Pre-eclampsia

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Pre-eclampsia remains a leading cause of maternal and perinatal mortality and morbidity. It is a pregnancy-specific disease characterised by de-novo development of concurrent hypertension and proteinuria, sometimes progressing into a multiorgan cluster of varying clinical features. Poor early placentation is especially associated with early onset disease. Predisposing cardiovascular or metabolic risks for endothelial dysfunction, as part of an exaggerated systemic inflammatory response, might dominate in the origins of late onset pre-eclampsia. Because the multifactorial pathogenesis of different pre-eclampsia phenotypes has not been fully elucidated, prevention and prediction are still not possible, and symptomatic clinical management should be mainly directed to prevent maternal morbidity (eg, eclampsia) and mortality. Expectant management of women with early onset disease to improve perinatal outcome should not preclude timely delivery—the only definitive cure. Pre-eclampsia foretells raised rates of cardiovascular and metabolic disease in later life, which could be reason for subsequent lifestyle education and intervention.

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Introduction

Complicating 2–8% of pregnancies, pre-eclampsia, along with the other hypertensive disorders of pregnancy, is a major contributor to maternal mortality worldwide.[1,2] In Latin America and the Caribbean, hypertensive disorders are responsible for almost 26% of maternal deaths, whereas in Africa and Asia they contribute to 9% of deaths. Although maternal mortality is much lower in high-income countries than in developing countries, 16% of maternal deaths can be assigned to hypertensive disorders.[1] The incidence of pre-eclampsia has risen in the USA.[3,4] This finding might be related to an increased prevalence of predisposing disorders, such as chronic hypertension, diabetes, and obesity.[3] Some ethnic groups (eg, African-American and Filipino women[5,6]) and low socioeconomic status are associated with a heightened risk.[7] Furthermore, severe pre-eclampsia is a major cause of severe maternal morbidity (eg, stroke and liver rupture) and adverse perinatal outcomes, such as prematurity and intrauterine growth restriction.[2] Although the generalised seizures of eclampsia complicate 2–3 cases per 10 000 births in Europe, eclampsia is 10–30 times more common in developing countries than in high-income countries.[2]

Other hypertensive disorders in pregnancy are pre-existing hypertension and gestational hypertension. Pre-eclampsia is generally defined as new hypertension (diastolic blood pressure of ≥90 mm Hg) and substantial proteinuria (≥300 mg in 24 h) at or after 20 weeks' gestation.[8] However, how best to define the maternal syndrome of pre-eclampsia, and how to differentiate mild from severe disease is being debated.[9–12] Table 1 shows recent classification frameworks, evolving from previous work of the American College of Obstetricians and Gynecologists[13] and the International Society for the Study of Hypertension in Pregnancy.[14] The main differences between the classification systems are: (1) inclusion or exclusion of complicated non-proteinuric gestational hypertension as pre-eclampsia; (2) differentiation between clinical and research definitions in the Australasian guideline; (3) use of early-onset pre-eclampsia as a severity criterion in Canada (<34 weeks) and the USA (<35 weeks); (4) clinical importance of assessing white-coat hypertension; and (5) definition of severe hypertension. Although perinatal risks have long been recognised to be highest remote from term, the 20-fold increase in maternal mortality that is associated with pre-eclampsia arising at less than 32 weeks (compared with that at ≥37 weeks)[15] seems not to have been, emphasising the importance of early-onset pre-eclampsia as a severity criterion. The debate between setting the systolic blood pressure definition of severe hypertension at either 160 mm Hg or 170 mm Hg needs to be resolved because of rising concerns about lethal maternal stroke risks at the lower threshold for blood pressure.[16,17] None of these classification systems seems to have been independently assessed for the ability to identify women and fetuses at heightened risk of the adverse events that make pre-eclampsia so important.

Pathogenesis

Although the cause of pre-eclampsia remains largely unknown, the leading hypotheses strongly rely on disturbed placental function in early pregnancy (figure). Impaired remodelling of the spiral artery has especially been considered as an early, but not necessarily the primary, defect causing pre-eclampsia.[19] Remodelling is a multistep process[20] in which the first decidua-associated step should be initiated around implantation.

Search strategy and selection criteria

We searched PubMed and the Cochrane Library with the search terms "pre-eclampsia" and "hypertension and pregnancy", and cross-referenced them with the following terms: "epidemiology", "definition", "aetiology", "pathophysiology", "prediction", "prevention", "management", "clinical trials", "preconception care", and "thrombophilia". We mainly restricted our search to studies done in human beings. We largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those that we judged to be relevant. Review articles and book chapters are cited to provide readers with more details and references than this Seminar provides. Our reference list was modified on the basis of comments from peer reviewers.

	RCOG severe pre-eclampsia (2006)[9]	SOMANZ (2008)[10]	SOGC (2008)[11]	ASH (2008)[12]
Pre-existing or chronic hypertension (blood pressure ≥140/90 mm Hg before 20 weeks' gestation)	NA	Chronic hypertension: essential; secondary; white coat; with or without superimposed pre-eclampsia	Pre-existing hypertension: with or without comorbid conditions; with or without superimposed pre-eclampsia	Chronic hypertension of any cause: with or without superimposed pre-eclampsia
Gestational hypertension (blood pressure ≥140/90 mm Hg after 19 weeks' (+6 days) gestation	NA	Gestational hypertension without significant proteinuria returning to normal within 12 weeks' post partum	Gestational hypertension: with or without comorbid conditions; with or without superimposed pre-eclampsia	Gestational hypertension: transient hypertension; blood pressure returning to normal within 6 weeks' post partum; late post partum hypertension, with blood pressure rise developing weeks' to 6 months' post partum and normalised by 1 year post partum
Pre-eclampsia (clinical definition)	Gestational hypertension (pregnancy-induced hypertension) and significant proteinuria (>0·3 g/24 h)	Gestational hypertension plus one or more of the following: dipstick proteinuria confirmed by either random Pr:Cr ratio ≥30 mg/mmol or 0·3 g/24 h; serum or plasma creatinine >90 μmol/L; oliguria; thrombocytopenia; haemolysis; disseminated intravascular coagulation; raised serum transaminases; severe epigastric or right upper quadrant pain; eclampsia; hypereflexia with sustained clonus; severe headache; persistent visual disturbances; stroke; pulmonary oedema; fetal growth restriction; placental abruption	Pre-existing hypertension and resistant hypertension, new proteinuria, or adverse condition (see severity criteria below) Gestational hypertension and proteinuria (random Pr:Cr ratio ≥30 mg/mmol or 0·3 g/24 h), or adverse condition	Gestational hypertension or chronic hypertension and proteinuria (dipstick ≥1+, random Pr:Cr ratio ≥30 mg/mmol or 0·3 g/24 h)
Pre-eclampsia (research definition)	Not defined	De novo hypertension >20 weeks' gestation, returning to normal post partum with properly documented proteinuria	Not defined	Not defined
Severe hypertension	170/110 mm Hg	170/110 mm Hg	160/110 mm Hg	160/110 mm Hg
Heavy proteinuria	1 g/L	Not defined	3–5 g per day	3 g per day
Severity criteria				
Gestational age at onset	Not included	Not defined	<34 weeks' gestation	<35 weeks' gestation
Maternal symptoms	Severe headache; visual disturbance; epigastric pain or vomiting	Not defined	Persistent or new/unusual headache; visual disturbances; persistent abdominal or right upper quadrant pain; severe nausea or vomiting, chest pain or dyspnoea	Headache; visual disturbances; abdominal pain
Maternal signs of end-organ dysfunction	Eclampsia; severe hypertension; heavy proteinuria; liver tenderness; signs of clonus; papilloedema	Not defined	Eclampsia; severe hypertension; pulmonary oedema; or suspected placental abruption	Severe diastolic hypertension (≥110 mm Hg); heavy proteinuria, oliguria
Abnormal maternal laboratory testing	Platelet count <100×10^9/L, HELLP syndrome, abnormal liver enzymes (ALT or AST rising to above 70 U/L)	Not defined	Raised serum creatinine; increased AST, ALT, or LDH with symptoms; platelet count <100×10^9/L; or serum albumin <20 g/L	Raised serum creatinine, decreased glomerular filtration rate, or increased AST or LDH
Fetal morbidity or mortality	Not included	Not defined	Oligohydramnios; intrauterine growth restriction; absent or reversed end-diastolic flow in the umbilical artery by Doppler velocimetry; intrauterine fetal death	Fetal morbidity (non-reassuring fetal testing)

RCOG=Royal College of Obstericians and Gynaecologists. SOMANZ=Society of Obstetric Medicine of Australia and New Zealand. SOGC=Society of Obstetricians and Gynaecologists of Canada. ASH=American Society of Hypertension. NA=not applicable. Pr:Cr=protein-to-creatinine ratio. HELLP=haemolysis, elevated liver enzymes, and low platelet count. ALT=alanine transaminase. AST=aspartate transaminase. LDH=lactate dehydrogenase.

Table 1: **International comparison between recent classification systems**

Disturbances at this stage could increase risk of pre-eclampsia, and might explain its higher incidence in women with unexplained subfertility or recurrent miscarriage.[21,22] Decidua-associated vascular changes also arise in the inner (junctional zone) myometrium, followed by trophoblast invasion with associated remodelling.[23] Interaction of trophoblastic HLA-C, HLA-E, and HLA-G with uterine natural killer cells or dendritic cells, or both, is thought to be important in regulation of invasion,[24–26] and some combinations of HLA-C and killer cell immunoglobulin-like receptor isoforms predispose to pre-eclampsia.[27]

Intervillous flow seems to start 7–8 weeks of gestation by the appearance of connecting channels between spiral arteries and lacunae in the wall of the implanted blastocyst.[28] Early trophoblast plugging might protect the embryo against high oxygen concentrations. Researchers[29] have postulated that premature loss of these plugs could result in early miscarriage, or, dependent on timing, pre-eclampsia. Gradually plugs are resolved by intravascular migration of the trophoblast. Intervillous flow is thought to start in lateral regions,[29] whereas trophoblast invasion and associated deplugging of spiral artery outlets starts in the centre and spreads to the periphery. Peripheral onset of intervillous flow should result in high local oxidative stress, leading to villous regression and formation of the chorion leave. Insufficient lateral spread of endovascular plugging could therefore result in extensive chorionic regression and a small placenta,[29] contributing to intrauterine growth restriction, early-onset pre-eclampsia, or both.

Overlaying trophoblast invasion and spiral artery remodelling steps on Jauniaux's placental oxygen curve[30] shows that decidua-associated remodelling in decidua and junctional zone myometrium develops during the steep rise in placental oxygen (10–12 weeks), whereas at 10 weeks some decidual arteries are already filled with endovascular trophoblast over their entire length.[31] Placental flow defects can be detected as early as 12 weeks in women who subsequently develop pre-eclampsia.[32] Deep invasion of the myometrial arterial segments comes after the steep rise in placental oxygen from 15 weeks onwards, and can therefore be triggered by increased flow.[31] Thus, impaired invasion of myometrial spiral arteries in pre-eclampsia might result from, rather than cause, maternal flow defects. As myometrial spiral arteries have a more pronounced muscular coat and elastica than do the corresponding decidual vessels, failed remodelling at this level leads to reduced uteroplacental arterial flow and episodes of irregular placental perfusion. Such hypoxia or reoxygenation episodes in some cases generate reactive

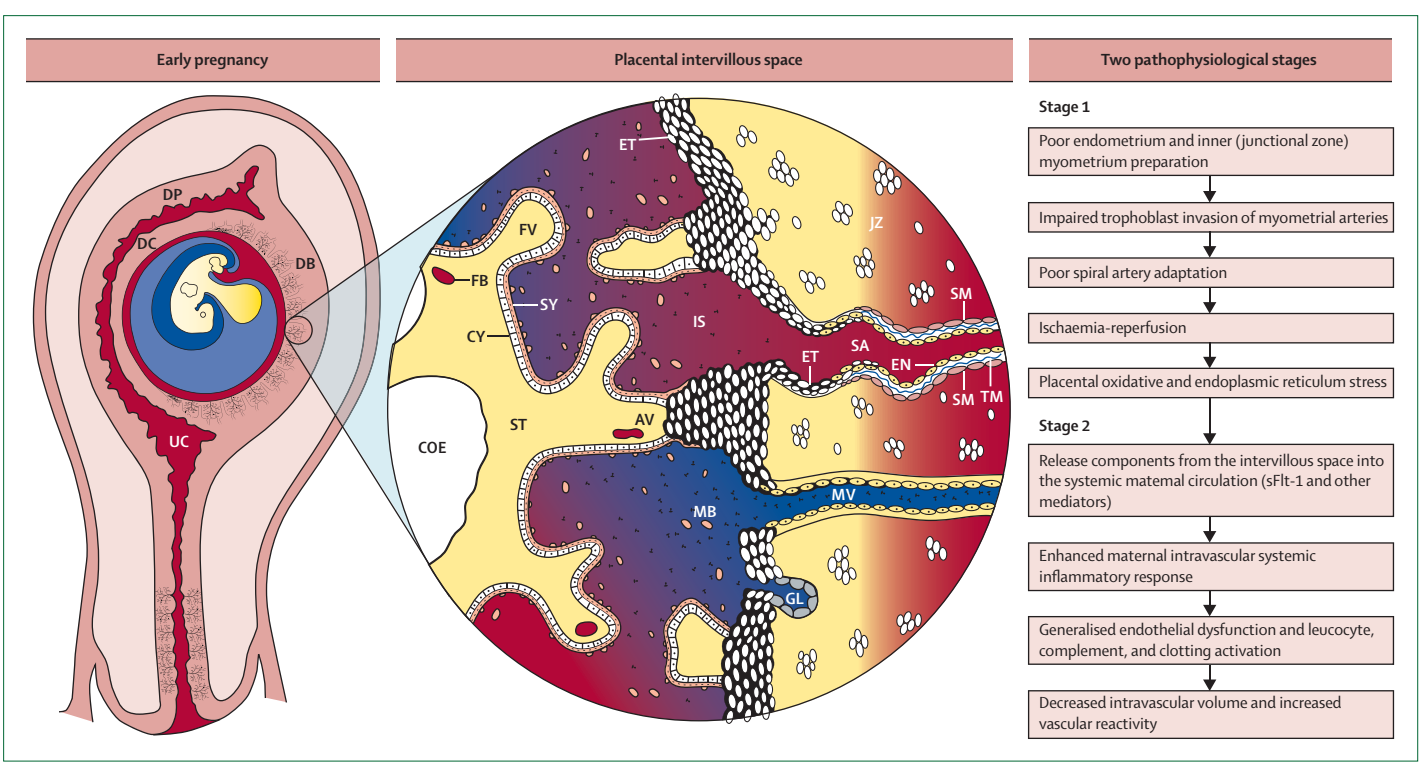

Figure: **Possible pathophysiological processes in pre-eclampsia**
AV=anchoring villus. COE=coelomic cavity. CY=cytotrophoblast. DB=decidua basalis. DC=decidua capsularis. DP=decidua parietalis. EN=endothelium. ET=extravillous trophoblast. FB=fetal blood vessel. FV=floating villus. GL=gland. IS=intervillous space. JZ=junctional zone myometrium. MB=maternal blood, leaving the intervillous space with various components such as antiangiogenic factors. MV=maternal vein. SA=spiral artery. SM=smooth muscle. ST=stroma. SY=syncytiotrophoblast. TM=tunica media. UC=uterine cavity. sFlt-1=soluble form of the vascular endothelial growth factor receptor. Centre panel of figure adapted from Karumanchi et al,[18] with permission from Elsevier.

	Unadjusted relative risks (95% CI)
Nulliparity	2·91 (1·28–6·61)
Multiparous women	
Pre-eclampsia in any previous pregnancy	7·19 (5·85–8·83)
10 years or more since last baby born	Increased*
Age 40 years or older	
Nulliparous women	1·68 (1·23–2·29)
Multiparous women	1·96 (1·34–2·87)
Body-mass index of 35 kg/m² or higher	1·55 (1·28–1·88)
Family history of pre-eclampsia (mother or sister)	2·90 (1·70–4·93)
Diastolic blood pressure of ≥80 mm Hg at booking	Increased*
Proteinuria at booking appointment (≥+on dipstick testing, on more than one occasion or quantified at ≥300 mg/24 h)	Increased*
Multiple pregnancy	2·93 (2·04–4·21)
Underlying medical disorders	
Pre-existing hypertension	Increased*
Pre-existing renal disease	Increased*
Pre-existing diabetes	3·56 (2·54–4·99)
Presence of antiphospholipid antibodies	9·72 (4·34–21·75)

*Risk for pre-eclampsia increased, but by how much is unknown.

Table 2: **Risk markers for pre-eclampsia at antenatal booking according to the PRE-eclampsia Community Guidelines (PRECOG[8])**

oxygen species,[33] leading to placental oxidative stress and placental dysfunction, with endoplasmic reticulum stress and impaired protein synthesis.[34] We believe that the unidentified causes of the first (placental) stage of pre-eclampsia[35] might include excessive or atypical maternal immune response to trophoblasts,[36] and either impaired decidualisation or failure of proper uterine preconditioning.[37] Thus, pre-eclampsia is a disease of failed interaction between two genetically different organisms. As such, Haig's maternal-fetal conflict hypothesis could be relevant.[38]

The second stage (figure) of systemic maternal disease is associated with an exaggerated endothelial activation and a generalised hyperinflammatory state compared with normal pregnancy.[39] Episodes of placental hypoxia or reperfusion result in oxidative stress, subsequent apoptotic and necrotic disruption of syncytial architecture,[40] and release of various components from the intervillous space into the maternal circulation, stimulating production of inflammatory cytokines.[41] The circulating bioactive trophoblast debris includes syncytiotrophoblast membrane microparticles[41] and an excess of syncytiotrophoblast-derived antiangiogenic factors, such as soluble endoglin and the soluble form of the vascular endothelial growth factor (VEGF) receptor (sFlt-1).[18] Increased production of anti-angiogenic factors by trophoblasts was also recently shown in molar pregnancy, a disorder known to predispose women to pre-eclampsia.[42,43] The excessive systemic inflammatory response of pre-eclampsia[44] results in endothelial dysfunction and associated increased vascular reactivity, preceding onset of symptomatic clinical disease.[45] Loss of endothelial integrity contributes to derangements of sodium-volume homoeostasis and reversal of many cardiovascular changes (eg, increased cardiac output and intravascular volume) accompanying normal pregnancy. Thus, pre-eclampsia is a low-output, high-resistance state with paradoxically decreased aldosterone and renin activity.[46]

Linking mechanisms between stages 1 and 2 can be different for several phenotypes of pre-eclampsia, including haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome,[47] and sometimes varies between individuals. Whether pre-eclampsia will be of early (often complicated by intrauterine growth restriction) or late onset can be dependent on whether the placenta in stage 1 becomes phenotypically small because of a greater angiogenic imbalance.[48] Poor placentation should not be regarded as the cause of pre-eclampsia, because not all of such pregnancies have poor outcomes, but instead as a powerful predisposing factor.[39] In the presence of a placenta with an appropriate size for gestational age, predisposing cardiovascular and metabolic syndrome-like disorders might also be able to set off a cascade of placental and systemic inflammation and oxidative stress, resulting in late onset pre-eclampsia (also called maternal pre-eclampsia).[49] This view is substantiated by findings of normal villous morphology in late-onset pre-eclampsia, by contrast with early-onset pre-eclampsia,[50] although no such data seem to exist for the placental bed.

Although interactions between maternal genetic and constitutional factors with environmental factors contribute to the second stage, such factors are now thought to have an effect on the first stage of the disease.[49] Decreased antioxidant and phase I and phase II biotransformation activities in the maternal blood and decidual and placental tissue probably contribute to an increased risk of pre-eclampsia.[51] The protective effect of smoking against pre-eclampsia[52] could result from beneficial carbon monoxide effects on trophoblast invasion and spiral artery remodelling, increased stage 1 placental blood flow, and decreased stage 2 inflammatory responses.[53] Decreased placental release of sFlt-1 is possibly associated with this protective effect.[54]

Screening

Table 2 shows factors that can easily be measured at the first prenatal appointment and that increase the likelihood of pre-eclampsia in any pregnancy.[8,55] In risk assessments done after 20 weeks' gestation, attention should be paid to the possible onset of pre-eclampsia by identification of any of the following signs and symptoms: new hypertension, new proteinuria, symptoms of headache, visual disturbance, epigastric pain, vomiting, reduced fetal movements, and an infant that is small for gestational age.[56] Such risk assessment before and after 20 weeks can be used in the community to offer referral for specialist input.

Next to history taking, physical examination including measurement of blood pressure and assessment for presence of proteinuria, are the cornerstones of screening in antenatal care. Blood pressure should be measured as for non-pregnancy, with the woman at rest, sitting upright, with the arm supported, and the sphygmomanometer cuff at the level of the patient's heart.[11] Korotkoff sound V (disappearance of turbulence) should be used to define diastolic blood pressure and values recorded to the nearest 2 mm Hg. Thigh cuffs (18×36 cm) should be used for women with an arm circumference of 41 cm or more.[56] Of the automated blood pressure measuring devices on the market, only the Microlife 3BTO-A and Microlife WatchBP Home[57] have met the British Hypertension Society's criteria for accuracy. Mean arterial blood pressure might be a better predictor for pre-eclampsia than is systolic or diastolic blood pressure or an increase in blood pressure.[58] Although dipstick testing for screening of proteinuria is prone to issues of intraobserver and interobserver variability and limited sensitivity and specificity,[59] it is readily available, widely used, and might be the only test available in low-income and middle-income countries. Although 24 h urine collection is still used to confirm and quantify a substantial amount of proteinuria,[56] this method seems vulnerable to issues of overcollection, undercollection, and large coefficients of variation between tests in the same women.[60] The spot urinary protein-to-creatinine ratio, often used as a screening method,[56] is less cumbersome than is 24 h urine collection, and is suggested to be an equivalently accurate measure of clinically significant proteinuria in pregnancy.[61] Still to be established, however, is whether this ratio remains constant throughout a 24 h period.[62]

Prediction

Early prediction of pre-eclampsia would allow for close surveillance and preventive strategies. Many tests have been assessed for their relation to placental perfusion, vascular resistance, and placental products, including tests for Down's serum screening analytes and hormones, renal and endothelial dysfunction, oxidative stress, and fetal-derived products. Of 27 tests reviewed by Meads and colleagues,[63] only a few reached specificities above 90%. These were body-mass index of 34 kg/m² or higher, α-fetoprotein, and bilateral uterine artery Doppler notching. Sensitivity of higher than 60% was achieved only by uterine artery Doppler resistance index and combinations of indices. Kallikreinuria (sensitivity >80% and specificity >90%) and cellular and total fibronectin (specificity >90%) seem worthy of further investigation. No single test, however, met the clinical standards for a predictive test—a conclusion also drawn by authors of another systematic review.[64]

Because any single biomarker is unlikely to be effective in prediction of the onset of a disorder as heterogeneous as pre-eclampsia, researchers[65] have suggested that combinations of tests such as ultrasound assessment of uterine artery Doppler waveforms, placental thickness and homogeneity, and serum markers raise the effectiveness of history and physical-based screening. Logistic regression analysis combining information on uterine artery pulsatility index, mean arterial pressure, serum pregnancy-associated plasma protein-A, serum-free placental growth factor, body-mass index, and presence of nulliparity or previous pre-eclampsia showed promising high sensitivity and specificity in prediction of early pre-eclampsia.[66] Similarly, ratios of antiangiogenic and proangiogenic factors (eg, ratio of sFlt-1 to placental growth factor)[67,68] might have better discriminatory power than do other methods.[69] However, whether or not these tests will also be useful across the range of placenta-related complications remains unknown.

Clinical presentation

Maternal organ systems that are susceptible to excessive inflammation and endothelial damage are the CNS, lungs, liver, kidneys, systemic vasculature, coagulation, and the heart—the placenta and fetus are also at risk. The more organ systems that are affected, the more maternal and perinatal complications arise. Clinicians should take caution not to undervalue clinical signs and symptoms in (severe) pre-eclampsia (table 1) because they can be non-specific (eg, nausea and vomiting). Caregivers should always remember that pre-eclampsia can potentially fulminate, and therefore they should not be given a false sense of security because mild disease has been designated. Some risks pertain to development of the HELLP syndrome of microangiopathic haemolysis and platelet consumption, and hepatocellular damage from periportal or focal parenchymal necrosis. Patients frequently (40–90%) have epigastric or right upper quadrant pain.[70] These clinical symptoms, along with headache, visual changes, and nausea or vomiting seem to be more predictive than are laboratory parameters for adverse maternal outcomes.[71]

HELLP syndrome complicates 10–20% of cases of severe pre-eclampsia, and develops mostly preterm (50%). In 20% of women, however, it presents in late gestation, or in 30% post partum.[72] HELLP without hypertension or proteinuria is reported in 10–20% of cases. Direct complications of HELLP syndrome are abruptio placentae (9–20%), disseminated intravascular coagulation (5–56%) and acute renal failure (7–36%). Less frequent complications are eclampsia (4–9%), pulmonary oedema (3–10%), and subcapsular liver haematoma (less than 2%).[72] Estimates of complication rates can be quite high because they are derived mainly from tertiary care centres. Overall, significant maternal morbidity is encountered in about 15% of women with severe pre-eclampsia,[73] including retinal detachment and cerebrovascular bleeding, and complications related to HELLP syndrome, but with lowered frequencies. The brain is at risk because of impaired cerebral

Panel 1: **Differential diagnoses in severe pre-eclampsia by organ system**

Vasculature
- Phaeochromocytoma
- Hyperaldosteronism
- Cushing's disease
- Thyrotoxicosis
- Aorta coarctation

Renal system
- Lupus nephritis
- Acute and chronic glomerulonephritis
- Interstitial nephritis
- Pyelonephritis

Liver
- Acute fatty liver of pregnancy
- Pregnancy cholestasis
- Hyperemesis gravidarum
- Cholecystitis
- Cholangitis
- Viral hepatitis
- Acute pancreatitis
- Gastritis
- Gastric ulcer

Haemostasis
- Benign thrombocytopenia of pregnancy
- Thrombotic thrombocytopenic purpura
- Haemolytic uraemic syndrome
- Idiopathic thrombocytopenic purpura
- Antiphospholipid syndrome
- Folate deficiency
- Systemic lupus erythematosus
- Septic or haemorrhagic shock

Respiratory system
- Pneumonia
- Pulmonary embolus
- (Catastrophic) antiphospholipid syndrome

(Continues in next column)

(Continued from previous column)

Cardiovascular system
- Peripartum cardiomyopathy
- Myocardial infarction or ischaemia

Brain
- Cerebral systemic lupus erythematosus
- Epilepsy
- Brain tumour
- Cerebrovascular accident
- Hypertensive encephalopathy
- Metabolic disease

Eyes
- Retinal arterial or venous thrombosis
- Retinal ischaemia
- Retinal detachment
- Persistent spasm of retinal vessels
- Central serous retinopathy
- Uveal melanoma
- Choroidal osteoma

autoregulation due to endothelial damage together with decreased sympathetic innervation in the posterior cerebral circulation, and a lessened ability for neurogenic response to increase blood pressure. Cortical blindness and some cases of eclampsia could evolve from the acute cerebral illness, posterior reversible leukoencephalopathy syndrome (PRES).[74]

Eclampsia, complicating 1–2% of severe pre-eclampsia,[75] is defined as the occurrence of tonic-clonic seizures in a pregnant or recently delivered woman that cannot be attributed to other causes. Although difficult to predict, in 79% of cases promonitory signs and symptoms are present during the week before the first eclamptic seizure: headache (56%), visual disturbances (23%), epigastric pain (17%), hypertension (48%), proteinuria (46%), and concurrent hypertension and proteinuria (38%).[76] Hypertension and proteinuria can last for several weeks post partum.[77] Pre-eclampsia can also deteriorate or present de novo after delivery, occasionally evolving into severe forms that are similar to eclampsia.[78] Women with symptoms and signs of pre-eclampsia might have other maternal diseases,[79] and therefore differential diagnoses should be considered and excluded (panel 1). Perinatal concerns in women with pre-eclampsia relate to risks of placental abruption (0–6%), intrauterine growth restriction (5–18%), and perinatal mortality (0–9%), dependent on severity and gestational onset of disease.[80]

Management

For women with pre-eclampsia, dependent on severity, review at day assessment units or admission to hospital is indicated according to local guidelines.[56] Table 3 and panel 2 show our suggested management paradigms according to gestational age at presentation. Although we recognise that there is no universally accepted standard of care, which is dependent on local facilities, we believe that risk reduction for women with pre-eclampsia needs a series of strategies—namely standardised assessment and surveillance, avoidance and management of severe systolic and diastolic hypertension, prevention and treatment of seizures of eclampsia, and avoidance of use of aggressive rehydration in women admitted with severe pre-eclampsia. Although debate exists about routine use of some individual tests, standardised assessment and surveillance of all vulnerable organ systems in women with pre-eclampsia has been associated with reduced adverse maternal outcomes,[86] and proposals for blood tests have been developed.[56] Tests for uric acid is one of the controversial tests that has been

	20 weeks (+0 days)—fetal viability*	Fetal viability*—29 weeks (+6 days)	30 weeks (+0 days) to 33 weeks (+6 days)	34 weeks (+0 days) to 36 weeks (+6 days)	37 weeks (+0 days) or more
Perinatal prognosis on admission with pre-eclampsia: cohort data of 2128 women admitted to tertiary units with pre-eclampsia†	18–50% survival; 2–45% intact survival	60–95% survival; 15–90% intact survival‡	98% survival; 88–96% intact survival‡	>99% survival; 96% intact survival‡	>99% survival; >96% intact survival‡
Increase in maternal risks[15] (compared with normotensive pregnancy)	Substantial	Substantial	Substantial	Moderate	Minimum
Consider in-utero transfer to tertiary centre with NICU	Optional; centre should be competent with midtrimester termination of pregnancy or expectant management	Yes, if mother stable for transfer	Ideally, but perinatal outcomes might be unchanged if transfer post partum	Optional, but centre should be competent with expectant management if considered as management option	Optional; in case of severe disease
Expectant management[81-83]	No; although in very few patients at 22–23 weeks' gestation clinician might attempt sufficient pregnancy prolongation to attain perinatal survival	Optional; could be considered in view of possible perinatal gains	Optional; could be considered in view of possible perinatal gains	Optional; could be considered, but in severe disease balance towards delivery	No
Betamethasone for fetal lung maturation[84]	Optional; dependent on gestational age	Yes	Yes	No	No
Suggested route of delivery	Vaginal (misoprostol induction of labour)[85]	Probable caesarean section, unless intrauterine fetal death	Vaginal, depending on fetal and cervical status	Vaginal, depending on fetal and cervical status	Vaginal, depending on fetal and cervical status

NICU=neonatal intensive care unit. *As defined locally (usually between 23 weeks' [+0 days] and 24 weeks' [+6 days] gestation). †Unpublised data from PIERS.[86] ‡Chance of living to discharge from a NICU without major morbidity (≥grade 3 intraventricular haemorrhage, stage 3 or 4 retinopathy of prematurity, necrotising enterocolitis, and chronic lung disease).

Table 3: **Antepartum management options for women with pre-eclampsia by gestational age at diagnosis**

suggested. Although researchers have suggested that uric acid is as important as proteinuria for identification of fetal risk in women with gestational hypertension,[93] it is a poor predictor of maternal and fetal complications in women with pre-eclampsia.[94] In a review,[62] researchers concluded that the amount of proteinuria is not a good marker of severity of pre-eclampsia, and that this measure should not guide management.

For women who are remote from term (<34 weeks' gestation), there is both randomised controlled trial and cohort-based evidence[81] that expectant management (compared with stabilisation and delivery, which is the sole cure for pre-eclampsia) confers some perinatal benefit with a minimum amount of additional maternal risk. However, insufficient data are available for straightforward recommendations for either expectant or interventionist care,[82] and policies could differ for women cared for in low-resource settings. For women who present before 24 weeks' gestation, expectant management is unlikely to offer any perinatal advantages, although maternal risks accumulate.[81,83] Women at term with pre-eclampsia (and non-proteinuric gestational hypertension) are best managed by a policy of induction of labour.[95] In the case of women with HELLP syndrome at or near term, expedited delivery should be standard management. Remote from term, clinicians could consider expectant management in some cases with vigilant expectancy, but no evidence exists to advise for which women such policy can be applied without substantial maternal risks.[81,82] Such practices should only be attempted in institutions with much experience in management of pre-eclampsia. Failure to exhibit due clinical care in combination with a policy of expectant management can prove lethal.[96] Corticosteroids have not been shown to benefit primary maternal and perinatal outcomes in women with HELLP.[72,97,98]

The present Cochrane review[99] does not support the choice of any one antihypertensive agent over another for management of severe pregnancy hypertension, concluding that the choice should depend on the clinician's experience with a specific drug. It does, however, advise against use of diazoxide because, although more effective for reduction of blood pressure than is hydralazine,[100] diazoxide might result in increased rates of maternal hypotension. Ketanserin seems to be less effective than is hydralazine. Neither magnesium sulphate ($MgSO_4$) nor nimodipine are recommended as antihypertensive agents.[99] In another systematic review,[89] nifedipine (within the class of calcium-channel blockers) seemed to be more effective in bringing blood pressure within the target range, with less hypotension, than was hydralazine. By comparison, labetalol was less effective but was associated with fewer adverse maternal and perinatal events than was hydralazine.[89] Nifedipine capsules (5 mg or 10 mg) are no longer available in all markets, and should not be used in women with known coronary artery disease, those who have had diabetes mellitus for more than 15 years, or those who are older than 45 years because of the risks of sudden cardiac death.[101] Clinicians who

Panel 2: Suggested antepartum management options for women with pre-eclampsia at any stage of diagnosis*

Optional assessment and surveillance[56,86]

On admission, on day of delivery, and additional testing as indicated by changes in clinical state.

Maternal

Blood: haemoglobin, platelet count, creatinine, uric acid, AST or ALT, further testing if indicated

Fetal

CTG, ultrasound, AFI, umbilical artery Doppler

$MgSO_4$

Regimen: $MgSO_4$ 4 g IV loading dose over 15–20 min, followed by an infusion of 1 g/h; recurrent seizure(s) treated with additional 2–4 g IV loading dose(s); clinical monitoring by measurement of urinary output, respiratory rate, and tendon reflexes.

Eclampsia prophylaxis[87]

Yes; for severe pre-eclampsia during initial stabilisation and peripartum (delivery +24 h)

Eclampsia treatment[88]

Yes

Antihypertensive therapy (other doses possible)[89,90]

Severe hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg)

- Nifedipine capsule (5 mg orally for first dose, 10 mg orally subsequently) every 30 min; nifedipine intermediate acting (10 mg orally) every 45 min; labetalol (100 mg orally) every 45 min, maximum 1200 mg/day; labetalol (20 mg IV first dose, repeat 20–80 mg IV every 30 min, or 1–2 mg/min, maximum 300 mg); hydralazine (5–10 mg IV) every 30 min, maximum 20 mg
- Nifedipine capsules are safe to use contemporaneously with $MgSO_4$; nifedipine capsules should not be used in women with known coronary artery disease, aortic stenosis, or longstanding diabetes (eg, >15 years); after two consecutive doses of acute therapy (ie, nifedipine, labetalol, hydralazine), start or increase maintenance therapy with agents listed below

(Continues in next column)

(Continued from previous column)

Non-severe hypertension (systolic BP <160 mm Hg and diastolic BP 90–109 mm Hg)

- Labetalol (100–400 mg orally 2–4 times daily, maximum 1200 mg/day); intermediate-acting nifedipine (10–20 mg orally 2–3 times daily, maximum 120 mg/day); nifedipine sustained release preparation (20–60 mg orally daily, maximum 120 mg/day); methyldopa (250–500 mg orally 2–4 times daily, maximum 2 g/day); other β blockers (other than atenolol)
- In the absence of renal disease, pre-pregnancy diabetes, or other indications for strict maintenance of strict normotension, whether BP targets should be high normotension (eg, diastolic BP 85 mm Hg) or non-severe hypertension (eg, diastolic BP 105 mm Hg) is unknown; ACE inhibitors, ARBs, atenolol, and prazosin should be avoided

Plasma volume expansion[11,91]

No; because of risks of maternal mortality associated with pulmonary oedema, in women with severe pre-eclampsia infusion of sodium-containing fluids might need to be restricted and balanced against urine output over 4 h or more and creatinine concentrations

Thromboprophylaxis[92]

Yes; if on bed rest for 4 days or more

*Please refer to local practice guidelines. AST=aspartate transaminase. ALT=alanine transaminase. CTG=cardiotrocography. AFI=amniotic fluid index. IV=intravenous. BP=blood pressure. ACE=angiotensin converting enzyme. ARB=angiotensin II receptor blocker.

choose the alternative of intermediate-acting nifedipine tablets should recognise the slow onset of action so that women are not over-treated because of an expectation of a rapid blood pressure response.[102] Nifedipine and $MgSO_4$ can be used together effectively and safely.[103] Antihypertensives for use in women with non-severe hypertension, although generally not related to improved pregnancy outcome except for less severe hypertension,[90,104] are also shown in panel 2.

Prevention and management of eclampsia seizures is based on giving $MgSO_4$.[87,88] Women with severe pre-eclampsia should be considered for $MgSO_4$ prophylaxis.[104] Findings from randomised controlled trials[87,88] support a regimen of $MgSO_4$ given as a 4 g intravenous loading dose during a 15–20 min period, followed by an infusion of 1 g/h, with a first or recurrent seizure treated with another 2–4 g intravenous loading dose. This regimen does not need testing of blood concentrations of $MgSO_4$ because clinical effect can be monitored with deep tendon reflexes. Additionally, it adds a wider therapeutic index between effect and toxicity risk than does the historical 2 g/h regimen. Despite a reduced intravascular volume in pre-eclampsia, plasma volume expansion has not proven to provide any benefit.[91]

Timing of delivery should be designed to keep perinatal outcomes at an optimum while obviating maternal risks. In pre-eclampsia, this timing should be based on criteria of fetal wellbeing and gains to be made in terms of perinatal outcomes by achievement of additional intrauterine time. Fetal wellbeing is assessed by ultrasound (biometry, umbilical artery Doppler, ductus venosus Doppler, and amniotic fluid) and cardiotocography (preferably computerised).[105] Antenatal corticosteroids for fetal lung maturation should be given to all women at risk of delivery at less than 34 weeks of gestation.[84] Previable fetuses can be delivered with misoprostol induction.[85] In early-onset pre-eclampsia and often concurrent intrauterine growth restriction and placental pathology, the fetus is unlikely to tolerate

labour. However, the closer the pregnancy gets to term, the more reasonable an attempt at induction of labour is for women with pre-eclampsia who require timely, but not emergency, delivery.

When women have severe disease, issues of peripartum management of thrombocytopenia and HELLP syndrome arise.[11,72] Although routine prophylactic platelet transfusions are not recommended, ordering blood products, including platelets, should be considered when platelet counts are fewer than 50×10^9 platelets per L, falling rapidly, or when coagulopathy is present. Platelet transfusion is always indicated before, during, or after either caesarean section or vaginal delivery when platelet counts are fewer than 20×10^9/L or in case of significant bleeding (eg, ecchymosis, bleeding from gums or wound).[70] Preanaesthetic assessment of a woman with pre-eclampsia is essential, including an airway examination and assessment of coagulation status (such as platelet count). There is no role for tests of platelet function.[9,11,106] Use of regional analgesia or anaesthesia, or both, is not contraindicated in women when platelet counts are higher than 75×10^9/L in the absence of a coagulopathy, falling platelet count, or concomitant use of either an antiplatelet agent (eg, aspirin) or anticoagulant (eg, heparin).

Regional anaesthesia (epidural, spinal, or combined spinal-epidural) is appropriate for women taking low-dose aspirin (without either coagulopathy or platelets $<75\times10^9$/L), and those given low-molecular-weight heparin at least 12 h after a prophylactic dose or 24 h after a therapeutic dose.[107] Early insertion of a spinal or epidural catheter for obstetric or anaesthetic indications should be considered (in the absence of contraindications) to reduce the need for general anaesthesia in case of caesarean section. A difficult airway due to pharyngolaryngeal oedema should always be anticipated. Intubation could increase risk of severe hypertension (and subsequent cerebral events) and aspiration. Measures should be taken to avoid a speed that compromises maternal safety, even in the presence of acute fetal compromise. Central venous access or pulmonary artery catheterisation should only be used for specific disorders (ie, pulmonary oedema and cardiac disease) in a high dependency setting. Ergot alkaloids should be omitted for active management of the third stage of labour if the mother is hypertensive.[16]

Preconception care and future health

Women at high risk for pre-eclampsia, including those with a history of the disease or other complications in their obstetric history, should be offered preconception care by obstetricians with experience in management of the disorder. If present, severity of chronic hypertension, diabetes, connective tissue, or renal disease should be assessed and pharmacological treatment adjusted for safety in pregnancy. Risks of occurrence and recurrence (10% for previous mild disease and up to 40% for severe disease) and perinatal mortality and morbidity should be explained and a management plan, available for all associated caretakers, should be drawn up. Obesity and an increase in body-mass index between pregnancies[108] increases risk of (recurrent) pre-eclampsia,[109] and partly neutralises the protective effect of smoking.[52] Although preconception weight loss has not yet been properly investigated, studies after bariatric surgery suggest positive effects.[110] Other risk factors (table 2), should also be discussed.

Nutritional preventive measures should not be advised for management of the occurrence or recurrence of pre-eclampsia in women at high risk or the general population. Neither diets low in energy or salt, nor supplementation with either antioxidants vitamins C or E, fish oil, garlic, zinc, selenium, folic acid, or magnesium are effective.[63,111,112] An evidence-based review[113] showed no relation between calcium supplementation and risk reduction of pre-eclampsia, although supplementation might have some effects in high-risk populations that are calcium-deficient. Low-dose aspirin prophylaxis has long been of interest because it is thought to correct an imbalance in the ratio of thromboxane A_2 to prostacyclin that is associated with increased vasoreactivity. Findings from a meta-analysis[114] of individual patients' data from 31 randomised trials showed that asprin was associated with a 10% reduction in pre-eclampsia and prematurity (less than 34 weeks' gestation), and that aspirin seemed to be safe. The number needed to treat to obtain these results was, however, very large. Low-dose aspirin should be offered on an individual basis and decisions made on the basis of the woman's risk profile from their obstetric and medical history. Neither progesterone or diuretics nor antihypertensives in women with chronic hypertension reduce risk of pre-eclampsia.[111] The damaging effects of smoking on general health and perinatal outcomes especially[115] outweigh its incidence-lowering effects on pre-eclampsia.[52]

Inherited or acquired thrombophilias are a heterogeneous group of coagulation disorders that predispose women to an extra risk of thromboembolic events during pregnancy and puerperium.[116] Although pre-eclampsia is related to reduced uteroplacental blood flow, its direct correlation with thrombophilia remains controversial. Placental thrombotic and inflammatory lesions associated with early-onset pre-eclampsia or fetal growth restriction do not arise more often in women with thrombophilia or hyperhomocysteinaemia than in those without these disorders.[117] Meta-analyses[118] often showed positive, though mostly weak, associations of thrombophilia with pre-eclampsia, although there were instances of heterogeneity between studies. Results from three large, prospectively designed studies[119–121] showed no associations with any of the inherited thrombophilias for mild or severe pre-eclampsia. In small studies,[122,123] investigation of recurrence rates of pre-eclampsia in women with thrombophilias showed conflicting results. Associations with hyperhomocysteinaemia are often biased by delivery to test-time interval and maternal age.[124] There are no completed trials to establish the effects of heparin on

pregnancy outcomes for women with a thrombophilia.[125] Therefore, in view of WHO criteria by Wilson and Jungner,[126] routine screening of women who had pre-eclampsia and treatment when they were positive for thrombophilia does not yet seems justified, unless the intent is to randomly assign women in definitive randomised controlled trials. Thrombophilia testing, however, should be recommended for those with a personal or family history of thrombosis.[127]

Pre-eclampsia, especially of early onset, can be followed by symptoms of maternal post-traumatic stress.[128,129] Timely recognition of those women at risk and referral reduces the duration of treatment necessary.[129] Women with pre-eclampsia are at increased risk for future cardiovascular disease. Pooled relative risks for hypertension, fatal and non-fatal ischaemic heart disease, and fatal and non-fatal stroke are 3·70 (95% CI 2·70–5·05), 2·26 (1·86–2·52), and 1·81 (1·45–2·27), respectively, 10–14 years after the index pregnancy.[130] Early-onset disease and other additional concurrent placental pathology confer cumulative risk.[131] Increased pre-pregnancy serum concentrations of triglycerides, cholesterol, LDL cholesterol, non-HDL cholesterol, and blood pressure are positively associated with risk of subsequent pre-eclampsia and could explain, together with abdominal obesity, the link with future cardiovascular disease.[132,133] Identification of such young women possibly offers opportunities for strategies to decrease remote cardiovascular risk.[130] As the absolute risk for disease within 12 years is low (less than 0·5–1·5% dependent on pre-eclampsia severity)[130] a first focus might be on lifestyle modifications, including smoking cessation, weight reduction, healthy diet, and exercise,[134] in individualised intervention programmes, including use of the internet. Because the risk of developing chronic hypertension could be higher than 20%,[130] blood pressure should be checked regularly. Other individual cardiovascular risk factors should be treated as indicated, but there seems to be no place for further screening or preventive drug interventions until further evidence is available. Pre-eclampsia has been suggested to predispose to reduced thyroid function in later years.[135]

Perspectives

Although genetic contributions to the risk of pre-eclampsia are recognised by familial clustering of this disorder, underlying mechanisms remain uncertain.[136] Maternal constitutional and environmental risk factors for pre-eclampsia could be implicated by interference with the epigenetic programming of the gametes, placenta, and fetus.[137] Derangements in genomic imprinting in placental tissue, resulting in disturbed paternal versus maternal gene expression, have additionally been suggested to contribute to pre-eclampsia.[137,138] Therefore, high priority will be given in the near future to elucidation of gene-gene and gene-environment interactions and underlying epigenetic mechanisms[139] that are associated with the programming of trophoblast cells and how they relate to placental causes and systemic linkages of different phenotypes of pre-eclampsia. Such phenotypes include that for HELLP syndrome and other placental complications such as isolated intrauterine growth restriction. These insights could direct future specific preconception and early pregnancy preventive measures to favourably affect placentation in women at high risk. Such measures might also be targeted at decreasing excessive inflammatory and oxidative stress (eg, by statins or metformin) or improvement of endothelial health.

A lowered incidence of hypertensive disease in pregnancy was suggested after periconception low-dose aspirin treatment.[140] Trophoblast complement inhibitory therapy with heparin might seem beneficial in some subgroups of patients.[141] However, to be able to keep spiral artery remodelling at an optimum with prophylactic treatment, a need for more comparative research to understand the placental bed remains. Additionally, pharmacological approaches to counteract the anti-angiogenic state in the second stage of the disease could be promising. Epigenetic modification of fetal vascular tissue during a pregnancy that is complicated by pre-eclampsia might also relate to future reproductive status and cardiovascular health.[137,142] Men and women exposed to pre-eclampsia as a fetus,[143] and women born small for gestational age,[144] have an increased risk of having (or fathering) a future pregnancy that is complicated by pre-eclampsia. These children also have a heightened risk of high blood pressure, features of metabolic syndrome, and cardiovascular diseases at relative early age.[145,146]

In preconception care, development of simple rules for prediction of recurrent early-onset hypertensive disease in pregnancy is important.[147] During pregnancy, proteomics-based identification of clinically useful predictive biomarkers might become feasible.[148,149] Furthermore, development and validation of disease severity criteria that objectively identify women at incremental risk of adverse outcomes need to be developed. Randomised controlled trials are much needed to establish recommendations for management of early-onset severe pre-eclampsia. In the UK, substandard care contributes to 72% of maternal deaths that are related to hypertensive disease in pregnancy,[16] and to 96% of those in the Netherlands.[96] In the Dutch enquiry,[96] no instructions about danger signs to women had been documented in 80% of cases. Therefore, patient education is of major importance. The need for drills and simulations for obstetric emergencies such as severe hypertension and eclampsia, and for audits of pre-eclampsia-related maternal mortality and severe morbidity should be further advocated.

Contributors

EAS designed the structure of the review and coordinated writing of the Seminar. All authors contributed to the literature search, writing of the Seminar, and addressing of reviewers' comments.

Conflicts of interest

We declare that we have no conflicts of interest.

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