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Pre-eclampsia part 2: prediction, prevention and management

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Abstract

An antiangiogenic state might constitute a terminal pathway for the multiple aetiologies of pre-eclampsia, especially those resulting from placental abnormalities. The levels of angiogenic and antiangiogenic proteins in maternal blood change prior to a diagnosis of pre-eclampsia, correlate with disease severity and have prognostic value in identifying women who will develop maternal and/or perinatal complications. Potential interventions exist to ameliorate the imbalance of angiogenesis and, hence, might provide opportunities to improve maternal and/or perinatal outcomes in pre-eclampsia. Current strategies for managing pre-eclampsia consist of controlling hypertension, preventing seizures and timely delivery of the fetus. Prediction of pre-eclampsia in the first trimester is of great interest, as early administration of aspirin might reduce the risk of pre-eclampsia, albeit modestly. Combinations of biomarkers typically predict pre-eclampsia better than single biomarkers; however, the encouraging initial results of biomarker studies require external validation in other populations before they can be used to facilitate intervention in patients identified as at increased risk. Angiogenic and antiangiogenic factors might also be useful in triage of symptomatic patients with suspected pre-eclampsia, differentiating pre-eclampsia from exacerbations of pre-existing medical conditions and performing risk assessment in asymptomatic women. This Review article discusses the performance of predictive and prognostic biomarkers for pre-eclampsia, current strategies for preventing and managing the condition and its long-term consequences.

Introduction

Current management of pre-eclampsia consists of controlling maternal hypertension, prevention of seizures and timely delivery of the fetus. Although understanding of the pathophysiology of this important obstetric syndrome remains elusive,[1] efforts are underway to identify biomarkers that can predict pre-eclampsia as early as the first trimester.[2]

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Author contributions

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Subgroup findings from meta-analyses and small randomized controlled trials of aspirin[3–6] and combinations of nitric oxide donors (L-arginine) and antioxidants (vitamins E and C)[5] for the prevention of pre-eclampsia are promising. However, these preventive strategies remain investigational. An imbalance between angiogenic and antiangiogenic factors has emerged as an important pathogenetic mechanism in pre-eclampsia.[7–11] The levels of these proteins in maternal blood, especially when measured in patients suspected of having pre-eclampsia <34 weeks of gestation, have prognostic value in identifying patients who will develop maternal and/or perinatal complications.[12–16] Importantly, several potential interventions could ameliorate an imbalance between angiogenic and antiangiogenic factors[17–22] and, hence, might provide opportunities to improve maternal and/or perinatal outcomes. Patients with pre-eclampsia are at increased risk of long-term complications, such as cardiovascular disease,[23] renal disease[24] and metabolic syndrome.[23] This Review discusses the potential clinical value of biomarkers, focusing on the use of angiogenic and antiangiogenic factors for prediction and monitoring of pre-eclampsia. Current management, possible interventions and long-term consequences of pre-eclampsia are also discussed.

Biomarkers that predict pre-eclampsia

Considerable efforts have been made to identify biomarkers that can predict pre-eclampsia as early as the first trimester,[2] as some evidence suggests that patients could benefit from early (<16 weeks of gestation) administration of aspirin or combinations of nitric oxide donors and antioxidants.[3–6] Risk assessment of patients with pre-eclampsia using biochemical markers[25,26] (such as pregnancy-associated plasma protein A [PAPP-A],[27] inhibin A, activin A, α-fetoprotein [AFP] and free choriogonadotropin subunit β [CG-β][28,29]), placental morphology and/or perfusion[30] and uterine artery Doppler velocimetry (UtADV) in the first or second trimesters (Figure 1),[31] has not provided encouraging results. Plasma levels of placental protein 13 (PP13, also known as galactoside-binding soluble lectin 13 or galectin-13) in the first trimester were predictive of early pre-eclampsia in two studies,[32,33] but these findings were not subsequently corroborated.[27,34,35]

Combinations of biomarkers generally have better diagnostic performance than single biomarkers in predicting pre-eclampsia.[2,25] In a systematic review, combinations of two or more of the seven most widely studied serum biomarkers—A disintegrin and metalloproteinase domain-containing protein 12 (ADAM 12), free CG-β, inhibin A, activin A, PP13, placental growth factor (PlGF) and PAPP-A)—in the first trimester identified 55–75% of patients with early pre-eclampsia (delivery <34 weeks) and 30–40% of all patients with pre-eclampsia, with a false-positive rate of 10%.[2] Three studies have reported strong prognostic performance for multiple biomarkers in the prediction of pre-eclampsia as early as in the first trimester; however, these studies involved imputed or simulated data and are, accordingly, not directly comparable to those that used traditional analytical methods.[36–38] In the first study, an estimated 91.0%, 79.4% and 60.9% of individuals with early (<34 weeks), intermediate (34–36 weeks) and late (>37 weeks) pre-eclampsia (on the basis of gestational age at delivery), respectively, could be identified with a 10% false-positive rate.[36] The first study used a combination of maternal characteristics, obstetric history, UtADV measurements, mean arterial pressure and maternal serum levels of PAPP-A, PP13, inhibin A, lifeactivin A, soluble endoglin, pentraxin-3 and P-selectin, determined in the first

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trimester (11–13 weeks of gestation).[36] The second and third studies used competing risk models (survival function) to predict pre-eclampsia. In the second, an estimated 80.0%, 54.6% and 34.9% of patients with pre-eclampsia who delivered at <34 weeks, <37 weeks and <42 weeks, respectively, could be identified using a combination of maternal characteristics, UtADV results and mean arterial pressure, with a 10% false-positive rate.[37] The third study additionally incorporated serum biomarkers (PAPP-A and PlGF), with the result that an estimated 96.3%, 76.6% and 53.6% of these patients could be identified with the same false-positive rate.[38]

Although several marker combinations (especially those including UtADV measurements in the first trimester) have poor performance for detecting all cases of pre-eclampsia, they are much better at identifying early pre-eclampsia.[39] The encouraging results of these biomarker studies nonetheless require validation in independent sets of samples.[40,41] In addition, for these biomarkers to have clinical utility, effective interventions must be developed for those identified as at increased risk, before their use can be implemented in clinical practice. [42]

Other systems biology approaches to identify biomarkers for pre-eclampsia include proteomics,[43,44] metabolomics,[45–47] measuring cell-free fetal DNA[48,49] and quantifying cell-free mRNAs encoding relevant proteins, such as corticotrophin-releasing hormone, placenta-specific protein 1, P-selectin,[50] vascular endothelial growth factor (VEGF) receptor 1 (VEGFR-1) and endoglin.[51] Early studies that quantified cell-free fetal DNA (which is thought to originate from apoptotic trophoblasts) for the prediction of pre-eclampsia before 20 weeks of gestation yielded encouraging results.[48,52] However, subsequent studies could not replicate these findings.[53,54] Studies using transcriptomic,[50,55,56] proteomic[43,44] and metabolomic[45–47] approaches have shown promising results, even in the first trimester, according to several case-control studies; however, large prospective cohort studies are required to validate these results.

Research in this area focuses not only on the identification of biomarkers that can predict pre-eclampsia, but also on predictors of adverse perinatal outcomes after diagnosis of pre-eclampsia. For example, the full PIERS (pre-eclampsia integrated estimate of risk) model was developed in 2011 to predict fatal or life-threatening maternal complications of pre-eclampsia within 48 h of admission, using standard clinical and laboratory information.[57] This model was validated using a threshold of ≥10% predicted probability to define a positive test, and predictive variables obtained within 6 h and 24 h of admission. The full PIERS model identified 44% and 57% of the women who would later develop adverse outcomes at these two respective time points, resulting in positive predictive values (PPVs) of 24% and 26%.[58]

An imbalance between angiogenic and antiangiogenic factors has emerged as an important pathogenetic mechanism in pre-eclampsia,[59,60] and evidence indicates that maternal plasma levels of these factors can identify the majority of patients who will develop early pre-eclampsia.[61,62] Moreover, levels of these biomarkers correlate with disease severity[59,60,63,64] and have prognostic value in identifying women who subsequently develop maternal and/or perinatal complications, especially in patients suspected of having pre-eclampsia at <34 weeks of gestation.[12–15,65,66]

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An emerging debate is whether pre-eclampsia is a homogeneous disease.[67] Critics argue that assessing a few biomarkers involved in only one pathway of disease (angiogenesis) is unlikely to predict or detect all women with pre-eclampsia, a disease that has multiple aetiologies.[68] Some investigators counter this argument with the proposal that the forms of pre-eclampsia associated with an angiogenic imbalance are those that result in adverse outcomes.[67,69] Furthermore, reported evidence of heterogeneity in the literature might be largely due to misclassification of other diseases as pre-eclampsia, as the criteria for its diagnosis (such as hypertension and proteinuria) are nonspecific.[67] However, several questions should be answered prior to concluding that pre-eclampsia is a homogenous disease. For example, the criteria used to define angiogenic imbalance (including fixed cut-offs derived from receiver operating characteristic [ROC] curve analyses, multiples of median values or percentile distributions of analyte levels) have yet to be agreed. Consequently, it is difficult to ascertain what proportion of patients with pre-eclampsia truly has an angiogenic imbalance. Most women with preterm pre-eclampsia have abnormal profiles of angiogenic and/or antiangiogenic factors, but this is not the case in women with pre-eclampsia at term (≥37 weeks of gestation).[64,61] It is uncertain that patients who do not have abnormal ratios of angiogenic to antiangiogenic factors at term have been misclassified as having pre-eclampsia. Most patients with pre-eclampsia are diagnosed at term, and eclampsia is also not uncommon after 37 weeks gestation. Moreover, what causes the antiangiogenic state in the first place remains unclear.

Our view is that if an imbalance between angiogenic and antiangiogenic factors represents the terminal pathway of multiple aetiologies, it is possible that assessing biomarkers of angiogenesis might identify most patients with pre-eclampsia, especially the forms of this disorder resulting from placental abnormalities (such as early pre-eclampsia), which have a major adverse effect on perinatal outcomes.[61,67,70] Indeed, our research group has observed that ~80–90% of women with preterm pre-eclampsia and 40–50% of those with pre-eclampsia at term have abnormal plasma PlGF:sVEGFR-1 or PlGF:soluble endoglin ratios, (defined as being below the 10th percentile for gestational age of uncomplicated pregnancies) within the 7 days prior to delivery (Chaiworapongsa *et al.*, unpublished work).

Clinical value of biomarker assessment

Potential interventions exist to ameliorate an imbalance between angiogenic and antiangiogenic factors, and hence provide opportunities to improve maternal and/or perinatal outcomes in patients with pre-eclampsia. Studies evaluating the potential clinical utility of measuring angiogenic and antiangiogenic factors in pre-eclampsia have focused on three scenarios: firstly, triage of symptomatic patients suspected of having pre-eclampsia; secondly, differentiation of pre-eclampsia from exacerbations of pre-existing medical conditions; and thirdly, risk assessment in asymptomatic women.

Triage of women with suspected pre-eclampsia

Patients with pre-eclampsia can present with some, but not all, of the symptoms of pre-eclampsia and/or features similar to other conditions. Accurate diagnosis of pre-eclampsia by a combination of clinical symptoms and biomarkers might improve the management of

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patients who are at risk of adverse outcomes. Indeed, determination of plasma levels of angiogenic and antiangiogenic factors in combination with assessment of clinical variables, in patients with suspected pre-eclampsia who present before 34–35 weeks of gestation, improves the detection of patients who are likely to require preterm delivery or develop adverse outcomes within 2 weeks, compared with standard evaluations based on clinical factors or standard laboratory tests for pre-eclampsia alone.[12–15,65,66,71] Moreover, implementation of this strategy reduced costs and usage of health-care resources, according to a cost-effectiveness analysis.[72] Larger studies, using appropriate algorithms for management of patients with suspected pre-eclampsia according to the results of these biomarkers, are urgently needed.

Differentiation from pre-existing conditions

The diagnosis of pre-eclampsia in patients with chronic kidney disease (CKD) is challenging, especially in patients who have proteinuria or high blood pressure before 20 weeks of gestation. Indeed, in nonpregnant women, higher plasma levels of sVEGFR-1 have been observed in patients with CKD than in healthy controls.[73] This elevation correlates with serum levels of von Willebrand factor (a marker of endothelial dysfunction), suggesting that sVEGFR-1 might be associated with endothelial dysfunction and future cardiovascular risk in these patients.[74]

The potential clinical utility of angiogenic and antiangiogenic factors in differentiating superimposed pre-eclampsia from exacerbations of pre-existing medical conditions has been proposed in several case reports relating to pregnant women with nephrotic syndrome,[75] systemic lupus erythematosus[76] or those with end-stage renal disease undergoing haemodialysis.[77] Subsequently, in two case–control studies, higher serum levels of sVEGFR-1 and lower serum levels of PlGF were reported in patients with CKD having superimposed pre-eclampsia than in women with CKD having normal pregnancies.[78,79] However, the diagnostic performance of these biomarkers in a clinical setting has yet to be reported.

Risk assessment in asymptomatic women

Observational studies examining the predictive performance of measuring angiogenic and antiangiogenic factors in asymptomatic pregnant women have yielded inconsistent results.[61,80–84] This observation is partly explained by differences in the timing of sample collection (first, second or third trimester), case definitions (early, late or all pre-eclampsia) and statistical methods (logistic regression, fixed specificity or ROC curve analysis).[7–11] However, most data suggest that these factors are unlikely to be useful as early biomarkers of pre-eclampsia in asymptomatic patients at <16 weeks of gestation.[84] The predictive performance of these biomarkers for identifying patients at risk of developing pre-eclampsia generally increases with advancing gestational age at the time of sample collection (that is, they perform best when the evaluation is done within 5 weeks before the clinical presentation), or when trying to predict early rather than late disease.[61,82] The magnitude of the association between maternal plasma levels of angiogenic and antiangiogenic factors evaluated in the late second trimester (20–25 weeks) is stronger for early pre-eclampsia than

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for late disease.[61] The predictive performance of biomarkers for late pre-eclampsia is improved if the evaluation is performed in the third trimester.[85,86] However, in most studies, the majority of patients with an imbalance between angiogenic and antiangiogenic factors do not subsequently develop pre-eclampsia.[81–87] Such tests, therefore, have low PPVs regardless of the timing of sample collection.[81–87]

Although a low PPV is often interpreted as a lack of clinical utility in biomarker studies,[61,81,82,84] PPV is also a function of disease prevalence; the prevalence of pre-eclampsia is typically 3–5%.[85] A test with 90% sensitivity and 90% specificity for identifying patients at risk of a condition that has this prevalence would achieve a PPV of only approximately 30%. PPV by itself is, therefore, generally a poor indicator of biomarker utility in uncommon diseases.[86] Evidence supporting this view comes from the quadruple screening programme for Down syndrome, which has a prevalence of 1:800.[89] Screening has a PPV <1% for a positive test result, which represents a >1:273 chance of the fetus being affected.[89] Nevertheless, without safe and effective interventions, it is difficult to establish the clinical utility of screening for pre-eclampsia on the basis of angiogenic and antiangiogenic factors or other biomarkers.

Management of pre-eclampsia

The management of pre-eclampsia focuses on the control of acute hypertension, the prevention of seizures and timely delivery of the fetus. In a patient with pre-eclampsia who is near or at term (≥37 weeks gestation), when the fetus is mature, delivery is an effective way to treat the disorder and optimize pregnancy outcomes (Figure 2). In preterm gestations, the risk of continuing the pregnancy in the face of a multisystemic disorder must be balanced against the risks of premature birth.[90] Delivery is indicated when life-threatening maternal complications are present or impending, such as severe hypertension refractory to treatment (which places the mother at risk of stroke), pulmonary oedema, acute renal failure, hepatic rupture or eclampsia.[90] Delivery would also be indicated if a viable fetus is at risk of impending death. The mode of delivery (vaginal versus caesarean) depends on obstetric indications (such as fetal distress or previous classic caesarian deliveries). Attempted induction of labour does not seem to increase neonatal morbidity, but is rarely successful at <28 weeks in these patients.[91] Detailed discussion of the expectant management of women who have pre-eclampsia with severe features at <34 weeks of gestation, including patient selection, treatment and delivery indications, can be found elsewhere.[90,92]

Acute onset, severe hypertension

The primary goal of treating hypertension in patients with pre-eclampsia is to prevent an acute hypertensive crisis, which might lead to intracranial haemorrhage or stroke. Acute-onset, persistent (lasting ≥15 min) and severe hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg) requires immediate treatment.[90,93] This recommendation is based on a report describing 28 women with severe pre-eclampsia who developed stroke; all but one of these individuals had a systolic blood pressure ≥160 mmHg just before haemorrhagic stroke, whereas 13% had a diastolic blood pressure ≥110 mmHg within 6–12 h preceding stroke.[94] Thus, the goal of antihypertensive therapy is not to

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normalize blood pressure, but to maintain uteroplacental perfusion and achieve a blood pressure within the range of 140–160/90–100 mmHg, above which loss of autoregulation of cerebral vasculature occurs.

Every professional organization uses different blood pressure thresholds to prompt antihypertensive treatment in women with pre-eclampsia during the nonacute setting. For example, the National Institute for Health and Clinical Excellence in the UK recommends antihypertensive medication if blood pressure is >150/100 mmHg.[95] The Society of Obstetricians and Gynaecologists of Canada recommends starting antihypertensive therapy at blood pressure levels of 160/110 mmHg,[96] as does the American Congress of Obstetricians and Gynecologists.[90] By contrast, the Society of Obstetric Medicine of Australia and New Zealand recommends antihypertensive treatment if systolic blood pressure is >170 mmHg or diastolic blood pressure >110 mmHg.[97] Additional information can be found in various professional organizations' guidelines.[90,95–97]

Control of blood pressure should be achieved before delivery, even in urgent circumstances, such as eclampsia;[98] endotracheal intubation for a caesarean delivery increases maternal blood pressure, sometimes to severe levels.[98] Hydralazine, labetalol and nifedipine are the three most commonly used agents in the acute setting (Table 1).[99] Nimodepine, ketanserin and diazoxide were not recommended for the management of severe hypertension during pregnancy because nimodepine and ketanserin were associated with more persistent high blood pressure than hydralazine and diazoxide was associated with a higher risk of hypotension than labetalol.[100] Sodium nitroprusside is reserved only for the rare patients in whom hypertension is refractory to other agents, because of concerns related to cyanide and thiocyanate toxicity in the mother and baby, and potential worsening of cerebral oedema in the mother.[93]

Prevention of seizures

The development of seizures and/or coma is a characteristic of eclampsia, and increases the risk of maternal and perinatal death, as well as other complications (such as disseminated intravascular coagulation, pulmonary oedema, acute renal failure and cardiopulmonary arrest). The onset of eclampsia can be antepartum (38–53%), during labour (18–36%) or postpartum (11–44%).[101] Although most patients with postpartum eclampsia present within 48 h after delivery, some can occur as late as 23 days postpartum.[101]

The agent of choice for the prevention of seizures or recurrent seizure episodes in eclampsia is magnesium sulfate (Box 1),[102] which reduces the rate of seizures by 52% when compared to diazepam, and by 67% when compared with phenytoin.[103] Clinicians generally agree that magnesium sulfate should be administered to patients with pre-eclampsia who have severe features (number needed to treat [NNT] 63–71).[104] However, whether this agent is required in the management of pre-eclampsia without severe features (NNT 109–400) is currently unknown.[104] Treatment with magnesium sulfate is associated with a reduced rate of eclampsia (RR 0.4) and placental abruption (RR 0.64), but an increased rate of caesarean delivery (RR 1.05) compared with placebo or no anticonvulsant.[105]

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Prevention of pre-eclampsia

A broad range of interventions has been tested for the prevention of pre-eclampsia, including low-salt diets, diuretics, fish oil, calcium supplementation, antioxidants, aspirin and heparin.[106] However, most of these interventions have not been proven effective.

Antiplatelet agents

An imbalance between prostacyclin and thromboxane has been proposed to be one of the mechanisms mediating pre-eclampsia;[107] thus, antiplatelet agents (in particular, aspirin, which blocks platelet production of thromboxane B2)[108] have been extensively tested in randomized clinical trials to prevent pre-eclampsia. In a multicentre randomized clinical trial of low-dose aspirin for the prevention and treatment of pre-eclampsia in 9,364 pregnant women, the use of aspirin was associated with a nonsignificant reduction (12%) in the incidence of proteinuric pre-eclampsia.[109] This treatment had no significant effect on the incidence of intrauterine growth restriction, stillbirth or neonatal death. Aspirin did, however, significantly reduce the likelihood of preterm delivery: 19.7% in patients receiving aspirin versus 22.2% in controls, an absolute reduction of 2.5 events per 100 women treated ($P = 0.003$).[109] Subsequently, a meta-analysis of data from 32,217 women showed that patients receiving aspirin for the prevention of pre-eclampsia had a significant (10%) reduction in the incidence of pre-eclampsia, preterm birth (<34 weeks of gestation) and a composite of serious adverse pregnancy outcomes (pre-eclampsia, small for gestational age infant, fetal death or maternal death).[3]

In another meta-analysis, the incidence of early pre-eclampsia was reduced by 50% (RR 0.47, 95% CI 0.34–0.65) in women considered to be at risk of pre-eclampsia owing to a history of pre-eclampsia or abnormal UtADV findings, who started taking low-dose aspirin ≤16 weeks of gestation. [4] Expanded meta-analyses have confirmed these findings, and also suggest that this intervention is associated with a decrease in the rate of severe pre-eclampsia.[6,110,111] However, these findings were obtained in subgroup analyses, and remain to be confirmed by randomized controlled trials.

Antioxidants

Although oxidative stress has been implicated in the pathophysiology of pre-eclampsia, a meta-analysis of randomized controlled trials of vitamins C and E failed to show a beneficial effect for preventing pre-eclampsia and might increase risk of gestational hypertension and prelabour rupture of membranes.[112] However, pre-eclampsia was reduced by 63% in patients considered to be at risk of developing the condition (owing to a personal or family history of pre-eclampsia) who received L-arginine (5.4 g daily) in combination with vitamin C (500 mg daily) and vitamin E (400 IU daily) before 24 weeks of gestation.[5] Treatment after 24 weeks of gestation with antioxidant or vitamins alone was ineffective in preventing pre-eclampsia.[5] The results from this study are promising, and further investigation is warranted to confirm these interesting findings.

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Calcium supplementation

As calcium deficiency has been implicated in the pathogenesis of pre-eclampsia,[113] several randomized controlled trials have examined whether calcium supplementation can prevent its development.[114–116] One such trial in the USA included 4,589 pregnant women who received either calcium supplementation (2 g daily) or placebo.[117] The results showed no significant reduction in the incidence or severity of pre-eclampsia, or delay in its onset, in the women receiving supplemental calcium.[117] By contrast, a Cochrane systematic review and meta-analysis concluded that women who received calcium supplementation (≥l g daily) had a reduced incidence of pre-eclampsia (RR 0.45, 95% CI 0.31–0.65).[118,119] The beneficial effect was greatest for patients with low baseline calcium intake (RR 0.36, 95% CI 0.20–0.65), and those with a high risk of pre-eclampsia (RR 0.22, 95% CI 0.12–0.42).[118] Currently, calcium supplementation for prevention of pre-eclampsia is only considered in pregnant women from populations with low calcium intake (<600 mg daily).[90]

Other potential interventions

Considerable efforts are underway to identify treatments that can reverse the imbalance of angiogenic and antiangiogenic factors associated with pre-eclampsia. Statins are cholesterol-lowing agents that have the potential to reverse this angiogenic imbalance through their pleiotropic effects, which include stimulating trophoblast production of PlGF, improving endothelial function, upregulating haeme oxygenase 1, decreasing oxidative stress or inflammation and inhibiting complement as well as tissue factor activation.[120] Statins might, therefore, represent a suitable intervention for patients at risk of pre-eclampsia or those with an imbalance between angiogenic and antiangiogenic factors. Pravastatin (as opposed to other statins with lipophilic properties) is a water-soluble agent that crosses the placenta slowly and, consequently, might have fewer adverse effects for the fetus than do the lipophilic statins.[121] The reported congenital anomalies of statins include isolated anomalies, such as central nervous system or limb defects and the VACTERL association.[122] However, abnormal pregnancy outcomes were not reported following exposure to pravastatin or fluvastatin.[122] In an experiment conducted in a dually perfused at-term human placental lobule, 14% of pravastatin was retained in placental tissue, 68% remained in the maternal circulation and only 18% was transferred to the fetal circulation.[123] These favourable findings support the use of pravastatin during pregnancy.

Other proposed therapeutic interventions to reverse an antiangiogenic state in pregnant women at risk of pre-eclampsia include the administration of $VEGF_{121}$ [17,18,21] or extracorporeal removal of soluble VEGFR-1 (sVEGFR-1).[20] Supplemental choline intake during the third trimester of pregnancy can reduce maternal serum levels of sVEGFR-1 and placental expression of total (soluble and membrane-bound) VEGFR-1. However, whether this approach can reduce the incidence of pre-eclampsia remains to be determined.[22] These preventive interventions probably will not reverse established pre-eclampsia, as the antiangiogenic state is an adaptive response to various insults, rather than being the primary abnormality leading to pre-eclampsia. However, as delivery of the placenta remains the only therapeutic option available for women with established pre-eclampsia, any interventions that enable the safe prolongation of pregnancy might result in improved perinatal outcomes.

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Long-term sequelae of pre-eclampsia

Although pre-eclampsia is a pregnancy-specific disorder that resolves on delivery of the placenta, women with pre-eclampsia are at increased risk of subsequent cardiovascular disease. The results of a systematic review and meta-analysis support prior observations that women with pre-eclampsia are more likely than those without pre-eclampsia to develop long-term sequelae, including chronic hypertension (OR 3.13), cardiovascular disease (OR 2.28), stroke (OR 1.76), diabetes (OR 1.80)[23] and end-stage renal disease (RR 4.70).[24] The risk of end-stage renal disease seems to increase progressively with the number of pregnancies affected by pre-eclampsia.[24] Moreover, women with pre-eclampsia are more likely to have microalbuminuria 3–5 years after delivery than women with a normal pregnancy.[124] These findings might reflect undiagnosed renal disease,[125] which is common in patients with pre-eclampsia,[126] or, alternatively, might suggest that pre-eclampsia compromises renal function. Glomerular endotheliosis, a typical renal lesion observed in pre-eclampsia and previously thought to resolve after delivery, can be detected long after pregnancy in some women affected by pre-eclampsia.[127]

Receiving a diagnosis of pre-eclampsia could have profound long-term health-care implications, as it identifies a group of women at risk of adverse health outcomes and potentially enables the early implementation of preventative interventions (for example diet, exercise and/or pharmacological treatment).[128,129]

Conclusions

Current management of pre-eclampsia consists of controlling hypertension, preventing seizures and timely delivery of the fetus. Considerable effort has been made to identify biomarkers that can predict pre-eclampsia. In the absence of safe and effective interventions, however, the low prevalence of pre-eclampsia (which necessarily results in low PPVs for identified biomarkers) means that establishing the clinical utility of any biomarker as a screening test for pre-eclampsia is difficult. A few preventive interventions for pre-eclampsia —such as low-dose aspirin or the combination of nitric oxide donors and antioxidant vitamins—remain to be fully investigated. Potential interventions exist to ameliorate the imbalance between angiogenic and antiangiogenic factors observed in some patients with pre-eclampsia, and hence might provide opportunities to improve maternal and/or perinatal outcomes. The diagnosis of pre-eclampsia can have profound long-term health-care implications, as it identifies a subgroup of women at increased risk of adverse health outcomes. Further studies are required to improve screening strategies to identify women at risk of pre-eclampsia who could benefit from targeted preventive interventions. Evaluation of the cost-effectiveness of any intervention should also be considered.

Review criteria

A search for original research and review articles published in English between 1840 and 2013 focusing on pre-eclampsia was performed in PubMed using the following search terms alone or in combination: “pre-eclampsia,” “toxaemia,” “pregnancy-induced hypertension”

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and “eclampsia.” The bibliographies of pertinent articles were also examined to identify further relevant papers.

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Key points

- Combinations of biomarkers perform better than single biomarkers for predicting pre-eclampsia, but require external validation before they can be used routinely.
- Potentially effective interventions to prevent pre-eclampsia in patients at risk include early administration of low-dose aspirin or l-arginine in combination with oral antioxidants (vitamins C and E).
- Maternal plasma levels of angiogenic and antiangiogenic factors identify most patients who will develop early pre-eclampsia, correlate with disease severity and have prognostic value for maternal and/or perinatal complications.
- Management of pre-eclampsia includes control of hypertension, prevention of seizures and timely delivery; steroids are administered to enhance fetal lung maturity if induction of labour before 34 weeks is contemplated.
- In pre-eclampsia at ≥37 weeks of gestation, delivery effectively optimizes pregnancy outcomes; for preterm gestations, the risk of continued pregnancy must be balanced against that of premature birth.
- Women with pre-eclampsia are at increased risk of developing cardiovascular disease, including chronic hypertension, stroke, coronary artery disease, diabetes and end-stage renal disease later in life.

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Box 1

Use of magnesium sulfate for seizure prophylaxis in pre-eclampsia

Continuous intravenous infusion

- Loading dose of magnesium sulfate (4–6 g administered over 15–20 min)
- Maintenance infusion with 1–2 g/h
- Maintain magnesium sulfate concentration between 480 mg/l and 840 mg/l
- Monitor urinary output and if <25–30 ml over 2 consecutive hours, oliguria is diagnosed; fluid status and magnesium level should be assessed and magnesium infusion should be decreased or discontinued
- Monitor magnesium toxicity by combination of assessment of deep tendon reflexes and respiratory rate
- Discontinue infusion 24 h after delivery

Intermittent intramuscular injection (when intravenous administration is not possible)

- 20% magnesium sulfate solution (4 g intravenously at rate not exceeding 1 g/min)
- 50% magnesium sulfate solution (10 g, 5 g injected deeply in the upper outer quadrant of both buttocks). If convulsions persist after 15 min, give up to 20% solution of magnesium sulfate (2 g) intravenously at a rate not exceeding 1 g/min
- Every 4 h thereafter give 50% magnesium sulfate solution (5 g) injected deeply in the upper outer quadrant of alternate buttocks, but only after confirming that the patellar reflex is present, respiration is not depressed and urinary output in the previous 4 h exceeds 100 ml
- Discontinue treatment 24 h after delivery

Adverse effects

- Flushing, nausea and vomiting, muscle weakness, thirst, headache, drowsiness, confusion and respiratory depression

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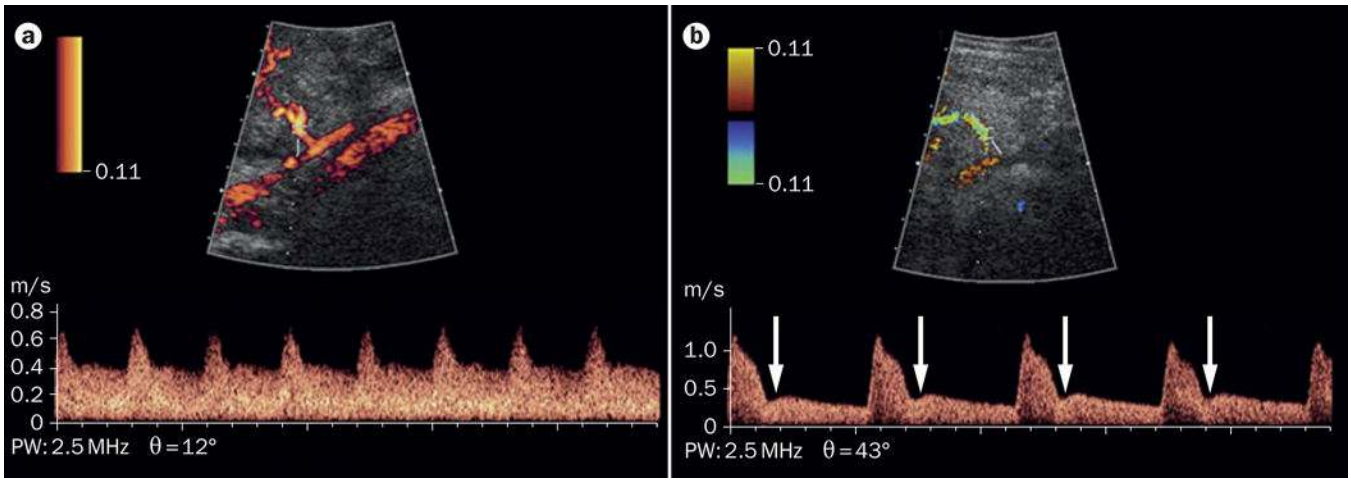

Figure 1. Uterine artery Doppler velocimetry findings in the second trimester of pregnancy

A. Normal findings. **B.** Abnormal findings, indicated by either the presence of bilateral uterine artery early diastolic notches (arrows) or a mean pulsatility index (calculated as [peak systolic velocity – end diastolic velocity]/time averaged velocity, averaged across both uterine arteries), above the 95th percentile for gestational age.

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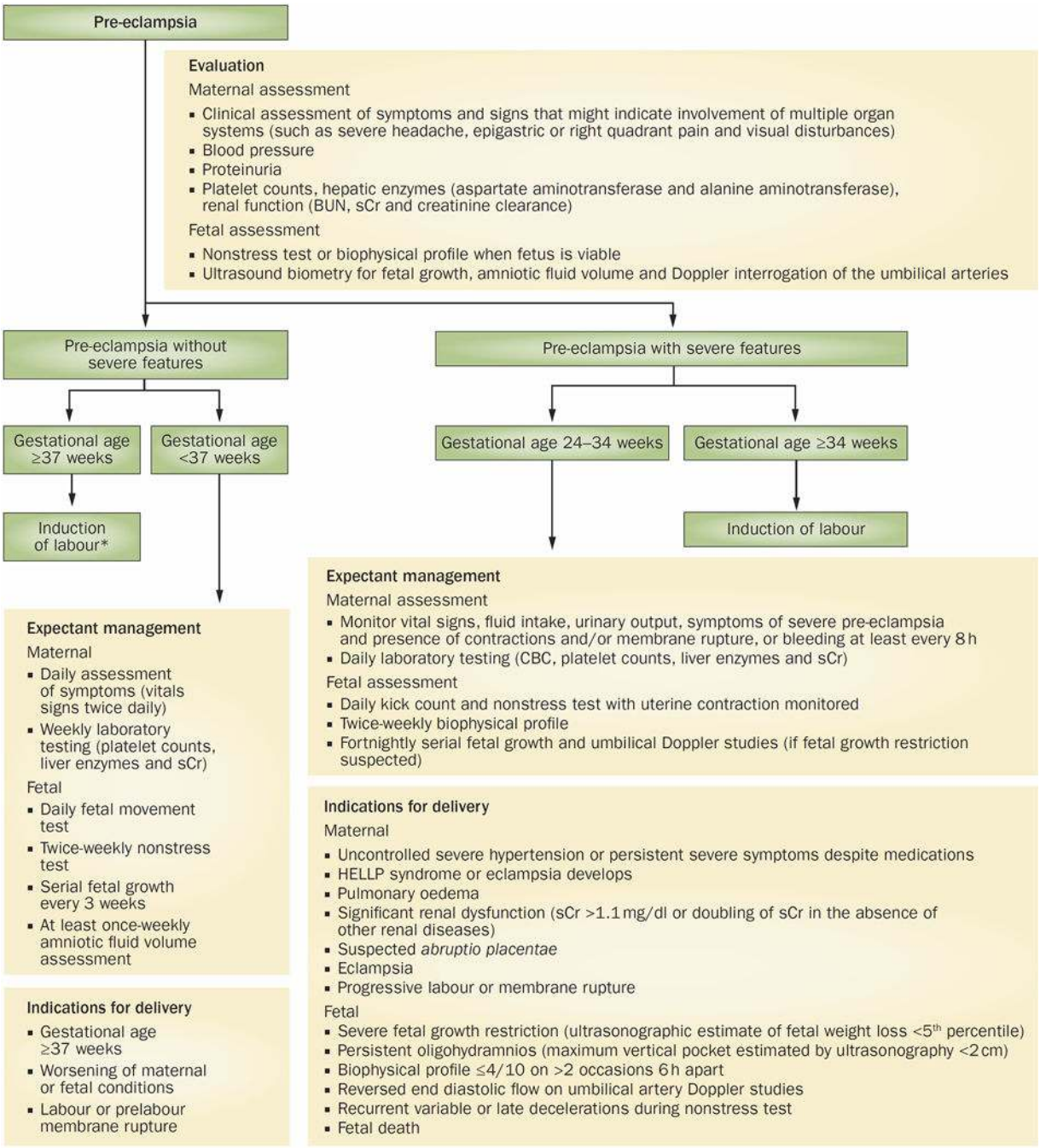

Figure 2. Management of pre-eclampsia

Management of pre-eclampsia depends on the severity of the disease (with or without severe features) and gestational age at diagnosis.[134] For pre-eclampsia without severe features, delivery is recommended at term (≥37 weeks). For pre-eclampsia with severe features, delivery is recommended if gestational age is at ≥34 weeks. Before 34 weeks of gestation, the decision to deliver should be balanced between risk of maternal or fetal complications and benefit of continuing pregnancy to fetal maturity.

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*Patients with gestational hypertension or mild pre-eclampsia after 36 weeks who undergo induction of labour have a reduced rate of adverse maternal outcomes (especially the development of severe hypertension), lower incidence of caesarean delivery and a better quality of life than those who had expectant management.[130–133] If preterm induction of labour is contemplated, steroids are administered between 24 weeks and 34 weeks of gestation to improve fetal lung maturity. Magnesium sulfate is administered during labour and the first 24 h after delivery for seizure prophylaxis.[104]

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; GA, gestational age; HELLP, haemolysis, elevated liver transaminases, low platelets; sCr, serum creatinine.

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Table 1

Therapeutic agents for control of severe hypertension in pregnancy

Agent	Mechanism	Dose	Adverse effects	Comments
Hydralazine	Vasodilator	5 mg (intravenous or intramuscular), then 5–10 mg every 10–40 min, or constant infusion of 0.5–10 mg/h	Risk of delayed maternal hypotensionFetal bradycardia	Substantial experience of safety and efficacy
Labetalol	α- and β-blocker	20 mg (intravenous), then 20–80 mg every 5–15 min (maximum 300 mg), or constant infusion of 1–2 mg/min	Risk of neonatal bradycardia Should be avoided in women with asthma or heart failure	Lower risk of tachycardia and arrhythmia than vasodilators Increasingly preferred as first-line agent
Nifedipine	Calcium channel antagonist	10–30 mg (oral), repeat after 45 min if needed *	Tachycardia, but is seldom associated with palpitations Flushing, headache, sweaty palms133	Possible interference with labour or synergistic effects with magnesium sulfate have not been proven[134]

* Blood pressure falls within 5–10 min of a capsule being bitten and swallowed, and 10–30 min with oral administration.[133] All agents are FDA category C. Information in this Table is used with permission and was partly obtained from Chesley's Hypertensive Disorders in Pregnancy, Lindheimer, M. D. et al. (eds)