal tissues. It is essential that a robust shell is formed, as it seals off the conceptus and protects it from excessive levels of oxygen and xenobiotics during the critical phase of organogenesis.[32] The stimulus for this development is the histotroph or "uterine milk" derived from the endometrial glands. These secretions, which are rich in nutrients and mitogenic growth factors, are deliv-

Box 1 | Risk factors for pre-eclampsia from three systematic reviews[13 18 19]

- Chronic hypertension
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus
- Pre-gestational diabetes
- Chronic renal disease
- Multifetal pregnancy
- Pre-pregnancy BMI >30
- Previous stillbirth
- Nulliparity
- Maternal age >40
- Increased pre-pregnancy BMI
- Long inter-pregnancy interval (>5 years)
- Reduced school education
- Previous pre-eclampsia
- Assisted reproduction
- Previous intrauterine growth restriction
- Previous placental abruption

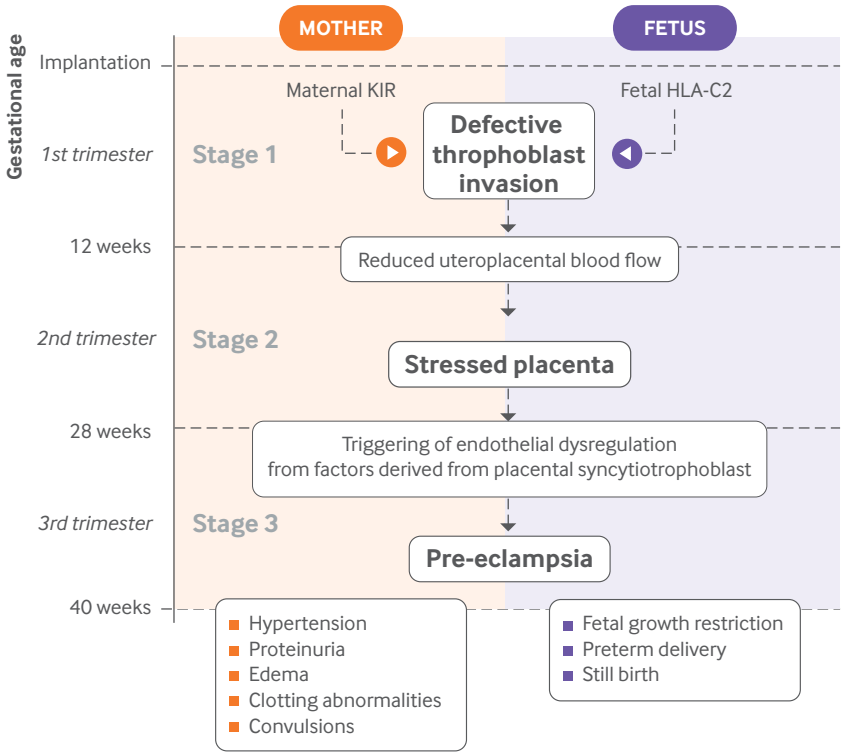

Fig 2 | Pathogenesis of pre-eclampsia with the subsequent effects on mother and fetus. The failure of trophoblast uterine interactions in the first trimester leads to a stress response in the placenta. This may affect growth and development of the villous tree, affecting transfer of oxygen and nutrients to the fetus. The stress to the syncytiotrophoblast leads to shedding of a range of factors into the systemic circulation. These factors cause a systemic inflammatory response resulting from disruption of the homoeostatic functions of the maternal endothelium, including regulation of clotting, fluid transfer, and blood pressure

ered into the placenta where they bathe the early villi, which contain the progenitor trophoblast cells.[33] Suppression of gland development in sheep and mice shows that the secretions are essential for early placental development.[34] Growth factor expression in the glands is up regulated during early pregnancy in response to lactogenic hormones derived from the trophoblast. The placenta is therefore able to stimulate its own development through a dialogue involving the decidua and the endometrial glands. We speculate that the same dialogue operates in humans, although there are no firm data at present.[35] It is possible to address this question directly now that organoid cultures of the endometrial glands[3] and of the trophoblast[4 5] can be generated. Co-culture experiments will enable identification of the impact of trophoblast signals on the gland secretome, and assessment of the impact of that secretome on trophoblast proliferation and differentiation.

Failure of that dialogue could cause incomplete development of the cytotrophoblast shell and lay the pathophysiological foundations for most placentally related complications. When severe, deficient formation of the shell is associated with spontaneous miscarriage, even in karyotypically normal pregnancies.[36] It seems likely that, in less severe cases compatible with an ongoing pregnancy, it predisposes to pre-eclampsia, as the shell is also the source of the extravillous trophoblast cells (EVT) which are required for remodeling the maternal spiral arteries that ultimately supply the placenta. Evidence to support this hypothesis is lacking, but transcriptional profiling reveals defects in decidualization in women who either develop or have experienced pre-eclampsia.[37 38] In addition, the risk of pre-eclampsia is increased following two miscarriages,[39] pointing to defective interactions between trophoblast and the decidua.

The EVT arise from the outer surface of the shell through a partial epithelial mesenchymal transition, transforming into invasive cells characterized by expression of HLA-G. The cues and signalling pathways regulating this transition are not known, but the recent ability to derive EVT from trophoblast stem cells[40] and from trophoblast organoid cultures[5] will provide a powerful tool in understanding the process. Individual EVT migrate through the actions of matrix metalloproteinases via two routes. Initially, interstitial EVT migrate through the stroma towards the spiral arteries. These are the terminal branches of the uterine vasculature within the endometrium that ultimately supply the placenta. In the non-pregnant state, the arterial walls contain extensive smooth muscle that is highly responsive to endocrine and vasoactive stimuli. During normal pregnancy, EVT destroy the smooth muscle and elastin, which are replaced by inert fibrinoid material.[41] Although the mechanisms underpinning remodeling are not fully

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understood,[42] the presence of EVT around the artery is essential. Endovascular trophoblasts then pass down the lumens of the spiral arteries, forming aggregates of cells that effectively plug the arteries during the first weeks of gestation.[43] Eventually, interstitial EVT move through the stroma to reach the inner third of the myometrium where they fuse to generate static, multinucleated giant cells.

Many studies have focused on control of this invasion,[44] and have largely used reductionist systems in vitro involving choriocarcinoma and other trophoblast-like cell lines. Extrapolating the results in vivo is difficult as local interactions that occur with multiple maternal cells, cytokines, and glycoproteins will be critical. Single cell RNA sequencing of the maternal and fetal cells present in the placental bed during the first trimester has predicted several potential receptor-ligand-receptor interactions.[45] Reports on the extent of the invasion in pre-eclampsia have been conflicting. Some describe it as superficial,[46] but others found that it extends as deep as normal, but that the EVT fail to destroy the arterial walls.[47] This confusion reflects the difficulty in sampling all the spiral arteries in the placental bed in early human pregnancy.

Remodeling has two principal consequences for uteroplacental blood flow. Firstly, the terminal segments of the arteries dilate in a funnel shape as they approach the placenta. Remodeling in itself has a relatively minor impact on the volume of blood flow to the placenta, and hence oxygenation. By contrast, mathematical modeling suggests it reduces the velocity and pulsatility of the inflowing maternal blood by an order of magnitude to approximately 10 $cm.s^{-1}$ (fig 3).[48] This reduction is essential to prevent damage to the delicate placental villi and microvilli, as can happen during placental perfusion in vitro if the flow rate is too high.[49] Secondly, trophoblast transformation of spiral arteries normally extends as far as the inner third of the myometrium. Hence, it includes the hypercontractile segment of the artery located in the junctional zone between the endometrium and myometrium that restricts blood loss during menstruation. This segment must be remodeled to prevent compromise of placental blood flow, while the more proximal elements of the uteroplacental vasculature dilate under other stimuli.

Recognizing that pre-eclampsia was associated with defective spiral artery remodeling during early pregnancy was a major step forward in the understanding of its pathophysiology.[50 51] However, subsequent histological studies of placental bed biopsies revealed that deficient arterial remodeling is not specific to pre-eclampsia, being common to the other disorders of placentation.[1] Indeed, non-transformed arteries can be seen in normal pregnancies.[52] Nonetheless, there is general agreement that maternal vascular lesions are more severe in cases of pre-eclampsia than in cases of fetal growth restriction alone, which in turn are more severe than in normotensive pregnancies.[47 52 53 54]

A further arterial lesion, acute atherosis, is seen at the end of gestation in the most severe cases. In a retrospective examination of 16 345 placentas, the lesion was found in 0.4% of uncomplicated pregnancies, compared with 10.2% of pre-eclamptic cases, most commonly the early onset form associated with growth restricted neonates.[55] The lesion is characterized by fibrinoid necrosis and accumulation of lipid laden intimal macrophages. Acute atherosis is not restricted to the placental bed and can affect any decidual non-transformed arteries. The location of the lesions suggests they arise because of the altered haemodynamics occurring when remodeling is deficient.[48] Unlike defective remodeling in itself, acute atherosis can severely restrict the caliber of the uteroplacental vessels, exacerbated by secondary thrombotic lesions, limiting the volume of blood entering the placenta and causing infarction with a risk of fetal demise. This effect has been seen using magnetic resonance imaging (MRI) in cases of early but not late onset pre-eclampsia.[56]

Deficient remodeling of the spiral arteries is often associated with high resistance uterine artery Doppler waveforms, leading to the assumption that one causes the other, although the physics of waveform determinants is complex.[57] In addition, challenging this assumption is the observation that identical changes in uterine artery waveform are seen during both normal and extra-uterine pregnancies where there can be no spiral artery remodeling.[58] Often overlooked is that the more proximal sections of the uterine vasculature: the radial, arcuate, and uterine arteries, undergo considerable dilation independent of trophoblast invasion. These effects are mediated through other factors, such as oestrogen and placental growth factor. Measurements taken from micro-computed tomography scans in mice show that the radial arteries account for ~90% of total uteroplacental vascular resistance,[59] and computational modeling indicates the same is true for humans.[60] Hence, more attention should be paid to more proximal elements of the uteroplacental vascular tree in future[6]1

Placental changes in pre-eclampsia

The gross placental lesions in pre-eclampsia principally reflect maternal malperfusion, with infarcts of the villous tissue at different stages of resolution, villous-free placental lakes, fibrin deposition, and inflammation. These lesions are not specific to the syndrome, but a meta-analysis found them to be four- to seven times more common in pre-eclamptic pregnancies than in normotensive controls,[61-63] with a spectrum of pathology that is more severe in early compared with late onset disease[64-68] (table 1).

At the microscopical level, there is focal necrosis of the syncytiotrophoblast with loss and distortion of the microvilli, dilation of the endoplasmic reticulum cisternae, and swelling of the mitochondria.[101 102] Hyperplasia of the underlying cytotrophoblast cells may be present, but some cells undergo degeneration or apoptosis.[101 103] Not surprisingly, these lesions are associated with shedding of trophoblastic debris.[96]

These morphological differences are backed by reports showing higher levels of placental stress at the molecular level. Thus, oxidative stress and activation of the unfolded protein response (UPR) are greater in early than in late onset pre-eclampsia.[94] One consequence of activation of the UPR is the suppression of non-essential protein

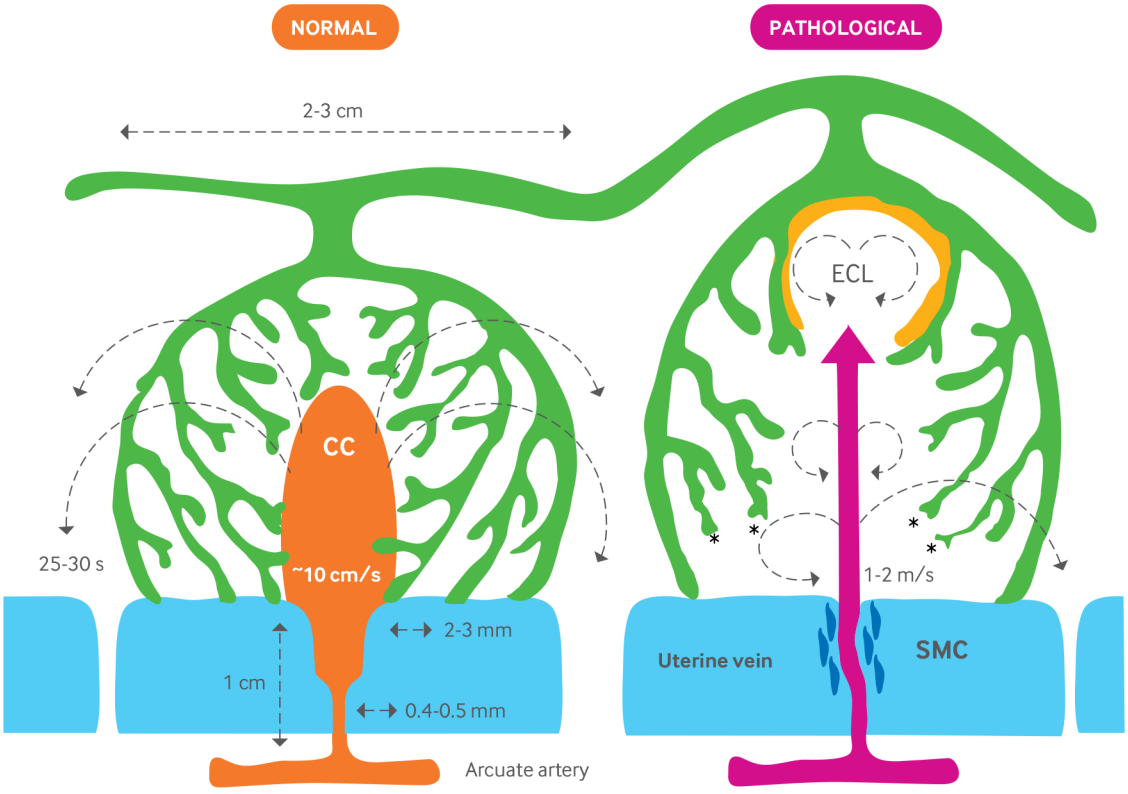

Fig 3 | Diagrammatic representation of the effects of spiral artery remodeling on the inflow of maternal blood into the intervillous space in normal and pathological pregnancies. Dilation of the distal segment of the spiral artery in normal pregnancies reduces the velocity of incoming blood, and the residual momentum carries the blood into the central cavity (CC) of a placental lobule, from where it disperses evenly between the villi. Transit time to the uterine vein is estimated to be in the order of 25-30 s, allowing adequate time for oxygen exchange. In pathological pregnancies, where no or very limited conversion occurs, the maternal blood enters the intervillous space in a jet-like spurt at speeds of 1-2 m/s. Flow is likely to be turbulent, indicated by the circular arrows, and the high momentum damages the villi, forming echogenic cystic lesions (ECL) lined by thrombus (stippled). The transit time will be reduced, so that oxygen exchange is impaired. Trophoblastic microparticulate debris may be dislodged from the villous surface. The retention of smooth muscle cells (SMC) around the spiral artery will increase the risk of spontaneous vasoconstriction and ischemia-reperfusion injury (Modified from[48] with permission)

synthesis, explaining the growth restriction often associated with early onset pre-eclampsia.[104] Particles from syncytiotrophoblast surface are released into the maternal circulation as microvesicles or secreted from internal multivesicular bodies as exosomes (nanovesicles). Both carry complex cargoes, including microRNAs,[105] and are potential liquid biopsies of the syncytiotrophoblast.[106] Shedding of placental microparticles is greater in early onset pre-eclampsia than in the late onset form,[96] while levels of exosomes in maternal serum are increased in early onset but not in late onset pre-eclampsia compared with age matched controls.[83] Exosomes may become important biomarkers of placental stress in the near future.[107]

Pre-eclampsia is also associated with changes in placental DNA methylation[93] and gene expression.[98 100] However, caution is needed in interpreting data, because the changes are likely to reflect the pathophysiology rather than being causal. Oxidative stress and similar changes in gene expression can be induced, for example, by the rigors of labor when the placenta is subjected to intermittent perfusion.[108] Mode of delivery and sample processing have major impacts on the placental transcriptome, metabolome, and activation of stress response pathways, and represent important confounding variables.[109] Additional factors, such as maternal administration of glucocorticoids and other therapeutics, and the sex of the placenta should also be taken into account,[24 110] but are seldom reported. A further difficulty is the lack of non-labored, healthy pre-term control placental samples, as caesarean sections are rarely performed in obstetrically normal pregnancies at gestational ages equivalent to those in early onset pre-eclampsia. Placentas from spontaneous pre-term deliveries display high levels of stress due to either the predisposing pathology or vaginal delivery,[111] and so are often unsuitable as controls.

From placental stress to the maternal syndrome

In the classic two-stage model, placental stress leads to dysfunction of maternal peripheral endothelial cells, a systemic inflammatory response,[112] and the clinical syndrome of pre-eclampsia. Blood flow to maternal organs is reduced, and physiological assessment indicates vasospasm, activation of the coagulation cascade, and reduced plasma volume before clinical disease.[113-115]

Numerous placental factors could trigger the systemic syndrome, but the absence of a spontaneous pre-clinical model makes it difficult to elucidate their importance. As an alternative, an informative comparison may be that between FGR alone and FGR associated with pre-eclamp-

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sia, because FGR shares much the same pathophysiology of deficient spiral artery remodeling with early onset pre-eclampsia, though to a lesser degree.[53 104 116 117] Different levels of placental cell stress may distinguish between the two conditions,[118] because at high levels of activation, the UPR switches from principally homoeostatic to pro-apoptotic and pro-inflammatory pathways.[119] Hence, the higher levels of placental senescence,[120] maternal serum pro-inflammatory cytokines,[121] cell-free fetal DNA,[122] leptin,[123] placental apoptotic debris,[124] soluble receptor (sFLT) for vascular endothelial growth factor (VEGF),[125 126] and the lower levels of placental growth factor (PlGF)[127] reported in early onset pre-eclampsia compared with FGR alone may reflect the severity of the initiating maternal malperfusion. Differences in the maternal responses to these factors will obviously contribute to the clinical manifestations.

Of the potential mediators listed, the balance between sFLT and PlGF is of particular clinical importance.[71] The elevated levels of sFlt are thought to bind and reduce the bioavailability of VEGF to the maternal endothelial cells, impairing their endogenous production of nitric oxide and causing vasoconstriction. By itself, sFlt does not cause activation of human umbilical endothelial cells in vitro, but it does render them more sensitive to pro-inflammatory cytokines.[128] This synergistic effect may explain why pre-eclampsia has proved so hard to treat, as it is likely that the peripheral aspects of the syndrome are caused by a complex mix of factors rather than any one mediator alone.

Because of the involvement of the endothelium, pre-eclampsia is a global systemic syndrome affecting many organs including the central nervous system, kidney, liver, and the coagulation cascade to varying degrees in different women. Metabolic abnormalities, including dyslipidaemia, insulin resistance, and inflammatory markers, are also characteristic.[129 130 131] There are striking differences in the severity and rate of progression of the disorder. Pre-eclampsia can present as a mild disorder that progresses slowly or one that develops rapidly to a life threatening condition. Changes in the maternal liver, adrenal glands, heart, and brain are consistent with decreased organ perfusion, and many are identical to those found in hypovolemic shock. The histological changes in the kidney are characteristic: these are concentrated in the glomerulus with profound endothelial swelling and disruption of the basement membrane and podocytes.[132] Seen in no other form of hypertension and reminiscent of hemolytic uremic syndrome (a thrombotic microangiopathy) these changes indicate that pre-eclampsia is not simply an unmasking of a propensity to hypertension. Pre-eclampsia usually resolves shortly postpartum. If removal of the placenta is delayed, for example in cases of extra-uterine pregnancies, the risk may continue for weeks or months until the placenta is reabsorbed.[133]

Genetics

A family history of pre-eclampsia and risk of recurrence has long been recognized, especially in those with the early onset form, stimulating a long search for the genetic predisposition to the disorder. However, pregnant women who have a monozygotic twin show no concordance, pointing to the role of maternal-fetal gene interactions.[134] That paternal genes are important is seen from the change of partner effect, and the increased risk with fathers born of an affected pregnancy or who previously fathered a pre-eclamptic pregnancy with another woman. The influence of the mother dominates, however, with variance of heritability estimated as 35% maternal, 20% fetal, 13% to a couple effect, and the rest to other effects.[135 136]

Pregnancy involves an interaction between maternal and fetal genes, which may explain the lack of success in finding genes associated with pre-eclampsia from studying maternal genomes alone. Using a candidate gene approach, the focus has been on genes likely to be involved in the final systemic stage of the disorder—particularly genes affecting endothelial function (eg, renin-angiotensin system), the oxidative stress, and thrombophilia pathways. Family linkage studies have also met with equally limited success. More recently, genome wide association studies (GWAS) have been performed. As with the candidate gene studies, these GWAS have been hampered by small numbers, lack of reproducibility, different ethnicities of participants, and problems with rigorous diagnostic criteria for pre-eclampsia. To date, no maternal sequence variants have been identified that can be replicated in independent datasets. However, one GWAS looking at fetal variants involving 4380 cases and 310 328 controls recently identified a variant near the gene encoding Fms-like tyrosine kinase 1 (FLT1), the receptor for vascular endothelial growth factor, in the fetal genome.[137] The association was strongest in cases of late onset pre-eclampsia, and when the birth weight exceeded the 10th centile. Thus, altered production of sFLT by the placenta in response to placental stress secondary to malperfusion may be affected by fetal genetic variants.

Since Medawar's seminal essay[138] pointing out that the fetus is "nature's transplant," the role of the maternal immune system in regulating successful pregnancy has been extensively studied. In addition, the key features of the immune system are memory and specificity, and pre-eclampsia occurs particularly in first pregnancies (memory) and after a change of father (specificity). Ideas in the field became dominated by the idea that immunosuppression is essential for successful pregnancy. A breakdown in maternal T cell tolerance was invoked as a cause of pregnancy disorders, but in humans multiple mechanisms exist to avoid decidual or systemic T cells killing placental trophoblast cells, and there is no evidence this is ever a cause of failing pregnancies.[139] Nonetheless, the immune system is programmed to discriminate between self and non-self, and thus uterine immune cells are likely to be able to detect the invading fetal trophoblast cells and potentially regulate the depth of invasion and transformation of the spiral arteries.

The main maternal leukocytes present at the time of implantation are not T cells but different types of lymphocytes, natural killer (NK) cells. Killer immunoglobulin-like receptors (KIR) are expressed by uterine NK cells (uNK)

Table 1 | Differences between early and late onset forms of pre-eclampsia

	Early onset	Late onset	System affected	Reference
Maternal serum				
Asymmetric dimethylarginine (ADMA)	↑	–	Vasoreactivity	69
Apelin	↑	–	Blood pressure, angiogenesis	70
sFlt/PlGF ratio	↑↑	↑/–	Angiogenesis, endothelial cell dysfunction	71 73
Brain natriuretic peptide	↑↑	↑	Cardiac dysfunction	74
Complement activation	↑	↑	Immune response	75
Copeptin	↑	–	Metabolic syndrome, insulin resistance	76
Fetuin-A	↓	↑	Inflammatory modulator, metabolism	77
Fibronectin	↑↑	↑	Clotting cascade	78
Growth differentiation factor-15 (GDF-15)	↓	↓↓	Cell injury, oxidative stress	79
HtrA1	↑	↓	Cell stress	80
Irisin	↓↓	↓	Adipomyokine, metabolism	81
Leptin	↑↑	↑	Metabolism	82
Placental exosomes	↑	↓	Placental stress	83
Progranulin	↑↑	↑	Cell growth	84
Pro-inflammatory cytokines	↑	–*	Inflammation	85
sVCAM-1	↑↑	↑	Endothelial dysfunction	78
R gulatory T cells	↓↓	↓	Inflammatory response	86
Maternal CVS function		▪		
Baroreceptor sensitivity	–	↑	Blood pressure	87
Heart rate variability	–	↑	Cardiac dysfunction	87
Left ventricular concentric hypertrophy	↑↑	↑	Cardiac dysfunction	74
Bilateral u erine artery notching	↑↑	↑	Uteroplacental blood flow	88
Placental perfusion	↓	↑	MRI placental blood flow	56
Placental				
Width	–	↑	Placental development	89
Pathological changes	↑	–*	Malperfusion	65 90
Villous volume, surface area	↓	–	Placental develpment	91
Total oxidant status	↑↑	↑	Oxidative stress	92
Altered methylation	↑	–	Oxidative stress	93
Placental stress	↑	–	Cell stress	94 95
Trophoblast debris	↑↑	↑	Maternal endothelial dysfunction	96
Mitochondrial copy number	↑	–	Metabolism	97
G-prote n coupled receptor signalling	↓	-	Immune and inflammatory responses	98
TLR4	↑	–	Immune regulation	99
EGFL7, ACVRL1	↓	–	Angiogenesis	100

*comparisons limited to early onset against late onset pre-eclampsia rather than age matched controls

and bind to HLA-C molecules on EVT. Because the maternal genes encoding KIR and the fetal genes encoding HLA-C are both highly polymorphic, there are different maternal KIR/fetal HLA-C genetic combinations in each pregnancy. Immunogenetic studies show that interactions of EVT with uNK cells are an important determinant of the risk of pre-eclampsia and other placentally related complications in both European and African populations.[140 141] From these, it appears that a degree of activation of the uNK cells is beneficial for successful pregnancy. uNK cells cluster around the spiral arteries, and it is presumed their activation causes the release of cytokines and proteases that stimulate the remodelling process, although evidence is still limited for how they function in normal and abnormal pregnancies.[142] This maternal/fetal genetic interaction system is only likely to account for a small amount of the genetic contribution to pre-eclampsia operating at the site of placentation. Other genetic influences will affect the stress response in the placenta (eg, sFLT1) and the maternal susceptibility to the systemic syndrome.

Screening

Pre-eclampsia is usually symptomless, making the syndrome hard to predict. Symptoms such as epigastric pain or severe headache frequently herald a terminal crisis, for example eclampsia or the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, which requires prompt termination of pregnancy.[143] Screening of well women for the early stages of pre-eclampsia has been highly successful in limiting maternal and perinatal problems.[144] Antenatal care is based on predictions of the chances of pre-eclampsia developing before the next screening tests are due. Pre-eclampsia is uncommon before 20 weeks, but then progressively becomes more frequent towards term and beyond.[145] Hence, the frequency of checks is higher during the third trimester. Until recently, screening was based on timely detection of new onset hypertension and proteinuria, because they were the first features to be documented and their measurement is easy and cheap. They were introduced empirically and are effective overall. Confirmatory evidence comes from studies in LMIC, which consistently document the importance of adequate antenatal screening.[16 146]

In high income countries this situation has changed substantially. Impending or active pre-eclampsia can be detected by circulating biomarkers or Doppler ultrasound assessment of the uteroplacental circulation. This can be useful for the early onset but not late onset form of the

syndrome.[147 148] Circulating biomarkers may be placental or maternal. New hypertension or proteinuria are maternal markers of endothelial activation, whereas placental syncytiotrophoblast factors are further upstream in the pathophysiology and likely to be more precise. An increased ratio of sFlt-1/PlGF is a good marker of the placental component of pre-eclampsia, and of fetal growth restriction induced by placental malperfusion.[71]

The ability to exclude pre-eclampsia is also important, and before 35 weeks the PlGF value can rule out the need for delivery within the next two weeks with 98% probability.[149] When combined in the sFlt-1/PlGF ratio, this increases to a probability of more than 99% within the next week.[150] As with uterine artery Doppler assessment, the ratio does not predict late onset pre-eclampsia well. Ideally, diagnosis should be made early in pregnancy, when interventions could begin before the clinical features are manifest. Combinations of demographic and clinical factors with maternal blood pressure, uterine artery Doppler measurements, and blood biomarker assessments factors have been assembled to improve predictive efficiency.[31] A version of enhanced first trimester screening has been used in a trial of prophylactic low dose aspirin with encouraging results, identifying primarily early onset pre-eclampsia.[151] Whatever the outcome of these developments, measured rather than subjective estimates of the risk of pre-eclampsia should be robust.

Therapy

Prevention

Pharmacological and behavioural efforts to prevent pre-eclampsia are at best minimally effective. Evidence that a "healthy" diet,[152] "appropriate" weight gain and exercise,[153] and stress reduction[154] can reduce the riskis less than compelling; however, the general advantages of a healthy lifestyle justify these in pregnancy. Meta-analyses of the more than 40 000 women treated with aspirin in doses of less than 165 mg started in early pregnancy indicate a small beneficial effect to reduce the incidence of pre-eclampsia, fetal prematurity, and mortality.[155] Current recommendations for aspirin are for women with modest to high risk.[156] Calcium supplements of 1.5 to 2 g daily in settings with low calcium intake reduce the severity of blood pressure and adverse outcomes, and may reduce the incidence of pre-eclampsia or preterm birth.[157] The World Health Organization currently recommends this therapy for women in settings with low calcium intake.

The central role of placental oxidative stress in the pathophysiology provided a rationale for the administration of antioxidant vitamins. Clinical trials of antioxidant vitamins (C and E) have proved to be ineffective in several large interventional studies,[158] possibly because treatment was started between 10 and 20 weeks of gestation, after trophoblast transformation of spiral arteries. Alternatively, these vitamins may not be the appropriate antioxidants and others should be considered.[159 160 161] Whether therapy with vitamins or nutritional supplements before or in early pregnancy are effective[162 163] requires careful clinical testing. Preventive therapies for pre-eclampsia have been successful in small trials involving homogenous populations, but have not been supported by larger multicenter findings.[164]

Treatment of overt pre-eclampsia

Pre-eclampsia is a disease of two individuals, the mother and her fetus. Careful monitoring of the maternal condition and timely delivery with increasing progression of disease explain the difference in maternal mortality between HIC and LMIC, and the dramatic reduction of maternal mortality in HIC in the mid 20th century.[144] There were no deaths from pre-eclampsia in the latest Confidential Enquiry into Maternal Deaths in the UK. However, for the fetus, delivery may exchange a dangerous situation in utero for the morbidity and mortality of premature delivery. The maternal condition may be palliated to slightly prolong pregnancy and gain fetal maturation, but there is nothing currently that reverses the pathophysiology to improve outcome. Prolongation of the pregnancy increases the risk of fetal death in utero probably because of obstruction of uterine arteries by acute atherosis.

Palliation primarily involves antihypertensive therapy to avoid maternal intracranial bleeding, and magnesium sulphate as anticonvulsant therapy. The choice of antihypertensive agents, as determined by efficacy and safety for mother and fetus, is guided by a few trials but largely by experience.[130 165] Magnesium sulphate is more effective to treat or prevent seizures than other pharmacological agents,[166-168] and is safe if used appropriately. However, over-dosage results in respiratory and cardiac failure, and so its use should be monitored[169] and reserved for women where the risk-benefit ratio is acceptable.[130]

Long term implications

The consequences of pre-eclampsia for the mother and her baby are lifelong. Meta-analyses indicate a twofold increase in cardiovascular risk and death in women with previous pre-eclampsia.[170] This increases to six- to ninefold if pre-eclampsia occurs in more than one pregnancy, or before 37 weeks' gestation.[171] Specific risk increases are estimated as 3.7-fold for hypertension and 1.8-fold for stroke.[170] Less well studied, but related, is an increased risk of heart failure, particularly with preserved ejection fraction (HFpEF).[172] In addition, women with early onset pre-eclampsia can have diastolic dysfunction that persists in a subset for at least a year.[173] Microvascular disease with reduced capillary density is also more prevalent.[174]

An important question is whether similar risk factors cause pre-eclampsia and later life cardiovascular disease, or does pre-eclampsia cause later life cardiovascular disease? The answer requires information gathered before pregnancy. In the large HUNT study in Norway in which young women and men were recruited and followed, thus far for 20 years, 3225 women provided information before and after pregnancy.[175] Cardiovascular risk markers were compared before, and following, normal and pre-eclamptic pregnancies. Most, but not all, risk was present before the pre-eclamptic pregnancy. For example, women with pre-eclampsia have an increased prevalence of a gene variant known to be associated with

cardiomyopathy, and, indeed, 40% of women with peripartum cardiomyopathy have pre-eclampsia, both conditions commoner in women of African ancestry.[176 177]

The American Heart Association has emphasised that evaluation of cardiovascular risk for women should include a pregnancy history and that pre-eclampsia be considered a risk factor.[178] How this risk should be translated into follow-up is "work in progress."[179 180] Evidence based assessment of whether increased or earlier surveillance or pharmacological interventions are beneficial is currently underway.

An emerging area of some concern is the suggestion of increased cognitive dysfunction[181] and white matter lesions on MRI in the brains of formerly pre-eclamptic women.[182] Another intriguing relationship, but this time beneficial, is the reduced risk of breast cancer in women with a history of pre-eclampsia, which appears much greater if the fetus is male.[183]

The infant from a pre-eclamptic pregnancy also appears at increased risk for cardiovascular disease, although the relationship is not as well established as for the mother. Infants of pre-eclamptic mothers have higher blood pressure during young adulthood[184] and an increased risk for stroke in later life.[185] There are also disturbing reports of increased "mental disorders" including mood and anxiety in infants of women with pre-eclampsia, especially in females.[186] One third of infants of pre-eclamptic pregnancies are growth restricted and have the same increased risk of obesity, diabetes, hypertension, and other chronic diseases as other growth restricted infants.[187]

For the infant, the question is whether the associations are genetic and/or related to the post-delivery environment, or due to in utero exposure to the mother's pre-eclamptic pregnancy inducing epigenetic changes? At least one study suggests in utero exposure is not important, since adults exposed to pre-eclampsia in utero had the same cardiovascular risk as their siblings born from a non-pre-eclamptic pregnancy.[188]

Guidelines

Guidelines for the clinical management of the syndrome have recently been published by the ISSHP.[8]

Emerging therapies

There are several trials of drugs to alter the pathophysiology of pre-eclampsia. The statin pravastatin, administered from early pregnancy, is safe for mother and neonate.[189] Pre-eclampsia was less common in women receiving pravastatin (4 in placebo, 0 in cases n=10 in each group), although the trial was under powered.

A trial of the PDE5 inhibitor sildenafil citrate to prevent FGR found no prolongation of pregnancy,[190] with some adverse neonatal effects, including pulmonary hypertension, and should be discontinued.[191] Although a definitive benefit of the nitric oxide precursor arginine has not been established because of sample size and study design, potential benefit suggests further studies.[192 193]

An experimental approach is to reduce the concentration of sFlt in the maternal circulation using apheresis with a charge specific dextran sulfate column. In women presenting with very early onset pre-eclampsia, the pregnancy could be prolonged by eight and 15 days following single or multiple treatments, compared with three days in untreated controls.[194]

An alternative approach only tested in pre-clinical models is to knock down expression of sFlt in the placenta using interference RNA technology.[195] Other possible therapies are modifiers of endoplasmic reticulum stress, hydrogen sulphide donors,[161] and scavengers of fetal haemoglobin.[196]

Conclusion

Advances have been made in our understanding of the pathophysiology and clinical management of pre-eclampsia, but several research questions remain (box 2). The variability of clinical presentation, long range outcome, laboratory findings, and inconsistent response to preventive therapies and inaccuracy of prediction suggest different subtypes of pre-eclampsia.[164] As clinical phenotyping improves, complemented by analytical techniques[197] and data from large cohorts,[198] it is likely that the spectrum of pre-eclampsia will be better understood. At present, the early and late onset forms are the probable extremes of a spectrum. The early onset form is predominantly due to defective placentation during the first few weeks of pregnancy, and shares a common initiating pathophysiology to other disorders of placentation, especially FGR. Various strands of evidence indicate that the level of placental insult is greater in pre-eclampsia than in FGR, stimulating the release of a heavier burden of placental pro-inflammatory factors. The concentration of these factors, and their interactions with the maternal constitution, will determine the inflammatory response that distinguishes between the two conditions. By contrast, late onset pre-eclampsia appears to be driven by oxidative changes in the placenta induced by a progressive mismatch between maternal perfusion and feto-placental demands, coupled with a maternal predisposition to cardiovascular disease.

There are other current gaps in our knowledge. Racial disparities and differences in the frequency and severity of pre-eclampsia[199] are only partly explained by genetics

QUESTIONS FOR FUTURE RESEARCH

General

- What are the most accurate ways to predict pre-eclampsia?
- How many sub-types of pre-eclampsia exist?
- Does pre-eclampsia cause or exacerbate a predisposition to maternal cardiovascular disease?
- What impact will treatments designed to ameliorate the systemic syndrome have on fetal growth and survival?

Placenta related

- Can pre- or peri-conceptional interventions aimed at enhancing maternal wellbeing and endometrial function prevent pre-eclampsia?
- Why is pre-eclampsia seen particularly in first pregnancies?
- What is the role of paternally derived fetal genes in placental development?
- What are the similarities and differences in the pathophysiologies of other placental-related complications (eg, preterm labour, fetal growth restriction, unexplained stillbirth, and abruption) compared with pre-eclampsia?

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and socioeconomic status. There is an increased risk of all disorders of placentation in women with recent African ancestry that remains unexplained. What are the other causal factors? Can we learn about the unique features of cardiovascular disease in women by understanding the pathophysiology of pre-eclampsia? What are the short and long term implications of pre-eclampsia for the offspring? Are the effects of pre-eclampsia due to more than prematurity or fetal growth restriction? These and other poorly understood features of pre-eclampsia suggest targets for future research.[200]

The substantial reduction in maternal and fetal mortality and morbidity that has been achieved over recent years has depended almost entirely on improved clinical awareness and care. To improve prediction and prevention it is now important to augment these advances with increased understanding of placental development, interactions with the uterine lining, and pathophysiology across the entire duration of pregnancy.

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