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Editorial

First-trimester screening for pre-eclampsia: moving from personalized risk prediction to prevention

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Introduction

Maternal gestational hypertensive disorders and their complications have ranked consistently as the primary cause of adverse maternal and neonatal outcome since the institution of prenatal care[1]. The recognition of predisposing circumstances, such as nulliparity, familial disposition, prior pre-eclampsia, renal disease, hypertension and diabetes, reaches back as far as four centuries. In 1984, Leon Chesley concluded that: 'it does not seem likely that pre-eclampsia can be prevented on the basis of current knowledge. A major purpose of prenatal care is to detect incipient pre-eclampsia and to prevent its progression'[1]. Since then, research that has evolved around first-trimester screening algorithms for pre-eclampsia has offered a significant opportunity to rethink the potential for preventive strategies.

First-trimester screening for pre-eclampsia

In the context of current practice, a desire for prediction of pre-eclampsia with subsequent prevention means that Wilson's criteria[2] can only be met for screening performed in the first trimester. At this time, a woman's risk can be identified in the latent stage of the disease, when prevention still has the opportunity for a beneficial impact[3–7]. The 11–14-week nuchal translucency (NT) screening examination is an established point of contact in contemporary prenatal care and therefore an ideal point at which to integrate screening for pre-eclampsia[8]. The most effective prediction has been achieved by the concurrent evaluation of variables that are associated with pre-eclampsia and calculation of a personalized risk score for each woman. Such factors that affect risk have been recognized since the beginning of the last century and include parity[9], family history of pre-eclampsia[1,6], diabetes mellitus[10], chronic hypertension and blood pressure[11], maternal age[1,12], body mass index (BMI)[13], ethnicity[14] and socioeconomic status[1]. However, it is only relatively recently that we have been able to estimate statistically the individual risk that is attributable to each factor[6,15,16], and this has allowed us to incorporate into screening algorithms additional first-trimester markers of placental success, such as uterine artery Doppler waveforms and maternal serum biomarkers[6,15,17–25].

There are several advantages that first-trimester screening for pre-eclampsia offers today. These include a personalized risk estimate that is available to the entire obstetric population, including nulliparae, a 97.5–99.8% certainty that pre-eclampsia will not occur in screen-negative women[26] and the ability to evaluate the impact of preventive therapies on the observed-to-expected pre-eclampsia rate, thus improving the statistical and clinical validity of intervention trials[27–29]. The disadvantages of first-trimester screening algorithms are their low positive predictive value, ranging between 6% and 10%[30,31], limited validity in external populations[26,32], the preferential prediction of early-onset disease with severe hypertensive features[33] and the apparent absence of effective preventive interventions[30,31].

However, the latter apparent disadvantage in particular can be addressed by utilizing first-trimester algorithms not only to predict a personalized risk for pre-eclampsia but also to identify treatable conditions in screen-positive women. As pre-eclampsia results from the convergence of multiple risk factors, evaluating the characteristics of women in whom prevention fails may point towards additional risk factors that require attention.

Failure of pre-eclampsia prevention: an opportunity to rethink how better to utilize first-trimester screening

Therapies for the prevention of pre-eclampsia that have received recently the greatest attention include low-dose aspirin, antioxidant vitamins and calcium supplementation. For low-dose aspirin, reduction of pre-eclampsia and fetal growth restriction by up to 50% have been demonstrated for women initiating therapy by 16 weeks' gestation[3,34,35]. This reduction is dose-related and most notable for early-onset pre-eclampsia. Later initiation not only produces no benefit but also is associated with a potential increase in complications, such as placental abruption, while earlier initiation has been implicated in fetal abdominal wall defects[36,37]. Accordingly, the United States Preventive Services Task Force issued the recommendation to initiate 81 mg aspirin after 12 weeks in women at risk for pre-eclampsia who have no adverse effects or contraindications[38]. This places the first-trimester NT screen at the ideal point in gestation at which to implement this recommendation. However, even when aspirin is initiated this early, the rate of pre-eclampsia is still 9.3%[3], much higher than that in the general obstetric population. While it could be concluded that aspirin has limited efficiency, it is also possible

that women develop pre-eclampsia because they have additional risk factors that are not addressed by aspirin. Two recent studies indicate that women at high risk for pre-eclampsia, and in whom low-dose aspirin fails, are more likely to have chronic hypertension, with higher blood pressure at enrolment and pre-existing diabetes, with an elevated BMI[28,39].

With respect to the other therapies that have been studied, L-arginine and perhaps also antioxidant vitamins C and E reduce the rate of pre-eclampsia, but only in a subset of women with prior or family history of pre-eclampsia and when therapy is initiated by 24 weeks' gestation[4,40]. Calcium supplementation can reduce the rate of pre-eclampsia in up to 64% of women with low calcium intake (< 600 mg daily) and in 78% of women at high risk for pre-eclampsia[41,42]. In women receiving antioxidant vitamins C and E or dietary supplementation, only the risk attributable to having a BMI > 30 was reduced, while women with a prior history of pre-eclampsia, chronic hypertension, diabetes[43] or abnormal uterine artery Doppler did not benefit[44].

These studies illustrate several important points. First, the therapeutic gestational window that offers maximum benefit combined with the lowest risk for complications precedes the interstitial wave of trophoblast migration[45] in the late first and early second trimesters. Second, preventive therapies appear to address specific risk, while women with unaddressed risks continue to develop pre-eclampsia. In these women, cardiovascular and metabolic risks emerge as important factors that require attention. In this context, the individual variables that constitute current first-trimester screening models need closer scrutiny.

Cardiovascular, metabolic and prothrombotic risk profiles: the primary treatable contributors to gestational and long-term health in women

Recently, Scholten and coworkers[46] evaluated the prevalence of cardiovascular, metabolic and prothrombotic risk profiles in women with a prior history of pre-eclampsia. They identified that 77% of women had at least one risk profile. Of these, the cardiovascular risk profile was most prevalent (66.1%), followed by hyperhomocysteinemia (18.7%), metabolic syndrome (15.4%) and thrombophilia (10.8%). While there was considerable overlap between circulatory, metabolic and prothrombotic risk profiles (hyperhomocysteinemia and thrombophilia), there was < 2% overlap between the metabolic and prothrombotic risk profiles. The presence of circulatory and metabolic risk profiles was associated with earlier onset of pre-eclampsia in the prior pregnancy. Because these women were studied after pregnancy, these risk profiles may be not purely a residual effect of pre-eclampsia but also a cause for future recurrence. While the physiological tendency with increasing parity is to have lower first-trimester blood pressure, women with prior pre-eclampsia behave against this trend; remaining prehypertensive in a future pregnancy, they have a six-fold increased recurrence risk[47,48]. The parallel rise in pre-eclampsia rate and associated long-term cardiovascular, renal and metabolic complications further supports the importance of these risk profiles as being causative[30,49–54]. However, the most compelling proof for this concept comes from studies that developed first-trimester prediction rules from variables that were measured prior to the onset of pre-eclampsia.

First-trimester multivariable predictive models for pre-eclampsia have been developed using various study methodologies[6,15,17–25,55–68]. The components that are included in these prediction rules are typically categorized as maternal historic factors, maternal physical characteristics, uterine artery Doppler studies and biomarkers (Figure 1). Within these categories, multivariate prediction models identify maternal BMI, hypertension, prior pre-eclampsia, uterine artery Doppler and biomarkers among the top 10 independent predictors of pre-eclampsia (Figure 2). An alternate way to categorize these screening variables is by their representation of risk profiles (Figure 1). A prior history of hypertension, renal disease and elevated blood pressure can be considered as representative of a cardiovascular risk profile, while increased BMI, prior diabetes or gestational diabetes represent a metabolic risk profile and a history of thrombophilia represents a prothrombotic one. Maternal historic variables are personal *a-priori* risk modifiers, while placental Doppler studies and serum biomarkers can be considered as early markers of placental success. When categorized in this way, it is apparent that all variables utilized in multimarker algorithms fall into one of these risk profiles (Figure 1). This categorization has the advantage of allowing estimation of the contribution of treatable conditions to a woman's personalized pre-eclampsia risk (Figure 3). Accordingly, these algorithms could be applied with a dual purpose: calculation of individualized pre-eclampsia risk, and identification of the primary contributing treatable risk profile (Figures 1 and 4).

The metabolic risk profile

Insulin resistance, obesity, hypertension and dyslipidemia characterize the metabolic syndrome and the World Health Organization has put forward specific diagnostic criteria relating to BMI, blood pressure, proteinuria and triglyceride and high-density lipoproteins (HDL) (Table 1)[69–71]. In pregnancy, a state of relative insulin resistance, each additional component of the metabolic syndrome increases risk for pre-eclampsia by 30–40% and the odds are increased almost four-fold when C-reactive protein is increased[72,73]. Those women that develop pre-eclampsia exhibit more pronounced insulin resistance and dyslipidemia and many retain these metabolic risk factors after pregnancy[74–78]. When features of metabolic syndrome persisted after pregnancy, pre-eclampsia recurrence increased up to three-fold with each additional component of the metabolic syndrome, with hypertension and hyerinsulinemia as the leading risk factors[79].

Parameter	Classified by category	Classified by risk profile	Amenable to treatment
Maternal age	Personal history	Personal risk profile	No
Maternal ethnicity			
Tobacco use in pregnancy			
Parity			
Education level			
Conception method			
Family history of pre-eclampsia			
Prior pre-eclampsia			
Prior preterm birth			
Renal disease	Past medical conditions	Cardiovascular risk profile	Yes: antihypertensives
Hypertension			
Systolic blood pressure	Physical examination		
Diastolic blood pressure			
Mean arterial blood pressure			
Prior gestational diabetes	History	Metabolic risk profile	Yes: metformin, pravastatin
Pre-existing diabetes mellitus	Past medical conditions		
Maternal height	Physical examination		
Maternal weight			
Maternal body mass index			
Thrombophilia	Past medical conditions	Prothrombotic risk profile	Yes: heparin, aspirin
Uterine artery Doppler index	Placental blood flow	Placental risk profile	No
Uterine artery notching			
free beta-human chorionic gonadotropin	Placental biomarker		
Pregnancy-associated plasma protein-A			
Placental growth factor			
Placental protein-13			
A disintegrin and metalloproteinase-12			
Soluble endoglin			
Soluble fms-like tyrosine kinase-1			
P-selectin			
Neutrophil gelatinase-associated lipocalin			
Inhibin-A			
Vascular endothelial growth factor			
Tumor necrosis factor			
Pentraxin-3			
Angiopoietin			

Figure 1 First-trimester variables associated with pre-eclampsia, listed by category, risk profile and treatability.

Hyperinsulinemia-related risks could potentially be addressed by administration of metformin, an insulin-sensitizing agent. The potential benefit of metformin is suggested by a recent meta-analysis of women with polycystic ovary syndrome who continued therapy after conception[80]. In these women, metformin reduced pre-eclampsia by almost 50%, with a pooled odds ratio of 0.53 (95% CI, 0.30–0.95). Interestingly, women with lower complication rates also had reduced uterine artery impedance in the first and second trimesters, raising the possibility that accelerated reduction of uteroplacental blood flow resistance is in part responsible for the beneficial effect of metformin[81]. Importantly, as there appear to be no adverse effects on the mother and offspring, these studies indicate that metformin can be continued safely after conception[78,82,83].

Because several lipid abnormalities, including hypertriglyceridemia, increased low-density lipoprotein (LDL) and lower HDL levels, have been shown to predate development of pre-eclampsia, lipid-lowering agents such as statins are also being considered for prevention[84–90]. Pravastatin crosses the placenta slowly and therefore is considered to carry the lowest risk for fetal side

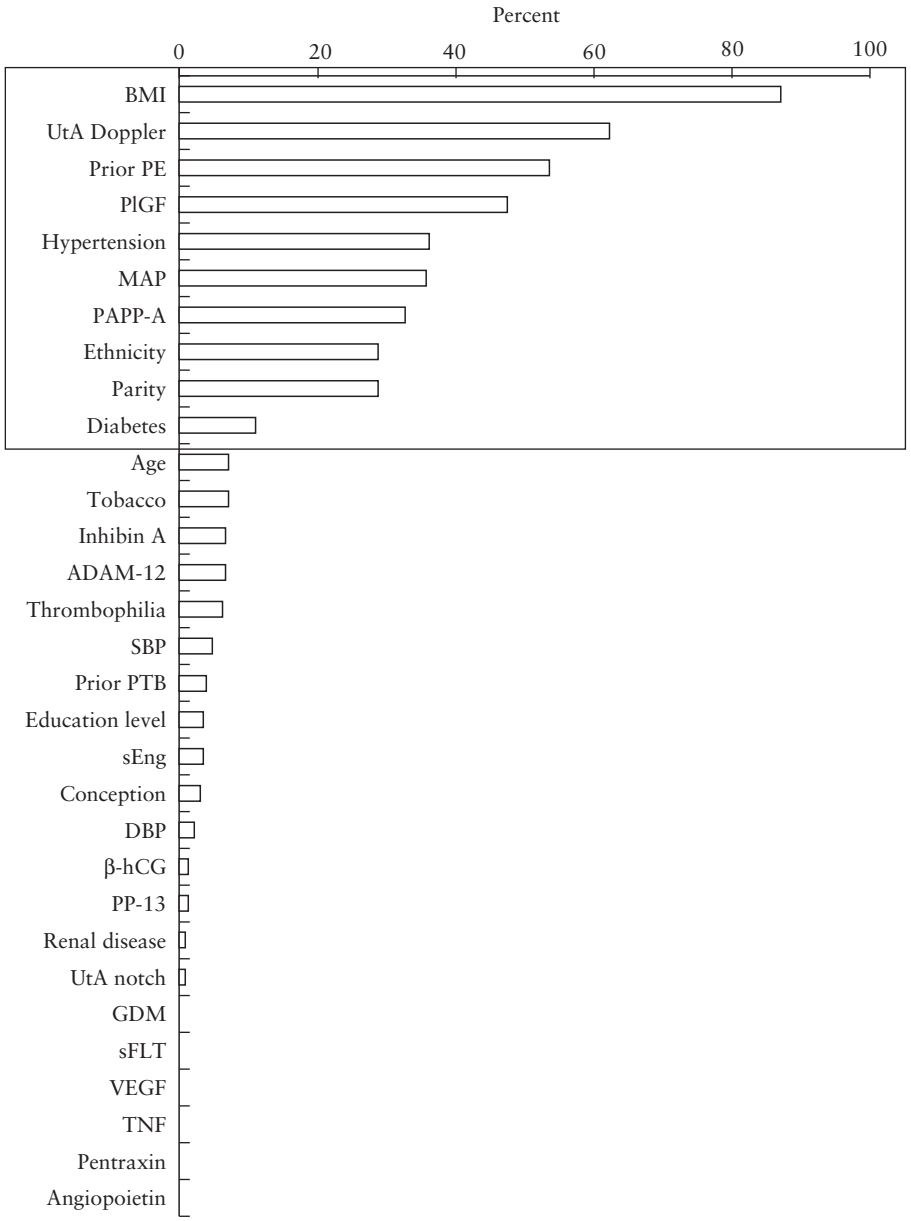

Figure 2 Adjusted proportional distribution of individual variables to pre-eclampsia risk. Percentages were calculated for studies that utilized multivariate prediction statistics[17–25]. ADAM-12, A disintegrin and metalloproteinase-12; BMI, body mass index; DBP, diastolic blood pressure; GDM, prior gestational diabetes; β-hCG, beta-human chorionic gonadotropin; MAP, mean arterial blood pressure; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PlGF, placental growth factor; PP-13, placental protein 13; PTB, preterm birth; SBP, systolic blood pressure; sEng, soluble endoglin; sFLT, soluble fms-like tyrosine kinase-1; TNF, tumor necrosis factor; UtA, uterine artery; VEGF, vascular endothelial growth factor.

effects[91,92]. Animal studies show that pravastatin not only ameliorates pre-eclampsia but also induces placental growth factor production, potentially addressing the placental risk profile[93]. Two randomized controlled trials to evaluate the use of pravastatin in women at high risk for pre-eclampsia are currently underway[94,95].

Hypertension is a treatable element that is a component of both the metabolic syndrome, as defined by the World Health Organization, and the cardiovascular risk profile. Understanding the relationship between first-trimester blood pressure and the development of pre-eclampsia is therefore essential in order to determine if specific blood-pressure thresholds should be part of a personalized preventive approach.

The cardiovascular risk profile

While blood pressure ranges have been classified by several professional bodies for pregnant and non-pregnant women (Table 2), there is discrepancy in the nomenclature and thresholds for the classification of hypertension in pregnancy[96–101]. The importance of increased first-trimester blood pressure as a precursor to pre-eclampsia is emphasized by its independent risk contribution in all first-trimester screening algorithms. Women with normal outcome have a mean first-trimester systolic blood pressure between 115 and 120 mmHg and mean diastolic blood pressure between 65 and 75 mmHg[102]. In contrast, women who

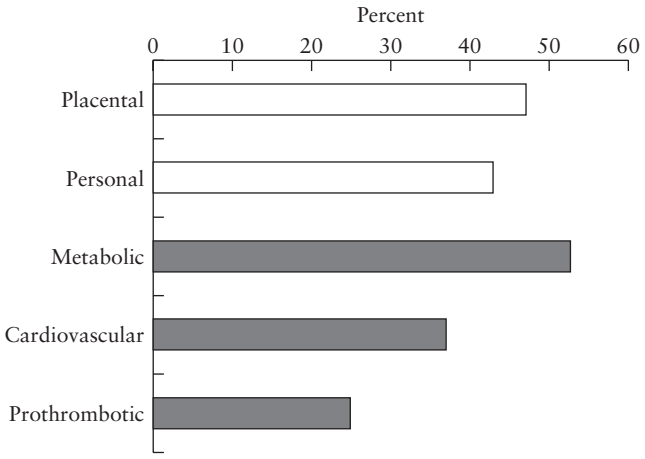

Figure 3 Adjusted proportional contribution of individual risk profiles to pre-eclampsia risk, according to whether they are not treatable (□) or treatable (■).

develop gestational hypertension or pre-eclampsia have mean blood pressures above this threshold and delivery of a small-for-gestational-age (SGA) infant is more likely for diastolic blood pressure exceeding 80 mmHg[103]. Birth weight and perinatal mortality appear to be related more closely to diastolic blood pressure, and optimal growth and perinatal outcome are observed for diastolic blood pressures between 70 and 80 mmHg and systolic blood pressure > 110 mmHg (Figure 5)[104,105]. Once they become established in the first trimester, women maintain their blood pressure category throughout pregnancy and it is the systolic and diastolic blood pressure changes from second to third trimester, modified by maternal characteristics, that are associated with the risk of pre-eclampsia[106,107].

First-trimester systolic and diastolic blood pressure values that are associated with normal outcome are notably lower than any recommended treatment threshold utilized in pregnancy[108,109]. The concept of first-trimester normalization of blood pressure to a value below 140/80 mmHg for prevention of pre-eclampsia is unexplored and likely to be considered controversial. Central to this controversy is the concern that therapy offers no benefit and increases the risk of growth restriction, presumably due to uteroplacental underperfusion[109–111].

Table 1 Diagnostic criteria of the metabolic syndrome according to World Health Organization (WHO)[69–71]

Components	*Cut-off*
Hyperinsulinemia	Fasting glucose ≥ 6.1 mmol/L
Obesity	Body mass index ≥ 30 kg/m^2
Hypertension	Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 85 mmHg
Proteinuria	Microalbuminuria ≥ 2.5 g/mL or proteinuria ≥ 0.30 g/24 h

The WHO defines metabolic syndrome as the presence of hyperinsulinemia with at least two of the other three components.

At the same time, animal and human studies suggest that high blood pressure can damage the placental vasculature and that it is the severity of hypertension that is the predominant risk factor for SGA[112–114]. Similarly, placental perfusion dependence on maternal cardiac output increases predominantly from the second trimester onwards and some trials have demonstrated higher birth weight in treated groups despite a greater antihypertensive effect[115–117]. The preventative potential of early blood pressure normalization is suggested by the significantly decreased pre-eclampsia prevalence and hypertensive disease severity in women receiving antihypertensive therapy from the second trimester[111,112,117–119]. First-trimester, observational data indicate that high-risk women who are normotensive in the first trimester have a 50% reduction of pre-eclampsia, while those with pre-hypertension or hypertension have a greater than two-fold increased risk[28].

Since maternal hypertension is the most prevalent and consistently demonstrated first-trimester risk factor, there is a most urgent need for research to clarify the preventive potential of first-trimester antihypertensives and the thresholds and treatment targets for such therapy.

The thrombotic risk profile

The maternal adaptation of the coagulation system makes pregnancy a natural prothrombotic state. In this setting, coagulation disorders such as thrombophilia or systemic lupus erythematosus are recognized risk factors for placental dysfunction and pre-eclampsia. In patients with specific coagulation disorders, targeted therapy decreases

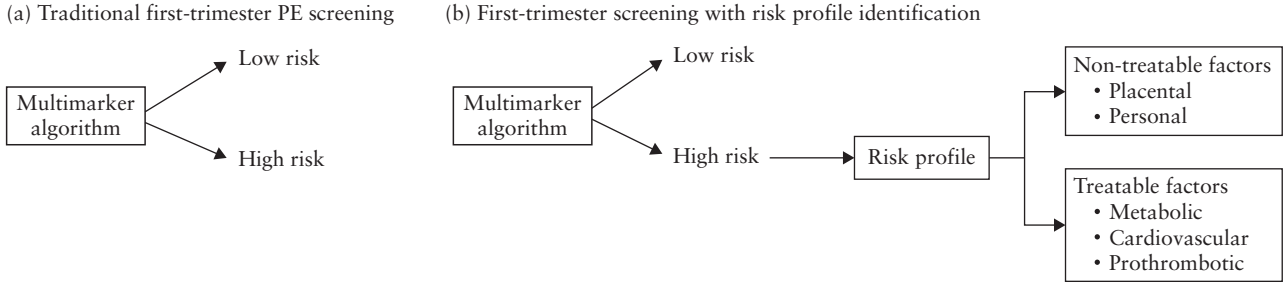

Figure 4 Flowcharts comparing traditional (a) and risk-profile-based (b) first-trimester screening for pre-eclampsia (PE). Traditional first-trimester screening provides a risk estimate based on a number of variables. First-trimester screening with risk profile identification also determines the treatable and non-treatable factors that confer the increased risk in screen-positive women.

Table 2 Blood pressure classifications according to several international professional bodies

Definition	*JNC 7 and 8*	*NHBPEP*	*NICE*	*ESC*
Normotension	SBP < 120 mmHg and DBP < 80 mmHg	SBP < 140 mmHg and DBP < 90 mmHg	SBP < 140 mmHg and DBP < 90 mmHg	SBP < 140 mmHg and DBP < 90 mmHg
Prehypertension	SBP 120–139 mmHg or DBP 80–89 mmHg	Not defined	Not defined	Not defined
Stage I (mild) hypertension	SBP 140–159 mmHg or DBP 90–99 mmHg	SBP 140–159 mmHg or DBP 90–109 mmHg	SBP 140–149 mmHg or DBP 90–99 mmHg	SBP ≥140 mmHg or DBP ≥ 90 mmHg
Moderate hypertension	Not defined	Not defined	SBP 150–159 mmHg or DBP 100–109 mmHg	SBP ≥ 150 mmHg or DBP ≥ 95 mmHg
Stage II (severe) hypertension	SBP ≥ 160 mmHg or DBP ≥ 100 mmHg	SBP ≥ 160 mmHg or DBP ≥ 110 mmHg	SBP ≥ 160 mmHg or DBP ≥ 110 mmHg	SBP ≥ 170 mmHg or DBP ≥ 110 mmHg

DBP, diastolic blood pressure; ESC, European Society of Cardiology; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NHBPEP, National High Blood Pressure Education Program's Working Group on High Blood Pressure in Pregnancy; NICE, National Institute for Health and Care Excellence; SBP, systolic blood pressure.

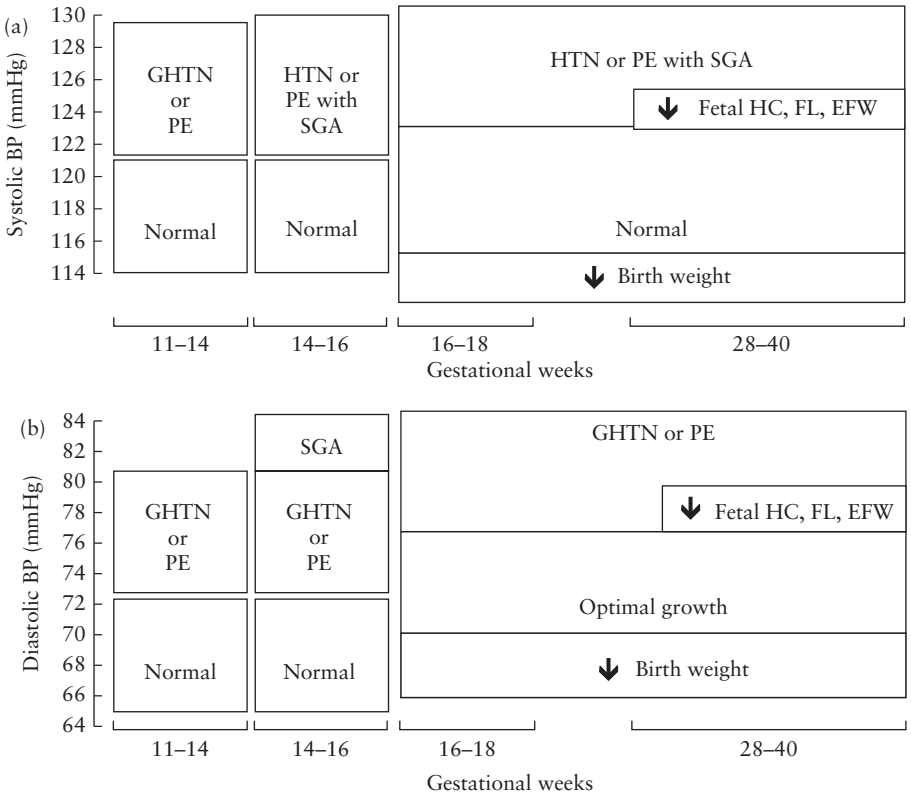

Figure 5 Median gestational blood pressures (BP) and maternal and neonatal outcomes. Displayed are the outcomes for ranges of systolic (a) and diastolic (b) BP during different gestational periods. Mean systolic BP >120 mmHg and mean diastolic BP > 72 mmHg in the first trimester is associated with an increased risk for gestational hypertensive disorders (GHTN) and delivery of a small-for-gestational-age (SGA) neonate. Increased blood pressure in the third trimester is associated with decreasing fetal growth and SGA. Overall, growth is related more closely to diastolic BP from 16 weeks onward. EFW, estimated fetal weight; FL, femur length; HC, head circumference; PE, pre-eclampsia.

significantly the rate of pre-eclampsia and adverse perinatal outcome[120,121]. However, other than for these specific applications, the risks involved do not currently support the generalized administration of anticoagulants for pre-eclampsia prevention, and we must await demonstration of their benefit by randomized trials[121–123].

While low-dose aspirin is likely to address many underlying factors that promote a prothrombotic risk profile, therapy of hyperhomocysteinemia may be a worthwhile target. In the study by Scholten *et al.*[46], hyperhomocysteinemia was present in almost 19% of women with prior pre-eclampsia. During early pregnancy, higher plasma homocysteine levels increase the risk of pre-eclampsia three- to four-fold[124,125]. Low dietary folate intake is an important contributor to increased homocysteine levels and is significantly more common in women who develop pre-eclampsia[126]. Modification of homocysteine levels requires high-dose folate and a randomized trial evaluating a daily folate dose of 4 mg is currently underway[127,128]. It remains to be determined if folate will benefit all women or specifically those with elevated homocysteine levels, in which case elevated

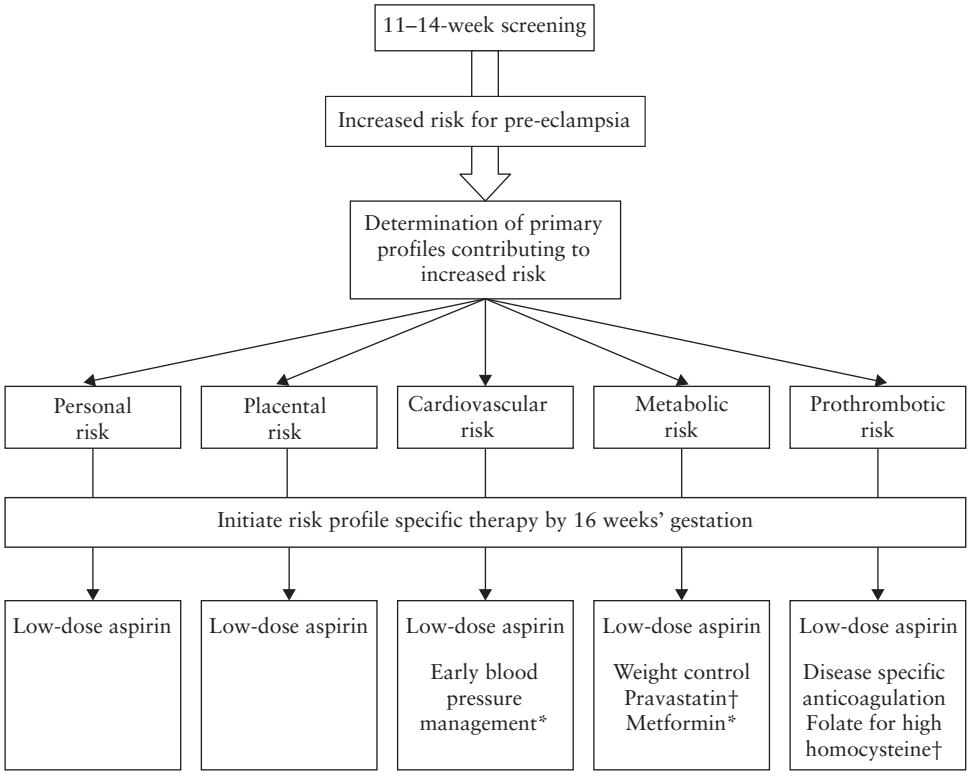

Figure 6 Personalized pre-eclampsia prevention: flowchart illustrating a personalized approach to pre-eclampsia that addresses all risk factors contributing to a woman's risk. *Randomized trials are needed. †Randomized trials are currently underway.

homocysteine may be incorporated as a first-trimester risk factor into multimarker algorithms to identify personalized treatment needs.

First-trimester personalized prevention of pre-eclampsia

Pre-eclampsia is a condition with multifactorial origins. First-trimester screening algorithms confirm historic observations and show that cardiovascular, metabolic and prothrombotic risks are the primary treatable factors that converge and determine a woman's risk of developing pre-eclampsia at a time in gestation when intervention has the most favorable risk-to-benefit ratio. Current prevention strategies largely target downstream effects rather than the primary inciting conditions. As a result, benefits are mostly apparent for patients falling into the target range of the therapeutic agent concerned, and risk profiles that are not targeted continue to place women at risk for pre-eclampsia while women in whom these risk profiles are addressed have significantly lower risks. As pre-eclampsia is multifactorial in origin, it is intuitive that prevention needs to address multiple factors. Modification of first-trimester screening algorithms to not only calculate the risk, but also identify individualized treatment targets, would offer an opportunity to provide personalized prevention of pre-eclampsia (Figure 6).

In this context, the greatest impact is likely to arise from early optimization of blood pressure; trials in this direction are urgently needed. This risk factor is most frequent numerically and carries a high risk for subsequent pre-eclampsia. Trials to address metabolic risks are already underway and will hopefully clarify the most effective preventive agents. First-trimester initiation of low-dose aspirin is already supported by many professional organizations. However, a personalized-risk-directed preventative approach may not only have a greater statistical impact, but also open up possibilities for a significant move towards improving long-term cardiovascular health in women.

Conclusion

Pre-eclampsia is a disease with multifactorial origins. First-trimester screening algorithms for pre-eclampsia incorporate multiple risk factors into the appropriate statistical context to offer personalized risk prediction early in pregnancy. All these factors fall into one of five risk profiles: personal, placental, cardiovascular, metabolic and prothrombotic. While low-dose aspirin initiated by 16 weeks' gestation reduces significantly the incidence of pre-eclampsia in women with personal and placental risk profiles, women with unaddressed cardiovascular and metabolic risks continue to develop it. Early management of blood pressure, insulin insensitivity, abnormal lipid profile, dietary calcium deficiency or hyperhomocysteinemia can all significantly reduce the rate of pre-eclampsia in appropriately selected patients. This selection can be achieved most effectively by first-trimester screening algorithms, with subsequent identification of the risk profiles that require specific therapy. In this context, research into

the management of appropriate blood pressure thresholds requires most urgent attention, as first-trimester hypertension is the most consistent and prevalent contributing risk factor for subsequent pre-eclampsia.

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