Pre-eclampsia

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Pre-eclampsia is a major cause of maternal mortality (15–20% in developed countries) and morbidities (acute and long-term), perinatal deaths, preterm birth, and intrauterine growth restriction. Key findings support a causal or pathogenetic model of superficial placentation driven by immune maladaptation, with subsequently reduced concentrations of angiogenic growth factors and increased placental debris in the maternal circulation resulting in a (mainly hypertensive) maternal inflammatory response. The final phenotype, maternal pre-eclamptic syndrome, is further modulated by pre-existing maternal cardiovascular or metabolic fitness. Currently, women at risk are identified on the basis of epidemiological and clinical risk factors, but the diagnostic criteria of pre-eclampsia remain unclear, with no known biomarkers. Treatment is still prenatal care, timely diagnosis, proper management, and timely delivery. Many interventions to lengthen pregnancy (eg, treatment for mild hypertension, plasma-volume expansion, and corticosteroid use) have a poor evidence base. We review findings on the diagnosis, risk factors, and pathogenesis of pre-eclampsia and the present status of its prediction, prevention, and management.

Pre-eclampsia is a multisystem disorder of unknown cause that is unique to human pregnancy. It is characterised by abnormal vascular response to placentation that is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system, and endothelial-cell dysfunction. The clinical findings of pre-eclampsia can manifest as either a maternal syndrome (hypertension and proteinuria with or without other multisystem abnormalities) or fetal syndrome (fetal growth restriction, reduced amniotic fluid, and abnormal oxygenation). In clinical practice, the maternal syndrome is probably more than one disease with major differences between near-term pre-eclampsia without demonstrable fetal involvement and pre-eclampsia that is associated with low birthweight and preterm delivery. The disorder is heterogeneous for which pathogenesis can differ in women with various risk factors. Pathogenesis of pre-eclampsia in nulliparous women may differ to that in women with pre-existing vascular disease, multifetal gestation, diabetes mellitus, or previous pre-eclampsia. Additionally, the pathophysiology of the disorder leading to onset before 34 weeks’ gestation could differ to that developing at term, during labour, or postpartum.

Despite advances in perinatal care, frequency of pre-eclampsia has not changed. Research addressing this disorder has been extensive during the past decade, but has not resulted in substantial improvement in methods of prediction or prevention of the disorder. A major impediment in the development of such methods is our poor understanding of the various pathological mechanisms that lead to pre-eclampsia as well as the inconsistent criteria used to define it. Indeed, diagnostic criteria for the disorder and its subtypes have not been standardised or well defined and have varied between countries and over time during the past 20 years. However, criteria have been refined, and since 2000, there has been considerable agreement regarding the recommended definition of pre-eclampsia between international working groups. Consequently, we focus on studies published during the past 5 years.

Maternal and perinatal outcome

Pre-eclampsia is a major obstetric problem leading to substantial maternal and perinatal morbidity and mortality worldwide, especially in developing countries. Maternal and perinatal outcomes in pre-eclampsia depend on one or more of the following: gestational age at time of disease onset, severity of disease, quality of management, and presence or absence of pre-existing medical disorders. In general, maternal and perinatal outcomes are usually favourable in women with mild pre-eclampsia developing beyond 36 weeks’ gestation. By contrast, maternal and perinatal morbidities and mortalities are increased in women who develop the disorder before 33 weeks’ gestation, in those with pre-existing medical disorders, and in those from developing countries (panel 1).

Several studies have suggested that women who develop pre-eclampsia are at increased risk of cardiovascular complications later in life. Indeed, many risk factors and pathophysiological abnormalities of pre-eclampsia are similar to those of coronary-artery disease. Insulin resistance has been implicated as a common factor. Ramsay and colleagues first showed...

Search strategy and selection criteria

We searched MEDLINE, PubMed, and the Cochrane Library for published work relevant to this Seminar with the search words: "preeclampsia", "epidemiology", "definition", "pathophysiology", "prediction", "prevention", and "management". This search was updated from 2000, to November, 2004. Publications were selected for review based on original research, randomised controlled trials, and meta-analyses and evidence-based reviews of assessment of interventions. We also included highly regarded earlier publications and recent comprehensive review articles.
Seminar

by use of laser doppler imaging in vivo, impaired microvascular function in women aged 15–25 years with pregnancies complicated by pre-eclampsia. Thus, microvascular dysfunction, which is associated with insulin resistance, could predispose to both coronary heart disease and pre-eclampsia. Pregnancies complicated by pre-eclampsia could identify women at risk of vascular disease in later life and provide the opportunity for lifestyle and risk-factor modification.25 Additionally, growth restriction is now recognised as a major risk factor for premature atherosclerosis, according to the so-called fetal origins of the adult disease hypothesis. Again, the insulin-resistance syndrome seems to be the main pathway through which an adverse intrauterine environment—eg, growth-restricted fetuses, or low-birthweight infants in the case of severe pre-eclampsia—negatively affects long-term adult health.18,27

Diagnosis

Pre-eclampsia is usually diagnosed in the presence of hypertension associated with proteinuria.1,2,16 Hypertension is defined as a blood pressure of at least 140 mm Hg (systolic) or at least 90 mm Hg (diastolic) on at least two occasions and at least 4–6 h apart.1,2,7 The urine dipstick measurements used to establish proteinuria should be no more than 7 days apart.1,2,7 However, these criteria are not endorsed by working groups outside the USA.10,28 Accurate diagnosis of pre-eclampsia depends on precise blood-pressure measurements (ie, cuff size, position of arm at heart level, and calibration of equipment), which is important in obese women. Studies have shown that urinary dipstick determinations as well as random protein-to-creatinine ratios correlate poorly with the amount of proteinuria found in 24-h urine samples of women with gestational hypertension.1,2,29,30 Therefore, the definitive test to diagnose proteinuria should be quantitative protein excretion over 24 h.29 In the absence of proteinuria, pre-eclampsia should be considered when hypertension is associated with persistent cerebral symptoms, epigastric or right upper-quadrant pain with nausea or vomiting, or with thrombocytopenia and abnormal liver enzymes.1,10

Pre-eclampsia is regarded as serious if severe hypertension is associated with proteinuria or if hypertension is associated with severe proteinuria (>5 g per day).2,29 Furthermore, pre-eclampsia is regarded as severe in the presence of multiorgan involvement such as pulmonary oedema, seizures, oliguria (<500 mL per day), thrombocytopenia (platelet count <100 000 per μL), abnormal liver enzymes associated with persistent epigastric or right upper-quadrant pain, or persistent and severe CNS symptoms (eg, altered mental status, headaches, blurred vision, or blindness).2,29

The traditional criteria to confirm a diagnosis of pre-eclampsia (new onset of both hypertension and proteinuria after 20 weeks’ gestation) are appropriate to use for most healthy, nulliparous women. However, in some women, development of severe gestational hypertension (absent proteinuria) is associated with higher maternal and perinatal morbidity than in those with mild pre-eclampsia.29 Additionally, hypertension or proteinuria might be absent in 10–15% of women who develop haemolysis, elevated liver enzymes, or low platelet counts (ie, HELLP syndrome),32 and in 38% of those who develop eclampsia.32 These signs are associated with substantially higher rates of maternal and perinatal morbidity than mild pre-eclampsia.32,33 Therefore, we should apply this knowledge prudently as we continue to search for future methods to predict or prevent pre-eclampsia.

The criteria mentioned so far are not reliable in women who have either hypertension or proteinuria before 20 weeks’ gestation, especially those receiving antihypertensive drugs.10,11,14 Because of the physiological changes leading to raised maternal blood pressure and increased protein excretion with advanced gestation in such women, more stringent criteria should be used to
Panel 2: Risk factors for pre-eclampsia

**Couple-related risk factors**
- Limited sperm exposure
- Primipaternity
- Pregnancies after donor insemination, oocyte donation, or embryo donation
- Protective effect of partner change in the case of previous pre-eclamptic pregnancy
- Maternal or pregnancy-related risk factors
- Extreme of maternal age
- Multifetal gestation
- Pre-eclampsia in a previous pregnancy
- Chronic hypertension or renal disease
- Rheumatic disease
- Maternal low birthweight
- Obesity and insulin resistance
- Pregestational diabetes mellitus
- Maternal infections
- Pre-existing thrombophilia
- Maternal susceptibility genes
- Family history of pre-eclampsia
- Smoking (reduced risk)
- Hydropic degeneration of placenta

With whole population data, Lie and colleagues showed that men who fathered one pre-eclamptic pregnancy were nearly twice as likely to father a pre-eclamptic pregnancy in a different woman, irrespective of whether she had already had a pre-eclamptic pregnancy or not. Thus, mothers had a substantially increased risk in their second pregnancy (almost 3%) if they became pregnant by a man who had fathered a pre-eclamptic first pregnancy in another woman. This risk was nearly as high as the average risk in first pregnancies.

The primipaternity concept was challenged by Skjaerven and co-workers who, by using the Medical Birth Registry of Norway, recorded that for women with no previous pre-eclampsia, the risk of disease rose with increasing time interval between births. Notably, for those with previous pre-eclampsia, the risk tended to fall with increasing time interval between deliveries. They concluded that the increase in pre-eclampsia risk ascribed to a new father by other investigators is due to insufficient control for interbirth interval. Although the researchers used a large database, the study had several major weaknesses, such as the high percentage of falsely claimed paternities in birth registries in stable couples and a questionable diagnosis in up to 60% of the pre-eclamptic patients. Other biological inconsistencies in the data are discussed by Dekker and Robillard.

These findings make the birth-interval hypothesis not very plausible. However, the main problem is that couples with extended birth intervals include a high percentage of women with secondary infertility and one or more miscarriages. Infertility, especially if caused by polycystic ovarian disease, and recurrent miscarriages are recognised risk factors for pre-eclampsia.

Advances in assisted reproductive technology have introduced several challenges for the maternal immune system that also increase the risk of pre-eclampsia. These include women who are older than 40 years, are infertile during their first gestation or obese with polycystic ovaries syndrome, and are pregnant by donated gametes—ie, donor insemination, oocyte donation, or even embryo donation. The use of donated gametes will affect the maternal–fetal immune interaction, and many of these women will have multifetal gestations.

Obesity is a definite risk for pre-eclampsia. Risk increases with a greater body-mass index. The worldwide increase in obesity is likely to raise the frequency of pre-eclampsia. Obesity has a strong link with insulin resistance, which is a risk factor for pre-eclampsia. The exact mechanism by which obesity or insulin resistance is associated with the disorder are not completely understood. Possible explanations are increased shear stress, associated with a hyperdynamic circulation; dyslipidaemia or enhanced cytokine-mediated oxidative stress; amplified sympathetic activity...
An overall increased rate of thrombophilia has been seen in women with pre-eclampsia compared with controls.\textsuperscript{27,38} However, there have been several reports that are unable to reproduce these findings.\textsuperscript{39,35} The apparent controversy could indicate the heterogeneity of patients being studied. Most negative studies included mainly (late) third-trimester cases. van Pampus and colleagues,\textsuperscript{39} who investigated the largest series of pre-eclamptic patients so far, clearly showed the differential presence of thrombophilias in women with very early-onset disease (delivery \(< 28\) weeks) versus those needing delivery in the third trimester—even though they still delivered before 36 weeks’ gestation.

### Pathophysiology

It should be emphasised that the causes of pre-eclampsia remain unknown. Therefore, the current attempt to distil recent pathophysiological data in one causal framework represents another one of the many hypotheses proposed to explain the pathogenesis of pre-eclampsia. Typically, progress of any new theory starts with a flurry of studies bolstering one hypothesis and leading to tremendous excitement and interest, which then is invariably followed by studies that do not confirm such a hypothesis (figure 1).

Pre-eclampsia is caused by presence of the placenta or the maternal response to placentation. However, it is now clear that poor placentation is not the cause of pre-eclampsia, but rather a powerful predisposing factor—ie, poor placentation is a separate disorder that once established usually leads to the maternal syndrome, depending on the extent to which it causes inflammatory signals (which may depend on fetal genes) and the nature of the maternal response to those signals (which would depend on maternal genes). If placental ischaemia was the only cause of pre-eclampsia one would expect a significant degree of concordance between the maternal and fetal disease phenotypes. Practising obstetricians will appreciate how often we encounter a fetus in excellent condition with, paradoxically, an extremely sick mother, and vice versa.\textsuperscript{37}

Indeed, theories on the cause of pre-eclampsia are often depicted as two opposing schools of thoughts—the vascularists, for whom ischaemia-reperfusion leads to oxidative stress and vascular disease, and the immunologists, who see pre-eclampsia as a maternal–paternal immune maladaptation (ie, a maternal alloimmune reaction triggered by a rejection of the fetal allograft). Chaouat and colleagues\textsuperscript{39} correctly emphasised that the distinction between vascular and immune events is no longer tenable in view of what is now known of the molecules secreted within the immune system. Most, if not all, cytokines are endowed with pleiotropic properties, of which action on the vascular endothelium and smooth muscle, coagulation, and other immune cells are most relevant to pre-eclampsia.\textsuperscript{14}
Placentation and the immune theory of pre-eclampsia

Epidemiological studies support the concept of maternal–fetal (paternal) immune maladaptation being centrally implicated in the causation of pre-eclampsia. Deposition of semen in the female genital tract provokes a cascade of cellular and molecular events that resemble a classic inflammatory response. The critical seminal factor seems to be seminal-vesicle-derived transforming growth factor β1 (TGFβ1)—it initiates a postmating inflammatory reaction, allowing an increased ability to sample and process paternal antigens, and a strong type-2 immune reaction. By initiating a type-2 immune response towards paternal antigens, seminal TGFβ1 may inhibit the induction of type-1 responses against the semi-allogenic conceptus that are thought to be associated with poor placental development and fetal growth.

Peters and colleagues recently confirmed that sperm exposure causes mucosal alloimmunisation. Limited sperm exposure is the most likely explanation for the high incidence of pre-eclampsia in teenagers. Wang and co-workers showed that the antigen, and as such a major part of the protective effect of previous sperm exposure, is conveyed by sperm cells. They noted that the risk for pre-eclampsia was three times higher in women conceiving via intracytoplasmic sperm injection (ICSI) with surgically obtained sperm (from men with complete azoospermia) than in those with standard in-vitro fertilisation and ICSI using sperm obtained by masturbation. Repeated intercourse with sustained antigen exposure (sperm cell) in the appropriate cytokine environment (ie, TGFβ1) is now thought to be essential in this partner-specific mucosal tolerance.

During the early weeks of gestation, cytotrophoblast cells stream out of the tips of the anchoring villi and penetrate the trophoblast shell and overlying syncytiotrophoblast to form cytotrophoblast columns that develop into the cytotrophoblast shell. Trophoblast cells continue to migrate into the decidua and eventually colonise the placental bed’s myometrium. Once the cytotrophoblast shell makes contact with spiral-artery openings, trophoblast cells stream into arterial lumina to form intraluminal plugs. Endovascular trophoblast cells replace the endothelium of spiral arteries and then invade the media, resulting in destruction of the medial elastic, muscular, and neural tissue. Trophoblast cells become incorporated into the vessel wall, and the endothelial lining is finally reconstituted.

Zhou and colleagues showed that endovascular cytotrophoblasts usually transform their adhesion-receptor phenotype to resemble the endothelial cells they replace and that pre-eclampsia is associated with a failure of cytotrophoblasts to mimic a vascular-adhesion phenotype. Initial vascular changes seem to precede endovascular trophoblast invasion, showing that interstitial trophoblast and decidual leucocytes (especially natural-killer cells) have a role in early disruption. These physiological changes create a low-resistance arteriolar system and no maternal vasomotor control, which allows the substantial increase in blood supply to the growing fetus. During the early stages of implantation, cytotrophoblast plugs might act as valves regulating blood flow in the intervillous space and protect the embryo from forceful maternal blood flow.

This initial physiological degree of hypoxia seems relevant in switching on hypoxia-inducible factor-1α, with subsequently increased production of several angiogenic and growth factors by trophoblasts, in particular the insulin growth factors. Results of doppler studies suggest that the presence of continuous intervillous space flow in the first trimester is associated with a complicated pregnancy outcome, and that true flow is established only by about 12 weeks’ gestation in healthy pregnancies.

Additionally, endovascular trophoblast invasion has been shown as a side route of interstitial invasion. A true decidua is only formed in species with an invasive form of placentation. Human beings have a particularly extensive placental invasion, possibly because of the long intrauterine period needed for fetal brain development. The mucosal lining of the uterus is transformed from the endometrium in the non-pregnant state to the decidua in pregnancy. A major leucocyte infiltration is the major cellular characteristic of this change. The process begins in the luteal phase before potential implantation. During early pregnancy, natural-killer cells in the uterus (probably derived from those in the blood) accumulate as a dense infiltrate around the invading cytotrophoblast cells. From mid-gestation onwards, these killer cells progressively disappear, which coincides with cytotrophoblast invasion, since human placenta is complete by about 20 weeks’ gestation. Natural-killer cells affect both trophoblast invasion and vascular changes in the maternal placental bed. The uterine natural-killer cells produce several cytokines that are implicated in angiogenesis and vascular stability, including vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and angiopoietin 2.

Trophoblast-cell invasion into the decidua with its massive leucocyte infiltration and the subsequent arterial transformation needs, and results in, close tissue contact between allogeneic cells. What immune mechanisms allow this deeply controlled trophoblast invasion? Syncytiotrophoblasts do not produce classic HLA mRNA or HLA protein in their membranes. Although all the classic class-I HLA antigens are absent (apart from HLA-C), the invading cytotrophoblast does express the non-classic HLA-G and HLA-E antigens. The non-polymorphic HLA-G has an important role protecting the trophoblast from cytotoxic effects mediated by natural-killer cells, but activation of the natural-killer cells by HLA-G is probably highly important in mediating major vascular changes.
One of the major products of natural-killer cells is interferon (IFN)γ. Animal studies (mainly in mice) have shown that proinflammatory IFNγ derived from uterine natural-killer cells is essential and acts physiologically in triggering pregnancy-induced spiral-artery modification.69 Release of IFNγ upregulates genes that stimulate α2-macroglobulin production. α2-macroglobulin regulates proteases, cytokines, and other molecules that signal vascular dilatation. Croy and colleagues67 reviewed data suggesting that α2-macroglobulin works mainly via local binding of VEGF, although other mechanisms such as increased activity of inducible nitric oxide synthase are probably also implicated.68

Because T cells were thought to be the unique cells needed for adaptive immune responses, absence of major T-cell interaction in pre-eclampsia seemed to negate the immune maladaptation hypothesis.70 This concept was radically changed by the realisation of the major role of decidual natural-killer cells, representing the predominant population of decidua lymphoid cells. Natural-killer cells function by cell killing or by cytokine production, and maternal decidual natural-killer cells, representing the predominant population of decidua lymphoid cells. Natural-killer cells function by cell killing or by cytokine production, which is enhanced by cytokines such as IFNα, IFNβ, interleukin (IL) 2, IL12, and IL15.66 They express killer inhibitory and activatory receptors that recognise HLA-class-I molecules. HLA-G is important for activation of uterine natural-killer cells but being monomorphic cannot convey any partner-specific signal. By contrast, HLA-C loci are dimorphic for residues 77–80 and these two HLA-C groups interact with different natural-killer cell receptors.

There is great diversity of haplotypes of killer-cell immunoglobulin-like receptors (KIR) in humans, and because HLA-C is polymorphic, every pregnancy will have different combinations of paternally-derived fetal HLA-C and maternal KIRs. These new insights provide an attractive model that would explain how pregnancy is based on a unique couple-specific immune interaction not involving T-cells but natural-killer cells interacting with paternal HLA-C molecules.44 Hiby and colleagues45 postulated that recognition of these molecules by KIRs on maternal decidual natural-killer cells was important in the development of pre-eclampsia. Mothers lacking most of all activating KIRs (AA genotype) when the fetus had HLA-C (belonging to the HLA-C2 group) were at a substantial risk of pre-eclampsia. This effect was true even if mothers had HLA-C2, indicating that neither non-self nor missing-self discrimination was an effect. Thus, this interaction between maternal KIRs and trophoblast seems not to be a typical immune function, but shows how cells from the innate immune system have a physiological role in placental development.

**Placental debris hypothesis—syncytiotrophoblast shedding**

Shedding of syncytiotrophoblasts, a feature of healthy pregnancy, is increased in pre-eclampsia. This shedding is now viewed as part of syncytial renewal.65 Enhanced deportation of microvillous membrane particles of syncytiotrophoblasts71 and raised concentrations of free fetal DNA and cytokeratin in the maternal circulation have been recorded in pre-eclampsia.74,75 Increased cell-free fetal DNA was noted at 16–18 weeks in future pre-eclamptic women, but these concentrations did not correlate with those of maternal C-reactive protein.75

Apoptosis causes controlled cell fragmentation to allow continuous renewal of the syncytiotrophoblast surface, and is amplified in pre-eclampsia.76,77 What causes this increased apoptosis? Placental ischaemia and reperfusion with subsequent oxidative stress have been regarded as major pathogenetic drivers. In established disease, especially with fetal involvement, these mechanisms are clearly operational.78 Acute atherosis and spiral-artery thrombosis, as late events, have been implicated in causing severe placental ischaemia and even infarction.60

The absence of a close correlation between the presence of maternal, placental, and fetal components of the disease69 and the chronology of maternal components of the syndrome seem to contradict placental ischaemia as the major or only mechanism.79 The placental environment in the first trimester is typically low in oxygen; this relative hypoxia is probably physiologically important because increased intervillous flow is associated with adverse pregnancy outcome.80 Signs of placental involvement (eg, increased amounts of inhibit A) are noticeable in future pre-eclamptic patients already in their first trimester long before any degree of placental hypoxia.79 Placental ischaemia, especially in the advanced stages of disease, is probably only one of several predisposing factors for the pre-eclampsia syndrome.7

Immune or inflammatory processes provide an alternative explanation. Apoptosis could be due to maternal or fetal immune maladaptation; several cytokines (especially IL2, IFNγ, and tumour necrosis factor [TNF])81 and FAS–FAS ligand are well known mediators of apoptosis. Maternal serum of pre-eclamptic women reduces trophoblast viability with evidence for enhanced sensitivity to FAS-mediated apoptosis.82 Increased placental apoptotic debris in pre-eclampsia could participate in pathogenesis by enhancing the inflammatory stimulus with or without specific immune recognition. Monocytes and neutrophils binding to syncytiotrophoblast microparticles result in raised production of TNF and IL12, and superoxide radicals, respectively.83 Low-level ingestion of apoptotic cells by macrophages is known to elicit the production of anti-inflammatory cytokines, whereas excessive apoptosis (creating danger signals) activates macrophages towards a proinflammatory-cytokine profile.82

Many other placental factors seen in the maternal circulation during healthy pregnancy are increased in pre-eclampsia. These include several inflammatory cytokines, corticotropin-releasing hormone, free-radical species, and activin A; all could stimulate the maternal inflammatory response.75 Much of the controversy about oxidative stress
is related to the non-specificity of the markers. Moretti and co-workers measured oxidative stress in exhaled breath that was not subjected to in-vitro artifacts and recorded greater oxidative stress in women with pre-eclampsia than in those with uncomplicated pregnancies and non-pregnant controls.

In particular, TNF, with its ability to activate endothelial cells, cause microvascular protein leakage, and reduce acetylcholine-induced vasorelaxation, has received a lot of attention as a having a potential key role. Increased TNF amounts in the pre-eclamptic placenta are probably produced by villous stromal cells, especially macrophages, but sources other than the placenta seem to contribute to raised plasma TNF and IL6 concentrations seen in the disease. IL12 derived from monocytes or macrophages is important in driving T-helper-1 reactions in pre-eclampsia. IL12 is a potent stimulus of IFNγ release by natural-killer cells and naive T cells. Importantly, IFNγ efficiently primes monocytes for further IL12 release that triggers a feed-forward cycle, which could explain the very rapid deterioration in some severely ill pre-eclamptic patients.

In summary, maternal–fetal immune maladaptation could be the main cause for superficial placenta. Subsequent increased syncytiotrophoblast shedding might trigger a systemic inflammatory response in mothers, possibly by creating an antigenic stimulus and the so-called danger signal leading to substantial T-helper-1 activation.

**Endothelial activation and inflammation**

It is still uncertain whether pre-eclampsia is caused by the damaged ischaemic or reperfused placenta or by the inappropriate or exaggerated maternal inflammatory response towards the presence of the trophoblast, although the endothelium is associated with the pathophysiology of disease. Many endothelial studies have focused on the importance of prostacyclin and thromboxane A2 imbalance in women with pre-eclampsia. Recent studies confirming increased concentrations of asymmetric dimethylarginine at 23–25 weeks in pregnant women who subsequently develop pre-eclampsia underline the importance of the nitric oxide-cGMP pathway.

Endothelial dysfunction or inappropriate endothelial-cell activation are the most common clinical manifestations in pre-eclampsia, including enhanced endothelial-cell permeability and platelet aggregation. Redman and colleagues showed that such endothelial activation is part of a more general (intravascular) inflammatory reaction, including intravascular leucocytes as well as the clotting and complement systems. A key finding was that this maternal inflammatory response was also a feature of healthy pregnancy in the third trimester, but less severe than in pre-eclampsia. Even typical pregnancy is characterised by a pronounced inflammatory response, and the differences between pre-eclampsia and healthy pregnancy are less obvious than those between pregnancy and non-pregnancy.

The absence of the typical stimulation of the renin–angiotensin system (despite substantial hypovolaemia); the enhanced vascular sensitivity to angiotensin II and norepinephrine with subsequent vasoconstriction and hypertension; and the raised endothelial-cell permeability in established pre-eclampsia can all be explained by this endothelial activation. Endothelial dysfunction will cause a fall in production and activity of vasodilator prostaglandins, especially prostacyclin and nitric oxide. The raised ratio of thromboxane A2 to prostacyclin might further reduce uteroplacental blood flow with spiral-artery thrombosis and placental infarction. In pre-eclampsia, endothelial-cell dysfunction and platelet aggregation precede the rise in thrombin and fibrin formation. Inadequate production of antiaggregatory prostacyclin, nitric oxide, or both, provide a plausible explanation for surface-mediated platelet activation occurring on the inner lining of spiral arteries. Platelets adhere to and release α-granule and dense-granule constituents, specifically thromboxane A2 and serotonin, contributing to platelet aggregation and inducing fibrin formation, especially in the uteroplacental circulation.

Thrombophilia is probably only one of the contributing factors. In a two-hit model of pre-eclampsia, in which a triggering event is exacerbated by other factors, thrombophilias are the exacerbating factor, or second hit. Cytotrophoblasts in spiral arteries, apoptosis, or increased syncytiotrophoblast apoptosis could elicit fibrin deposition, as well as platelet activation. Additionally, annexin-V production by trophoblasts is reduced in pre-eclampsia, possibly as a result of inflammatory cytokine and free-radical activity. The degree of annexin-V reduction correlates with the increase of markers of coagulation activation, maternal disease severity, and severity of intrauterine growth restriction. Any pre-existing underlying thrombophilia will augment this pathophysiological process. The role of fetal thrombophilias in the causation of placental vasculopathy is still controversial with evidence supporting and refuting this association.

**Genes, the genetic-conflict hypothesis, and genetic imprinting**

According to the genetic-conflict theory, fetal genes will be selected to increase the transfer of nutrients to the fetus, and maternal genes will be selected to restrict transfer exceeding a specific maternal optimum. With genomic imprinting, a similar conflict exists within fetal cells between genes that are maternally derived and those that are paternally derived. The conflict hypothesis predicts that placental factors (fetal genes) will act to raise maternal blood pressure, whereas maternal factors will act to reduce blood pressure. Endothelial-cell dysfunction
could have evolved as a fetal-rescue strategy to enhance non-placental resistance when the uteroplacental blood supply is inadequate.7

VEGF and its soluble receptor, sFlt, provide a prime example of the molecular pathways predicted by Haig.89 In healthy pregnancy, the appropriate interaction between endovascular trophoblast and decidual leucocytes, especially natural-killer cells, results in substantial VEGF and PlGF release.90 Raised concentrations of free VEGF are important in maintaining the quiescent endothelial state under the existing increased shear and inflammatory stress of typical pregnancy.101 Maynard and colleagues102 showed that placenta-derived sFlt (sFlt1), an antagonist of VEGF and PlGF, is upregulated in pre-eclampsia, leading to increased systemic amounts of sFlt1 that fall after delivery. Raised circulating sFlt1 in pre-eclampsia is associated with lowered circulating concentrations of free VEGF and PlGF, resulting in endothelial dysfunction. The magnitude of increase in sFlt correlates with disease severity,92,103 lending further support to the theory that the balance of VEGF and soluble Flt is closely implicated in one of the final pathophysiological pathways.

In the first trimester, PI GF concentrations are decreased in pregnancies with future pre-eclampsia and intrauterine growth restriction, whereas sFlt amounts do not differ from controls.104 These data are again compatible with the role of decidal angiogenic growth factors, in particular PI GF, being essential for early placental development (low concentrations of PI GF in both intrauterine growth restriction and pre-eclampsia) with the later involvement of sFlt as fetal-rescue signal steering the maternal response (ie, the degree of maternal systemic hypertension). This hypothesis is supported by Levine and co-workers,105 who showed that during the last 2 months of pregnancy in normotensive controls, concentrations of sFlt1 and PI GF rose and fell, respectively.

Nilsson and colleagues106 published a model estimating a heritability of 31% for pre-eclampsia and 20% for gestational hypertension. Although one major pre-eclampsia gene is unlikely, such a gene has committed evolutionary suicide, unless it had a major reproductive advantage. We are more likely to see a rapidly growing number of susceptibility genes, many of which interact with the maternal cardiovascular or haemostatic system, or with the regulation of maternal inflammatory responses. Genome-wide linkage studies have identified at least three pre-eclampsia loci showing substantial linkage: 2p12, 2p25,94 and 9p13.95 These loci segregate with different populations.96 Notably, these loci only explain a small percentage of the overall cases of pre-eclampsia. Moreover, although these linkage studies indicate maternal susceptibility, they do not exclude the additional involvement of fetal genes. One concern in any genetic study on pre-eclampsia is the confounding effect of the so-called fetal origins of adult disease hypothesis suggesting that a hostile intrauterine environment for a female fetus would form the basis for the insulin-resistance syndrome with its associated endothelial dysfunction, and therefore a raised risk of pre-eclampsia.97

Epigenetic features—ie, imprinting—are implicated in the pathogenesis of pre-eclampsia.97,100 Oudejans and colleagues98 confirmed the susceptibility locus on chromosome 10q22.1. Haplotype analysis showed a parent-of-origin effect: maximum allele sharing in the affected siblings was seen for maternally derived alleles in all families, but not for paternally derived alleles.99

Prediction of pre-eclampsia

Many biochemical markers have been proposed to predict which women are likely to develop pre-eclampsia.8,94 These markers were generally chosen on the basis of specific pathophysiological abnormalities that have been reported in association with pre-eclampsia—ie, those of placental dysfunction,101 endothelial and coagulation activation,9,80,106 and systemic inflammation.73,75,107 Maternal concentrations of these biomarkers have been reported to be either increased or reduced early in gestation before the onset of pre-eclampsia. However, data for the reliability of these markers in indicating pre-eclampsia have been inconsistent, and many markers are not specific or predictive enough for routine use in clinical practice.8,106

Doppler ultrasonography is a useful method to assess the velocity of uterine-artery blood flow in the second trimester. An abnormal velocity wave form is characterised by a high resistance index or an early diastolic notch (unilateral or bilateral).108 Pregnancies complicated by abnormal uterine artery doppler findings in the second trimester are associated with more than a six-fold increase in rate of pre-eclampsia.109 However, the sensitivity of an abnormal uterine artery doppler for predicting the disorder ranges from 20% to 60%, with a positive predictive value of 6–40%.109–111 Chien and colleagues112 reviewed 27 studies (n=12 994) and concluded that uterine-artery doppler assessment has limited value as a screening test for pre-eclampsia. Current data do not support this test for routine screening of pregnant women for pre-eclampsia,9 but uterine-artery doppler could be beneficial as a test for those at very high risk for the disorder if an effective preventive treatment is available.1

Prevention of pre-eclampsia

During the past decade, several randomised trials reported the use of various methods to reduce the rate or severity (or both) of pre-eclampsia (table). Results of these studies have been the subject of several systemic reviews.14,136–138 In summary, there have been few trials assessing protein or salt restriction; zinc, magnesium, fish oil, or vitamins C and E supplementation; the use of diuretics and other antihypertensive drugs; or heparin to prevent pre-eclampsia in women with various risk factors.5,102,136,138 Even though these trials had limited sample sizes, results showed a minimum to no benefit.3

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Findings from observational studies also suggest that heparin reduces recurrent pre-eclampsia in women with thrombophilias.\textsuperscript{117}

**Calcium supplementation**

In a Cochrane review,\textsuperscript{116} calcium supplementation was associated with reduced hypertension and pre-eclampsia, particularly for those at high risk of the disease and with a low baseline dietary calcium intake (for those with an adequate calcium intake the difference was not significant). No side-effects of calcium supplementation were recorded in the trials reviewed.\textsuperscript{113} However, the reduction was not indicated in any overall effect on stillbirths or neonatal deaths. The data lend support to calcium supplementation for women at high risk of pre-eclampsia and in communities with low dietary calcium intake.\textsuperscript{113} The absence of convincing evidence of effectiveness from the largest trial (n=4589),\textsuperscript{120} which recorded no reduction in the rate or severity of pre-eclampsia or in the timing of onset, have discouraged the use of calcium supplementation in developed countries. The benefit of calcium supplementation for pre-eclampsia prevention in women with low dietary calcium intake still remains unclear.\textsuperscript{5,6}

**Aspirin and other antiplatelet drugs**

Most randomised trials investigating the prevention of pre-eclampsia have used low doses of aspirin (500–1500 mg/L).\textsuperscript{114} The rationale for recommending low-dose aspirin prophylaxis is that the vasospasm and coagulation abnormalities in the disorder are caused partly by an imbalance in the thromboxane-A2-to-prostacyclin ratio. Low-dose aspirin treatment in pregnancy inhibits biosynthesis of platelet thromboxane A2 with little effect on vascular prostacyclin production, thus altering the balance in favour of prostacyclin and preventing development of pre-eclampsia.\textsuperscript{121} An updated systematic Cochrane review\textsuperscript{115} of the effectiveness and safety of antiplatelet drugs (mainly aspirin) for the prevention of pre-eclampsia included 51 trials (n=36 500). Risk of the disorder associated with the use of antiplatelet drugs fell by 19%. 28 trials (n=31 845) reported preterm birth. There was a small (7%) reduction in the risk of delivery before 37 completed weeks. Fetal or neonatal deaths were reported in 38 trials (n=34 010). Overall, there was a 16% reduction in baby deaths in the antiplatelet group compared with controls. Babies small for gestational age were reported in 32 trials (n=24 310), with an 8% reduction in the incidence of small-for-gestational-age infants in the group receiving antiplatelet therapy.\textsuperscript{121} Treatment and control groups did not differ significantly in any other measures of outcome. The reviewers concluded that antiplatelet drugs, mainly low-dose aspirin, have small-moderate benefits when used to prevent pre-eclampsia. Low-dose aspirin was also noted to be safe.\textsuperscript{114,115} However, more information is needed to assess which women are most likely to benefit, at what gestational age treatment is best started, and what dose to use.

Results from a meta-analysis\textsuperscript{122} suggested that low-dose aspirin improves pregnancy outcome in women with persistent increases in uterine doppler resistance index at both 18 and 24 weeks’ gestation. However, in other studies with abnormal doppler measurements of uterine arteries at 22–24 weeks’ gestation, aspirin treatment after 23 weeks of gestation did not prevent pre-eclampsia.\textsuperscript{108,111} A large, multicentre study that included 2539 high-risk women with pre-gestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestation, or pre-eclampsia in a previous pregnancy showed no beneficial effects from low-dose aspirin treatment.\textsuperscript{11} However, almost all studies on the prevention of pre-eclampsia so far focus on poor or inconsistent definitions of the disorder.\textsuperscript{5} Aspirin use should be based on individualised risk assessment for pre-eclampsia.\textsuperscript{11,114,111}

**Management of pre-eclampsia**

Adequate and proper prenatal care is most important in the management of pre-eclampsia.\textsuperscript{1,2,10,28} Maternal antenatal monitoring includes identification of women at high risk, early detection by the recognition of clinical signs and symptoms, and progression of the condition to severe state.\textsuperscript{1,2,10,28} After diagnosis, subsequent treatment will depend on the results of initial maternal and fetal assessment. The main objective of management of pre-eclampsia must always be the safety of the mother. Although delivery is always appropriate for the mother, it might not be best for a very premature fetus. The decision between delivery and expectant management depends on fetal gestational age, fetal...
status, and severity of maternal condition at time of assessment. This objective can be achieved by formulating a management plan that considers one or more of the following: fetal gestational age, maternal and fetal status at time of initial assessment, presence of labour, or rupture of fetal membranes (figure 2). A detailed description of management of women with pre-eclampsia can be seen elsewhere.\textsuperscript{1,2,10} The proposed management algorithm and following recommendations that we discuss are based on observational studies and expert opinion. Individual components have not been subjected to appropriate large, prospective, randomised controlled clinical trials.

In general, women with mild disease developing at 38 weeks' gestation or longer have a pregnancy outcome similar to that seen in normotensive pregnancy.\textsuperscript{27} Thus, those patients should undergo induction of labour for delivery. Induction of labour or delivery is also recommended for those at or beyond 34 weeks' gestation in the presence of severe pre-eclampsia, labour, or rupture of membranes, or non-reassuring tests of fetal wellbeing (figure 2), because the mother is at a slightly increased risk of development of abruptio placentae and progression to eclampsia.\textsuperscript{1,2} In those who remain undelivered, close maternal and fetal monitoring is essential. The type of test and frequency of assessment will depend on fetal gestational age, severity of maternal condition, and presence or absence of fetal growth restriction.\textsuperscript{1,2,10} These tests should be repeated promptly in case of worsening maternal (progression to severe disease) or fetal condition (reduced movement or suspected growth restriction).\textsuperscript{1,2}

**Expectant management of severe pre-eclampsia**

The clinical course of severe pre-eclampsia can be characterised by progressive deterioration in both maternal and fetal conditions.\textsuperscript{126} Because these pregnancies have been associated with raised rates of maternal morbidity and mortality and with pronounced risks for the fetus, such patients should be delivered if the disease develops after 34 weeks' gestation.\textsuperscript{124} Delivery is also clearly indicated when there is imminent eclampsia (persistent, severe symptoms), multiorgan dysfunction, severe intrauterine growth restriction, suspected abruptio placentae, or non-reassuring fetal testing before 34 weeks' gestation.\textsuperscript{1,2,10,124} However, there is disagreement about treatment of severe pre-eclampsia before 34 weeks' gestation if the maternal condition is stable and fetal condition is reassuring.\textsuperscript{1,2,10} A Cochrane review on interventionist versus expectant care\textsuperscript{98} states that firm conclusions cannot be drawn, since only two small trials (n=133) have compared a policy of early elective delivery with that of delayed delivery, and the CIs for all outcomes are wide. However, the evidence is promising that short-term morbidity for the baby might be reduced by a policy of expectant care.\textsuperscript{125-127}

**Antihypertensive treatment**

Treatment of acute hypertension should prevent potential cerebrovascular and cardiovascular complications, which are the most common cause of maternal mortality and morbidity in developed countries.\textsuperscript{21,128} Although the use of antihypertensive drugs in women with pre-eclampsia and severe rises in blood pressure have been shown to prevent cerebrovascular problems, such treatment does not prevent or alter the natural course of the disease in women with mild pre-eclampsia.\textsuperscript{1,2,10}

The most recent Cochrane review\textsuperscript{119} included 40 studies (n=3797), 24 of which compared an antihypertensive drug with placebo and no antihypertensive drug (n=2815). Risk of severe hypertension associated with the use of antihypertensive drugs was halved, but little evidence showed a difference in the risk of pre-eclampsia. Similarly, there was no significant effect on the risk of perinatal death, preterm birth, or small-for-gestational-age babies,\textsuperscript{19} and there were no clear differences in other outcomes. Additionally, of 17 trials (n=1182) that compared one antihypertensive drug with another, no significant difference between any of these drugs was recorded in the risk of severe hypertension and proteinuria or pre-eclampsia. The reviewers concluded that it remains unclear whether antihypertensive drug treatment for mild-moderate hypertension during

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**Figure 2: Management of pre-eclampsia**

- **Pre-eclampsia**
  - Gestational age ≥ 38 weeks
  - At ≥ 34 weeks' gestation:
    - Severe pre-eclampsia
    - Labour or rupture of membranes
    - Abnormal fetal testing
    - Severe oligohydramnios or fetal growth restriction

- **Maternal and fetal assessment**
  - YES
    - Deliver
  - NO
    - Mild disease
    - Severe disease
    - < 23 weeks

- **Hospital or office management**
  - Maternal and fetal assessment

- **Worsening maternal or fetal condition**
  - ≥ 38 weeks
  - Labour or rupture of membranes

- **Steroids**
  - Delivery after 48 h

- **Antihypertensives**
  - Daily assessment of maternal-fetal conditions
  - Delivery at 34 weeks

**Expectant care**

- Delivery at 34 weeks
- Delivery after 48 h
- Steroids

**Antenatal care**

- Daily assessment of maternal-fetal conditions
- Delivery at 34 weeks

**Termination of pregnancy**

- Antihypertensives
- Delivery after 48 h

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**Conclusion**

The management of pre-eclampsia requires a comprehensive approach that considers the individual needs of each patient. This includes close monitoring of maternal and fetal wellbeing, timely delivery when indicated, and appropriate antihypertensive treatment. Further research is needed to clarify the optimal timing and type of antihypertensive therapy, as well as to develop strategies for reducing the risk of maternal and fetal complications associated with severe pre-eclampsia.
pregnancy is worthwhile. A meta-regression of antihypertensive drugs in pregnancy also suggested that lowered blood pressure in women with mild disease could increase the risk of a small-for-gestational-age baby.

Antihypertensive treatment is sometimes recommended for sustained values of systolic blood pressure of at least 160 mm Hg and for sustained diastolic values of at least 110 mm Hg. Parenteral hydralazine, labetalol, and short-acting oral nifedipine are the most commonly used drugs to control acute severe hypertension in women with pre-eclampsia. However, intravenous hydralazine is regarded as the first drug of choice for this purpose by several groups. Magee and colleagues did a meta-analysis of 21 trials (n=893); eight compared hydralazine with nifedipine, and five compared hydralazine with labetalol. Hydralazine was associated with significantly higher maternal side-effects and worse maternal and perinatal outcomes than either labetalol or nifedipine. The researchers concluded that adequately powered clinical trials are needed to compare labetalol with nifedipine for treating severe hypertension in women with pre-eclampsia.

Use of corticosteroids to improve pregnancy outcome in women with severe pre-eclampsia or HELLP syndrome

There has been uncertainty regarding the effectiveness and safety of corticosteroids in women with severe pre-eclampsia with or without HELLP syndrome. A prospective, double-blind, randomised trial of 218 women with severe pre-eclampsia and gestational age between 26 and 34 weeks were assigned either betamethasone or placebo. A significant reduction in the rate of respiratory distress syndrome in the steroids group was recorded. Corticosteroid use also was associated with reduced risks of neonatal intraventricular haemorrhage, infection, and neonatal death. No differences in maternal complications were seen between the two groups. Four trials compared dexamethasone plus standard treatment with standard treatment only in women with HELLP syndrome. There were no cases of liver haematoma or rupture, pulmonary oedema, renal failure, or placental abruption in either group and no difference in perinatal morbidities. Because of their small sample sizes, the reviewed trials showed no evidence that supports or refutes steroid use in HELLP syndrome antenatally and in postpartum to reduce or increase maternal and perinatal mortality. However, the data support the effectiveness and safety of corticosteroids to reduce neonatal complications in women with severe pre-eclampsia at 34 weeks' gestation or less.

Plasma-volume expansion

Some women with severe pre-eclampsia have a restricted circulating plasma volume and are haemo-concentrated. This has led to the recommendation that plasma volume should be expanded with either colloid or crystalloid solutions, to improve maternal systemic and uteroplacental circulation. However, intravascular volume expansion carries a serious risk of volume overload, which could lead to pulmonary or cerebral oedema. Also, large volume expansion often requires invasive monitoring of intravascular pressure, which includes procedures with risks of their own. Three small trials (n=61) compared a colloid solution with placebo or no infusion. Although too small for reliable conclusions, the findings suggest plasma-volume expansion is not beneficial. In view of the risks in such approach, use of colloid solutions should be avoided until data from large randomised trials become available.

Prevention of convulsions and control of acute convulsions

Eclampsia is defined as the onset of convulsions in women who have either gestational hypertension or pre-eclampsia. Several randomised trials have compared the efficacy of magnesium sulphate with other anticonvulsants in women with eclampsia. These trials compared magnesium sulphate with diazepam, phenytoin, or a lytic cocktail. Magnesium sulphate was associated with a significantly reduced rate of recurrent seizures and maternal death than that seen with other anticonvulsants. Magnesium-sulphate prophylaxis in women with pre-eclampsia should prevent or reduce the rate of eclampsia and its complications. Secondary benefits also include reduced maternal and perinatal morbidities in women with severe pre-eclampsia and lowered rate of progression to severe disease in those with mild pre-eclampsia. Four large, randomised controlled trials comparing the use of magnesium sulphate to prevent convulsions in patients with severe pre-eclampsia showed that magnesium-sulphate prophylaxis compared with placebo (two trials, n=10 795), nimodipine (one, n=1750), and with no treatment (one, n=228) in severe pre-eclampsia was associated with a significantly reduced rate of eclampsia. The largest trial so far, the Magpie trial, enrolled 10 141 women with pre-eclampsia (mainly in developing countries). Most patients had severe disease, and the rate of eclampsia was significantly lower in those assigned magnesium sulphate. However, of the 1560 women enrolled in developed countries, rates of eclampsia did not differ significantly between treatment and control groups. Nevertheless, the trial was not designed or powered to test the effectiveness of magnesium sulphate in patients in developed countries.

Another two randomised trials also compared magnesium sulphate with placebo in women with mild pre-eclampsia, and the results of all six trials showed no benefit of magnesium sulphate on perinatal outcome. Additionally, the treatment did not affect...
serious maternal complications of severe pre-eclampsia, such as pulmonary oedema, stroke, liver, haematomata, or renal failure.1,9,20 Available evidence has suggested that magnesium sulphate be given during labour and immediately postpartum in some women with severe pre-eclampsia, because the benefit of magnesium sulphate in those with mild disease remains unclear.1,19

Postpartum pre-eclampsia

In general, pre-eclampsia is cured by delivery of the placenta, although in some women the disease process could worsen during the first 48 h after delivery. Such women might be at risk for pulmonary oedema, renal failure, HELLP syndrome, postpartum eclampsia, and stroke.1,20 Therefore, women with diagnosed hypertension or pre-eclampsia (or both) need very close monitoring of blood pressure, maternal symptoms, and measurements of fluid intake and urine output.1,20

Severe hypertension or pre-eclampsia could develop for the first time postpartum.1,12,14 Hence, postpartum women should be educated about the signs and symptoms of pre-eclampsia. Additionally, all health-care providers should know about the importance of responding to these symptoms in time. Women who report persistent severe headaches, visual changes, epigastric pain with nausea or vomiting, or respiratory symptoms need immediate assessment and potential hospital care.1,12,14

Future directions

Many challenges remain regarding the prediction, prevention, and management of pre-eclampsia. Future research should expand our knowledge of biomarkers for early prediction of severe pre-eclampsia and aim to reduce the prevalence of the disorder that is associated with adverse pregnancy outcome (severe disease and onset before 33 weeks’ gestation). However, the lack of universal criteria to diagnose pre-eclampsia has hampered basic research into the cause, identifying biomarkers for prediction, and prevention of this condition. The diagnostic criteria for pre-eclampsia in the various risk groups should be sensitive and reliable in predicting adverse pregnancy outcome. Thus, hypothesis-driven studies based on large-scale genomic and proteomic approaches to identify new target molecules and diagnostic biomarkers should be designed and implemented, which will ultimately aid in formulating targeted interventions to prevent pre-eclampsia.

Progress in the next 5 years will be probably made to identify a rapidly growing list of susceptibility genes, and to have an improved understanding of (angiogenic) growth factors and their receptors, and normal and abnormal maternal-fetal immune interaction. From a clinical perspective, we can expect completion of several large randomised antioxidant trials (for vitamins E and C). Finally, there is an urgent need for large randomised trials to test new interventions that are designed to prevent cases of pre-eclampsia associated with adverse maternal and perinatal outcome.

Conflict of interest statement

We declare that we have no conflict of interest.

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