**Pre-eclampsia trio**

# Primary, secondary, and tertiary prevention of pre-eclampsia

*Gus Dekker, Baha Sibai*

**Pre-eclampsia remains one of the major obstetrical problems in less-developed countries. The causes of this condition are still unknown, thus effective primary prevention is not possible at this stage. Research in the past decade has identified some major risk factors for pre-eclampsia, and manipulation of these factors might result in a decrease in its frequency. In the early 1990s aspirin was thought to be the wonder drug in secondary prevention of pre-eclampsia. Results of large trials have shown that this is not the case: if there is an indication for using aspirin it is in the patient at a very high risk of developing severe early-onset disease. The calcium story followed a more or less similar pattern, with the difference that existing evidence shows that women with a low dietary calcium intake are likely to benefit from calcium supplementation. Proper antenatal care and timed delivery are of utmost importance in tertiary prevention of pre-eclampsia. There is evidence to suggest that the intrinsic direct effect of moderate degrees of maternal hypertension is beneficial to the fetus. Severe hypertension needs treatment. If antihypertensive is indicated, there is no clear choice of a drug. Hydralazine should no longer be thought of as the primary drug, most studies show a preference for calcium channel blockers.**

Pregnancy-induced hypertensive disorders have always been assumed to represent a pathological response. However, in more-developed countries non-proteinuric hypertension arising late in pregnancy, or gestational hypertension, is associated neither with any increase in perinatal mortality or morbidity nor with a decreased birthweight. Most studies quote higher birthweights in gestational hypertension, both in singleton and twin pregnancies.[1,2] In the rarer, severe form of the disease, usually arising in the late second or early third trimester and accompanied by substantial proteinuria, there is a striking increase in perinatal mortality and morbidity. These cases will be designated pre-eclampsia.

Prevention of pre-eclampsia would mean a big step forward in prenatal care. The general term prevention can have three different connotations: primary, secondary, or tertiary. Primary prevention means avoiding occurrence of a disease. Secondary prevention in the context of pre-eclampsia implies breaking off the disease process before emergence of clinically recognisable disease. Tertiary prevention means prevention of complications caused by the disease process, and is thus more or less synonymous with treatment.

## Primary prevention of pre-eclampsia

The best way to cope with human disease, by preventing it happening, is only achievable if the cause is understood and if it is feasible to avoid or manipulate those causes. Shallow endovascular cytotrophoblast invasion in the spiral arteries, an exaggerated inflammatory response, and inappropriate endothelial-cell activation are key features in the pathogenesis of pre-eclampsia.[3] But the mechanisms behind these features are unknown. Thus contraception is currently the only way to avoid pre-eclampsia. However, several risk factors have been identified (panel),[4] and manipulation of some of these risk factors might allow primary prevention.

### *Sperm exposure, the paternal factor, and age*

These factors point to potential primary peventive strategies because they can be manipulated. One popular hypothesis on the causes of pre-eclampsia is immune maladaptation.[3] Major support for this hypothesis comes from epidemiological studies that show the protective effect of sperm exposure, the impact of a change in partners, and the increased frequency of pre-eclampsia after donor insemination and oocyte donation.[5–9]

The mechanisms behind the protective effects of sperm exposure are unknown. Soluble HLA[10] and transforming growth factor-β1 in seminal fluid and the so-called

**Risk factors for pre-eclampsia**

**Preconceptional and/or chronic risk factors**
*Partner-related risk factors:*
Nulliparity/primipaternity
Limited sperm exposure, teenage pregnancy, donor insemination
Partner who fathered a pre-eclamptic pregnancy in another woman
*Maternal-specific risk factors:*
History of previous pre-eclampsia
Increasing maternal age, interval between pregnancies
Family history
Patient requiring oocyte donation
*Presence of specific underlying disorders:*
Chronic hypertension and renal disease
Obesity, insulin resistance, low maternal birthweight
Gestational diabetes, type-1 diabetes mellitus
Activated protein C resistance (factor V Leiden), protein S deficiency
Antiphospholipid antibodies
Hyperhomocysteinaemia
*Exogenous factors:*
Smoking (risk decrease)
Stress, work-related psychosocial strain

**Pregnancy-associated risk factors**
Multiple pregnancy
Urinary tract infection
Structural congenital anomalies
Hydrops fetalis
Chromosomal anomalies (trisomy 13, triploidy)
Hydatidiform moles

*Lancet* 2001; **357:** 209–15

**University of Adelaide, Lyell McEwin Hospital, North Western Adelaide Health Service, Elizabeth Vale, 5112 SA, Australia** (Prof G Dekker MD)**; and Department of Obstetrics and Gynecology, University of Cincinnati, Ohio, USA** (Prof B Sibai MD)

**Correspondence to:** Prof Gus Dekker
(e-mail: gustaaf.dekker@adelaide.edu.au)

postmating inflammatory response are being researched.[11] The protective effects of long-term sperm exposure might also provide an explanation for the high frequency of pre-eclampsia in teenage pregnancies.[12] A large prospective study[5] on the relation between sperm exposure and pre-eclampsia showed that (with women cohabiting for more than 12 months as reference) a cohabitation period of 0–4 months was associated with a typical odds ratio of 11·6, a period of 5–8 months with an odds ratio of 5·9, and a period of 9–12 months with an odds ratio of 4·2 for developing pre-eclampsia. Longer sperm exposure (after initial condom use to prevent HIV infection) could therefore be a preconception measure for optimum pregnancy outcome, similar to increased preconception folate intake. Future studies are needed to assess whether or not different routes of sperm exposure might have a beneficial effect on pregnancy outcome.[10]

Generally, pre-eclampsia is thought of as a disease of first pregnancies. Indeed, a previous normal pregnancy is associated with a strikingly lowered frequency of pre-eclampsia. The protective effect of multiparity, however, is lost with change of partner. Robillard and colleagues suggested use of the term primipaternity instead of primigravidity to describe the epidemiological standard of pre-eclampsia.[13] Data based on the complete Norwegian population (1967–92; about 60 000 births a year) clearly confirmed the impact of paternal factors on the risk of developing pre-eclampsia.[14] Men who fathered a pre-eclamptic pregnancy were nearly twice as likely to father a pre-eclamptic pregnancy in a different woman (OR [odds ratio] 1·8; 95% CI 1·2–2·6, after adjustment for parity), regardless of whether she had already had a pre-eclamptic pregnancy or not. The risk of pre-eclampsia in a second pregnancy increased with maternal age (1·3 per 5 years of increased age; $p<0·0001$) and with interval between pregnancies (1·5 per 5 years of interval between first and second pregnancies; $p<0·0001$).[14] Translated into primary prevention terms, these findings suggest that it is better to stay with the same partner if a first pregnancy was not complicated by pre-eclampsia, to have pregnancies only with low-risk men, and to have children at an age when the endothelium is still able to cope with the inflammatory stress associated with the pregnant state.[15] Health-care providers should realise that the antenatal care of a multiparous patient with a new partner should be the same as in a woman presenting with her first pregnancy, at least as far as the risk for pre-eclampsia is concerned.

*Obesity and insulin resistance*

Obesity is a definite risk for developing pregnancy-induced hypertensive disorders, including pre-eclampsia.[16–18] The typical odds ratio for obesity in most studies is about 3. In Conde-Agudelo and Belizan's study in a cohort of 878 680 pregnancies the frequency of pre-eclampsia for lean women (body mass index <19·8) was 2·6% versus 10·1% in obese women (body mass index >29·0).[18] Obesity has a strong link with insulin resistance The exact mechanisms by which obesity/insulin resistance are associated with an increased risk for pre-eclampsia are not completely understood. Possible explanations are: increased shear stress due to the hyperdynamic circulation associated with obesity;[19] dyslipidaemia or increased cytokine-mediated oxidative stress;[3] and direct haemodynamic effects of hyperinsulinaemia (increased sympathetic activity and increased tubular sodium resorption).

The almost worldwide increase in obesity is likely to lead to a rise in the frequency of pre-eclampsia. Prevention of or effective treatment of obesity, or both, could result in a substantial decrease in its frequency. Having a (too) low birthweight as a consequence of intrauterine growth restriction (IUGR) has also been identified as an important risk factor of the so-called insulin resistance syndrome in adult life. Prevention of IUGR could therefore, at least theortically, contribute to primary prevention of pre-eclampsia (and IUGR) in the next generation.[3,4]

*Smoking*

Cigarette smoking is associated with a 30–40% decrease in the risk of pre-eclampsia.[18] However, this benefit is cancelled out by the substantial negative effect of smoking on fetal growth, risk for placental abruption, and general health. However, understanding the mechanisms of the preventive effects of smoking on pre-eclampsia could help us to unravel important aspects of its pathophysiology. The beneficial effects might be mediated by nicotine through inhibition of interleukin-2 and tumour necrosis factor production by mononuclear cells.[15,20]

## Secondary prevention of pre-eclampsia

Secondary prevention of a disease is only possible if the following three requirements are met: knowledge of pathophysiological mechanisms (pathogenesis and genetics of pre-eclampsia were reviewed in the first part of this series); availability of methods of early detection; and means of intervention and correction of the pathophysiological changes.

*Availability of methods of early detection*

Many tests have been proposed to predict later development of the disease. Some of these methods are already used or could be easily introduced in most hospitals in more-developed countries.

Measuring blood pressure or second trimester mean arterial pressure is not useful for early diagnosis of pre-eclampsia.[21] If an increased diastolic blood pressure or second trimester mean arterial pressure predicts anything, it is gestational hypertension, not the real disease pre-eclampsia with its associated perinatal morbidity and mortality.[22] Also weight gain cannot be used to predict development of pregnancy-induced hypertensive disorders, and excess weight gain alone imparts no adverse prognosis to perinatal outcome.[23]

Most women with a pregnancy-induced hypertensive disorder are symptomless, which is an important part of the rationale for frequent antenatal visits in late pregnancy. Laboratory tests have been used for prediction, diagnosis, and monitoring of disease progress. The diagnosis of pre-eclampsia is even based on a laboratory test.

Uric acid clearance drops disproportionately in pre-eclampsia compared with creatinine and urea clearance. The explanation for this specific decrease in urate clearance lies in the biphasic pattern of renal involvement in pre-eclampsia. Tubular function is the first to be involved, and later in the disease process glomerular function is impaired. Uric acid is used as an indicator of disease severity in established pre-eclampsia and has been reported to be a better predictor for adverse perinatal outcome than blood pressure.[23] In most patients the increase in urate concentrations seems to coincide with the increase in blood pressure, and precedes development of the proteinuric stage (a sign of glomerular damage) of the disease. Uric acid concentrations have been used for early diagnosis of pre-eclampsia, but not for hypertension as such. The low sensitivity found in most studies renders uric acid measurement unhelpful for widespread use.[24]

Proteinuria is a late sign of pregnancy-induced hypertensive disorders, and HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome and eclampsia could occur in the absence of proteinuria. After blood pressure measurement, dipstick proteinuria analysis is the most common screening test for pre-eclampsia. Several studies have shown a large number of both false positives and false negatives when dipstick urine analysis is compared with biochemical analysis of total protein excreted in 24 h collections.[25] Poor sensitivity and specificity and the fact that proteinuria is such a late feature of the disease make routine use of dipsticks in a normotensive low-risk population just as ineffective in predicting pre-eclampsia as measuring maternal weight gain.[26] However, the dipstick is easy to use and cheap, and the aim of using a dipstick is to assist in timely diagnosis of pre-eclampsia (not to predict later pre-eclampsia), especially in those patients with borderline increases in blood pressure and in patients at a higher risk—eg, with chronic hypertension. However, the practitioner using dipsticks should be aware of the high false negative rates.

Women with raised second trimester maternal serum α-fetoprotein (MSAFP) concentrations whose fetuses do not have neural-tube defects have an increased risk of: fetal death, delivery of an infant who is small for gestational age, and preterm delivery. A similar association could exist between human chorionic gonadotropin (hCG) and fetal death, pre-eclampsia, preterm delivery, and placental pathology. The raised concentrations of MSAFP and maternal hCG are thought to reflect early placental pathology. Leakage of MSAFP through a defective placental barrier and an increased placental villous surface have been suggested as explanations.[27] Most studies have shown that in women at low risk, raised MSAFP or hCG are predictive of adverse pregnancy outcome. In women already at risk the presence of an abnormal serum hCG or AFP does not increase that risk. The negative predictive value is too low for these tests to be useful as a screening instrument. However, the positive predictive value of about 40% for adverse perinatal outcome could justify intensified obstetric surveillance in women with unexplained increased concentrations of AFP or hCG.[27,28]

Platelet lifespan is much shorter in pregnancy-induced hypertensive disorders, particularly when complicated by fetal growth retardation. However, the distributions of platelet counts in normotensive and pregnant women with hypertension overlap too much for platelet counts to be an effective method for early detection in low-risk nulliparous women.[29]

High maternal haemoglobin concentrations and haematocrits are associated with low birthweight and placental weight, increased frequency of prematurity and perinatal mortality, as well as maternal hypertension.

| Pooled likelihood ratio | Pre-eclampsia | IUGR | Perinatal death |
|---|---|---|---|
| Low risk populations | | | |
| Positive test | 6·4 (5·7–7·1) | 3·6 (3·2–4·0) | 1·8 (1·2–2·9) |
| Negative test | 0·7 (0·6–0·8) | 0·8 (0·8–0·9) | 0·9 (0·8–1·1) |
| High risk populations | | | |
| Positive test | 2·8 (2·3–3·4) | 2·7 (2·1–3·4) | 4·0 (2·4–6·6) |
| Negative test | 0·8 (0·7–0·9) | 0·7 (0·6–0·9) | 0·6 (0·4–0·9) |
| Diastolic notch* | | | |
| Positive test | 6·8 (5·9–7·9) | 3·5 (2·8–4·4) | · · |
| Negative test | 0·7 (0·6–0·8) | 0·8 (0·7–0·8) | · · |

Based on reference 32. *Data of studies only based on the presence or absence of a diastolic notch. IUGR=intrauterine growth restriction.

**Pooled likelihood ratios and 95% CIs for uterine artery doppler in the prediction of pre-eclampsia, IUGR, and perinatal death**

Serial measurements of haemoglobin and haematocrit are used to monitor pregnancies at high risk of uteroplacental insufficiency. Striking increases in concentrations of haemoglobin in the second trimester could predict development of pregnancy-induced hypertensive disorders. The predictive value of less pronounced haemoglobin concentrations is low.[30]

Impaired trophoblast invasion is one of the key features of pre-eclampsia and most cases of IUGR. The usefulness of uterine/uteroplacental doppler flow studies have been debated for the past 15 years because of differences in the anatomical sites of measurement, the indices used to describe an abnormal waveform, and the outcome measurement for which the test is predictive. Studies with any hypertension (instead of real pre-eclampsia) as the endpoint report a very poor predictive performance.[31] Chien and colleagues[32] have done a rigorous systematic review of all 27 studies and 12 994 participants (table).[32]

They concluded that uterine artery doppler assessment has limited ability to screen for pre-eclampsia. However, the data could be interpreted as showing that an abnormal doppler result increases the likelihood of pre-eclampsia six-fold, which is important to the woman and her obstetrician, and could be large enough for a health-service provider to recommend investment in this screening test. The development of transvaginal colour doppler is likely to improve performance as a screening test.[33]

Thus no one test is truly predictive, though some tests are useful to detect patients at risk. The multifactorial origin of pre-eclampsia suggests that it is highly unlikely that there will be one universal predictive test in the future.

### *Means of intervention and correction of pathophysiological changes*

To date, strategies aimed at secondary prevention of pre-eclampsia have all focused on mechanisms thought to be behind the pathophysiology of the disease process. We present here the results of the three preventive strategies which have been thoroughly assessed in the past 10–15 years: calcium supplementation; low-dose aspirin; and fish-oil supplementation.

Some, but not all, epidemiological studies have suggested that the frequency of pre-eclampsia/eclampsia is inversely proportional to nutritional calcium intake.[34] The most recent update of the Cochrane Library on calcium supplementation includes nine studies and over 6000 women.[35] The data show a modest decrease in the risk of pre-eclampsia (relative risk [RR] 0·72, 95% CI 0·60–0·86). The effect was greatest for women at high risk of hypertension (0·22, 0·11–0·43) and those with low baseline calcium intake (0·32, 0·21–0·49). It should be stressed that the results for women at high-risk remain equivocal since only 225 women have been analysed so far.[36] The idea that dietary calcium intake is the most important confounder in assessing effects of calcium supplementation is supported by the substantial protective effects of calcium supplementation in more-developed countries with a low calcium intake, such as Australia, versus complete absence of any beneficial effect of calcium supplementation in more-developed countries with a high calcium intake.[36–38] However, there is still pre-eclampsia in countries with a high calcium intake (USA, Netherlands), especially the type that kills babies and mothers, and preventing a definition—ie, hypertension and proteinuria—is not the same as improving perinatal outcome. The Cochrane review shows that calcium supplementation does not improve perinatal outcome. Is

there a place for calcium supplementation?[35] The answer is probably yes for populations with a low baseline calcium intake. Calcium supplementation will not improve perinatal outcome, but will, by decreasing the frequency of near-term pre-eclampsia, result in cost-savings, a relevant benefit in countries with limited budgets.

Several (mainly cross-sectional) studies in the 1980s and early 1990s suggested that pre-eclampsia is characterised by a prostacyclin/thromboxane-$A_2$ imbalance. This imbalance could explain many of the clinical manifestations of pre-eclampsia, and several attempts have been made to correct this imbalance or to diminish its consequences.[39,40]

Asprin acetylates the hydroxyl group of a single serine residue at the active site of the cyclo-oxygenase enzyme. Platelets are unable to resynthesise cyclo-oxygenase because they lack nuclei. Recovery of the ability to generate thromboxane-$A_2$ depends on the synthesis of new platelets, taking 10–12 days for a complete turnover. Aspirin also inhibits endothelial cyclo-oxygenase, but endothelial cells have the capacity to resynthesise new cyclo-oxygenase when aspirin is removed from their environment. Another mechanism involved in the causation of the paradoxical selectivity of low-dose aspirin on platelet cyclo-oxygenase is based on the pharmacokinetic characteristics of this drug. Absorption of a low oral dose of aspirin causes fairly high concentrations in the portal circulation leading to a cumulative inhibition of cyclo-oxygenase in platelets passing through the gut capillaries, whereas the concentration in the peripheral circulation (after deacetylation of aspirin in the liver) remains too low to affect endothelial cyclo-oxygenase.[40]

The Cochrane Collaboration have just updated their systematic review of effectiveness and safety of antiplatelet agents (predominantly aspirin) for prevention of pre-eclampsia.[41] They have shown that use of aspirin is associated with: a 15% decrease in the risk of pre-eclampsia (32 trials with 29 331 women; relative risk [RR] 0·85; 95% CI [0·78–0·92]. This decrease is irrespective of risk status but seems to be greater when a placebo is not used, when the dose of aspirin is greater, or when randomisation in a trial occurred at an earlier gestational age. They also showed that a 7% decrease in risk of delivery before 37 completed weeks (23 trials with 28 268 women; 0·92, 0·88–0·97) and a 14% decrease in fetal and/or neonatal death (30 trials with 30 093 women; 0·86, 0·75–0·99), which was greatest in women at high risk (4134 women; 0·73, CI 0·56–0·96). There were no significant differences between treatment and control groups in the frequency of infants who were small for gestational age (25 trials with 20 235 women, 0·91, 0·83–1·00), placental abruption, and induction of labour or caesarean section. The Cochrane reviewers concluded that, despite the potential benefits overall, it is not possible to make clear recommendations.

Low-dose aspirin does correct the prostacyclin/thromoxane-$A_2$ imbalance, so why is it not the wonder drug we all hoped for? The most likely explanation is that such an imbalance is not the only, and certainly not the major, pathogenic biochemical pathway.[42] Other investigators have stressed that the dose of aspirin should be high enough to inhibit placental synthase and thus a major part of placental lipid peroxide production, and to allow for other anti-inflammatory effects of aspirin.[43,44] The importance of a higher dose of aspirin is supported by several studies using biochemical or clinical endpoints.[45–47] Some of the larger trials could have looked at the wrong dose of aspirin used at the wrong time of pregnancy.[48] Thus it is unclear whether aspirin given in early pregnancy in an appropriate dose is effective in pre-eclampsia. A multicentre trial to address that question is in progress in France. Low-dose aspirin has been studied in combination with other antiplatelet drugs. In a South African study, addition of ketanserin to aspirin was associated with a substantial decrease in the frequency of superimposed pre-eclampsia and an improvement in pregnancy outcome among patients with mild to moderate midtrimester hypertension.[49]

There is interest in the protective effects of n-3 fatty acids because of the assumed importance of the prostacyclin/thromboxane-$A_2$ balance in pre-eclampsia. When n-3 fatty acids are included in the diet, eicosapentaenoic acid and docosahexaenoic acid compete with arachidonic acid in several ways: they inhibit synthesis of arachidonic acid from linoleic acid; they compete with arachidonic acid for the 2-position in membrane phospholipids, thereby lowering plasma and cellular concentrations of arachidonic acid; and eicosapentaenoic acid competes with arachidonic acid as the substrate for cyclo-oxygenase, inhibiting the production of thromboxane-$A_2$ by platelets and produces only small amounts of a physiologically inactive thromboxane-$A_3$. In endothelial cells, the production of prostaglandin $I_2$ is not inhibited much, and the physiological activity of prostaglandin $I_3$, which is synthesised from eicosapentaenoic acid, is added to that of prostaglandin $I_2$.[50] Because of these potentially beneficial effects, several trials have assessed the preventive effects of fish oil. Olsen and colleagues have done a large trial, the European Multicentre Fish Oil Supplementation trial (FOTIP trial).[51] In six multicentre trials, women with high-risk pregnancies were randomly assigned to receive fish oil or olive oil from around 20 weeks' gestation. Four of these trials were prophylactic trials and enrolled 232, 280, 386, and 579 women who had had previous preterm delivery, intrauterine growth restriction, or pregnancy-induced hypertension/pre-eclampsia, and twin pregnancies, respectively. Fish oil lowered risk of preterm delivery from 33% to 21% (OR 0·54; 95% CI 0·30–0·98) but did not affect any of the other outcomes. In twin pregnacies, the risks for all three outcomes were similar in the two intervention arms. So fish oil is not going to be the solution.

### *New developments*

In the past 5 years many studies have been published on the association between a variety of thrombophilic disorders and early-onset pre-eclampsia and other types of acute or chronic uteroplacental insufficiency. Some of these disorders, such as hyperhomocysteinaemia, can easily be corrected from the metabolic point of view,[52] but currently it is unknown whether or not metabolic correction translates into improved perinatal outcome. More or less the same is true for managing patients with previous adverse pregnancy outcome and documented activated protein-C resistance or protein-S deficiency with (low molecular weight) heparin. Several trials are now addressing these issues.

The beneficial effects of vitamin C and E on markers of oxidative stress,[53] endothelial activation, and the frequency of pre-eclampsia have been assessed. 283 women were identified as being at risk of pre-eclampsia by abnormal two-stage uterine artery doppler (17% frequency of pre-eclampsia in placebo group) and were randomly assigned vitamin C and E or placebo at 16–22 weeks' gestation. In the cohort who completed the study

the odds ratio was 0·24 (0·08–0·70; p=0·002) in favour of the women randomised for vitamin C and E. However, the 11 women in the vitamin group had a worse perinatal outcome than the 24 women in the control group. The mean gestational age at delivery in women given placebo women was 37·5 weeks (34·5–38·7) versus 36·1 weeks (32·7–39·0) in the vitamin group. The mean birthweight in the placebo group was 2670 g (3000–3553) versus 2200 g (1340–2940) in the vitamin group, and only the vitamin group had babies with a birthweight below 1500 g.

## Tertiary prevention

Without a doubt, proper antenatal care is the most important part of tertiary prevention. The decrease in maternal mortality and serious morbidity since the 1950s resulted not from the management of acute hypertension but mainly from the screening and intervention (such as timed delivery) that comes with organised antenatal care. There should be an effort to develop antenatal-care systems that allow close vigilance and easy referral for all pregnant women at risk. Greater attention should be made to identify patients with risk factors.

The aim of treating a pregnant woman with pre-eclampsia is the prevention of complications (tertiary prevention). What are we treating? There is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial.[54] The more controversial issues are the role of pharmacological treatment for conservative management in severe pre-eclampsia aimed at prolongation of pregnancy, the ability of such treatment to modify the course of the underlying systemic disorder, and the effect on fetal and maternal outcome.

IUGR is thought to be one of the major risks of the maternal increase in blood pressure in pre-eclampsia. However, although the association is quite common, it is not the blood pressure that harms the baby. To put this in the correct perspective, it is useful to consider the genetic conflict hypothesis.[55] Maternal and fetal genomes have different roles during development. Inheritable paternal, rather than maternal, imprinting of the genome is necessary for normal development of trophoblast and extraembryonic membranes. According to the genetic conflict theory, fetal genes will be selected to increase the transfer of nutrients to the fetus, and maternal genes will be selected to limit transfers in excess of some maternal optimum. The phenomenon of genomic imprinting means that a similar conflict exists within fetal cells between genes that are maternally derived and genes that are paternally derived. Haig stresses the fact that endovascular trophoblast invasion has three consequences. First, the fetus gains direct access to its mother's arterial blood. Therefore, a mother cannot lower the nutrient content of blood reaching the placenta without decreasing the nutrient supply to her own tissues. Second, the volume of blood reaching the placenta becomes largely independent of control by the local maternal vasculature. Third, the placenta is able to release hormones and other substances directly into the maternal circulation.[55] The conflict hypothesis predicts that placental factors (fetal genes) will act to increase maternal blood-pressure, whereas maternal factors will act to lower blood pressure. The conflict hypothesis suggests that the mother decreases vascular resistance early in pregnancy to ration fetal nutrients and that the subsequent physiological increase in vascular resistance represents the changing balance of power as the fetus grows larger. A corollary is that placental factors contribute to the increase in maternal cardiac output. Placental factors could preferentially increase non-placental resistance because uteroplacental arteries are highly modified and unresponsive to vasoconstrictors. The intrinsic effects of a high maternal systemic blood pressure are ultimately beneficial to the fetus.

Thus, Haig's conflict hypothesis predicts that fetal genes will enhance the flow of maternal blood through the intervillous space by increasing maternal blood-pressure (perfusion pressure).[55] Maternal blood-pressures form a continuum so that the dividing line between normotensive and hypertensive pregnancies is arbitrary. The conflict hypothesis predicts that a mother's position on this continuum is defined by the balance between fetal factors increasing blood pressure and maternal factors decreasing blood pressure. This mechanism could operate in gestational hypertension, when fetal prognosis is known to be good. By contrast, in established pre-eclampsia hypertension results from vasoconstriction rather than increased cardiac output. A hypoxic placenta might release cytotoxic factors that damage maternal endothelial cells, and thus cause vasoconstriction and an increase in maternal blood-pressure. In this situation, small increments in the birthweight of semistarved fetuses could often have caused major increases in subsequent survival despite substantial costs to the mother. Thus, endothelial cell activation could have evolved as a high risk fetal strategy to increase non-placental resistance when a fetus's uteroplacental blood supply is inadequate.[55] The genetic conflict theory fits with most observations and pathophysiological findings related to perinatal outcome in women with hypertension and with pre-eclampsia. However, advances in molecular genetics are needed if we are to confirm or refute this hypothesis.

The beneficial effects of blood pressure per se are shown by the US National Institutes of Health, study on twin pregnancies and blood pressure.[56] Among women with a twin gestation, those who remained normotensive were more likely to deliver at an earlier gestational age babies with a lower birthweight than those who developed hypertensive disorders. An iatrogenic decrease in blood pressure may also result in IUGR.[57] Von Dadelszen and colleagues did a meta-analysis of 45 randomised trials on the effect of oral antihypertensive treatment.[57] This meta-analysis included 3773 women with mild-to-moderate pregnancy hypertension and clearly showed that the greater the mean difference in mean arterial blood pressure before versus after initiation of the antihypertensive treatment the higher the proportion of infants who were small for gestational age. According to these researchers, any effect on fetal growth is important because the likely maternal benefits of treating mild to moderate hypertensive are small. A decrease in intrauterine growth could potentially lead to more premature iatrogenic intervention, neurodevelopmental abnormalities, and a higher frequency of the insulin-resistance syndrome, resulting in more cardiovascular disorders in adult life. These data should not be extrapolated to antihypertensive treatment for severe hypertension in pregnancy. In patients with severe pregnancy hypertension, the duration of (intravenous) treatment is mostly short, whereas the median length of treatment in the studies included in this meta-analysis was 10·3 weeks. Obviously, existing data cannot exclude a specific intrinsic (not blood-pressure related) negative effect on fetal growth of the different groups of antihypertensive drugs, or even of one particular antihypertensive drug within a group. Certain β-blockers received a lot of attention for that matter.

Acute falls in maternal systemic blood pressure can result in fetal distress. Administration of a powerful

vasodilator will result in a decreased intervillous blood flow unless the blood pressure decrease is accompanied by a (more or less specific) vasodilator response in the uteroplacental circulaton. This is a well-described phenomenon in patients treated with intravenous hydralazine if not pretreated with plasma volume expansion. According to a systematic review,[58] intravenous hydralazine should no longer be thought of as the drug of choice as its use is associated with more maternal and perinatal adverse effects than other drugs, particularly intravenous labetalol and/or oral (or sublingual) nifedipine. If antihypertensive treatment is chosen, there is no clear choice of drugs. By subgroup analysis, β blockers could be less effective than calcium channel blockers.[58]

There is an ongoing debate whether or not any conservative approach to severe early-onset pre-eclampsia is appropriate. However, this debate should stop since there is evidence from several randomised studies that a conservative approach will result in a better perinatal outcome without an increase in maternal risks.[58,59] Obviously, a perinatal centre with expertise and facilities for maternal and neonatal intensive care is needed for such treatments.

For prevention of recurrent seizures in women with eclampsia, magnesium is more effective and has less risks than phenytoin and diazepam.[60] The role of prophylactic magnesium in women with pre-eclampsia is less clear. If in doubt, it is probably safer to give magnesium than not, but it is not without risks, and in some series the only deaths were related to magnesium intoxication. The risk of eclampsia in women with pre-eclampsia is probably around 1 in 200 and there is no evidence that magnesium will lower it.[61] Hopefully the international multicentre Magpie trial, now in progress, will provide the answer. At this stage, it is appropriate to state that if a prophylactic anticonvulsant is to be used, magnesium is the drug of choice. Delivery is the ultimate cure of pre-eclampsia. The timing of delivery affects the outcome for mother and baby. However, most maternal deaths occur postpartum. A rushed delivery, especially a caesarean section in an unstable patient, adds to her risk rather than lowering it.

A major flaw in almost all studies on prevention of pre-eclampsia published so far is the focus on prevention of the definition of pre-eclampsia. Pre-eclampsia is defined as de novo hypertension plus proteinuria in the second half of pregnancy. But having pre-eclampsia is only a risk marker—most patients with pre-eclampsia feel fine and pregnancy outcome will be good. The study that showed that vitamin C and E supplementation could prevent pre-eclampsia was a good example of prevention of a definition rather than the actual pathology.[53]

Thus, there is a pressing need for: definition of biophysical/biochemical aspects of the pre-eclamptic syndrome that are best in prediction of poor maternal or perinatal outcome; further trials on the prevention of pre-eclampsia to focus on prevention of real pathology instead of just preventing a definition; and further basic and clinical studies to unravel its causes and pathogensis.

## References


1 Hauth JC, Ewell MG, Levine RJ, et al. Pregnancy outcomes in healthy nulliparas who developed hypertension. *Obstet Gynecol* 2000; **95:** 24–28.

2 Campbell DM, MacGillivray I. Preeclampsia in twin pregnancies: incidence and outcome. *Hypertens Pregnancy* 1999; **18:** 197–207.

3 Dekker GA, Sibai BM, Etiology and pathogenesis of preeclampsia: current concepts. *Am J Obstet Gynecol* 1998; **179:** 1359–75.

4 Dekker GA. Risk factors for preeclampsia. *Clin Obstet Gynecol* 1999; **42:** 422–35.

5 Robillard PY, Hulsey TC, Perianin J, Janky E, Miri EH, Papiernik E. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. *Lancet* 1994; **344:** 973–75.

6 Dekker GA, Robillard PY, Hulsey TC. Immune maladaptation in the etiology of preeclampsia. A review of corroborative epidemiologic studies. *Obstet Gynecol Survey* 1998; **58:** 377–82.

7 Robillard PY, Hulsey TC, Alexander GR, Keenan A, de Caunes F, Papiernik E. Paternity patterns and risk of preeclampsia in the last pregnancy in multiparae. *J Reprod Immunol* 1993; **24:** 1–12.

8 Trupin LS, Simon LP, Eskenazi B. Change in paternity: a risk factor for pre-eclampsia in multiparas. *Epidemiology* 1996; **7:** 240–44.

9 Tubbergen P, Lachmeijer AMA, Althuisius SM, Vlak MEJ, van Geijn HP, Dekker GA. Change in paternity: a risk factor for preeclampsia in multiparous women? *J Reprod Immunol* 1999; **45:** 81–88.

10 Koelman CA, Coumans AB, Nijman HW, Doxiadis II, Dekker GA, Glaas FH. Correlation between oral sex and a low incidence of preeclampsia: a role for soluble HLA in seminal fluid? *J Reprod Immunol* 2000; **46:** 155–66.

11 Tremellen KP, Seamark RF, Robertson SA. Seminal transforming growth factor beta1 stimulates granulocyte-macrophage colony-stimulating factor production and inflammatory cell recruitment in the murine uterus. *Biol Reprod* 1998; **58:** 1217–25.

12 Marti JJ, Hermann U. Immunogestosis: a new etiologic concept of "essential" EPH gestosis, with special consideration of the primigravid patient. *Am J Obstet Gynecol* 1977; **128:** 489–93.

13 Robillard PY, Dekker GA, Hulsey TC. Revisiting the epidemiological standard of preeclampsia: primigravidity or primipaternity. *Eur J Obstet Gynecol Reprod Biol* 1999; **84:** 37–41.

14 Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of preeclampsia. *BMJ* 1998; **316:** 1343–47.

15 Redman CWG, Sacks GP, Sargent IL. Pre-eclampsia, an excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynecol* 1999; **180:** 499–506.

16 Stone JL, Lockwood CJ, Berkowitz GS, Alvares M, Lapinski R, Berkowitz RL. Risk factors for severe preeclampsia. *Obstet Gynecol* 1994; **83:** 357–61.

17 Sibai BM, Gordon T, Thom E, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicentre study. *Am J Obstet Gynecol* 1995; **172:** 642–48.

18 Conde-Agudelo A, Belizan JM. Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women. *Br J Obstet Gynaecol* 2000; **107:** 75–83.

19 Bosio PM, McKenna PJ, Conroy R, O'Herlihy ??. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol* 1999; **94:** 978–84.

20 Madretsma GS, Donze GJ, van Dijk AP, Tak CJ, Wilson JH, Zijlstra FJ. Nicotine inhibits the in vitro production of interleukin 2 and tumor necrosis factor-alpha by human mononuclear cells. *Immunopharmacology* 1996; **35:** 47–51.

21 Villar MA, Sibai BM. Clinical significance of elevated mean arterial blood pressure in second trimester and threshold increase in systolic or diastolic blood pressure during the third trimester. *Am J Obstet Gynecol* 1989; **160:** 419–23.

22 Conde-Agudelo A, Belizan JM, Lede R, Bergel EF. What does an elevated mean arterial pressure in the second half of pregnancy predict: gestatonal hypertension or preeclampsia? *Am J Obstet Gynecol* 1993; **169:** 509–14.

23 Dekker GA, Sibai BM. Early detection of preeclampsia. *Am J Obstet Gynecol* 1991; **165:** 160–72.

24 Masse J, Forest J-C, Moutquin J-M, Marcoux S, Brideau N-A, Belanger M. A prospective study of several potential biologic markers for early prediction of preeclampsia. *Am J Obstet Gynecol* 1993; **169:** 501–08.

25 Halligan AW, Bell SC, Taylor DJ. Dipstick proteinuria: caveat emptor. *Br J Obstet Gynecol* 1999; **106:** 1113–15.

26 Dawes MG, Grudzinskas JG. Repeated measurement of maternal weight during pregnancy: is this a useful practice? *Br J Obstet Gynaecol* 1991; **98:** 189–94.

27 van Rijn M, van der Schouw YT, Hagenaars AM, Visser GHA, Christiaens GC. Adverse obstetric outcome in low-and high risk pregnancies: predictive value of maternal serum screening. *Obstet Gynecol* 1999; **94:** 929–34.

28 Walton DL, Norem CT, Schoen EJ, Ray T, Colby CJ. Second-trimester serum chorionic gonadotrophin concentrations and complications and outcome of pregnancy. *N Engl J Med* 1999; **341:** 2033–38.

29 Halligan A, Bonnar J, Sheppard B, Darling M, Walshe J. Haemostatic, fibrinolytic and endothelial variales in normal pregnancies and pre-eclampsia. *Br J Obstet Gynaecol* 1994; **101:** 488–92.

30 Murphy JF, Newcombe RG, O'Riordan JO, et al. Relation of haemoglobin levels in first and second trimesters to outcome. *Lancet* 1986; **1:** 992–94.

31 Chappel L, Bewley S. Pre-eclamptic toxaemia: the role of uterine artery Doppler. *Br J Obstet Gynaecol* 1998; **105:** 379–82.

32 Chien PF, Arnott N, Gordon A, Owen P, Khan KS. How useful is uterine artery doppler flow velocimetry in the prediction of pre-eclampsia, intra-uterine growth retardation and perinatal death? An overview. *Br J Obstet Gynaecol* 2000; **107:** 196–208.

33 Harrington K, Carpenter RG, Goldfrad C, Campbell S. Transvaginal doppler ultrasound of the uteroplacental arteries in the early prediction of pre-eclampsia and intrauterine growth retardaton. *Br J Obstet Gynaecol* 1997; **104:** 674–81.

34 Marcoux S, Brisson J, Fabia J. Calcium intake from dairy products and supplements and the risks of preeclampsia and gestational hypertension. *Am J Epidemiol* 1991; **133:** 1266–72.

35 Atallah AN, Hofmeyr GJ, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (Cochrane Review). In: *The Cochrane Library* **Issue 1.** Oxford: Update Software, 2000.

36 DerSimonian R, Levine RJ. Resolving discrepancies between a meta-analysis and a subsequent large controlled trial. *JAMA* 1999; **282:** 664–70.

37 Crowther CA, Hiller JE, Pridmore B, et al. Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, preeclampsia and preterm birth: an Australian randomized trial—FRACOG and the ACT Study Group. *Aust NZ J Obstet Gynaecol* 1999; **39:** 12–18.

38 Levine RJ and others. Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997; **337:** 69–76.

39 CLASP Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet* 1994; **343:** 619–29.

40 Dekker GA, Sibai BM. Low-dose aspirin in the prevention of preeclampsia and fetal growth retardation: rationale, mechanisms, and clinical trials. *Am J Obstet Gynecol* 1993; **168:** 214–27.

41 Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents and pre-eclampsia (Cochrane Review). In: *The Cochrane Library,* **Issue 1.** Oxford, Uptade Software, 2000.

42 Paarlberg KM, Jong de CLD, van Geijn HP, van Kamp GJ, Heinen AGLL, Dekker GA. Vasoactive mediators in pregnancy-induced hypertensive disorders: a longitudinal study. *Am J Obstet Gynecol* 1998; **179:** 1599–64.

43 Walsh SW. Lipid peroxidation in pregnancy. *Hypertens Pregnancy* 1994; **13:** 1–31.

44 Kaplanski G, Porat R, Aiura K, Erban JK, Gelfand JA, Dinarello CA. Activated platelets induce endothelial secretion of interleukin-8 in vitro via and interleukin-1 mediated event. *Blood* 1993; **81:** 2492–95.

45 Goldenberg RL, Hauth JC, DuBard MB, Copper RL, Cutter GR. Fetal growth in women using low-dose aspirin for the prevention of preeclampsia—effect of maternal size. *J Maternal Fetal Med* 1995; **4:** 218–24.

46 Dumont A, Flahault A, Beaufils M, Verdy E, Uzan S. Effect of aspirin in pregnant women is dependent on increase in bleeding time. *Am J Obstet Gynecol* 1999; **180:** 135–40.

47 Leitich H, Egarter C, Husslein P, Kaider A, Schemper M. A meta-analysis of low-dose aspirin for the prevention of intrauterine growth retardation. *Br J Obstet Gynaecol* 1997; **104:** 450–59.

48 Emeagi J, Patni S, Tikum HM, Mander AM. Low dose aspirin for preventing and treating pre-eclampsia. *BMJ* 1999; **319:** 316.

49 Steyn DW, Odendaal HJ. Randomised controlled trial of ketanserin and aspirin in prevention of pre-eclampsia. *Lancet* 1997; **350:** 1267–71.

50 Leaf A, PC Weber. Cardiovascular effects of n-3 fatty acids. *N Engl J Med* 1988; **318:** 549–57.

51 Olsen S, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies. *Br J Obstet Gynaecol* 2000; **107:** 382–95.

52 Leeda M, Riazi N, de Vries JIP, Jakobs C, van Geijn HP, Dekker GA. Effects of folic acid and vitamin B6 on women with hyperhomocysteinemia and a history of preeclampsia or fetal growth restriction. *Am J Obstet Gynecol* 1998; **179:** 135–39.

53 Chappell LC, Seed PT, Briley AL, et al. Effects of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999; **354:** 810–16.

54 Khedun SM, Moodley J, Naicker T, Maharaj B. Drug management of hypertensive disorders of pregnancy. *Pharmacol Ther* 1997; **74:** 221–28.

55 Haig D. Genetic conflicts in human pregnancy. *Quart Rev Biol* 1993; **68:** 495–532.

56 Sibai SM, Hauth J, Caritis S, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 2000; **182:** 938–42

57 von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet* 2000; **355:** 87–92.

58 Magee LA, Ornstein MP, von Dadelszen P. Management of hypertension in pregnancy. *BMJ* 1999; **318:** 1332–36.

59 Many A, Kupferminc MJ, Pausner D, Lessing JB. Treatment of severe preeclampsia from term: a clinical dilemma. *Obstet Gynecol Survey* 1999; **54:** 723–27.

60 Duley L, Carroli G, Belizan J, et al. Which anticonvulsant for women with eclampsia: evidence from the collaborative eclampsia trial. *Lancet* 1995; **345:** 1455–63.

61 Moodley J, Moodley VV. Prophylactic anticonvulsant therapy in hypertensive crisis of pregnancy: the need for a large, randomized trial. *Hypertens Pregnancy* 1994; **13:** 245–52.