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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 01/64/04. The contractual start date was in January 2004. The draft report began editorial review in August 2006 and was accepted for publication in August 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling

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Objectives: To investigate the accuracy of predictive tests for pre-eclampsia and the effectiveness of preventative interventions for pre-eclampsia. Also to assess the cost-effectiveness of strategies (test–intervention combinations) to predict and prevent pre-eclampsia.
Data sources: Major electronic databases were searched to January 2005 at least.
Review methods: Systematic reviews were carried out for test accuracy and effectiveness. Quality assessment was carried out using standard tools. For test accuracy, meta-analyses used a bivariate approach. Effectiveness reviews were conducted under the auspices of the Cochrane Pregnancy and Childbirth Group and used standard Cochrane review methods. The economic evaluation was from an NHS perspective and used a decision tree model.
Results: For the 27 tests reviewed, the quality of included studies was generally poor. Some tests appeared to have high specificity, but at the expense of compromised sensitivity. Tests that reached specificities above 90% were body mass index > 34, α-foetoprotein and uterine artery Doppler (bilateral notching). The only Doppler test with a sensitivity of over 60% was resistance index and combinations of indices. A few tests not commonly found in routine practice, such as kallikreinuria and SDS-PAGE proteinuria, seemed to offer the promise of high sensitivity, without compromising specificity, but these would require further investigation. For the 16 effectiveness reviews, the quality of included studies was variable. The largest review was of antiplatelet agents, primarily low-dose aspirin, and included 51 trials (36,500 women). This was the only review where the intervention was shown to prevent both pre-eclampsia and its consequences for the baby. Calcium supplementation also reduced the risk of pre-eclampsia, but with some uncertainty about the impact on outcomes for the baby. The only other intervention associated with a reduction in RR of pre-eclampsia was rest at home, with or without a nutritional supplement, for women with normal blood pressure. However, this review included just two small trials and its results should be interpreted with caution. The cost of most of the tests was modest, ranging from £5 for blood tests such as serum uric acid to approximately £20 for Doppler tests. Similarly, the cost of most interventions was also modest. In contrast, the best estimate of additional average cost associated with an average case of pre-eclampsia was high at approximately £9000. The results of the modelling revealed that prior testing with the test accuracy sensitivities and specificities identified appeared to offer little as a way of improving cost-effectiveness. Based on the

evidence reviewed, none of the tests appeared sufficiently accurate to be clinically useful and the results of the model favoured no-test/treat-all strategies. Rest at home without any initial testing appeared to be the most cost-effective 'test–treatment' combination. Calcium supplementation to all women, without any initial testing, appeared to be the second most cost-effective. The economic model provided little support that any form of Doppler test has sufficiently high sensitivity and specificity to be cost-effective for the early identification of pre-eclampsia. It also suggested that the pattern of cost-effectiveness was no different in high-risk mothers than the low-risk mothers considered in the base case.

Conclusions: The tests evaluated are not sufficiently accurate, in our opinion, to suggest their routine use in clinical practice. Calcium and antiplatelet agents, primarily low-dose aspirin, were the interventions shown to prevent pre-eclampsia. The most cost-effective approach to reducing pre-eclampsia is likely to be the provision of an effective, affordable and safe intervention applied to all mothers without prior testing to assess levels of risk. It is probably premature to suggest the implementation of a treat-all intervention strategy at present, however the feasibility and acceptability of this to women could be explored. Rigorous evaluation is needed of tests with modest cost whose initial assessments suggest that they may have high levels of both sensitivity and specificity. Similarly, there is a need for high-quality, adequately powered randomised controlled trials to investigate whether interventions such as advice to rest are indeed effective in reducing pre-eclampsia. In future, an economic model should be developed that considers not just pre-eclampsia, but other related outcomes, particularly those relevant to the infant such as perinatal death, preterm birth and small for gestational age. Such a modelling project should make provision for primary data collection on the safety of interventions and their associated costs.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Aneuploidy The condition of having less than or more than the normal diploid number of chromosomes.

Extra Domain A and B in fibronectin molecule Although fibronectin is encoded by only one gene, this protein exists in a number of variant isoforms due to alternate splicing and/or post-translational modifications.

I^2 statistic Indication of heterogeneity of studies in a forest plot.

Multiples of median When two analytical methods agree, or differ by a proportional amount, conversion to multiples of median can be used to simplify the clinical interpretation of results.

List of abbreviations

ACTH	adrenal corticotrophic hormone
AFP	α-foetoprotein
APEC	Action on Pre-Eclampsia
AUN	any unilateral notching
BMI	body mass index
BNF	British National Formulary
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
DHEA-s	dehydroepiandrosterone sulfate
DIC	disseminated intravascular coagulation
E3	unconjugated oestriol
ED-A, ED-B	extra domain A and B in fibronectin molecule
fDNA	foetal DNA
FN	fibronectin
fp, fn	false positive, false negative numbers
HCG	human chorionic gonadotrophin
HELLP	haemolysis, elevated liver enzymes and low platelets
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
MoM	multiples of median
NICU	neonatal intensive care unit
NNT	number-needed-to-treat
NPV	negative predictive value
PMS	premenstrual syndrome
PE	pre-eclampsia

continued

List of abbreviations *continued*

PPV	positive predictive value
PSA	probabilistic sensitivity analysis
RCT	randomised controlled trial
RD	risk difference
ROC	receiver–operator characteristic
RR	relative risk
SD	standard deviation
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SPSS	Statistical Package for the Social Sciences
sROC	summary receiver–operator characteristic
SUA	serum uric acid
tp, tn	true positive, true negative numbers
UCCR	urinary calcium/creatinine ratio
UCE	urinary calcium excretion
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Pre-eclampsia is part of a spectrum of conditions known as the hypertensive (high blood pressure) disorders of pregnancy and is defined as hypertension and proteinuria detected for the first time in the second half of pregnancy (after 20 weeks' gestation). Pre-eclampsia complicates 2–8% of pregnancies and may have serious effects on mother and child, which makes it an important threat to public health in both developed and developing countries. Once women are identified to be at high risk, they can be targeted for more intensive antenatal surveillance and prophylactic interventions. This report contains a health technology assessment of current strategies for risk stratification and prevention to guide clinical practice and future research in this field.

Objectives

The aim of the project was to identify combinations of test and treatments that would predict and help prevent pre-eclampsia. This study completed three distinct pieces of work to contribute to this goal:

- a series of systematic reviews on the accuracy of tests for the prediction of pre-eclampsia
- a series of systematic reviews of effectiveness of interventions with potential to reduce the number of cases of pre-eclampsia
- a health economic evaluation, including an economic model, of the combined effect of tests and interventions and their cost-effectiveness.

Methods

Protocols were developed for test accuracy and effectiveness systematic reviews which used up-to-date review methods, including searches without language restrictions, study quality assessment and meta-analysis where appropriate. Although there was a slight variation between the search end-date of different systematic reviews, searches were generally conducted to January 2005 at least. For test accuracy reviews, literature was identified from several sources, including databases: PubMED (MEDLINE), EMBASE (Ovid), The Cochrane Library (DARE, CCTR), MEDION, contact with experts including the Cochrane Pregnancy and Childbirth Group and checking of reference lists of accuracy review articles and papers that were eligible for the systematic reviews included in this report. Included were cohort and case–control studies of pregnant women where the test under review was performed before the 25th week of gestation and compared with the reference standard of pre-eclampsia and a 2×2 table was reported or could be calculated. Quality assessment was based on QUADAS criteria. Meta-analyses used a bivariate approach.

Effectiveness reviews were conducted under the auspices of the Cochrane Pregnancy and Childbirth Group. Studies were identified from the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Pregnancy and Childbirth Group's trials register, MEDLINE, EMBASE, handsearches of 30 journals and conference proceedings and reference lists of trial reports. Included were randomised or quasi-randomised controlled trials of the relevant intervention compared with placebo, no treatment or usual care in pregnant women that measured pre-eclampsia as an outcome. Quality assessment was as described in the Cochrane Handbook. Meta-analyses estimating relative risk (RR) were conducted in Review Manager software, using a fixed effects models or random effects if heterogeneity was detected.

For the economic evaluation, the model structure used was a decision tree constructed in DATA Treeage software. An NHS perspective was chosen. Four options (test no-one and treat all, test all and treat no-one, test all and treat only with positive test and test all and treat all) were compared with test no-one and treat no-one. Inputs to the model were test accuracy and effectiveness systematic review meta-analysis results, test accuracy and intervention costs, cost of pre-eclampsia as an outcome and the prevalence of pre-eclampsia. The primary analysis used point estimates of key parameters of all tests and the most effective interventions. Extensive deterministic and probabilistic sensitivity analyses were conducted.

The outputs were incremental cost-effectiveness ratios for test and treatment combinations.

Results

Main findings of test accuracy reviews

There were 27 tests reviewed [body mass index (BMI), α-foetoprotein, cellular and total fibronectin, foetal DNA, haemoglobin, haematocrit, human chorionic gonadotrophin, oestriol, uric acid, urinary calcium excretion, urinary calcium/creatinine ratio, several forms of proteinuria/albuminuria and several flow velocity waveforms of Doppler uterine artery]. The quality of studies and the accuracy of tests were generally poor. Some tests appeared to have high specificity, but at the expense of compromised sensitivity. Only a few tests reached specificities above 90%. These were BMI > 34, α-foetoprotein and uterine artery Doppler (bilateral notching). The only Doppler test with a sensitivity of over 60% was resistance index and combinations of indices. Kallikreinuria had a sensitivity of over 80%. Cellular and total fibronectin and kallikreinuria were found to have specificities above 90%. However, these estimates were based on single studies. Also, a few tests not commonly found in routine practice, such as kallikreinuria and sodium dodecyl sulfate polyacrylamide gel electrophoresis proteinuria, seemed to offer the promise of high sensitivity, without compromising specificity, but these too would require further investigation.

Main findings of effectiveness reviews

Sixteen systematic reviews of interventions are presented in this report, of which 15 provided estimates of effectiveness in preventing pre-eclampsia. The quality of included studies was variable; many reviews included only small, poor-quality trials and a small number of reviews included large, well-designed trials. The largest review was of antiplatelet agents, primarily low-dose aspirin, and included 51 trials (36,500 women). This was the only review where the intervention was shown to prevent both pre-eclampsia [RR 0.81, 95% confidence interval (CI) 0.75 to 0.88] and its consequences for the baby (death, preterm birth and small for gestational age). Calcium supplementation also reduced the risk of pre-eclampsia (12 trials, 15,206 women, RR 0.48, 95% CI 0.33 to 0.69) but with some uncertainty about the impact on outcomes for the baby. The only other intervention associated with a reduction in RR of pre-eclampsia was rest at home, with or without a nutritional supplement, for women with normal blood pressure. However, this review included just two small trials (106 women) and its results should be interpreted with caution. Although the review of antioxidant agents (vitamins C and E in particular) presented here reports a reduction in the relative risk of pre-eclampsia, two large trials have subsequently reported their results. In the recently updated Cochrane review, the effect on pre-eclampsia is no longer statistically significant.

Main findings from the economic evaluation

The cost of most of the tests was modest, ranging from £5 for blood tests such as serum uric acid to approximately £20 for Doppler tests. Similarly, the cost of most interventions was also modest. In contrast, the best estimate of additional average cost associated with an average case of pre-eclampsia was high at approximately £9000.

The results of the modelling revealed that prior testing with the test accuracy sensitivities and specificities identified appeared to offer little as a way of improving cost-effectiveness. Based on the evidence reviewed, none of the tests appeared sufficiently accurate to be clinically useful and the results of the model favoured no-test/treat-all strategies.

The treatments included in the main analysis were rest at home, antiplatelets, antioxidants and calcium as these were the interventions where the RRs and 95% CIs showed they were unlikely to be associated with a worse outcome of pre-eclampsia frequency. However, if the results of the updated Cochrane review on antioxidants had been available when the economic model was run, antioxidants would not have been so included.

Rest at home without any initial testing was the most cost-effective 'test–treatment' combination, delivering the greatest reduction in number of cases of pre-eclampsia at virtually zero additional cost (to the NHS). Calcium supplementation to all women, without any initial testing, was the second most cost-effective. The costs averted as a result of this reduction in cases of pre-eclampsia greatly exceed the cost of the calcium supplementation. Paradoxically, antiplatelet agents, the treatment about which there was greatest certainty of effectiveness, did not feature among the cost-effective options highlighted. This was because the size of the effect on number of cases of pre-eclampsia prevented, on current evidence, was smaller than the effect of rest at home and calcium supplementation. Thus, the very low cost associated with antiplatelet agents was outweighed

by the higher number of pre-eclampsia cases and the high associated cost. Calcium was more costly compared with antiplatelets but had fewer cases of pre-eclampsia and was therefore shown to be relatively much more cost-effective by the economic model.

All three main predictions of the economic model were affected by uncertainty. However, effective treatments (RR <0.7) with modest costs (<£50) applied to all women without prior testing were likely to be preferred from the perspective of cost-effectiveness. Threshold analyses conducted in the economic model suggested that tests with upper range costs would need substantially improved sensitivities (assuming best level of specificity achieved in any test was maintained). The economic model provided little support that any form of Doppler test has sufficiently high sensitivity and specificity to be cost-effective for the early identification of pre-eclampsia. The economic model also suggested that the pattern of cost-effectiveness was no different in high-risk mothers than the low-risk mothers considered in the base case.

Conclusions

None of the tests evaluated is sufficiently accurate, in our opinion, to suggest its routine use in clinical practice. Calcium and antiplatelet agents, primarily low-dose aspirin, are the interventions shown to prevent pre-eclampsia. The most cost-effective approach to reducing pre-eclampsia is likely to be the provision of an effective, affordable and safe intervention applied to all mothers without prior testing to assess levels of risk. However, we believe that it is probably premature to suggest the implementation of a treat-all intervention strategy such as advice to rest or pharmacological interventions such as low-dose aspirin or calcium supplementation at present. However, the feasibility and acceptability to women of offering universal application of interventions could be explored. Some consideration needs to be given to whether the health service should continue to do certain tests whose main perceived value is to help identify pre-eclampsia when their usefulness is questionable.

Recommendations for further research

Rigorous evaluation is needed of tests with modest cost whose initial assessments suggest that they may have high levels of both sensitivity and specificity. Similarly, there is a need for high-quality, adequately powered randomised controlled trials to investigate whether interventions such as advice to rest are indeed effective in reducing pre-eclampsia. In future, an economic model should be developed which considers not just pre-eclampsia, but other related outcomes, particularly those relevant to the infant such as perinatal death, preterm birth and small for gestational age. Such a modelling project should make provision for primary data collection on the safety of interventions and their associated costs.

Chapter 1

Objectives and background

Aims

The aims of this project were to investigate the accuracy of predictive tests for pre-eclampsia and the effectiveness of preventative interventions for pre-eclampsia, and also to assess the cost-effectiveness of strategies (test–intervention combinations) to predict and prevent pre-eclampsia.

Description of underlying health problem

Nature of pre-eclampsia and definitions

Pre-eclampsia (sometimes called toxaemia) is part of a spectrum of conditions known as the hypertensive (high blood pressure) disorders of pregnancy. These disorders have a continuum with normal pregnancy. In pregnant women, hypertension is usually defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg. Pre-eclampsia is defined as hypertension accompanied by proteinuria,[1] which usually occurs during the second half of pregnancy.[2] Proteinuria during pregnancy is defined as 300 mg of protein, or more, in a 24-hour urine collection (which correlates with 30 mg/dl or a spot ratio of $\geqslant$30 mg/ml).

There are four main categories of hypertensive disorders in pregnancy which are now widely agreed:

- **Pre-eclampsia**. Pre-eclampsia is defined as hypertension and proteinuria detected for the first time in the second half of pregnancy (after 20 weeks' gestation).
- **Gestational hypertension** or pregnancy-induced hypertension. This is hypertension detected for the first time during the second half of pregnancy (after 20 weeks' gestation) in the absence of proteinuria. It usually resolves within 3 months after delivery. Gestational hypertension that does not resolve after delivery should be reclassified as chronic hypertension.
- **Chronic hypertension**. This is hypertension known to be present before pregnancy, or detected before 20 weeks' gestation. It is classified as essential hypertension if there is no underlying cause and secondary hypertension if there is an underlying cause such as renal, cardiac or endocrine disease. Chronic hypertension may present for the first time as gestational hypertension.
- **Pre-eclampsia superimposed on chronic hypertension**. Women with chronic hypertension may then develop pre-eclampsia. This is diagnosed where there is new onset of proteinuria, or sudden worsening of either hypertension or proteinuria, or development of other signs and symptoms of pre-eclampsia after 20 weeks' gestation.

Attempts to classify the hypertensive disorders of pregnancy have, in the past, been confusing and sometimes misleading. More recently, there has been a shift towards standardising definitions, and ensuring they are relevant for both clinical practice and research. Internationally, there is now considerable agreement between the various widely used recommendations for classification.[1,3,4] The suggestion that a change in blood pressure is more important than any absolute level[5] is no longer included due to lack of evidence that it is related to outcome.[1,3,4] Oedema was originally one of the triad of signs of pre-eclampsia, but this has now been excluded from the definition.[1,3,6] This is mainly because oedema is a common feature of normal pregnancy, can only be assessed subjectively and does not define a group at risk of poor outcome. Oedema may be absent in some women with severe pre-eclampsia and eclampsia.

During normal pregnancy, cardiac output increases by about 40% in the first trimester. Blood pressure remains relatively unchanged in the first trimester, falling by about 5–10 mmHg in the second trimester, and rising back to pre-pregnancy levels by term. Kidney function also increases during normal pregnancy leading to increased protein excretion.

When measuring blood pressure, any rise found should be confirmed by a second measurement, ideally at least 4 hours later. Blood pressure should be measured with an auscultatory device, as oscillometric techniques systematically under-record during pregnancy.[7] The debate over which

auscultatory sound to use for assessment of diastolic blood pressure, muffling (Korotkoff phase IV) or disappearance (Korotkoff phase V), has been resolved, and Korotkoff V is now recommended as more reliable.[4,8] When measuring proteinuria, if only a single midstream urine sample is available, this correlates with 30 mg/dl, 1+ or more on a dipstick or a spot urine protein/creatinine ratio of at least 30 mg/mmol.[3,4]

For many women, developing pre-eclampsia can be a difficult and unexpected experience, especially if they become ill or deliver too early[9] or their baby dies. Women with mild pre-eclampsia generally have no symptoms. Women with severe pre-eclampsia or very high blood pressure may feel unwell with symptoms such as headache, upper abdominal pain or visual disturbances.

Aetiology

There has been an exponential increase in basic science literature exploring aetiology of pre-eclampsia, yet it remains a 'disease of theories'. Many aetiological (genetic, nutritional, immunological and infectious) and pathophysiological (abnormal placentation, oxidative stress and endothelial dysfunction) pathways have been proposed as causal hypotheses for pre-eclampsia.[10] Some of these are described below.

The placenta is believed to play a key role in pre-eclampsia. Pre-eclampsia occurs only in the presence of a placenta, and its resolution begins with the removal of the placenta at delivery. Pre-eclampsia can occur when there is no foetus, as in a molar pregnancy,[11] and when the pregnancy is not in the uterus, as in an abdominal pregnancy.[12] Abnormal implantation of the placenta[13] and excessive placental tissue have both been implicated as the underlying pathology in pre-eclampsia.

Pre-eclampsia is thought to occur as a result of inadequate blood supply to the placenta. In normal pregnancy, as the placenta implants in the uterus important changes take place in the blood vessels to ensure that the growing placenta and foetus have adequate blood supply from the mother. As the normal placenta implants it invades the spiral arterioles in the uterus, replacing their endothelial lining and remodelling them into large diameter vessels with a large capacity to handle blood flow to the placenta.[14] In pre-eclampsia, these vascular adaptations may be patchy or fail to extend into the deeper layers of the uterus,[13] resulting in small-diameter, high-resistance blood vessels that are unable to meet the increasing demand for blood supply to the placenta. Alternatively, implantation may be normal but there may be a relative reduction in placental perfusion if the placenta is large, and normal uterine blood flow is then inadequate to perfuse this large placenta, for example in a multiple pregnancy. Implantation and vascular changes are complete by 20–22 weeks' gestation. Hence, although pre-eclampsia is usually diagnosed in the second half of pregnancy, the antecedents are present much earlier.

Current thinking is that inadequate blood supply to the placenta leads to the release of unknown factors or materials into the maternal circulation. These factors then activate or injure the endothelial cells, resulting in endothelial dysfunction (abnormal functioning of endothelial cells).[15] Several pathways for this link between reduced perfusion of the placenta and endothelial dysfunction have been proposed. One hypothesis is that reduced placental perfusion may give rise to oxidative stress. In an environment where oxidants exceed neutralising antioxidant,[16] excessive formation of free radicals leads to lipid peroxidation and cell membrane damage.[17] Alternatively, lack of oxygen in the placenta may trigger the release of small proteins, known as cytokines, that start an inflammatory response in the endothelium.[18] Another proposed mediator for the endothelial cell injury is micro fragments of placental tissue. These are transferred into the maternal circulation, and have been shown to alter endothelial function in laboratory studies.[19]

Endothelial dysfunction results in a series of changes associated with narrowing of the blood vessels and an increased tendency to blood clots. These include reduced production of vasodilators and anticoagulants (such as prostacyclin and nitric oxide), increased production of vasoconstrictors and platelet aggregators (such as thromboxane A2 and endothelin), increased responsiveness of endothelium to the vasopressor angiotensin II and an elevation in the proteins of the coagulation cascade (such as von Willebrand factor). In addition to widespread vasoconstriction and activation of platelets and the coagulation system, these changes lead to leakage of fluid out of the blood vessels and into surrounding tissues, causing oedema and a reduction in the circulating blood volume. There is then inadequate blood flow to many of the woman's organs, especially the kidneys, liver and brain. It is the vasoconstriction, micro-clots, and reduced circulating blood volume that result in the clinical manifestations of pre-eclampsia.

However, reduced perfusion of the placenta is not sufficient to explain pre-eclampsia. The abnormal implantation may interact with maternal constitutional factors (genetic, environmental and behavioural) to produce the syndrome of pre-eclampsia. The contributions of reduced perfusion and maternal factors may be balanced differently in different pregnancies. For example, profoundly reduced perfusion could lead to pre-eclampsia in women with minimal predisposing risk, whereas for others the maternal constitution might present such a high risk that even minimal reduction of placental perfusion was sufficient.

Despite a growing understanding of the pathophysiology of pre-eclampsia, the underlying aetiology remains unclear. Factors that appear to have a role include the placenta, maternal immune response, genetic predisposition, maternal vascular disease and diet. Whether an individual woman will develop this syndrome probably depends on which of these factors she has and how they interact.

Normal pregnancy requires adaptation of the maternal immune response, so that the foetus, who also carries the father's genes, is not rejected as foreign tissue. It has been suggested that for some women pre-eclampsia may occur because this adaptation is inadequate, for example in a first pregnancy with a new partner.[20] In subsequent pregnancies with the same partner, the immune response is more complete, and the risk of pre-eclampsia is therefore lower. Even a first trimester miscarriage or termination provides some protection.[21]

Risk factors with a particularly high association with pre-eclampsia (more than a one in 10 risk) include maternal diabetes,[22–24] chronic hypertension[22,23,25] and renal disease.[26] Thrombophilias and autoimmune disease have a strong association with severe early-onset pre-eclampsia.[27] Obstetric factors associated with high risk are multiple pregnancy,[23,28] history of pre-eclampsia in a previous pregnancy, especially if severe or early onset,[22,29,30] and a current hydropic[11] or molar pregnancy.[31] Other factors linked with pre-eclampsia, but associated with a somewhat lower risk, include first pregnancies,[3,23,31] young (less than 20 years) or older age (more than 35 years),[23,24] a family history of pre-eclampsia[32,33] and obesity.[23,34,35]

Pre-eclampsia tends to run in families, suggesting that genetic predisposition may be a factor. The risk is higher for sisters and daughters of women who had eclampsia and pre-eclampsia.[32,33] A number of genes are currently under evaluation for possible links with pre-eclampsia.[36]

Medical conditions associated with vascular (blood vessel) disease also increase the risk of a woman developing pre-eclampsia. For example, the risk is doubled with diabetes[37] and one-fifth of women with chronic hypertension develop pre-eclampsia.[25] In addition, the thrombophilias are associated with severe early-onset pre-eclampsia.[27] This is a group of conditions with a tendency for thrombosis or blood clotting. They include protein S deficiency, activated protein C resistance and autoimmune diseases such as antiphospholipid syndrome and systemic lupus erythematosus. Recently, a raised blood level of homocysteine, a metabolite of the amino acid methionine, has been linked to pre-eclampsia,[38] although a systematic review of the relevant literature cast doubt on the likelihood of these being a causal association.[39]

Certain dietary factors have been linked to pre-eclampsia. For example, Mayan Indians in Guatemala, who traditionally soak their corn in lime before cooking, have a high calcium intake and a low incidence of pre-eclampsia and eclampsia. This led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of pre-eclampsia among women with low calcium intake. Similarly, the observation that Greenland Inuits who eat a lot of oily fish have a low incidence of pre-eclampsia provided the basis for the hypothesis that fish oil might prevent this condition.[40] Other dietary factors that have been suggested to have a role in preventing pre-eclampsia include magnesium, zinc, selenium, antioxidants such as vitamin C and E, folic acid, garlic and rhubarb.

It is clear that basic science literature has not so far provided a deep enough understanding of the biological mechanisms of disease in pre-eclampsia. This raises questions about the completeness of our basic knowledge and soundness of our interpretation of the available scientific information on disease mechanisms.[10] Systematic reviews have largely not been applied to study disease mechanisms and aetiology. The WHO programme to conquer pre-eclampsia has initiated systematic reviews to study aetiopathogenesis of pre-eclampsia.[41]

Epidemiology

Hypertension is common during pregnancy. Around 10% of women will have their blood

pressure recorded as above normal at some point before delivery. Pre-eclampsia complicates 2–8% of pregnancies;[2] however, the incidence varies according to risk factors. Among unselected women, the incidence rate of pre-eclampsia is estimated to be 2.5% [95% confidence interval (CI) 1.9 to 3.4%] from the control group event rate in a trial of antiplatelet agents for preventing pre-eclampsia and its complications.[42] Among primiparous women it is estimated to be 4.7% (95% CI 4.3 to 5.3%) by pooling control group event rates in five trials of antiplatelet agents for preventing pre-eclampsia.[43–47] Among high-risk women (e.g. previous pre-eclampsia or foetal growth restriction, pre-existing hypertension, nephropathy or diabetes, multiple pregnancy) it is estimated to be 10% (95% CI 9.3 to 10.8%) by pooling control group event rates in six trials of antiplatelet agents for preventing pre-eclampsia.[48–53] Overall, 15–25% of women with gestational hypertension progress to pre-eclampsia.[54]

Prognosis

For women who have hypertension alone, pregnancy outcome is similar to that for women with normal blood pressure. Once proteinuria develops, the outcome may be compromised. Pre-eclampsia can develop into severe pre-eclampsia and/or eclampsia. The clinical features or tests in pre-eclampsia that predict the risk of complications need delineation through systematic review. A recent review of the literature on the predictive value of serum uric acid showed imprecise, poor-quality evidence,[55] a feature likely to be prevalent in other related prognostic literature.

There is no widely accepted definition of severe pre-eclampsia. Nevertheless, it is generally agreed that two or more of the following indicate severe disease: severe hypertension (blood pressure at least 160 mmHg systolic or 110 mmHg diastolic), severe proteinuria [usually at least 3 g (range 2–5 g) of protein in 24 hours or 3+ on dipstick], reduced urinary volume (less than 400–500 ml in 24 hours), neurological disturbances such as headache, visual disturbances, and exaggerated tendon reflexes, upper abdominal pain, pulmonary oedema (fluid in the lungs), impaired liver function tests, high serum creatinine, low platelets, intrauterine growth restriction or reduced liquor volume.[3,4,56] Eclampsia is the occurrence of seizures in a woman with pre-eclampsia.

Severe pre-eclampsia can lead to problems in the liver, kidneys and brain and to abnormalities of the clotting system. Rare but particularly serious complications include eclampsia, stroke, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and disseminated intravascular coagulation (DIC). These serious complications are associated with an increased risk of maternal death.[57] As the placenta is also involved in pre-eclampsia, there are also increased risks for the baby. The most common are poor growth due to inadequate blood supply through the damaged placenta, and problems associated with prematurity, due either to planned early birth to protect the mother or the baby, or to the spontaneous onset of preterm labour.

Although the outcome following pre-eclampsia or eclampsia is good for most women, these conditions remain major causes of maternal mortality. There is also growing evidence that women who have had gestational hypertension or pre-eclampsia may be at increased risk later in life of hypertension, stroke and, to a lesser extent, ischaemic heart disease.[58,59] For the babies, pre-eclampsia is an antecedent for up 12% with growth restriction at birth[60] and for 19% of preterm births.[61] Being born too early, or with growth restriction, is associated with an increased risk of developmental delay and chronic ill health in childhood.

Burden of disease

Over half a million women die each year from pregnancy-related causes, and 99% of these deaths occur in the developing world.[2] However, there remain considerable gaps in burden of disease studies in the geographical coverage of causes of maternal mortality. An estimated 10–25% of maternal deaths in developing countries are associated with pre-eclampsia or eclampsia[62] (*Table 1*), as are 15% of the direct obstetric deaths in the UK[63] and USA.[56] Perinatal mortality is also increased following pre-eclampsia.[63,64]

There is less information about morbidity for either mother or baby, but it is likely that this too is high. For example, pre-eclampsia accounts for an estimated one-fifth of antenatal admissions,[65] two-thirds of referrals to day-care assessment units[66] and one-quarter of obstetric admissions to intensive care units.[67] Psychological morbidity following a difficult pregnancy or labour or perinatal death is well documented,[68] although there is little information specific to pre-eclampsia.

Current service provision

Screening for women at risk of pre-eclampsia is an important part of antenatal care. Routine

TABLE 1 *Proportion of maternal deaths attributed to hypertensive disorders according to geographical regions*

Region	Number of data sets	Number of maternal deaths (denominator)	Proportion of maternal deaths caused by hypertensive disorders (%)
Developed countries	5	2,823	16.1
Africa	8	4,508	9.1
Asia	11	16,089	9.1
Latin America and Caribbean	10	11,777	25.7

screening for pre-eclampsia is based on measurement of blood pressure and urinalysis for proteinuria. Once women have been identified as at high risk, they can be targeted for more intensive antenatal surveillance and prophylactic interventions such as early delivery. Most current strategies for risk assessment are based on the obstetric and medical history and clinical examination. Pregnant women are assessed at their first antenatal clinic (prior to 12 weeks if possible) for risk factors for pre-eclampsia including age, nulliparity, long pregnancy interval, prior history of pre-eclampsia, high body mass index (BMI), history of diabetes mellitus and hypertension. If a woman has any of the risk factors, an increased schedule of blood pressure screening is provided. Otherwise, they have blood pressure measurement and urinalysis for proteinuria at 16, 25, 28, 31, 34, 36, 38 and 40 weeks. No other blood tests to detect pre-eclampsia are recommended and routine Doppler ultrasound scans of the uterine or umbilical artery are not recommended.[69]

Primary prevention is preventing the onset of a disease, for example prevention of any signs or symptoms of pre-eclampsia. Secondary prevention is the reversing, stopping or slowing of its progress, for example prevention of proteinuria in a woman with gestational hypertension. Tertiary prevention is the prevention of complications in established disease, for example, prevention of eclampsia in a woman with pre-eclampsia. This project is mainly concerned with primary prevention.

As the cause of pre-eclampsia is not completely understood, it is difficult to develop rational strategies for prevention. Current strategies for prevention focus on antenatal surveillance, modification of lifestyle, dietary interventions and pharmacological therapy. Certain lifestyle choices may influence risk of hypertension, such as whether to exercise, how much to rest in bed and whether to modify the salt content in the diet. As these would normally be a matter of personal preference, it is important that any recommendation that women modify their life style should be based on adequate evidence.[70]

Antenatal care is a complex package of care. The components of this package vary considerably, depending on a range of factors such as country, setting and the characteristics of the individual woman. Evaluation of antenatal care should include evaluation of individual components, such as how to measure blood pressure or proteinuria, comparisons of packages with different components and frequencies and comparisons of different settings and providers of care. This project focuses on developing cost-effective prevention strategies for the UK NHS.

Various hypotheses have been put forward to link pre-eclampsia with specific dietary deficiencies, either before or during pregnancy. For example, calcium[71] and fish oil supplementation were suggested based on observations of an association between dietary intake and the incidence of pre-eclampsia in various communities. Zinc[72] and magnesium supplements[73] were suggested as interventions that might optimise normal physiological function during pregnancy. Antioxidants such as vitamin C and E, selenium and garlic have been suggested to counteract oxidative stress. Folic acid may correct raised blood levels of homocysteine.

A wide range of drugs have been advocated for primary and secondary prevention of pre-eclampsia. For example, diuretics were popular when oedema was considered to be an important symptom of pre-eclampsia. Antiplatelet agents were suggested based on the hypothesis that they would increase production of the vasodilator prostacyclin and reduce the vasoconstrictor thromboxane, hence reducing the risk of pre-eclampsia.[74] Anticoagulants have also been suggested for women at particularly high risk, such as those with thrombophilias.[75] Antihypertensive drugs are widely used for women with gestational or chronic hypertension in the

hope that early control of blood pressure may prevent progression to pre-eclampsia.[76] Recently, there has been interest in nitric oxide, a vasodilator and inhibitor of platelet aggregation.[77]

There is also considerable interest in this area from women's consumer groups. A small, unpublished survey was conducted between December 2005 and January 2006 by Action on Pre-Eclampsia (APEC) in direct response to the HTA effectiveness review project, which requested consumer feedback on the importance to consumers of each of the effectiveness review topics. APEC runs a helpline that receives between 3500 and 4000 information requests per year, of which approximately 20% are related to prevention of pre-eclampsia. The potential topics for the survey were reviewed by three members of APEC staff who run the APEC Helpline and information lines (via the telephone and website), who rated the importance of the topic to consumers. Staff members were also asked to report the most commonly asked questions. Responses were collated and rated as 2 (common question), 1 (occasionally asked question) and 0 (never asked – consumers unaware). In general, women were reported to be particularly concerned about things that they can do themselves (such as lifestyle and dietary interventions), but there were also questions about their healthcare professionals' actions (pharmacological interventions/antenatal care interventions). The results from the survey are given in *Table 2*.

This project will evaluate whether screening tests can be incorporated along with these interventions into a cost-effective prevention strategy. There are surprisingly few reliable evidence summaries on the individual risk factors for pre-eclampsia[2,78] and how these might interact. Similarly, the evidence concerning accuracy of various physiological, ultrasonographic and biochemical screening tests for predicting pre-eclampsia need to be systematically reviewed.

Objectives of this project

This research project was undertaken to meet the following objectives:

1. To determine, among women in early pregnancy, the accuracy of various tests (history, examination and investigations) for predicting the later development of pre-eclampsia and related complications (see *Table 3* for a list of tests).
2. To determine the effectiveness and safety of preventative interventions for pre-eclampsia and its complications (see *Table 4* for a list of interventions).
3. To determine the cost-effectiveness of testing and subsequent prevention strategies in terms of both human and financial costs.

The relationship of our objectives to the range of work required in this area is shown in *Figure 1*.

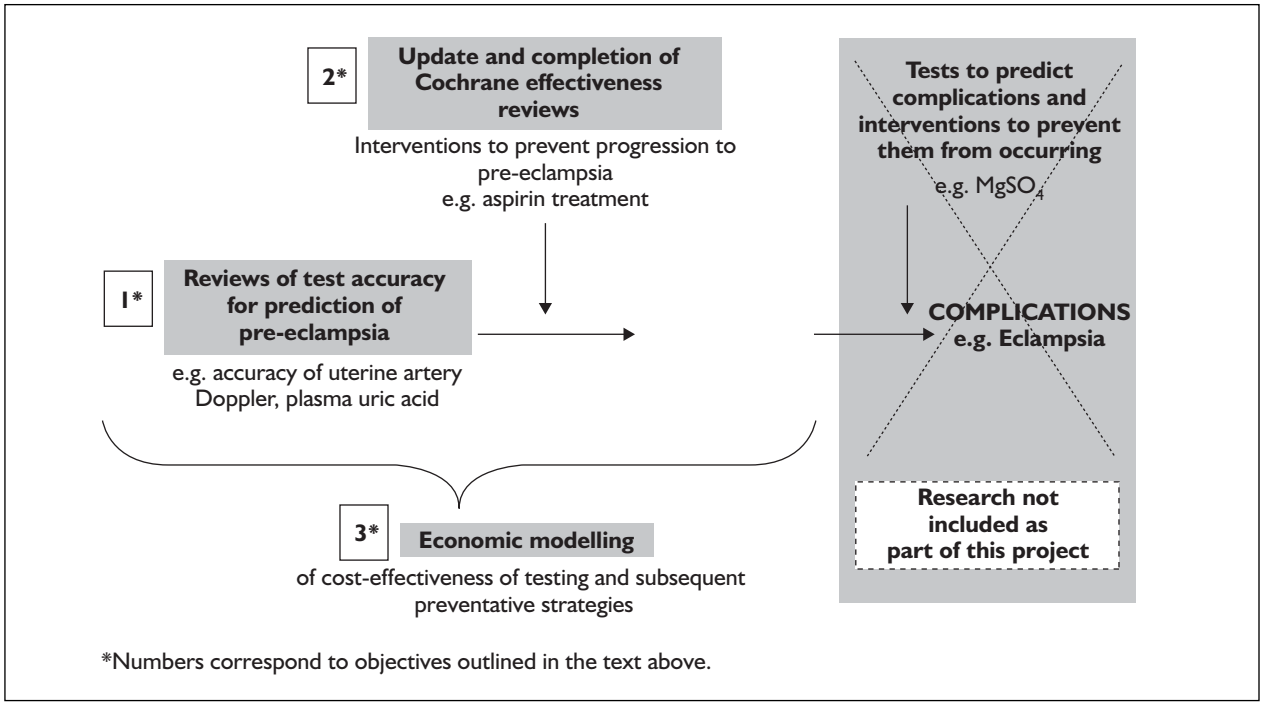

FIGURE 1 *Methods of predicting and preventing pre-eclampsia: an overview of objectives of this project*

TABLE 2 *Consumer priorities*

Review	Grading[a]	Comment
Lifestyle interventions		
Rest for preventing pre-eclampsia in women with normal blood pressure	2	More specifically, what is impact of working/stress in women (a) with increasing blood pressure that has not reached threshold or (b) women who have had pre-eclampsia and feeling guilty. Rest may have been advised by GP
Bed rest with or without hospitalisation for hypertension in pregnancy	2	
Exercise and other physical activity for preventing pre-eclampsia	0	
Aerobic exercise during pregnancy	0	Only asked as a normal antenatal question unrelated to pre-eclampsia
Dietary and nutritional interventions		
Antioxidants (vitamin C and E only)	2	Are they safe? Do they work? Women are self-medicating
Altered protein and energy intake	2	Specifically related to Brewer diet women find via the Internet
Garlic	1	
Magnesium	1	Only in relation to $MgSO_4$ and whether dietary Mg may have helped
Folate	1	
Calcium	1	
Fish oil and other prostaglandin precursors	1	
Chinese herbal medicine (including rhubarb)	0	
Zinc	0	
Altered dietary salt	0	
Pharmacological interventions		
Antiplatelet agents – specifically aspirin	2	Often asked if it is safe/effective after GP or consultant says it makes no difference. Potential for self-prescribing
Oral beta-blockers for mild to moderate hypertension	2	Questions concern long-term treatment and impact for asthmatics rather than severity of hypertension
Antihypertensive drugs for mild to moderate hypertension	1	Questions are more general; not related to severity of hypertension
Antihypertensive drugs for women with normal/borderline hypertension	0	
Diuretics	0	
Nitric oxide donors and precursors	0	
Progesterone	0	
Heparin in women with thrombophilia	0	
Antenatal care interventions		
Am I having the right pattern of antenatal care for my higher risk pregnancy?	2	This is a high priority additional question and is commonly asked by women who have had pre-eclampsia
Self blood pressure monitoring versus conventional blood pressure monitoring	1	Questions about the value of home monitoring for women (particularly who have had pre-eclampsia)
Patterns of antenatal care for low-risk pregnancies	1	Women are generally concerned about long interval between 16 and 28 weeks, not specifically regarding pre-eclampsia
Antenatal day-care units versus hospital admission for women with complicated pregnancies	1	Occasionally asked by a women who has been admitted
Ambulatory versus conventional methods for monitoring blood pressure	0	

[a] Grading: 2, common question; 1, occasional question; 0, never asked – consumers unaware.
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Chapter 2

Systematic review methods

Protocol development

Generic protocols were developed for undertaking the review work, one for systematic reviews of test accuracy studies and the other for the development and maintenance of Cochrane reviews evaluating interventions for prevention of pre-eclampsia.[79] These protocols outlined a common set of methods for the selection and assessment of studies and included a standard list of outcomes to be assessed. More details about the effectiveness reviews protocol can be found in Appendix 1.

The research question

The following structured question was addressed:

- Population: Normotensive women in early pregnancy at risk of developing hypertensive disorders of pregnancy.
- Index tests: See *Table 3*.
- Reference standard: Pre-eclampsia confirmed by presence of hypertension and proteinuria (and oedema as reported in older primary studies before definitions were revised).
- Interventions: See *Table 4*.
- Outcomes: Pre-eclampsia, perinatal deaths, small-for-gestational age babies, preterm birth, need for hospitalisation, neonatal intensive care and related healthcare costs.

Methods for test accuracy reviews

Search strategy

Literature was identified from several sources, including

- general health and biomedical databases: PubMED (MEDLINE), EMBASE (Ovid)
- specialist electronic databases: The Cochrane Library (DARE, CCTR), MEDION
- contact with experts including the Cochrane Pregnancy and Childbirth Group
- checking of reference lists of review articles and papers that were eligible for the systematic reviews included in this report.

The aim was to find all studies on all tests that predict or are believed to predict pre-eclampsia, using a single comprehensive search strategy. Therefore, search terms related to pre-eclampsia were combined with methodological filters for identification of aetiological and diagnostic test studies (see Appendix 2 for details). MEDLINE (PubMED) and EMBASE were searched from inception to February 2004. Other databases were searched from inception to December 2003. Experienced clinical librarians performed the searches and their updates (last update 30 May 2005). No language restrictions were applied. A comprehensive master database of articles relevant to any predictive test was constructed using Reference Manager 10.0 software.

Inclusion criteria

The criteria for study inclusion in the systematic reviews on predictive accuracy were as follows:

- **Population**: Any pregnant women in primary, secondary or tertiary care, at any level of risk of developing pre-eclampsia. Studies were included that tested women at risk of developing pre-eclampsia before 25 weeks of gestation. When gestational age at the time of the index test varied, the mean gestational age, as calculable from the descriptive statistics, had to be less than 25 weeks. If gestational age was unclear the study was excluded.
- **Setting**: Any setting including general practice, midwifery, outpatient clinics or based on national or regional registers.
- **Predictive tests (index tests)**: See *Table 3*. Tests used for the prediction of pre-eclampsia were prioritised on the basis of clinical relevance and after consultation with persons knowledgeable of NHS needs (we consulted with the Chair of the NHS Antenatal Sourcing Subgroup: Professor M Whittle; personal communication, November 2004. Foetal DNA was added to our original list based on the advice received.) We excluded studies that tested all women then

TABLE 3 *Tests for predicting pre-eclampsia in early pregnancy reviewed in this project*

Category	
History	None but data for tests subgrouped according to historical risk factors wherever possible
Examination	BMI
Investigations	
Blood	α-Foetoprotein (AFP) Serum fibronectin (total and cellular) Foetal DNA (fDNA) Haemoglobin/haematocrit Human chorionic gonadotrophin (HCG) Oestriol Serum uric acid
Urine	Urinary calcium excretion, urinary calcium to creatinine ratio Urinary proteinuria (24-hour or spot tests for total proteinuria, albuminuria, microalbuminuria, albumin to creatinine ratio, kallikrein, SDS-PAGE proteins)
Haemodynamic	Uterine artery Doppler (any/unilateral notching, bilateral notching, combinations of waveforms, pulsatility index, resistance index, other ratios)

SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis.

TABLE 4 *Cochrane effectiveness reviews updated in this project*

Category	
Antenatal care interventions	Ambulatory versus conventional methods for monitoring blood pressure
Lifestyle interventions	Bed rest with or without hospitalisation for hypertension Exercise for prevention of hypertension Rest in women with normal blood pressure
Dietary and nutritional interventions	Altered dietary salt intake Antioxidants Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems Nutritional advice Balanced protein/energy intake Isocaloric balanced protein supplementation Energy/protein restriction Garlic Magnesium Marine oil and other prostaglandin precursor supplementation during pregnancy for reducing pre-eclampsia
Pharmacological interventions	Antihypertensive drug therapy for mild to moderate hypertension Antiplatelet agents for preventing pre-eclampsia and its complications Diuretics for preventing pre-eclampsia Nitric oxide and precursors Progesterone

selected only some for follow-up on the basis of a specific range of index test results.

- **Reference standard**: Pre-eclampsia, using a variety of definitions. Pre-eclampsia was defined as hypertension (≥140/90 mmHg) with proteinuria (total protein of ≥300 mg in a 24-hour urine collection, or ≥30 mg/dl in a single sample of urine, or ≥1+ on a dipstick) developing for the first time after 20 weeks' gestation, with or without generalised oedema. For women with chronic hypertension, pre-eclampsia was defined as a sudden worsening of hypertension and/or proteinuria, or other signs and symptoms of pre-eclampsia after 20 weeks' gestation. When authors did not provide details of how pre-eclampsia was verified, pre-eclampsia rates as reported were accepted. At the stage of data extraction, the extent that pre-eclampsia definition complied with recent consensus was assessed.[3,4,80] All studies that compared a test or strategy with a reference standard according to international standards or variations of the

definition in pregnant women were included.[3,4] The prediction of clinical consequences of pre-eclampsia was not part of this work.

- **Study design**: Diverse study designs were included such as prospective cohorts, historic cohorts and (nested) case–control studies, all of which could be matched or unmatched on different variables. Studies had to report results so that a 2×2 table cross-classifying abnormal and normal test results and the occurrence or non-occurrence of pre-eclampsia could be calculated. Excluded were all cross-sectional studies in which the distribution of a non-stable indicator (often a blood constituent) among women with pre-eclampsia was compared with that of non-pre-eclamptic women. With any study design, the description of the distributions of test results among pre-eclamptic and non-pre-eclamptic women for clearly non-(log)-normal test results could not be transformed into proper 2×2 tables and were therefore excluded.
- **Subgroups**: Severe pre-eclampsia was defined as hypertension (systolic blood pressure $\geq$160 mmHg and/or diastolic blood pressure $\geq$110 mmHg) with proteinuria (total protein $\geq$2.0 g in a 24-hour urine collection or $\geq$3+ on a dipstick), with or without oedema. Also a distinction was made between early-onset (<34 weeks' gestation) and late-onset ($\geq$34 weeks' gestation) pre-eclampsia, but too few studies provided this information.

Study selection

The study selection process consisted of three steps. First, titles and/or abstracts of all citations in the master database (that is, irrespective of test type) were assessed by one reviewer. If a citation was considered potentially relevant, the full-text paper was retrieved for further consideration. Reviewers were instructed to include the paper if there was any doubt, thus enhancing the sensitivity of the initial selection step. Second, for each particular review, a search based on keywords in titles and abstracts in the master database was performed to find all studies on the test at issue. One reviewer again scrutinised titles and/or abstracts of studies on the particular test to ensure (almost) independent duplicate selection. Only papers that were judged as irrelevant twice were not ordered as full-text papers and all other papers were retrieved. Third, inclusion was performed independently by two reviewers who assessed against the selection criteria detailed above. Disagreements were resolved by consensus or by arbitration by a third reviewer when consensus could not be reached.

The reviewing team were fluent in English, French and German so could select papers, extract data and assess quality of papers in these languages. When necessary, papers in other languages, including Bulgarian, Chinese, Italian, Japanese, Russian and Spanish, were translated.

Data extraction

Clinical, methodological and statistical data extraction was conducted independently in duplicate, using a predesigned and piloted form that changed only slightly between different index tests. Data extraction was carried out using the Statistical Package for the Social Sciences (SPSS) database and/or paper forms. See Appendix 3 for a list of data items extracted.

Disagreements between reviewers were resolved by consensus or by arbitration by a third reviewer, if disagreement persisted. In case of serial index test measurements during pregnancy, a 2×2 data table was constructed for each serial measurement. Where multiple publications of the same study were identified, each publication was examined to ensure that all relevant information for that particular study was recorded. However, only the most complete report was used for extracting results.

Pairs of data extraction forms or SPSS files were checked for discrepancies. After disagreements were resolved information was entered into a dedicated SPSS database. Relevant variables were checked using descriptive statistics to detect implausible values or outliers. Extreme or outlying values were checked against the original data extraction forms and against the original publications if necessary to further exclude the possibility of data-entry errors.

Quality assessment

Quality items were included in the data extraction form (see Appendix 3). The following aspects of methodological quality of included test accuracy studies were assessed:[81,82]

- study design
- consecutive recruitment/random sample
- blinding of test results (both index and reference tests)
- greater than 90% verification of diagnosis
- incidence of pre-eclampsia less than 4%
- prospective data collection
- adequate index test description
- adequate reference standard.

Note that items on study design and incidence are not strictly related to internal validity, but help the

reader to put the findings in context. Study design was extracted and reported in tables. Study quality was assessed independently by two reviewers. Any disagreements were resolved by consensus or by arbitration by a third reviewer, if disagreement persisted.

The following items were included in quality diagrams in study summaries and assessed using the three criteria listed under each item:

- **Consecutive recruitment**
  Yes – adequate patient recruitment was present when there was a consecutive series of patients or the study used random sampling.
  Unclearly reported – selection criteria and patient recruitment were not clearly reported so that one could not tell what selection criteria were used.
  No – recruitment was considered inadequate where it was specifically described and was not consecutive or random.
- **Blinding of the test results (index test or reference test)**
  Yes – adequate blinding was present when it was explicitly stated that the results of each test were interpreted unaware of the results of the other test or when it might be inferred that they were interpreted before the other test results were available as applies to the index test result in prospective cohort studies.
  Unclearly reported – no description of whether either test was interpreted under blind conditions.
  No – inadequate blinding was present if it was clear from the text that neither test result was interpreted under blind conditions.
- **Verification of diagnosis**
  Yes – adequate verification of diagnosis was present where at least 90% of the women originally subjected to the index test and fulfilling the inclusion criteria were followed up and had verification by the reference standard.
  Unclearly reported – where the numbers of women excluded or lost to follow up were not calculable.
  No – inadequate where the follow-up level was below 90%.
- **Incidence of pre-eclampsia <4%**
  We dichotomised the item 'incidence of pre-eclampsia' using an incidence cut-off value of 4% in cohort studies (and based on the underlying cohort in nested case–control analyses where possible). This was done because in cohort studies with more than 10,000 women, which reflect more or less unselected populations, the incidence of pre-eclampsia varied between 1.3 and 3.2%.[83–85]
  Yes – unselected (low risk) patient spectrum where incidence of pre-eclampsia <4%.
  Unclearly reported – we could not determine the incidence of pre-eclampsia in the study.
  No – selected patient spectrum where incidence of pre-eclampsia was ⩾4%.
  The intention was to do subgroup analysis for high- and low-risk populations.
- **Prospective data collection**
  Yes – this was adequate when it was clear that the research protocol for the study had been written before data collection took place (prospective).
  Unclearly reported – we could not tell whether the data collection was conducted prospectively or retrospectively.
  No – this was inadequate when there was retrospective data collection or there was a mixture of prospective and retrospective data collection.
- **Adequate description of index test**
  Yes – adequate description of index test if the gestational age at the time of testing, type of test (e.g. assay/manufacturer) and cut-off level were all reported. For the Doppler review the criteria were type of Doppler, type of machine and probe used, level of high-pass filter, angle of insonation, size of sampling gate, number of consecutive waveforms measured, one or both uterine arteries, description of site of measurement, measurement parameter and cut-off level used, route (transvaginal or transabdominal).
  Unclearly reported – unclear description was the description of one or more items in addition to gestational age and cut-off level but not an adequate description.
  No – inadequate, gestational age and cut-off level reported only.
- **Adequate reference standard**
  Yes – adequate reference standard if strictly in accordance with current internationally accepted standards of definition of pre-eclampsia.
  Unclearly reported – unclear, if hypertension and/or proteinuria were not clearly defined in terms of cut-off level such as >140/90 mmHg or proteinuria >0.3 g in 24 hours.
  No – inadequate, when the definition of pre-eclampsia included other items such as a rise in systolic or diastolic blood pressure or hyperuricaemia or oedema, or when criteria were more loose or stringent.
  Adequacy of the reference standard for studies that reported on severe pre-eclampsia as an outcome was based on the definition of severe pre-eclampsia.

Methods of statistical analysis

Summary measures for predictive accuracy

The main focus of each review was a summary estimate of predictive accuracy as expressed by its sensitivity and specificity and their 95% CIs, for the studies that gave 2×2 tables. A secondary aim was to identify (clinically relevant) sources of heterogeneity, if any. If the calculation of a summary estimate was deemed not meaningful, individual study results were depicted using forest plots and receiver–operator characteristic (ROC) plots only.

Data exploration and statistical analysis

In each review, we used forest plots and ROC plots to display the precision by which sensitivity and specificity had been measured in each study and to illustrate the variation in estimates between studies. The 95% CIs were calculated using the exact binomial method, according to Wilson.[86] Extreme values, outliers and threshold phenomena (data points on a typical convex ROC curve) were explored. If appropriate, we used a bivariate meta-regression model to meta-analyse estimates of sensitivity and specificity.[87,88] Therefore, at least two studies with comparable data on test results had to be included. Rather than using a single outcome measure per study, such as the diagnostic odds ratio in the summary receiver–operator characteristic (sROC) approach, the bivariate model preserves the two-dimensional nature of diagnostic data by directly analysing the logit transformed sensitivity, log[sensitivity/(1 – sensitivity] and specificity, log[specificity/(1 – specificity)], of each study in a single model. This model estimates and incorporates the correlation that might exist between logit sensitivity and specificity within studies due to possible differences in threshold between studies. The bivariate model uses a random effects approach for both sensitivity and specificity, allowing for heterogeneity beyond chance due to clinical or methodological differences between studies. In addition, the model acknowledges the difference in precision by which sensitivity and specificity have been measured in each study. This means that studies with a larger number of patients with the target condition receive more weight in the calculation of the summary estimate of sensitivity, whereas studies with more patients without the target condition are more influential in the pooling of specificity. The model requires logit transformation of the sensitivity and specificity. A standard correction of adding 0.5 to all four cells of the 2×2 table was applied when either sensitivity or specificity was 100%. The model produces the following results: a random effect estimate of the mean sensitivity and specificity with corresponding 95% CIs, the amount of between-study variation for sensitivity and specificity separately and the strength and shape of the correlation between sensitivity and specificity. The results have been transformed back (anti-logit) to the original scale and used to calculate sROC curves with their 95% CIs. Where possible, covariates were added to the model to test explicitly whether either sensitivity, specificity or both are different in clinically cogent subgroups of studies. When possible the analysis aimed to estimate valid measures of predictive accuracy taking into account confounding by any methodological flaws. In the first instance, attempts were always made to quantify the extent to which the accuracy measures varied by clinical subgroups, such as early versus later determination. STATA SE 9.0 (StataCorp, College Station, TX, USA) was used for calculations except to fit the various bivariate models, for which the Proc Mixed procedure in SAS version 9.1 for Windows (SAS Institute, Cary, NC, USA) was used.

Data description

For each test, information on individual studies was summarised using:

- **A table with methodological and reporting characteristics of the included studies**. The number of women analysed was based on the total number of women tested before the 25th week of gestation in each study. The incidence of pre-eclampsia was based on the number of analysed cases divided by the total number of women at baseline (cohort studies and nested case–control studies). Results (such as age) are given as mean [± standard deviation (SD)] for the whole group unless stated otherwise.
- **A table with individual quality and reporting items of the included studies**. Symbols used in the table were classified as follows: +, study complies with item; –, study does not comply with item; ?, item unclearly or not reported.
- **A summary of quality and reporting items of the included studies**. Data were presented as 100% stacked bars, where figures in the stacks represent the number of studies. The item 'study design' is stated in the table with quality and reporting characteristics.
- **Forest plots of sensitivities (%) and specificities (%) and 95% CIs**. Studies are ranked according to decreasing specificity (within subgroups). Numbers of women analysed are tp/(tp + fn) for sensitivity and tn/(fp + tn) for specificity (fp, fn = false positive, false negative numbers; tp, tn = true positive, true negative numbers).

- **An ROC plot**. Estimates of predictive accuracy from individual studies are shown (separate for subgroups if appropriate) and where possible an sROC curve (according to the bivariate method) was drawn. In the sROC plots the vertical axis shows sensitivity, and the horizontal axis shows 1 – specificity.
- **A table with subgroup analyses** (if applicable). Significance level $p < 0.10$.

Methods for Cochrane reviews

Search strategy

The Cochrane Pregnancy and Childbirth Group's trials register was searched. This register is maintained by the Trials Search Coordinator and contains trials identified from:

- quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
- monthly searches of MEDLINE
- handsearches of 30 journals and proceedings of major conferences
- weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings and the list of journals reviewed via the current awareness service can be found under the heading 'Specialized register' within the information about the Cochrane Pregnancy and Childbirth Group at *The Cochrane Library* (http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/PREG/frame.html). Trials identified through the searching activities described above were given a code (or codes) depending on the topic. The codes were linked to review topics. The Trials Search Coordinator searches the register for each review using these codes rather than keywords.

In addition, CENTRAL (The Cochrane Library) and EMBASE (2002 to current) were searched using a generic search strategy to identify trials related to pre-eclampsia (see Appendix 4) in order to find trials that were not already listed in the trial register. For individual reviews this search could be expanded by including additional terms specific to the intervention being assessed. The journal *Hypertension in Pregnancy* was also handsearched for the years 2000–5. Reference lists of trial reports were checked for additional citations. Trial reports were also obtained through personal communication with trialists or experts in the area. There were no language restrictions for any aspect of the search.

Inclusion criteria

1. **Population**: Pregnant women, regardless of gestation at trial entry. The only participant exclusions were where women had given birth prior to trial entry or if they had established pre-eclampsia. In the Cochrane reviews, women were grouped according to normal blood pressure or hypertension (see Appendix 5 for details) but these subgroups have not been reported here.
2. **Intervention**: Any intervention or combination of interventions to prevent the occurrence of pre-eclampsia (see *Table 4*). Where appropriate for specific reviews, maximum and/or minimum intervention dosages were justified and specified. Based on current understanding of the aetiology of pre-eclampsia, it is implausible that very short-term interventions could have clinically important effects on pre-eclampsia. Therefore, the minimum duration of the intervention planned at trial entry was 7 days. If single-dose studies or those with a planned intervention of less than 7 days were included, this was justified and discussed in the individual review.
3. **Comparator**: Placebo or no intervention. Where one intervention was compared with another intervention in the Cochrane reviews, these results were not used in this report.
4. **Outcomes**: For the purposes of this report, the following outcomes were included:
   (a) For the woman – pre-eclampsia: defined where possible as hypertension (blood pressure ⩾140 mmHg systolic or ⩾90 mmHg diastolic) with proteinuria (⩾300 mg protein in a 24-hour urine collection or ⩾30 mg/dl in a single sample or ⩾1+ on dipstick). The definition does not include oedema. For a woman with chronic hypertension and proteinuria at trial entry, pre-eclampsia is defined as sudden worsening of proteinuria and/or hypertension, or other signs and symptoms of pre-eclampsia after 20 weeks' gestation.
   (b) For the baby – death: including all deaths before birth and up to 1 year after birth, or the closest outcome to this reported in the systematic review. Preterm birth: defined as birth before 37 completed weeks' gestation. Small for gestational age: defined as growth below the third centile, or lowest centile reported.
   A range of other outcomes were reported in the Cochrane reviews but have not been reported here. Details of these are available in Appendix 5.
5. **Study design**: Randomised controlled trials (RCTs) evaluating any interventions for prevention of pre-eclampsia and its

complications. Studies with a quasi-random design, such as allocation by alternation, day of week or hospital numbers, were included in some reviews. If a systematic review did include such studies, the subgroup results excluding studies with a quasi-random design were also used in a subgroup analysis.
Studies were excluded if:
(a) more than 20% loss to follow-up or withdrawal of participants
(b) more than 20% of analysis not in the groups to which the participants were randomised
(c) large difference (more than 10%) in loss of participants between groups.

6. **Subgroups**. A large number of subgroups were investigated in the Cochrane reviews and were included in the generic protocol but have not been reported here because they were not used to inform the economic model. Details of the subgroups can be found in Appendix 5.

Study selection

Each citation was assessed for inclusion in a review by at least two reviewers independently. Any differences in opinion were resolved by discussion. If agreement could not be reached, the full text copy was obtained and if necessary translated into English. If agreement still could not be reached based on the full text copy, further information was sought from the study authors. If the study authors could not be contacted, a third party was consulted.

Data extraction

Data on study characteristics, methodological quality and results were extracted on to data extraction sheets by at least two reviewers and discrepancies were resolved through discussion. If agreement was not reached, that item was excluded until further clarification was available from the authors. Where data for one or more main outcome were missing, authors were contacted whenever possible to obtain more information. The information was entered on to Review Manager software (RevMan 2003) and checked for accuracy by at least one other reviewer.

Quality assessment

The quality of each included trial was assessed independently by at least two reviewers using the criteria outlined in the Cochrane Handbook.[89] Each study was assessed for method of random allocation, quality of the concealment of allocation, completeness of follow up and blinding in the assessment of outcome.

1. ***Allocation concealment***
A quality category for concealment of allocation was assigned to each trial, using the following criteria:
(a) adequate concealment of allocation, such as telephone randomisation, consecutively numbered sealed opaque envelopes.
(b) unclear whether adequate concealment of allocation
(c) inadequate concealment of allocation such as random number tables, sealed envelopes that are not numbered or opaque.
Where the method of allocation concealment is unclear, whenever possible attempts were made to contact authors to provide further details.
2. ***Completeness of follow-up***
Completeness of follow-up was assessed using the following criteria:
(a) less than 5% loss to follow-up or withdrawal of participants
(b) 5% to 10% loss to follow-up or withdrawal of participants
(c) more than 10% and up to and including 20% loss to follow-up or withdrawal of participants. For most of the individual reviews, where information was missing, clarification was sought from the authors. For the purposes of this report, where reviews did not include information about follow-up (antiplatelets, energy and protein intake), this has been recorded in the absent/unclear/unreported category and individual trialists were not contacted.
3. ***Blinding***
Blinding was assessed using the following criteria:
(a) Blinding of patients (yes/no/unclear)
(b) Blinding of caregiver (yes/no/unclear)
(c) Blinding of outcome assessment (yes/no/unclear).

For this report, the quality of the studies for each systematic review was summarised in tables which were then used to create the quality diagram for each clinical effectiveness summary. Four categories were used: randomisation method (stated versus not stated or unclear), allocation concealment (present versus not present or unclear), blinding (any blinding versus none) and more than 80% follow-up (present versus not present or unclear). These were assessed using the characteristics of included studies published in each effectiveness review. If the characteristic of the trial in the characteristics table was marked as unclearly reported, that item was marked as unclear in the quality table. Individual trials were not examined. Data extraction from the Cochrane review tables of characteristics was carried out by two reviewers and discrepancies resolved by discussion.

Methods of statistical analysis

Statistical analyses were carried out using Revman (Revman 2003). Information was analysed based on the group to which the participants were randomised, regardless of whether they received the allocated intervention or not. For dichotomous data, results are presented as summary relative risk (RR) with 95% CI.

The I^2 statistic was used to assess heterogeneity between trials. In the absence of significant heterogeneity, results are pooled using a fixed effect model. If substantial heterogeneity was detected ($I^2 > 50\%$), possible causes were explored and subgroup analyses for the main outcomes performed. Heterogeneity that was not explained by subgroup analyses was modelled using random effects analysis, where appropriate

Methods of reporting

The full Cochrane review has been reported here rather than the trials that reported the pre-eclampsia outcome only. This is because we also report here baby outcomes of death, preterm birth and small for gestational age. Where the results have RR 0.9–1.1 and the 95% CIs cross 1, we describe the results as having no clear effect on pre-eclampsia. If the RR is more extreme than this but the 95% CIs cross 1, we describe the point estimate of effect but explain that these findings could have been accounted for by chance alone. Where the 95% CIs do not cross 1, we describe the results as unlikely to be accounted for by chance alone.

Modifications to the protocol and original grant proposal

Following approval of this HTA project, two key systematic reviews appeared in the literature that impacted on our plans.[78,90] Moreover, as we learned more about the subject after commencing the reviews, the knowledge gained was used to update our protocols. We sought input from the HTA programme at a monitoring visit (June 2005) concerning protocol modification. In all instances of modification to the original proposal/protocol, our decisions were driven by new knowledge about methods and definitions. We did not have knowledge of results among included studies until after changes were implemented into the protocols. The comparison between proposed diagnostic and screening tests and treatments for pre-eclampsia to be systematically reviewed in the protocol and original grant proposal and the final systematic reviews completed can be seen in Appendix 6.

Methods for economic evaluation

See the section 'Methods for economic evaluation' (p. 85) for a description of the methods used for the economic evaluation. This is because the methods include a description of inputs to the economic model that relies on information provided in Chapters 3 and 4.

Project reporting

The results of the three main parts of this review (test accuracy systematic reviews, effectiveness systematic reviews and economic modelling) are reported separately with a discussion section for each. Additional information (results and discussion) for effectiveness reviews is available in the Cochrane Library. The final section of the report considers all of the findings to draw conclusions overall. Recommendations for practice and research appear individually in each section and in the concluding chapter.

Chapter 3

Test accuracy reviews

Study selection

At the final update of 30 May 2005 there were 16,813 potentially relevant citations identified. These citations were screened for relevance to each of the 11 systematic review categories and retrieved if relevant. The numbers of included and excluded studies for each of the systematic reviews are shown in *Table 5*.

TABLE 5 *Process from initial search to final inclusion for accuracy reviews*

		Papers retrieved for detailed evaluation[a]			Reasons for exclusion						
Index test	**Total no. of citations**	**No. from electronic searches**	**No. from reference lists**	**Total no. of full text papers excluded**	**Not prediction and/or not test accuracy**	**Reviews/letters/editorials/comments**	**PE not separated/PIH only**	**(Mean) gestational age at time of index testing >25 weeks or unclear**	**Insufficient data to construct proper 2 × 2 table 2[b]**	**Other[c]**	**Total no. of papers included**
Body mass index[d]	NA	NA	13	2	1				1		11
α-Foetoprotein	117[f]	79	8	75	44	6	7	1	15	2	12
Fibronectin	136[f]	66	–	62	1	12	4	27	17	1	4
Cellular[e]											*2*
Total[e]											*3*
fDNA	52	33	–	30	15	6	–	5	3	1	3
Haemoglobin/haematocrit	1057	79	1	78	50	10	10	3	5	–	2
Human chorionic gonadotrophin	572[f]	149	3	136	85	17	9	1	21	3	16
Oestriol	431[f]	77	1	75	57	5	5	2	3	2	3
Uric acid	664[f]	186	6	187	139	40			5	3	5
Calcium/creatinine	1025[f]	195	5	192	146	22	6	12	4	2	8
Urinary calcium excretion[e]											*4*
Urinary calcium creatinine ratio[e]											*6*
Proteinuria/albuminuria	1718[f]	117	–	100	63	7	3	12	4	11	17
Doppler uterine artery	1072	229	3	166	69	23	26	22	16	13	63
Any/unilateral notching[e]											*19*
Bilateral notching[e]											*22*
Combinations of FVW[e]											*25*
Pulsatility index[e]											*8*
Resistance index[e]											*25*
Other ratios[e]											*7*

FVW, flow velocity waveform; NA, not applicable; PIH, pregnancy-induced hypertension.
[a] Based on topic specific search in Reference Manager.
[b] Including 2 × 2 tables with artificial test positive/test negative ratio.
[c] Other reasons for exclusion include duplicate publication, unobtainable, no translation available, no cut-off used.
[d] Review based on O'Brien and colleagues, *Epidemiology* 2003;**14**:368–74, where large cohort studies were available for precise estimation of accuracy.
[e] Italicised index tests are reviews performed after search immediately above mentioned.
[f] Search until October 2004.

Examinations

Body mass index

Pre-existing physical characteristics of pregnant women, such as BMI before pregnancy, have been proposed as potential risk factors for pre-eclampsia. BMI is calculated as weight (kg) per height squared (m^2) and is categorised as underweight (BMI < 20), normal weight (BMI 20–25), overweight (BMI > 25) and obese (BMI > 30). In particular, maternal obesity is associated with an increased risk of adverse pregnancy outcomes.

The review of diagnostic accuracy of BMI included 11 studies (452,615 women) (see Appendix 7). The quality of the studies is shown in *Figure 2* and Appendix 8. Sensitivities and specificities are shown in *Figure 3* and ROC space in *Figure 4*. Pooled estimates of sensitivity and specificity used in decision modelling were as follows:

- BMI ⩾ 34: 18% (95% CI 15 to 21%) and 93% (95% CI 87 to 97%)
- BMI > 29: 23% (95% CI 15 to 33%) and 88% (95% CI 80 to 93%)
- BMI > 24.2: 41% (95% CI 29 to 53%) and 75% (95% CI 62 to 84%)
- BMI < 19.8: 11% (95% CI 8 to 16%) and 80% (95% CI 73 to 86%).

Investigations – blood

Maternal serum α-foetoprotein

Determination of maternal serum α-foetoprotein (AFP) is used worldwide for screening of foetal aneuploidy and anomalies as part of the triple test and marker for neural tube defects. Free availability of this information has encouraged researchers to assess its predictive value for pre-eclampsia. AFP is a glycoprotein produced by the yolk sack and foetal gastrointestinal tract. Maternal serum AFP levels rise until 32 weeks of gestation, whereas foetal AFP peaks at 10–13 weeks and then declines progressively until term. Elevated AFP levels are associated with open spina bifida and anencephaly, whereas in Down's syndrome pregnancies AFP levels stabilise at 15–20 weeks of gestation.

The review of diagnostic accuracy of AFP included 12 studies (137,097 women) (see Appendix 7). The quality of the studies is shown in *Figure 5* and Appendix 8. The sensitivities and specificities are plotted in *Figure 6* and ROC space in *Figure 7*. Studies are classified by (1) counting all cases versus severe cases of pre-eclampsia only (Raty and colleagues, Stamilio and colleagues; for references referred to only within individual systematic reviews, see Appendix 12), (2) cut-off value 2.5 multiples of median (MoM) (top four

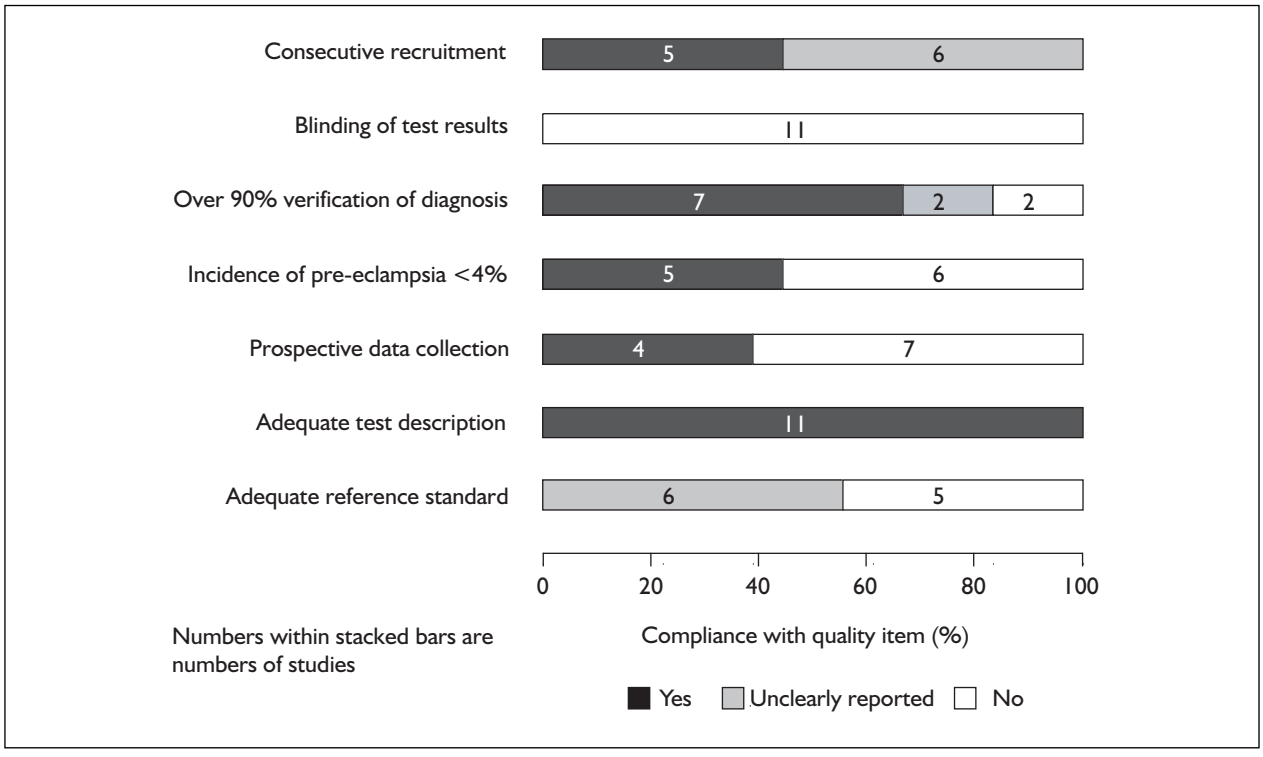


FIGURE 2 *Quality and reporting assessment of studies on BMI*

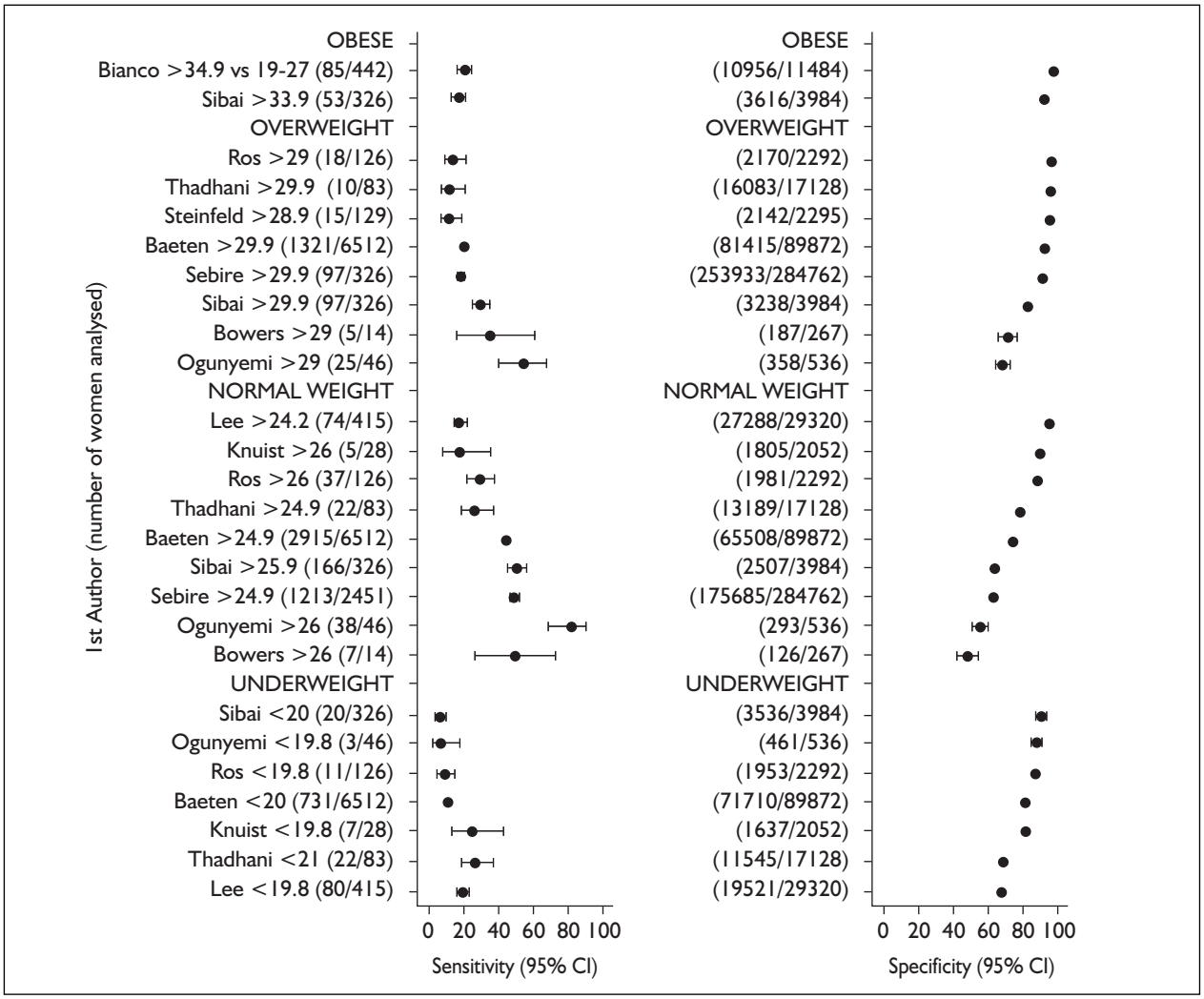


FIGURE 3 *BMI (prepregnancy) sensitivities, specificities and 95% CIs. Studies are categorised in subgroups by cut-off values, which are stated to the right of first author's name. For references referred to only within individual systematic reviews, see Appendix 12.*

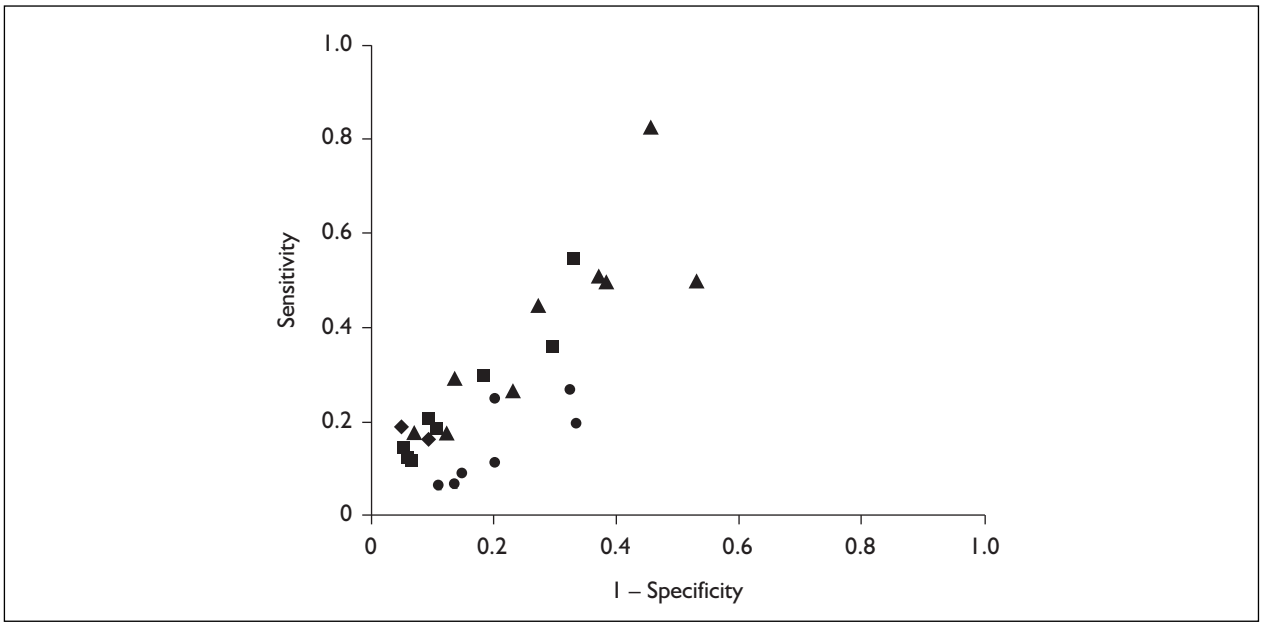


FIGURE 4 *BMI plotted in ROC space. Diamonds represent obesity, squares overweight, triangles normal weight and circles underweight.*

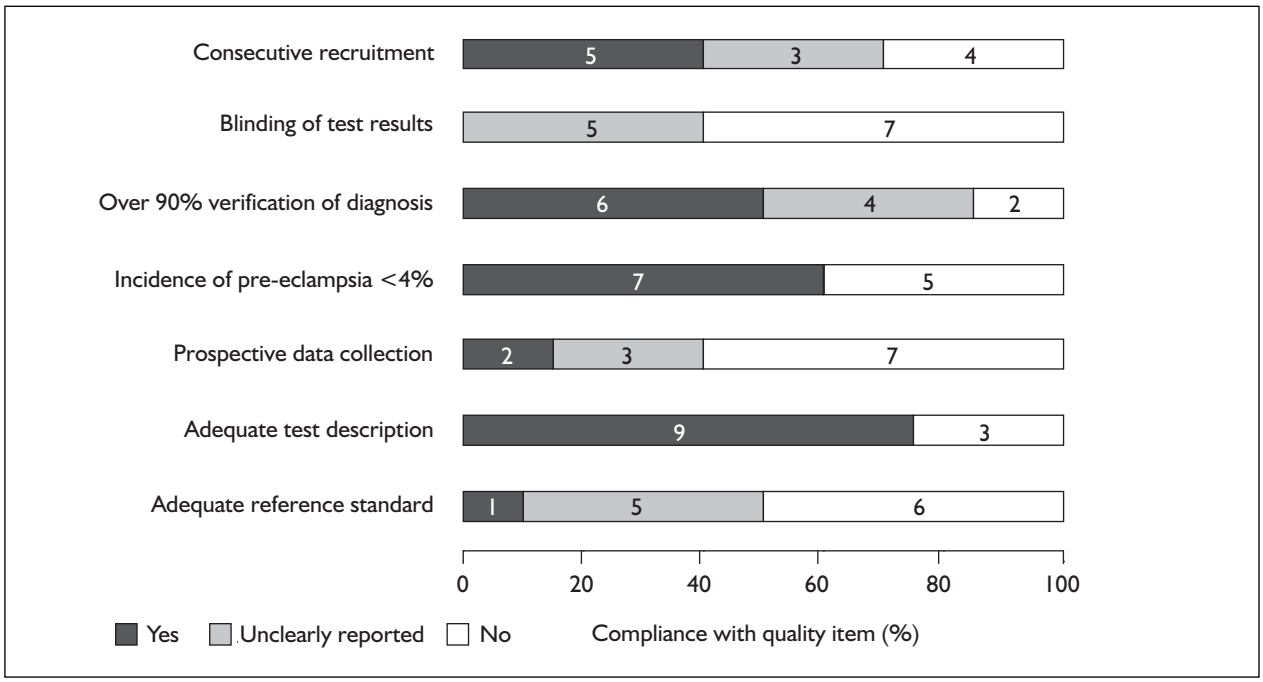


FIGURE 5 *Quality and reporting assessment of studies on AFP.*

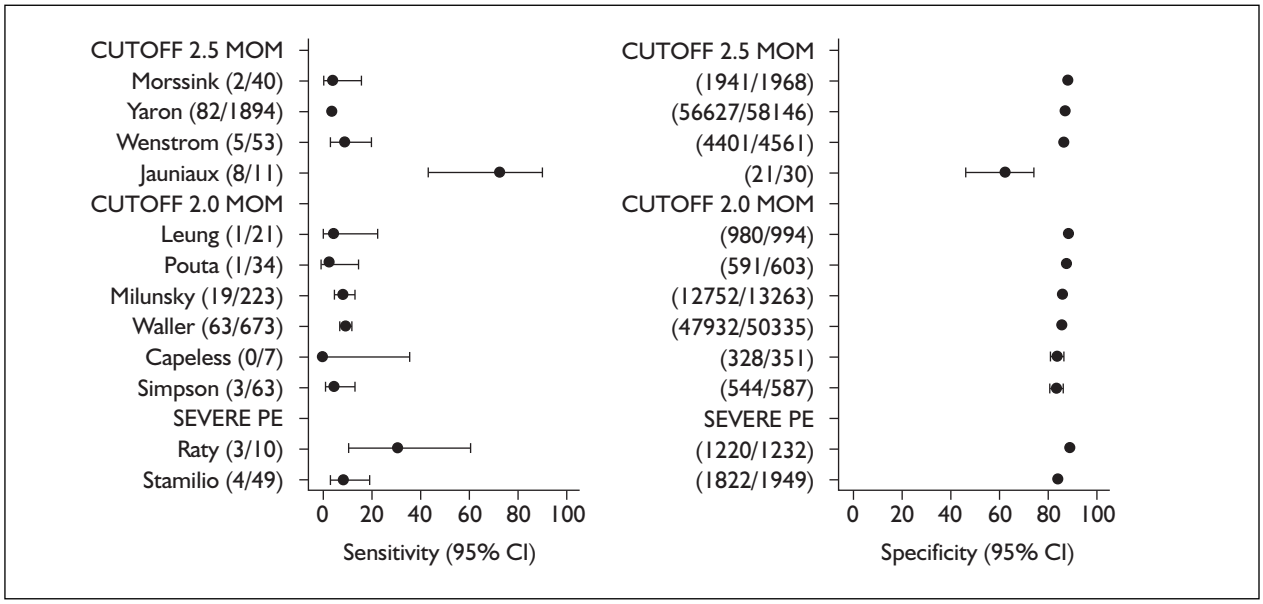


FIGURE 6 *AFP sensitivities, specificities and 95% CIs*

studies) versus 2.0 MoM (other studies). None of the subgroup analyses for AFP were statistically significant (see *Table 6*). We used pooled estimates of sensitivity and specificity of 9% (95% CI 5 to 16%) and 96% (95% CI 94 to 98%), respectively, in economic modelling.

Cellular and total fibronectin

Women destined to develop pre-eclampsia are reported to have higher plasma fibronectin (FN) concentrations than (pregnant) controls. FN is a glycoprotein of which several subtypes exist. Inflammation, vascular injury and malignancy are generally associated with increased expression of the extra domain A (ED-A) (also called ED-1+ or oncofoetal FN) and ED-B (also called ED-2+) forms of FN, particularly in the blood vessel walls. ED-A (oncofoetal) FN is also released by the placenta and has been used as a predictor for preterm birth. ED-A and ED-B are both called

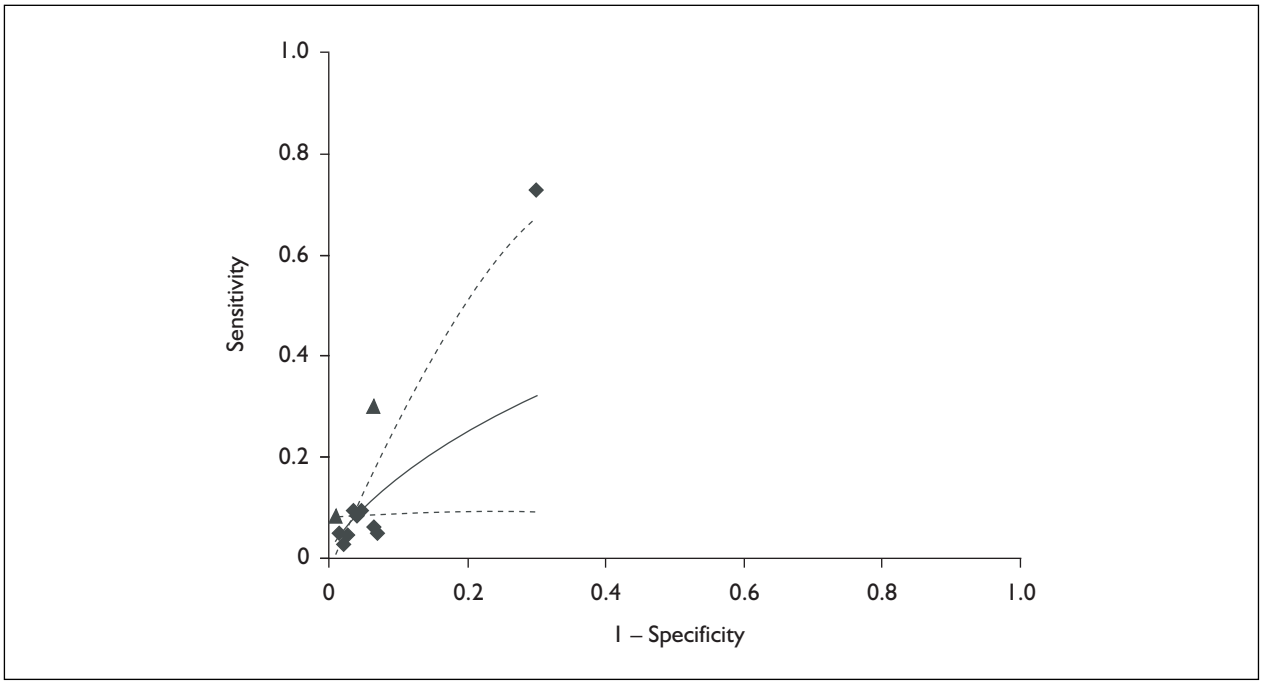


FIGURE 7 *AFP plotted in ROC space. The ROC space has triangles representing studies with severe pre-eclampsia as outcome, solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

TABLE 6 *Subgroup analysis (significance level p < 0.10) for maternal serum AFP testing based on 12 studies*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no. of studies)	9 (5 to 16)		96 (94 to 98)	
Severity of pre-eclampsia		0.528		0.618
Overall (10)	8 (4 to 16)		96 (93 to 98)	
Severe (2)	14 (3 to 46)		97 (89 to 99)	
Cut-off value		0.491		0.655
2.0 MoM (8)	8 (3 to 17)		97 (93 to 98)	
2.5 MoM (4)	12 (4 to 31)		95 (88 to 98)	
Incidence		0.177		0.329
<4% (6)	7 (3 to 14)		97 (94 to 99)	
⩾4% (5)	15 (6 to 32)		95 (88 to 98)	
Type of immunoassay		0.649		0.166
Radio (3)	7 (2 to 21)		97 (91 to 99)	
Enzyme (4)	13 (4 to 33)		93 (84 to 97)	
Fluorescent (2)	15 (3 to 54)		99 (95 to 100)	
Not reported (3)[a]	7 (2 to 25)		96 (89 to 99)	

[a] The category 'Not reported' was not used in calculating *p*-values.

cellular FN and contain only 5% of all FN in plasma whereas total FN contains all subtypes of FN.

The review of test accuracy of cellular FN included two studies (135 women) and total FN included three studies (373 women) (see Appendix 7). The quality of the four studies in total (one study reported both cellular and total FN) is shown in *Figure 8* and Appendix 8. Sensitivities and specificities are shown in *Figures 9* and *10* and ROC space in *Figures 11* and *12*. We were unable to derive meaningful pooled estimates of sensitivity and specificity. Three studies reported on several cut-off values, all shown in the forest plots and ROC plots. For cellular FN we used a sensitivity of 50% (95% CI 29.9 to 70.1%) at the highest specificity achieved of 96% (95% CI 79 to 99%) for economic modelling, measured in the second trimester at a cut-off value of 5.0 μg/ml. For total FN we used a sensitivity of 65% (95% CI 44 to 83%) at the highest specificity achieved of

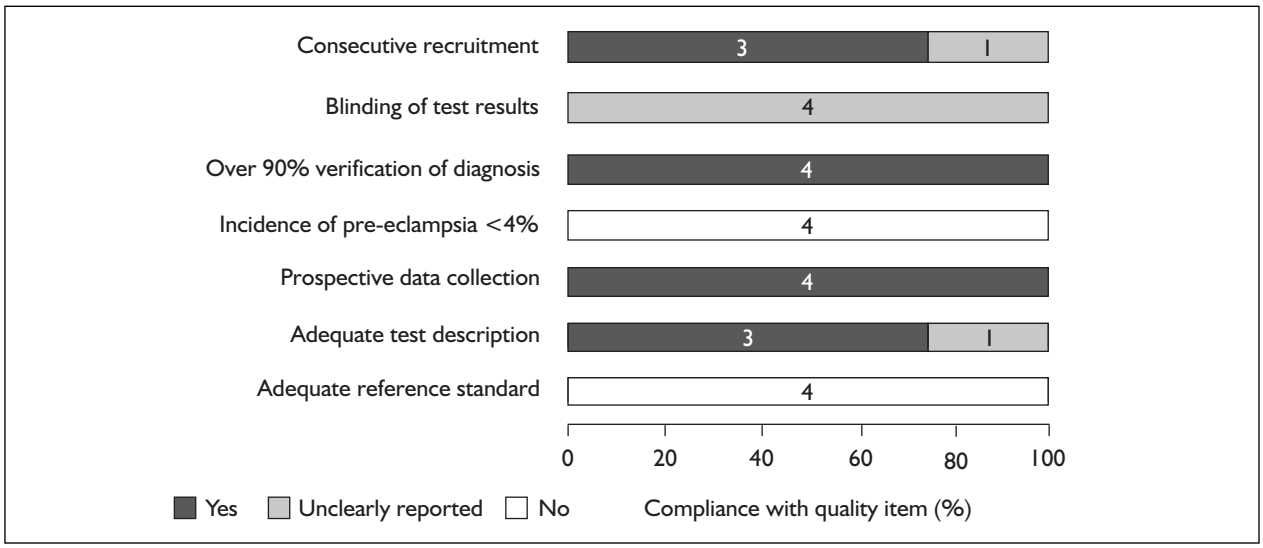


FIGURE 8 *Quality and reporting assessment of studies on cellular and total FN*

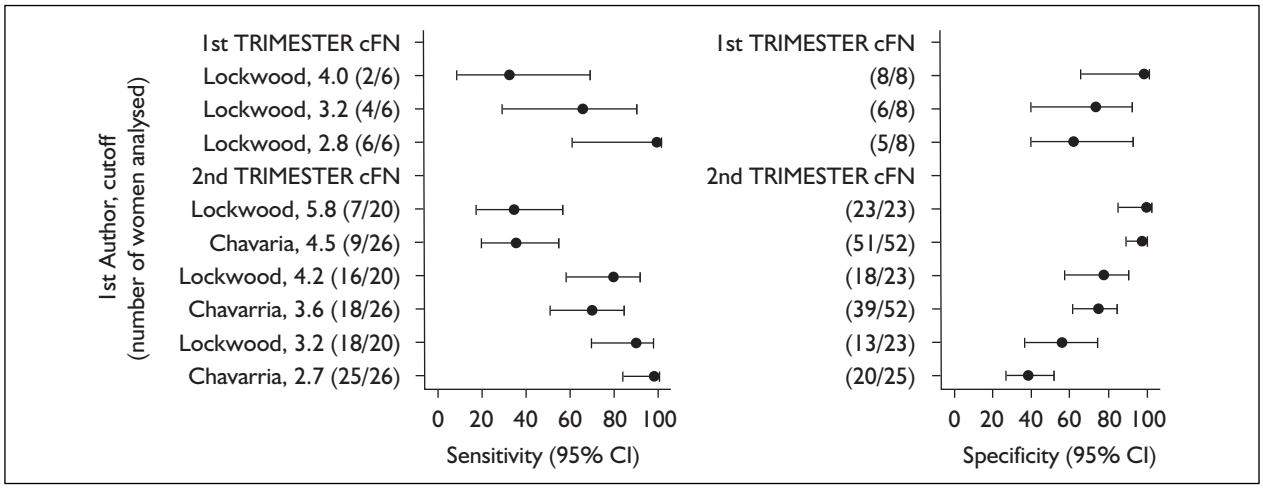


FIGURE 9 *Cellular FN sensitivities, specificities and 95% CIs. Numbers to the right of author's name are cut-off values in μg/ml.*

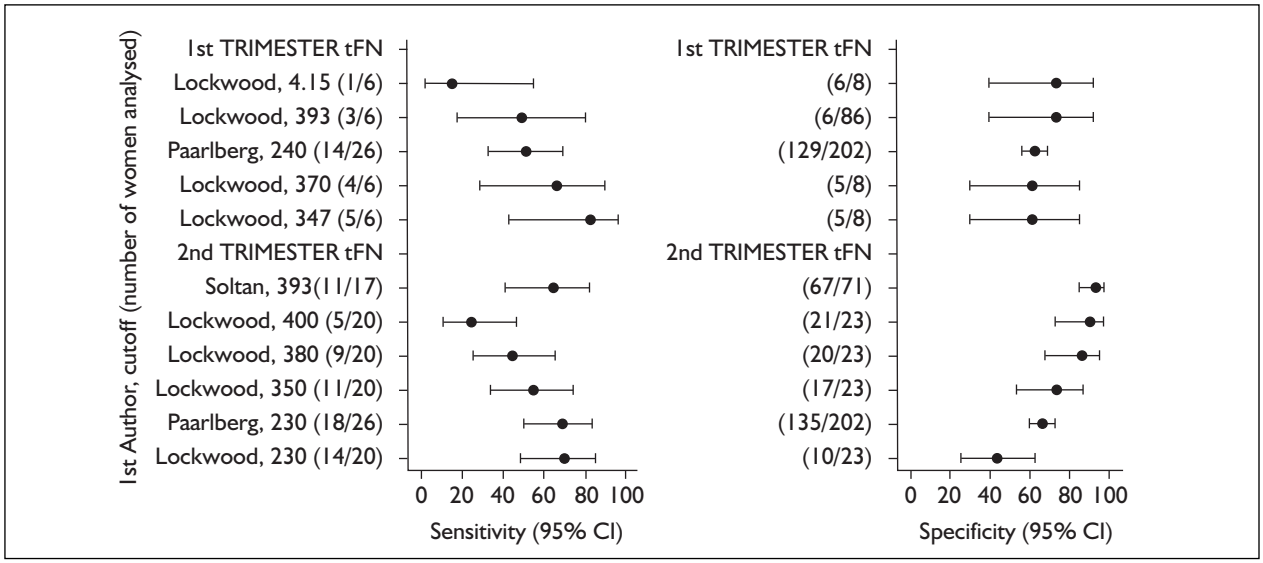


FIGURE 10 *Total FN sensitivities, specificities and 95% CIs. Numbers to the right of author's name are cut-off values in mg/l.*

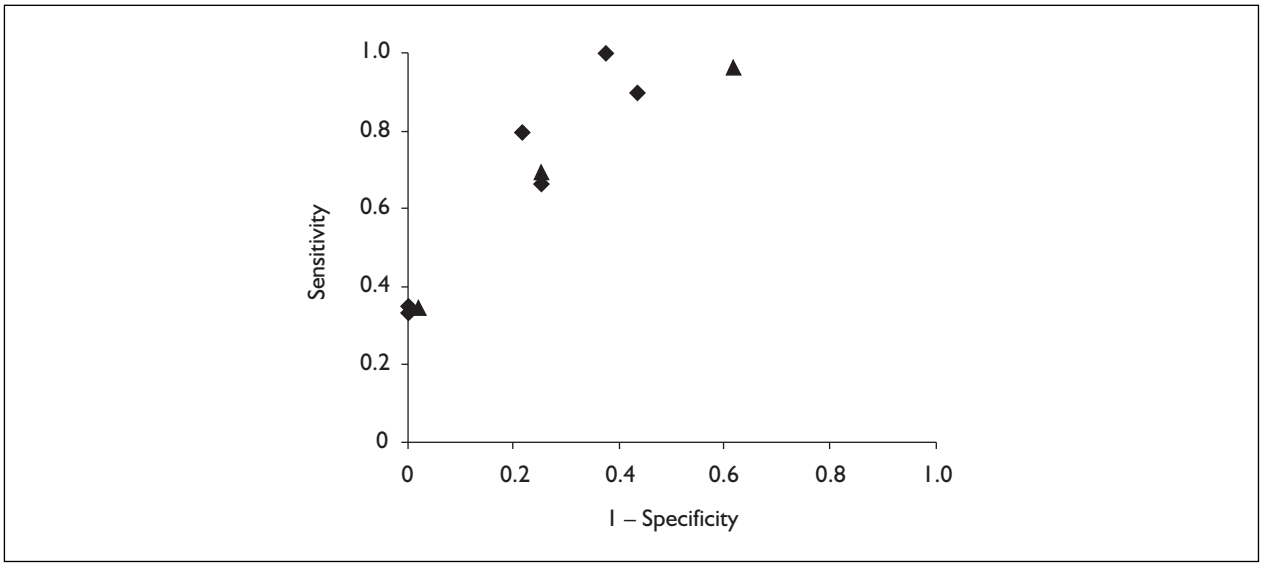


FIGURE 11 *Cellular FN plotted in ROC space. Diamonds represent results from Lockwood and colleagues and triangles Chavarria and colleagues.*

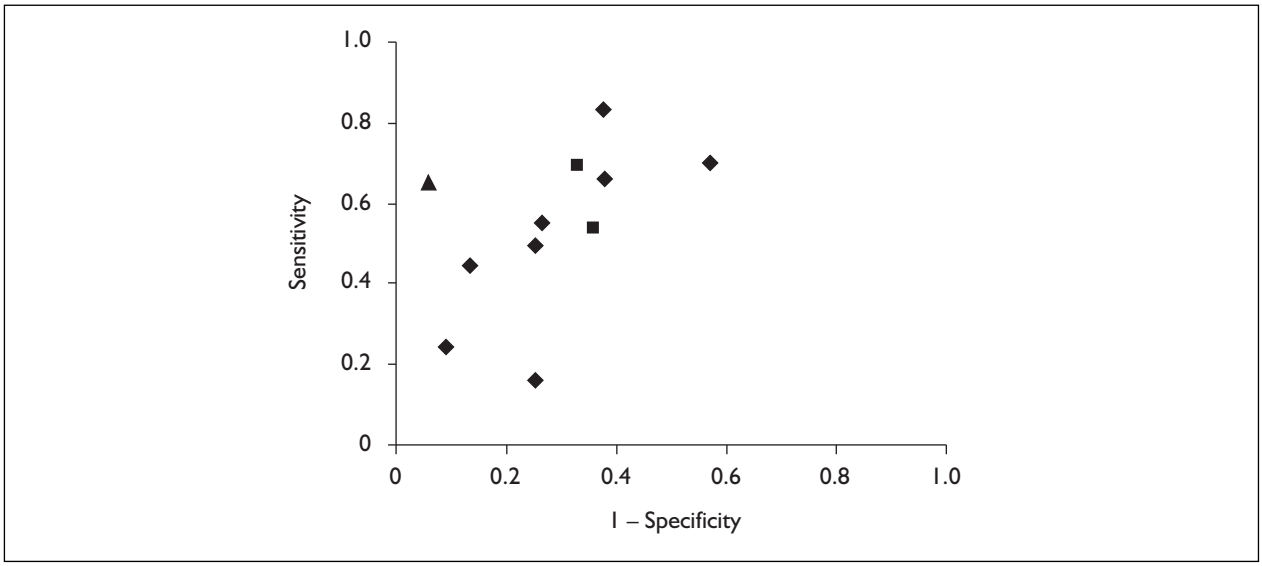


FIGURE 12 *Total FN plotted in ROC space. Diamonds represent results from Lockwood and colleagues, squares Paarlberg and colleagues and triangle Soltan and colleagues.*

94% (95% CI 86 to 98%) at a cut-off value of 293 μg/ml for economic modelling.

Foetal DNA

Pre-eclampsia is associated with an underlying placental lesion which facilitates increased trafficking of foetal cells and the release of cell-free foetal DNA (fDNA). A marked increase in the concentration of circulating cell-free fDNA has been found in the plasma of women with pre-eclampsia compared with normotensive women. In plasma of pregnant women carrying male foetuses, sequences from the SRY gene were amplified to distinguish fDNA from maternal DNA.

The review of diagnostic accuracy of fDNA included three studies (351 women) (see Appendix 7). The quality of the studies is shown in *Figure 13* and Appendix 8. Sensitivities and specificities are shown in *Figure 14* and the ROC space in *Figure 15*. We used pooled estimates of sensitivity and specificity of 50% (95% CI 31 to 69%) and 88% (95% CI 80 to 93%), respectively, for economic modelling. Each study was represented once in the pooled estimates [cut-off values: Cotter and colleagues >50,000 copies/ml, Farina and colleagues 10% false positive rate (FPR) and Leung and colleagues ⩾33.5 genome-equivalents (Geq)/mi].

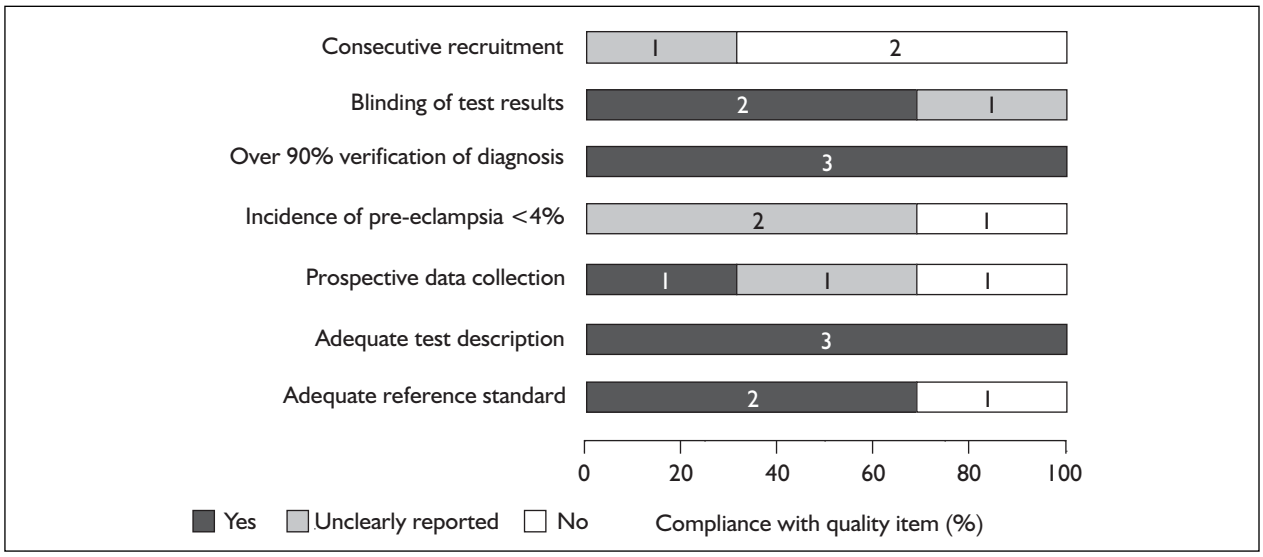


FIGURE 13 *Quality and reporting assessment of studies on foetal DNA*

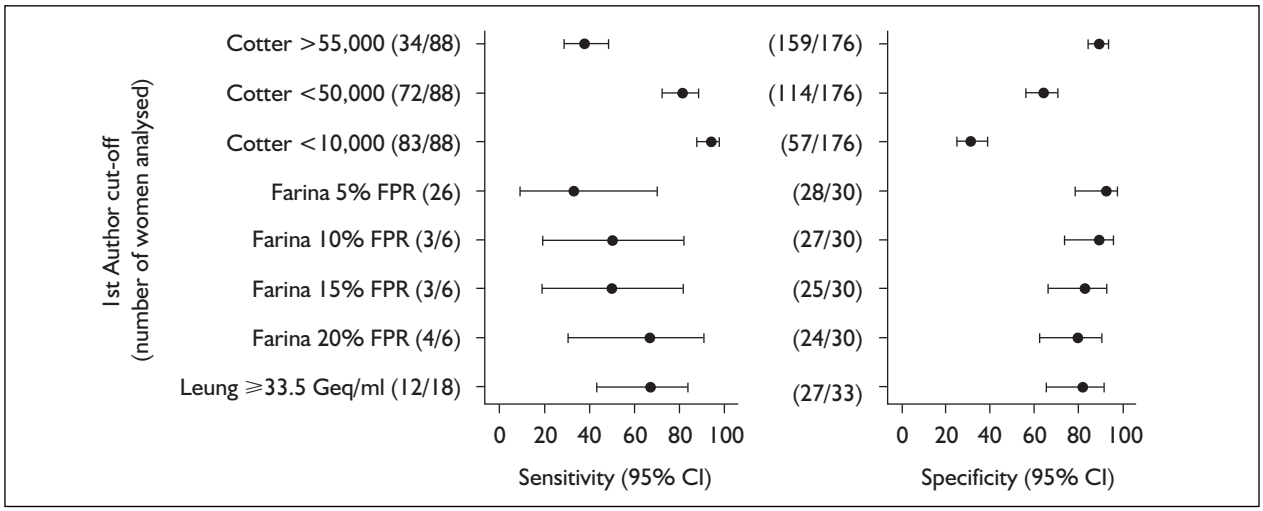


FIGURE 14 *fDNA sensitivities, specificities and 95% CIs*

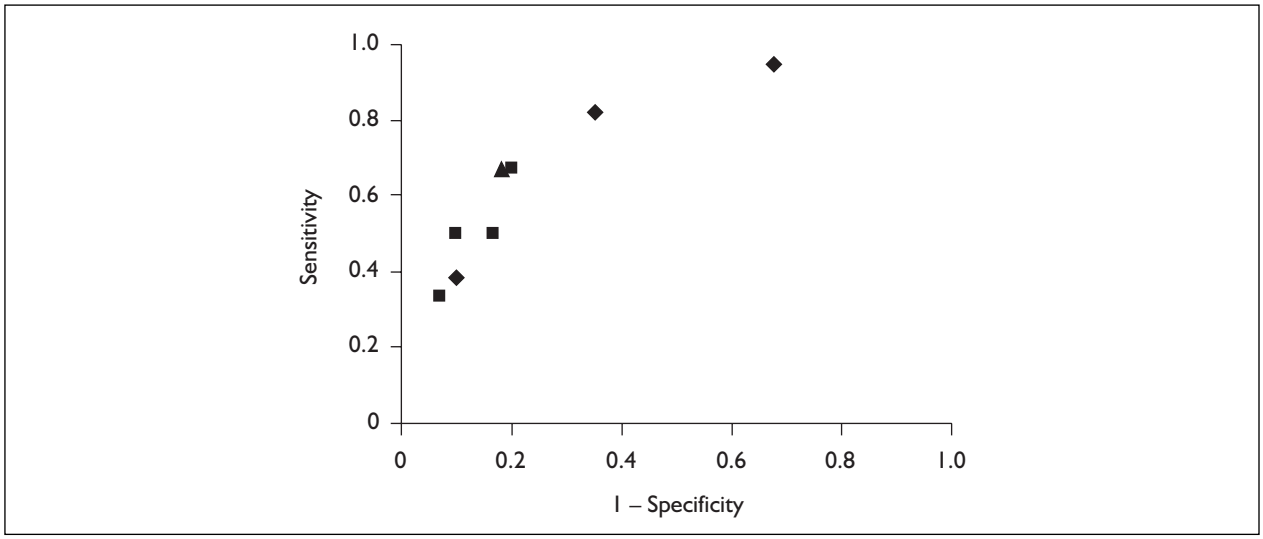


FIGURE 15 *fDNA plotted in ROC space. Diamonds represent results from Cotter and colleagues, squares Farina and colleagues and triangle Leung and colleagues.*

Haemoglobin/haematocrit

Pre-eclampsia, when it is severe, can be associated with a reduced cardiac output combined with an increased systemic vascular resistance and low plasma volume in comparison with normal pregnancy. Endothelial dysfunction and damage may lead to capillary leakage of plasma towards the interstitium and therefore low plasma volume and an increase in haematocrit and haemoglobin.

The review of diagnostic accuracy of haemoglobin and haematocrit included one study for haemoglobin (546 women) and one study for haematocrit (707 women) (see Appendix 7). The quality of the studies is shown in *Figure 16* and Appendix 8. The sensitivities and specificities are shown in *Figure 17* and the ROC space in *Figure 18*. Both studies were of poor quality so no further statistical analysis was possible and no results were used in economic modelling.

Maternal serum human chorionic gonadotrophin

Maternal serum HCG is used worldwide for screening of foetal aneuploidy, such as Down's syndrome, and anomalies as part of the triple test. This has also made the investigation of its predictiveness of pre-eclampsia possible. Maternal HCG levels seem to be increased in the second trimester in pregnancies that subsequently develop pre-eclampsia. HCG is a glycoprotein composed of two non-covalently linked subunits, α and β, and is produced mainly by the syncytiotrophoblast cells of the placenta after the luteo-placental shift (end

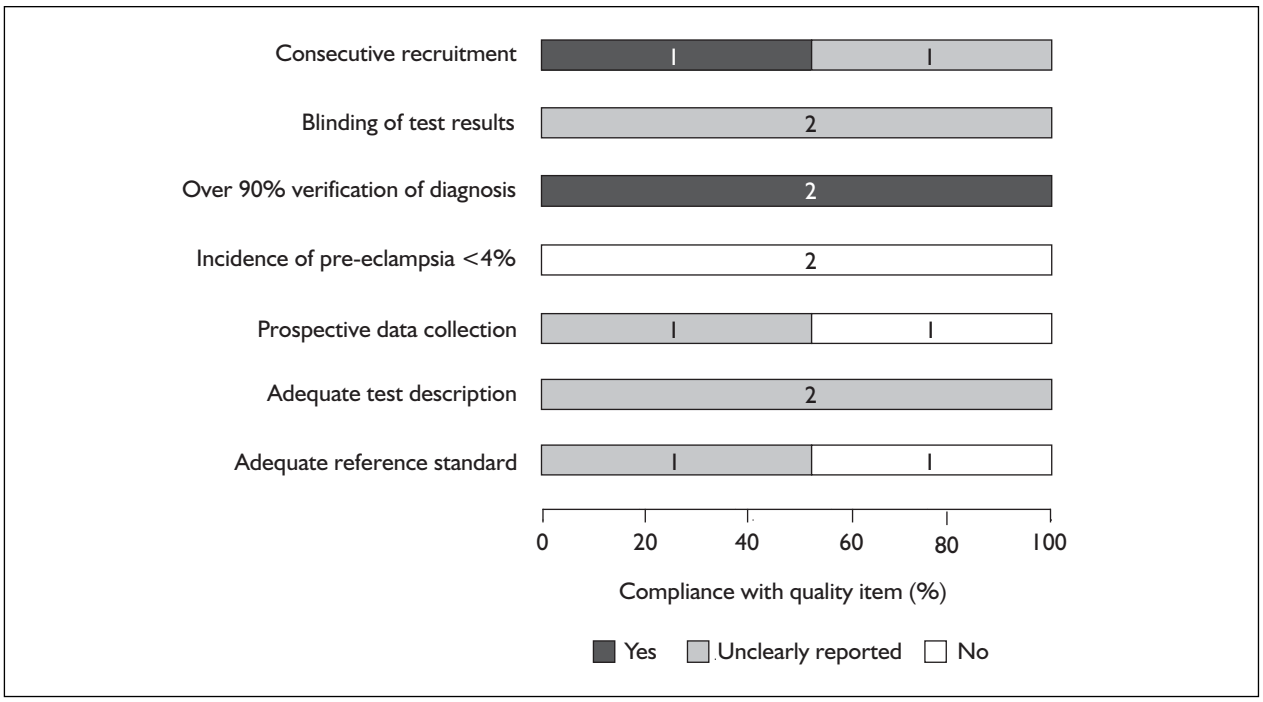


FIGURE 16 *Quality and reporting assessment of studies on haemoglobin and haematocrit*

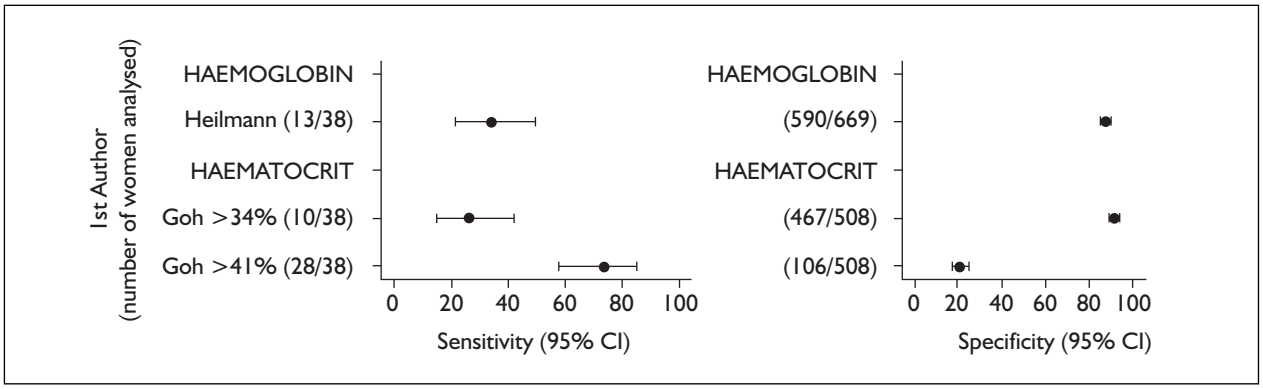


FIGURE 17 *Haemoglobin and haematocrit sensitivities, specificities and 95% CIs*

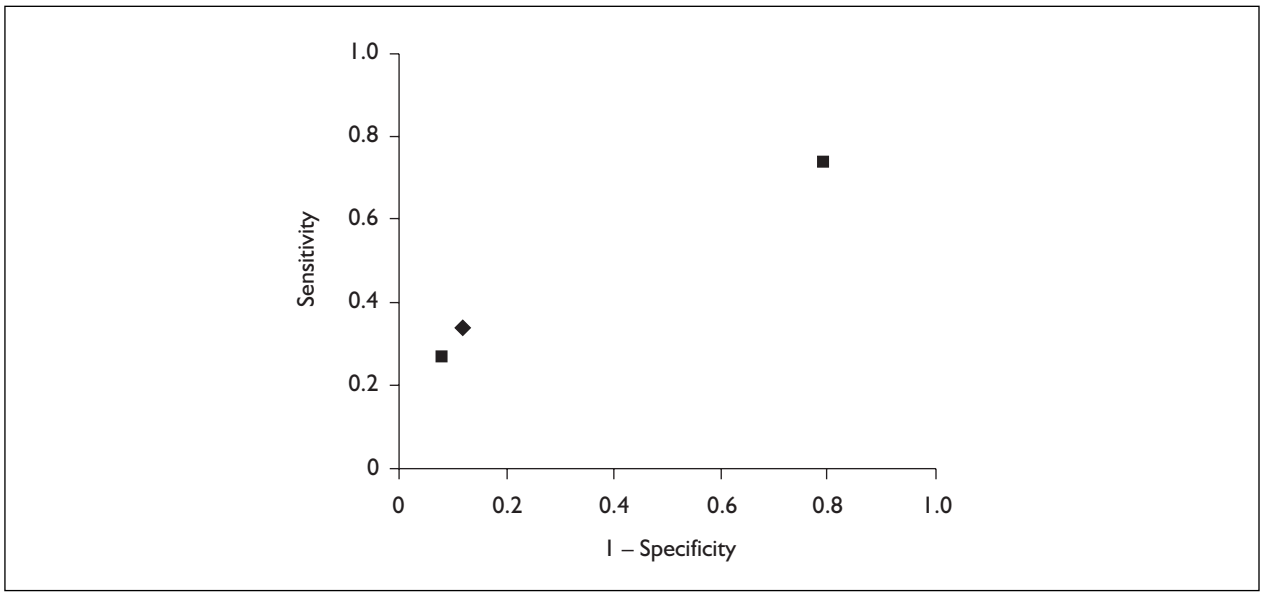


FIGURE 18 *Haemoglobin and haematocrit plotted in ROC space. Squares represent results from Goh and colleagues and diamond Heilmann and colleagues.*

of first trimester). HCG peaks at 8–10 weeks and then declines to reach a plateau at 18–20 weeks of gestation.

The review of diagnostic accuracy of maternal HCG included 16 studies (72,732 women) (see Appendix 7). The quality of the studies is shown in *Figure 19* and Appendix 8. Sensitivities and specificities are shown in *Figure 20*. *Table 7* shows the results of subgroup analyses for HCG where type of immunoassay affected both sensitivity and specificity. The ROC space is shown in *Figure 21*, where triangles represent studies with severe pre-eclampsia as outcome, the solid line represents the sROC curve and dashed lines represent the 95% CI of the sROC curve. We used pooled estimates of sensitivity and specificity of 24% (95% CI 16 to 35%) and 89% (95% CI 86 to 92%), respectively, in economic modelling.

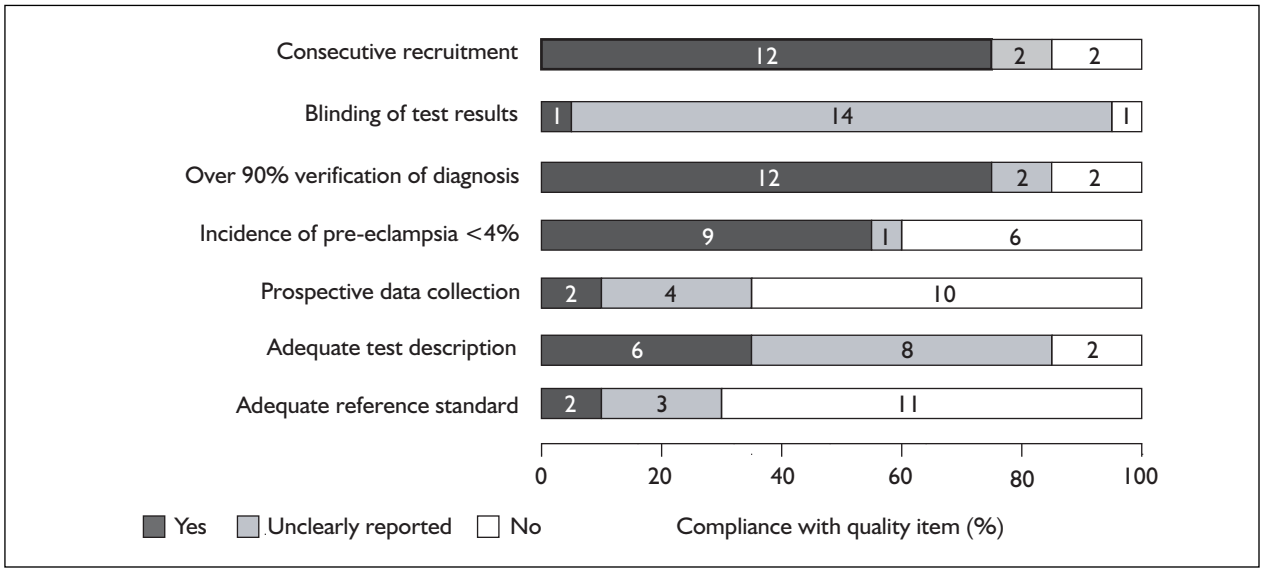


FIGURE 19 *Quality and reporting assessment of studies on maternal HCG*

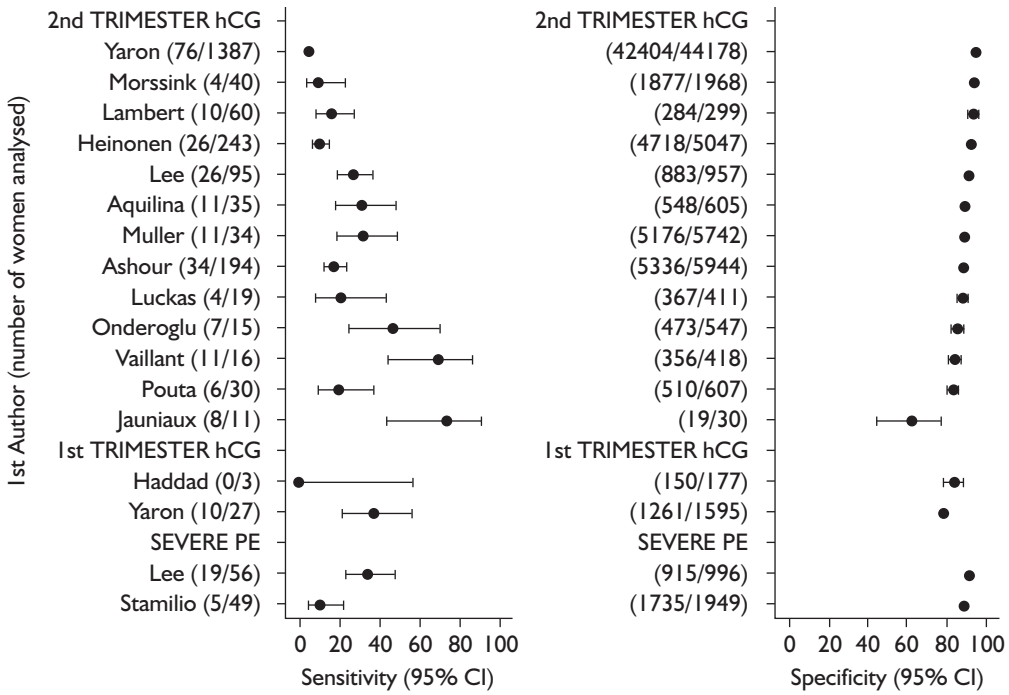


FIGURE 20 *Maternal HCG sensitivities, specificities and 95% CIs. Note that Lee and colleagues reported on both pre-eclampsia and severe pre-eclampsia.*

TABLE 7 *Subgroup analysis (significance level* p < *0.10) for maternal HCG testing based on 16 studies*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no. of studies)	24 (16 to 35)		89 (86 to 92)	
Definition of pre-eclampsia		0.474		0.435
Internationally accepted (2)	22 (8 to 47)		91 (82 to 96)	
Other variations (11)	31 (20 to 44)		88 (83 to 91)	
Unclearly/not reported (3)[a]	10 (4 to 24)		93 (88 to 97)	
Severity of pre-eclampsia		0.796		0.819
Overall (15)	26 (17 to 37)		89 (86 to 92)	
Severe (2)	22 (6 to 54)		90 (80 to 96)	
Cut-off value		0.728		0.252
2.0 MoM (9)	23 (14 to 37)		89 (84 to 92)	
2.3 or 2.5 MoM (5)	20 (9 to 38)		92 (87 to 95)	
Not reported in MoM (2)[a]	58 (20 to 88)		85 (71 to 93)	
Type of immunoassay		*0.011*		*0.037*
Radio (3)	12 (5 to 25)		93 (89 to 96)	
Enzyme (5)	45 (28 to 64)		87 (81 to 92)	
Fluorescent (2)	28 (10 to 57)		82 (69 to 90)	
Not reported (6)[a]	17 (9 to 29)		91 (86 to 94)	
Gestational age at testing		0.772		*0.105*
⩾14 weeks (14)	24 (15 to 35)		90 (87 to 93)	
<14 weeks (2)	28 (7 to 67)		82 (67 to 91)	

[a] The category 'Not reported' was not used in calculating *p*-values.

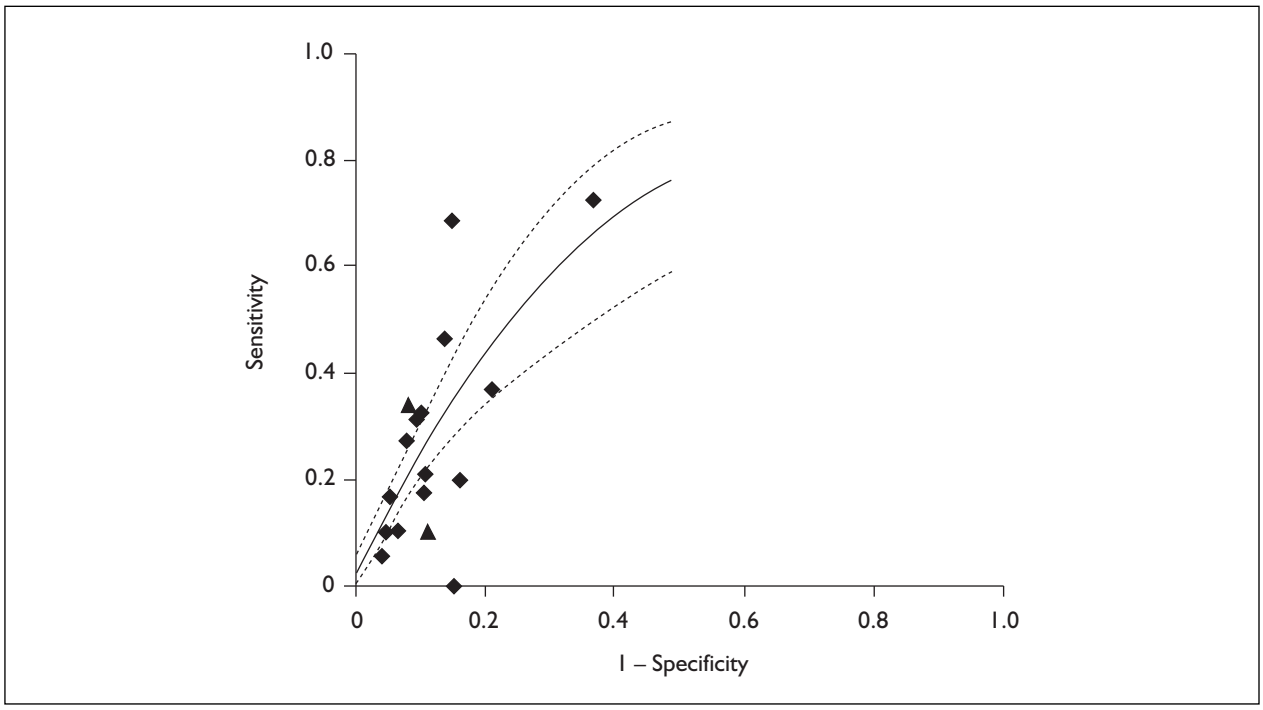


FIGURE 21 *Maternal HCG plotted in ROC space. The ROC space has triangles representing studies with severe pre-eclampsia as outcome, solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

Serum unconjugated oestriol

Determination of serum unconjugated oestriol is used worldwide for screening of foetal aneuploidy and anomalies as part of the triple test. Given the role of the placenta in determining the maternal serum level of this hormone, its predictive value in pregnancies with placental dysfunction such as in pre-eclampsia have also been investigated. Oestriol is produced by the placenta by conversion of foetal 16-α-hydroxydehydroepiandrosterone sulfate to androgens, which are subsequently aromatised to oestriol. It is first detected at 8 weeks of gestation. Early in pregnancy, dehydroepiandrosterone sulfate (DHEA-S) production by the foetal adrenal gland is independent of foetal adrenal corticotrophic hormone (ACTH); in the second trimester ACTH is required for adrenal function. Henceforward, 90% of oestriol production is accounted for by DHEA-S derived from the foetal adrenal glands. Either a placental or a foetal pathological condition, alone or in combination, could be associated with low serum oestriol levels.

The review of diagnostic accuracy of serum unconjugated oestriol included three studies (26,811 women) (see Appendix 7). The quality of the studies is shown in *Figure 22* and Appendix 8. Sensitivities and specificities are shown in *Figure 23* and the ROC space in *Figure 24*. We used pooled estimates of sensitivity and specificity of 26% (95% CI 9 to 56%) and 82% (95% CI 61 to 93%), respectively, in economic analysis.

Serum uric acid

High blood uric acid levels have been found to be associated with pre-eclampsia since 1917, but are also associated with other pathophysiological states. Renal impairment and an increased breakdown of purines in the ischaemic placenta leading to overproduction of uric acid may explain increased serum uric acid (SUA) levels in (future) pre-eclamptic patients. In normal pregnancy, after a decrease in SUA concentration, SUA levels rise in the third trimester, possibly due to increased foetal production, decreased binding to albumin and a decline in uric acid clearance. The National Heart, Lung and Blood Institute recommended the determination of SUA in high-risk women presenting with normal blood pressure.

The review of test accuracy of serum uric acid included five studies (514 women) (see Appendix 7). The quality of the studies is shown in *Figure 25* and Appendix 8. The sensitivities and specificities are shown in *Figure 26* and ROC space *in Figure 27*. We used pooled estimates of sensitivity and specificity of 36% (95% CI 22 to 53%) and 83% (95% CI 73 to 90%), respectively, in economic analysis.

FIGURE 22 *Quality and reporting assessment of studies on serum unconjugated oestriol*

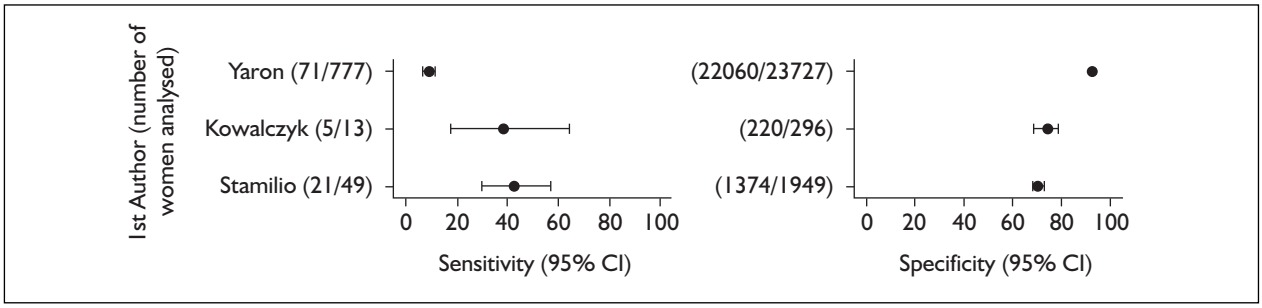


FIGURE 23 *Serum unconjugated oestriol sensitivities, specificities and 95% CIs. Note that Stamilio and colleagues reported on severe pre-eclampsia as an outcome.*

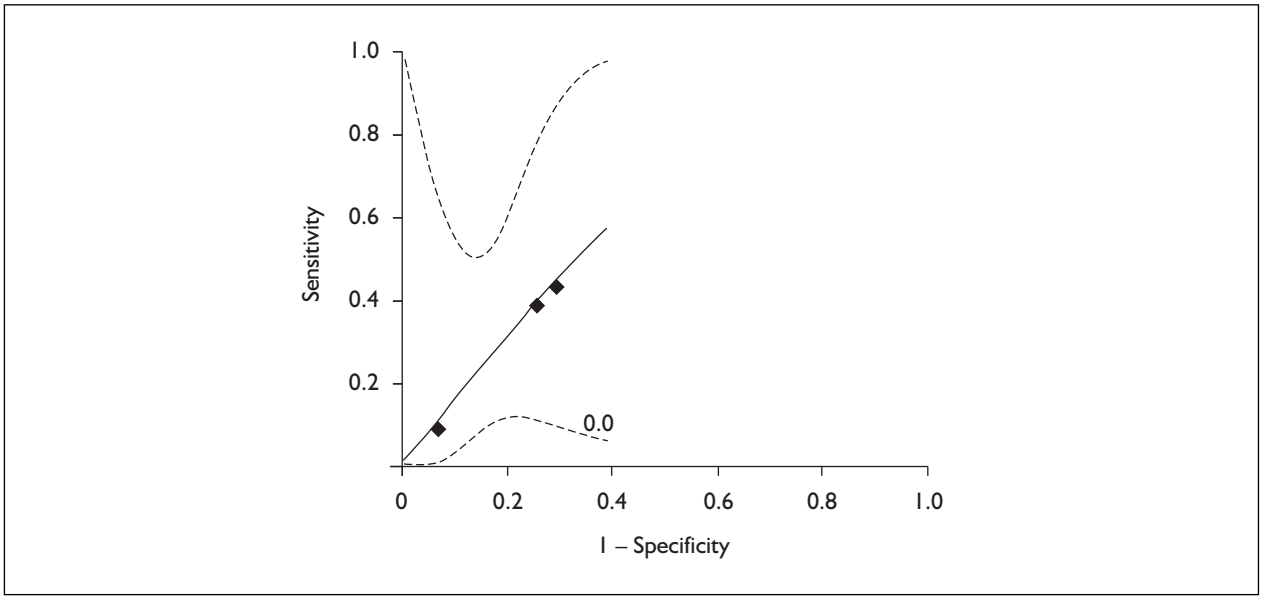


FIGURE 24 *Serum unconjugated oestriol plotted in ROC space. The ROC space has a solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

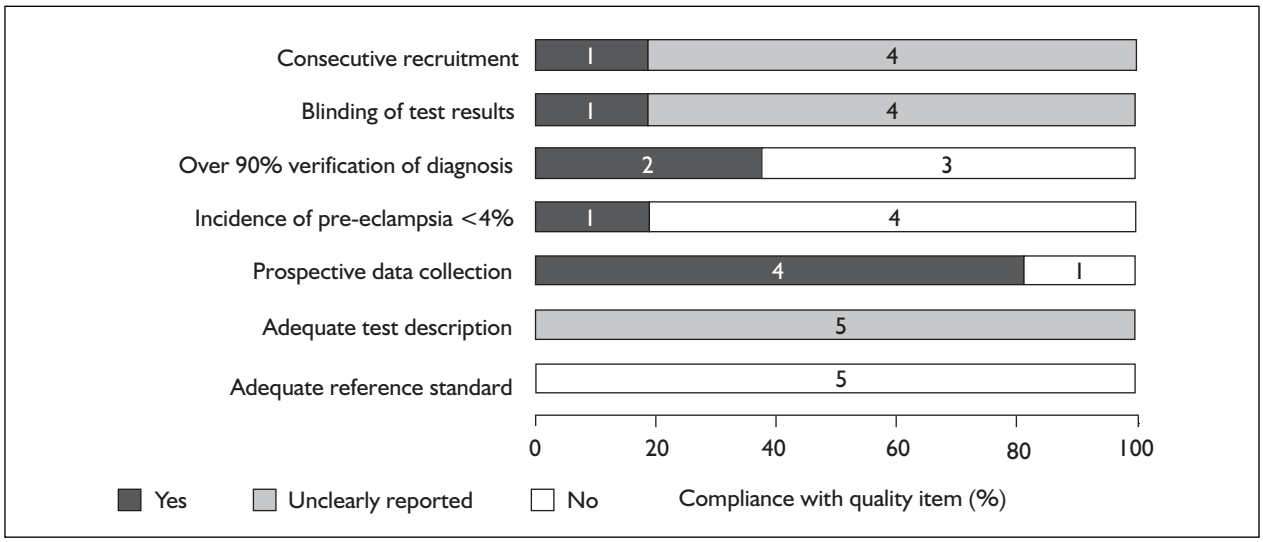


FIGURE 25 *Quality and reporting assessment of studies on serum uric acid*

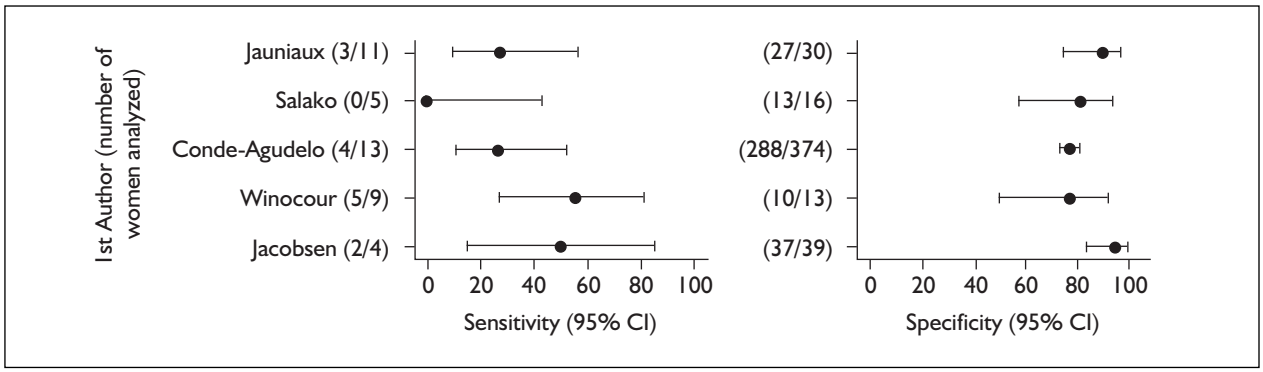


FIGURE 26 *SUA sensitivities, specificities and 95% CIs. Note that Jacobson and colleagues used a cut-off of rise above baseline rather than absolute value.*

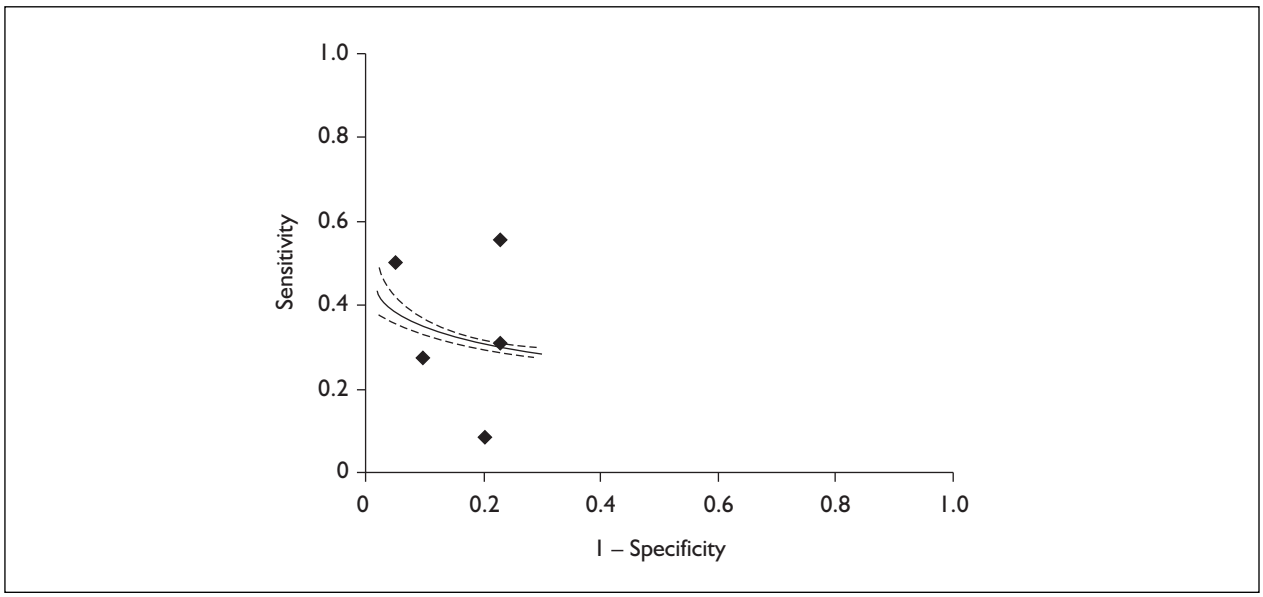


FIGURE 27 *SUA plotted in ROC space. The ROC space has solid line representing the sROC curve and dashed lines representing the 95% CI of sROC curve.*

Investigations – urine

Urinary calcium excretion/urinary calcium creatinine ratio

In normotensive pregnancies, renal excretion of calcium increases, reaching maximum levels in the third trimester. In normal pregnancy, urinary calcium excretion (UCE) is 350–620 mg/day, compared with 100–250 mg/day in non-pregnant women. Several studies have reported a decreased UCE in pre-eclampsia compared with normotensive pregnancies. UCE represents a balance between glomerular filtration and tubular (re)absorption; the latter may be increased in pre-eclampsia. The urinary calcium/creatinine ratio (UCCR) at 24–34 weeks was suggested to be predictive of pre-eclampsia.

The review of test accuracy of urinary calcium excretion included four studies (705 women) and urinary calcium creatinine ratio included six studies (1345 women) (see Appendix 7). The quality of the studies is shown in *Figures 28* and *29* and Appendix 8. The sensitivities and specificities

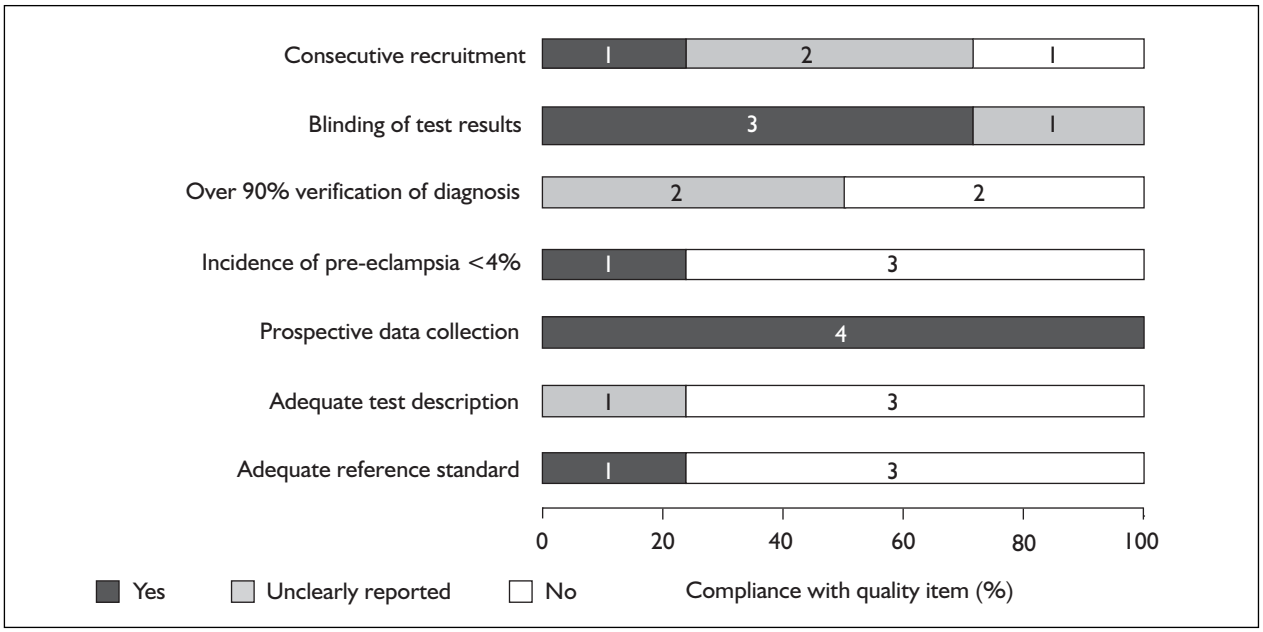


FIGURE 28 *Quality and reporting characteristics of studies on urinary calcium excretion*

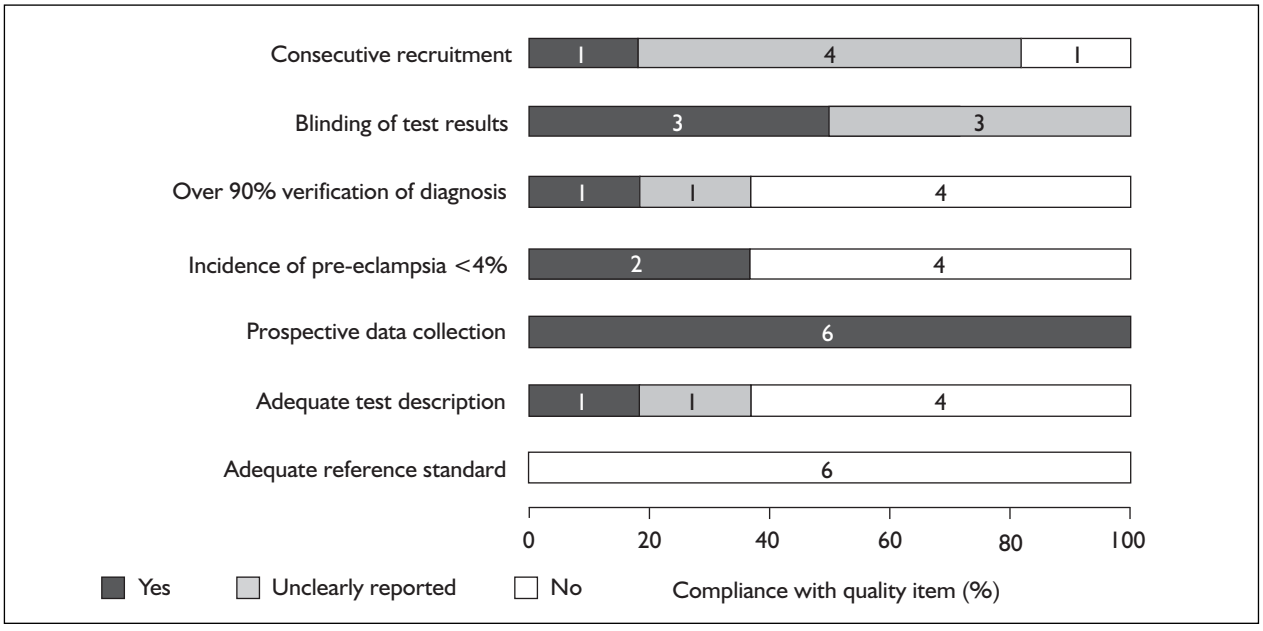


FIGURE 29 *Quality and reporting assessment of studies on urinary calcium/creatinine ratio*

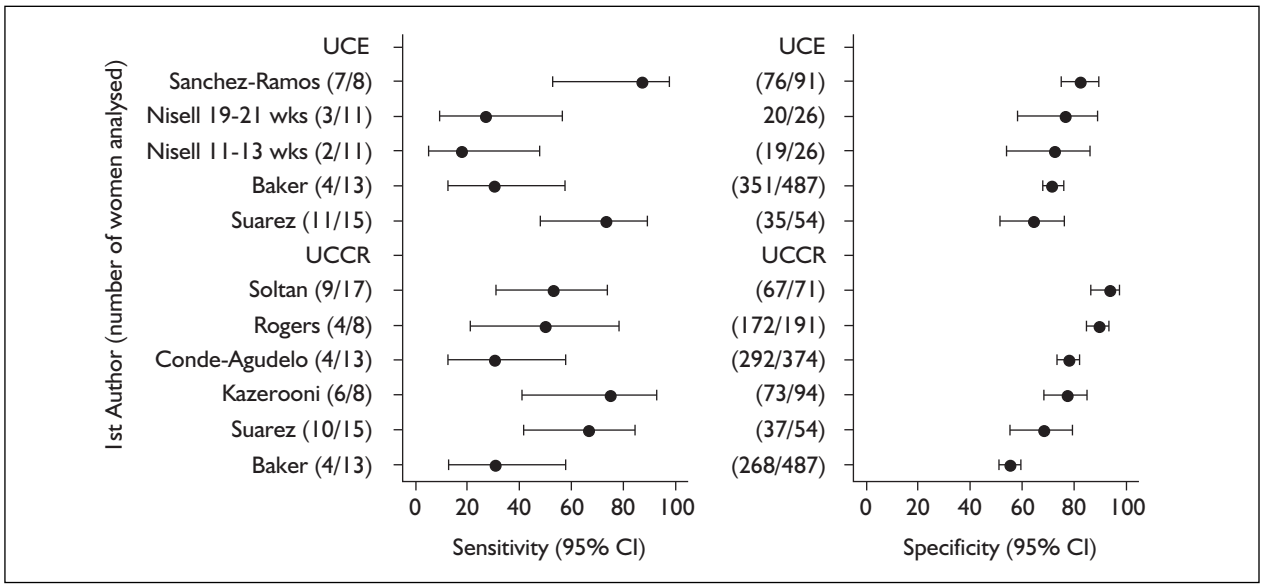


FIGURE 30 *UCE and UCCR sensitivities, specificities and 95% CIs*

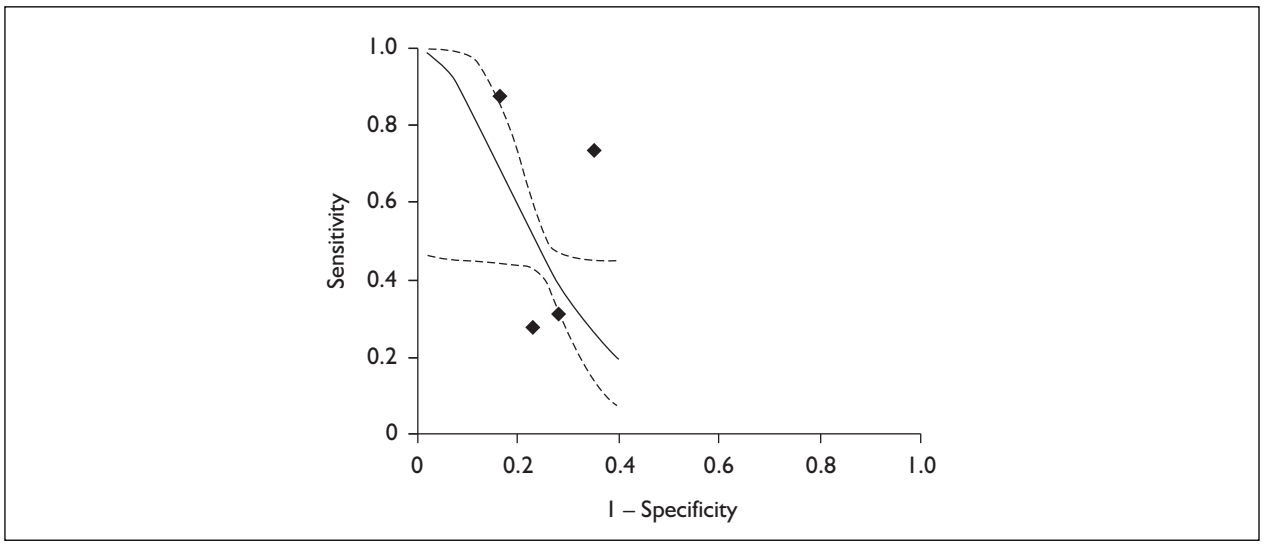


FIGURE 31 *UCE shown in ROC space. The ROC space has solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

are shown in *Figure 30* and ROC space in *Figures 31* and *32*. We used pooled estimates of sensitivity and specificity for UCE of 57% (95% CI 24 to 84%) and 74% (95% CI 69 to 79%), respectively, in economic analysis. We used pooled estimates of sensitivity and specificity for UCCR of 50% (95% CI 36 to 64%) and 80% (95% CI 66 to 89%), respectively, in economic analysis.

Proteinuria

Routine proteinuria urinalysis is conducted in antenatal clinics from first booking but there is little guidance to support this for pre-eclampsia prediction. Proteinuria measurement includes total protein or total albumin excretion in 24 hours, microalbuminuria, albumin/creatinine ratio, dipsticks for spot proteinuria or albuminuria and more unusual proteins such as kallikrein and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) proteins.

The review of diagnostic accuracy included 11 studies (4388 women), of which four reported total proteinuria (2228 women), two reported albuminuria (88 women), two reported microalbuminuria (190 women) and one each reported microalbuminuria/creatinine ratio (1422 women), kallikrein (307 women) and SDS-PAGE proteins (153 women) (see Appendix 7). The quality of the studies is

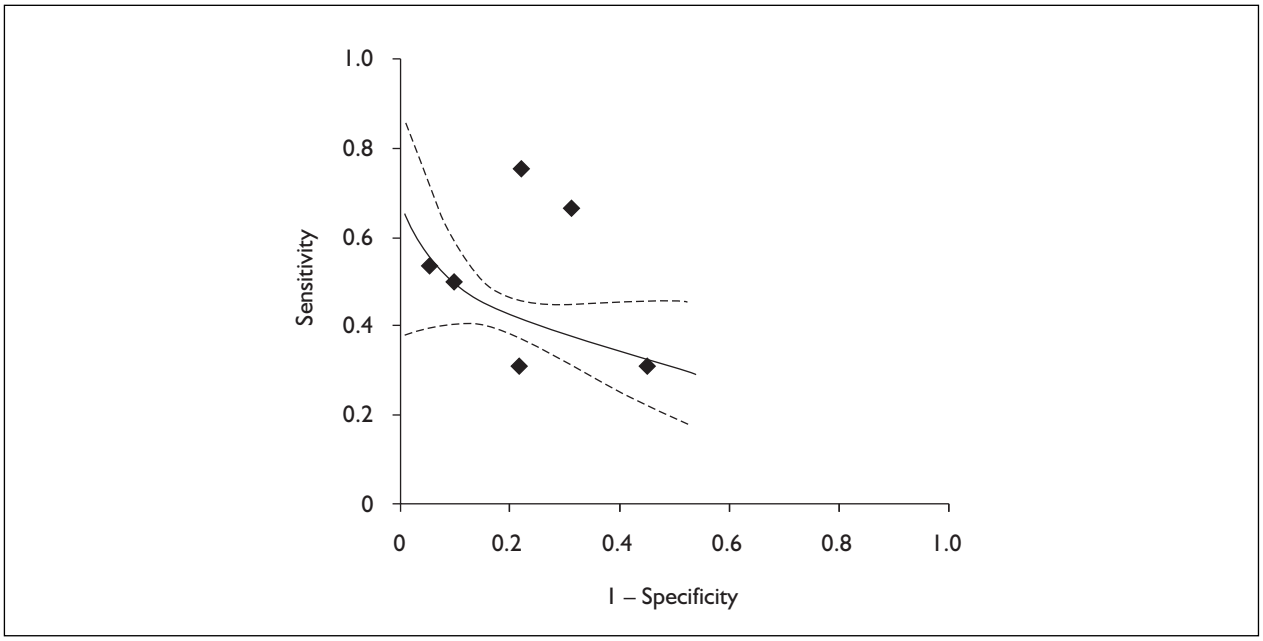


FIGURE 32 *UCCR shown in ROC space. The ROC space has solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

shown in *Figure 33* and Appendix 8. Sensitivities and specificities are shown in *Figure 34* and ROC space in *Figure 35*. Pooled estimates of sensitivity and specificity used in decision modelling were as follows: total proteinuria, 35% (95% CI 13 to 68%) and 89% (95% CI 79 to 94%); total albuminuria, 70% (95% CI 45 to 87%) and 89% (95% CI 79 to 94%); microalbuminuria, 62% (95% CI 23 to 90%) and 68% (95% CI 57 to 77%); and albumin/creatinine ratio, 19% (95% CI 12 to 28%) and 75% (95% CI 73 to 77%), respectively.

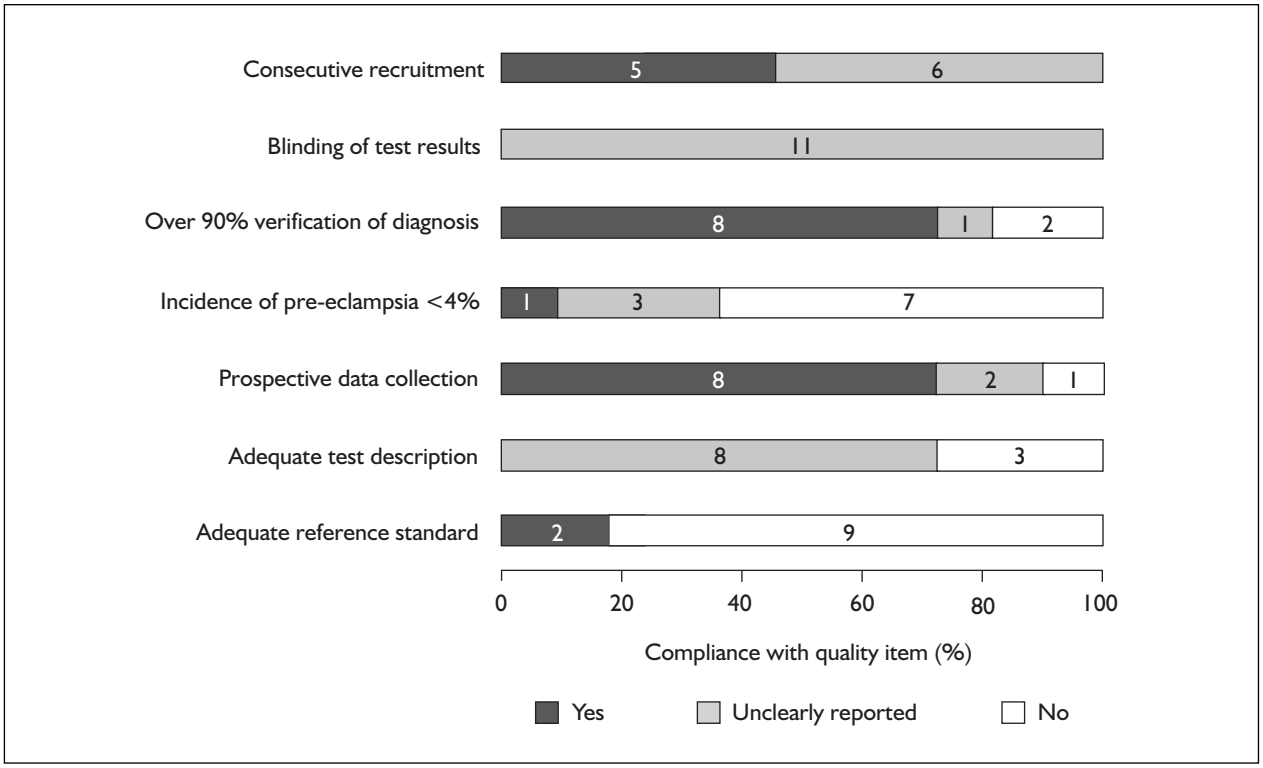


FIGURE 33 *Quality and reporting assessment of studies of proteinuria*

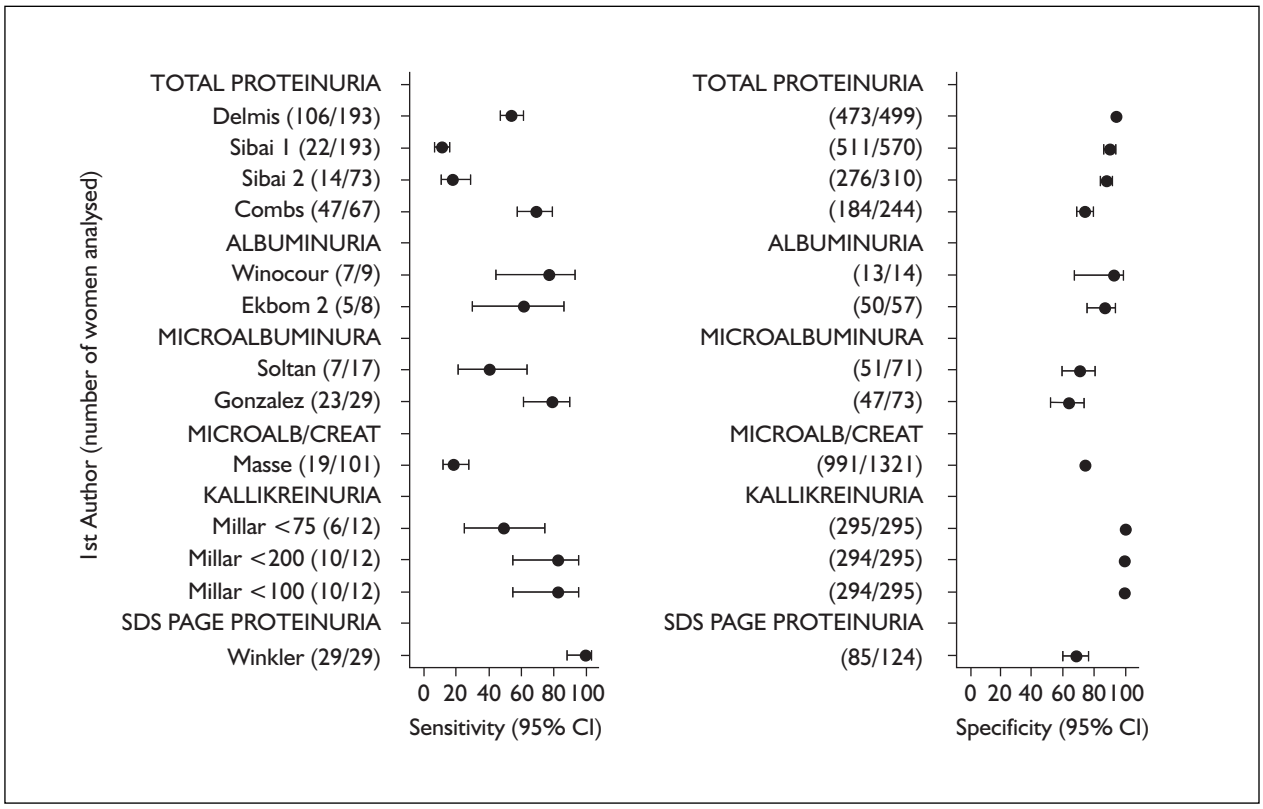


FIGURE 34 *Proteinuria tests sensitivities, specificities and 95% CIs*

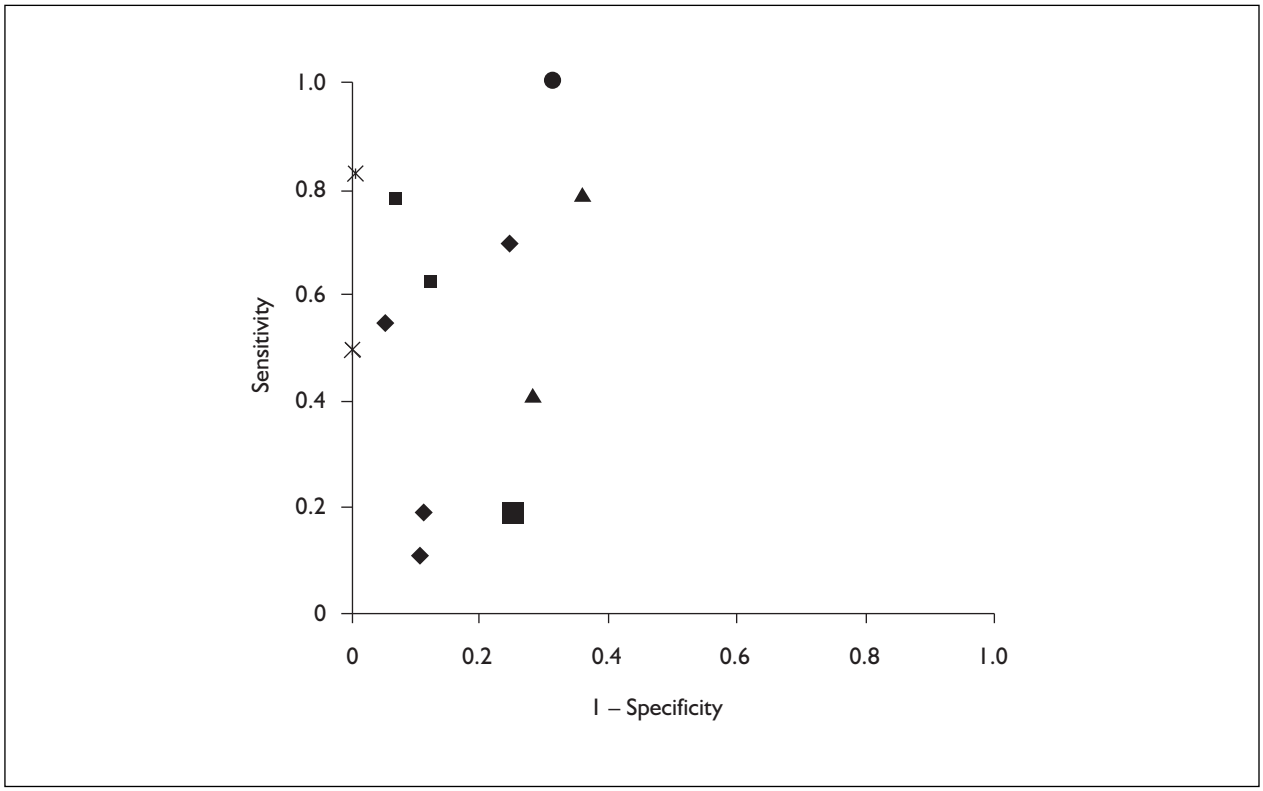


FIGURE 35 *Proteinuria tests shown in ROC space. Diamonds represent total proteinuria, small squares represent albuminuria, large square microalbumin/creatinine ratio, triangles microalbuminuria, circle SDS-PAGE proteinuria and crosses kallikreinuria.*

Investigations – haemodynamic

Uterine artery Doppler

Doppler ultrasound has been demonstrated to be a reliable, non-invasive method of examining uteroplacental perfusion. Alterations in flow velocity waveforms measured in the uterine arteries are associated with an increased risk for subsequent development of pre-eclampsia (and/or foetal growth restriction). There are six reviews of Doppler diagnostic tests which correspond to the six ways of reading a Doppler test:

1. A unilateral notch refers to an early diastolic notch measured in either the left or right main uterine artery; any notch refers to either a unilateral early diastolic notch or bilateral notches measured in the main uterine arteries.
2. Bilateral notching refers to early diastolic notches measured in both main uterine arteries.
3. All single ratios such as S/D ratio, A/C ratio and notch index.
4. The pulsatility index of the main uterine artery is calculated as peak systolic flow minus end diastolic flow divided by mean flow [= (A – B)/M].
5. The resistance index of the main uterine artery is calculated by peak systolic flow minus end diastolic flow divided by peak systolic flow [(A – B)/A].
6. Several flow velocity waveforms, single or combined, have been investigated for the prediction of pre-eclampsia. In this review, combinations of notching and resistance index, notching and pulsatility index, notching and other ratios are reported.

Any or unilateral notching of the main uterine arteries

The review of diagnostic accuracy of any or unilateral notching included 19 studies (14,345 women) (see Appendix 7). The quality of the studies is shown in *Figure 36* and Appendix 8. The sensitivities and specificities are shown in *Figure 37*. *Table 8* shows the results of subgroup analysis. The ROC space is shown in *Figure 38*, where the solid line represents the sROC curve and dashed lines represent 95% CIs. Studies with

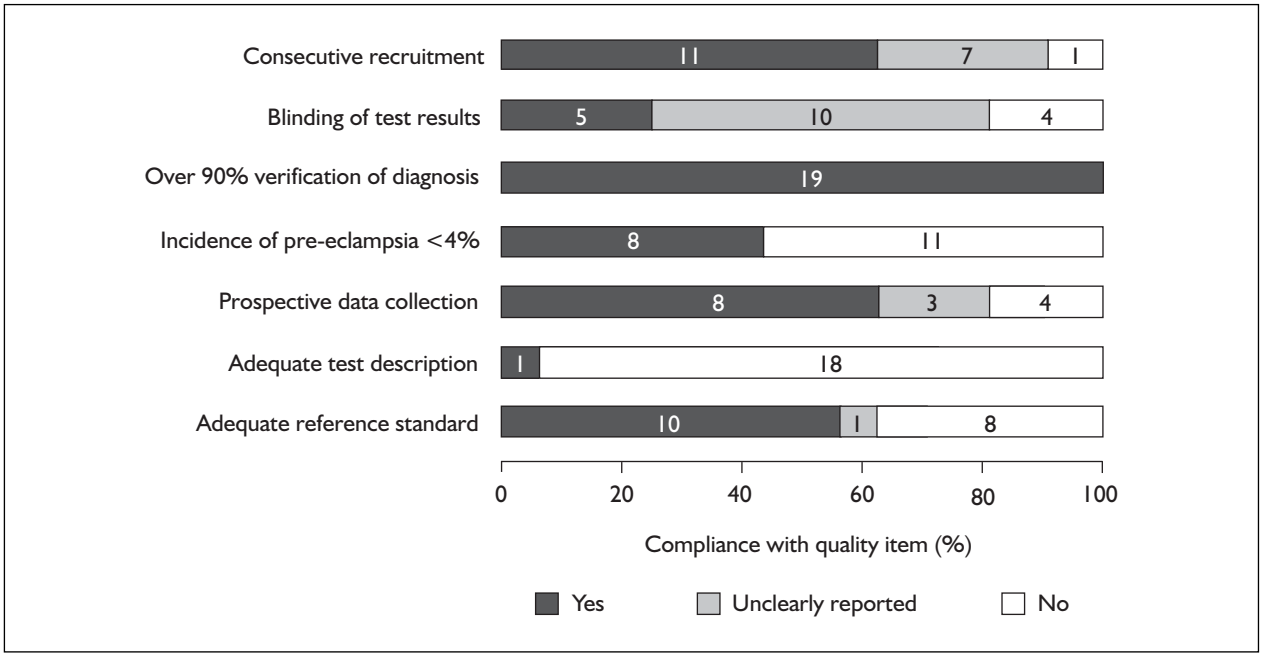


FIGURE 36 *Quality and reporting assessment of studies on Doppler any/unilateral notching*

TABLE 8 *Subgroup analysis (significance level p < 0.10) for any/unilateral notching of the main uterine artery*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no. of studies)	63 (51 to 74)		82 (74 to 87)	
Incidence		0.647		*0.025*
<4% (8)	66 (47 to 81)		88 (81 to 93)	
⩾4% (12)	61 (43 to 76)		75 (65 to 84)	

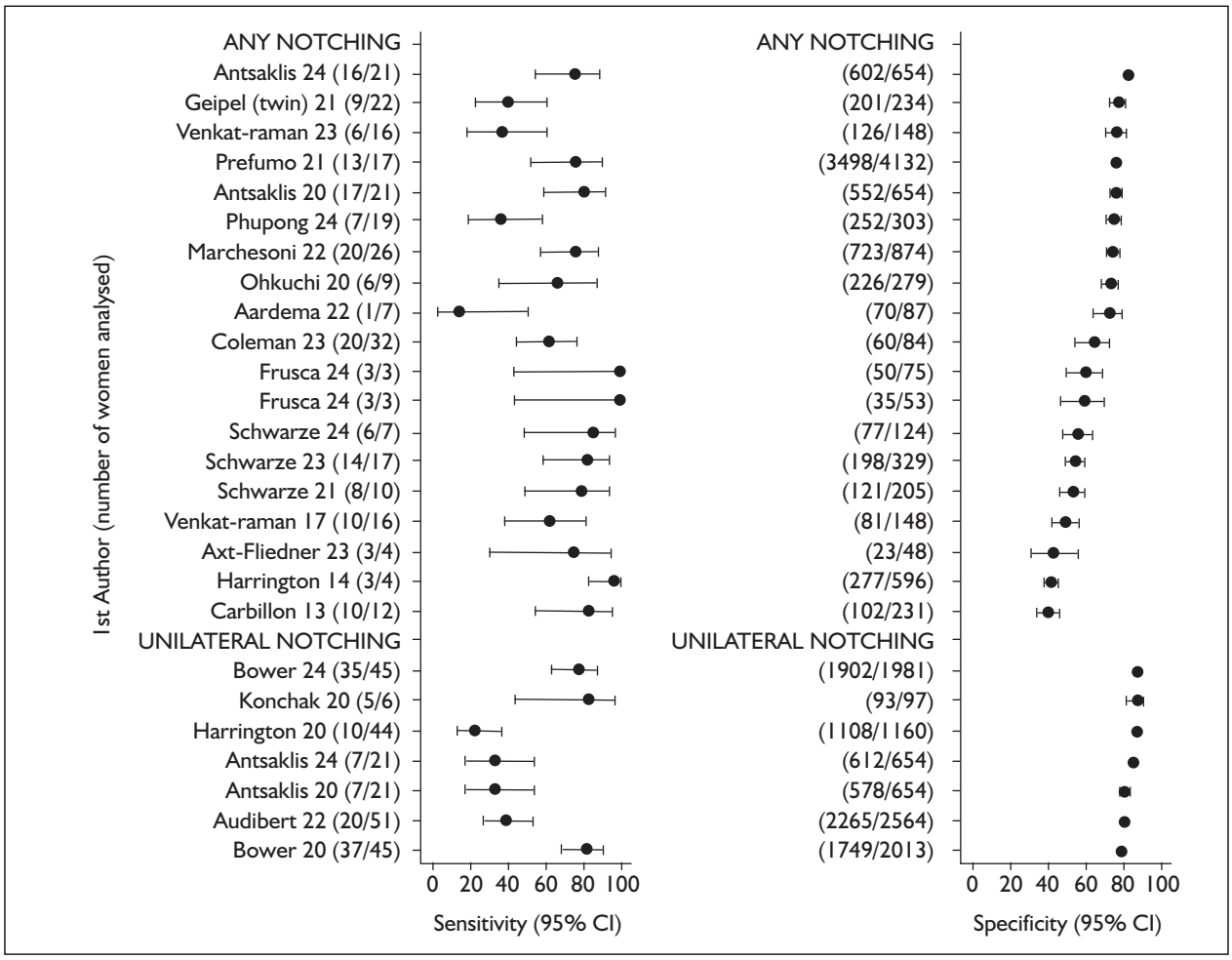


FIGURE 37 *Doppler any or unilateral notching of the main uterine arteries: sensitivities, specificities and 95% CIs. Studies are classified by any notching versus unilateral notching. Numbers to the right of the author's name indicate (average) gestational age at testing. Note that some authors reported data at several gestational ages.*

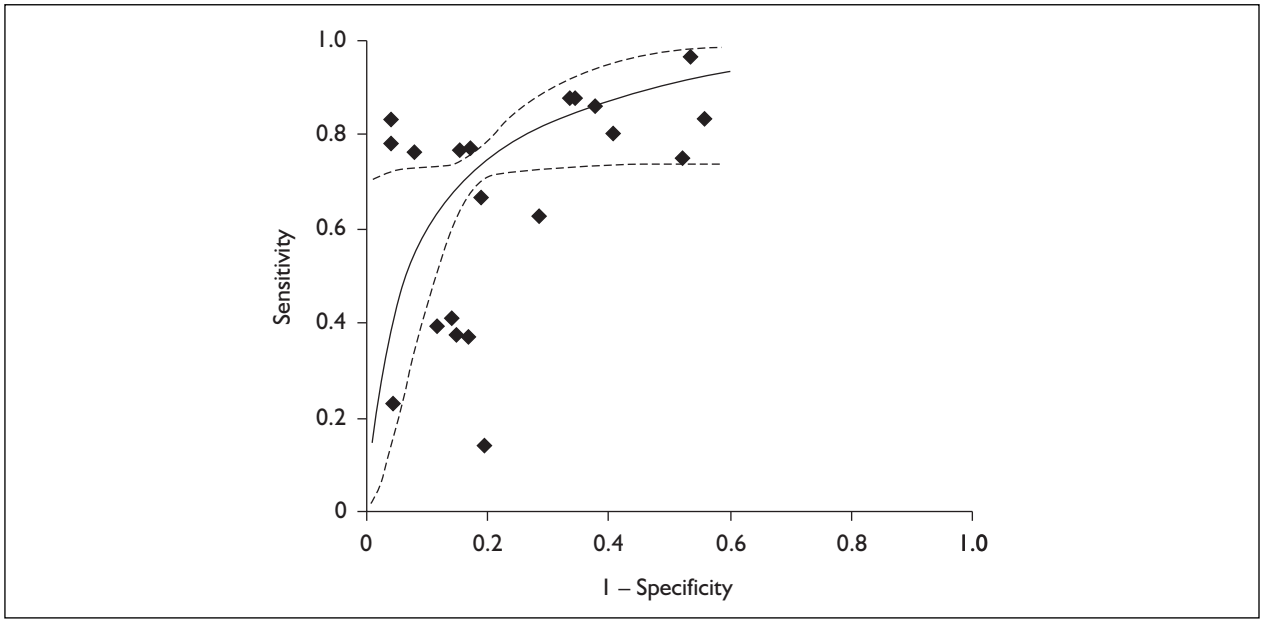


FIGURE 38 *Doppler any or unilateral notching plotted in ROC space. The ROC space has a solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

several measurements are represented once only. We used pooled estimates of sensitivity and specificity of 63% (95% CI 51 to 74%) and 82% (95% CI 74 to 87%), respectively, in decision modelling.

Bilateral notching of the main uterine arteries

The review of diagnostic accuracy of Doppler bilateral notching included 22 studies (29,395 women) (see Appendix 7). The quality of the studies is shown in *Figure 39* and Appendix 8. Sensitivities and specificities are shown in *Figure 40*. *Table 9* shows the results of subgroup analysis. The ROC space is shown in *Figure 41*, where the solid line represents sROC curve and dashed lines represent 95% CIs. Studies with several measurements are represented once only. We used pooled estimates of sensitivity and specificity of 48% (95% CI 34 to 62%) and 92% (95% CI 87 to 95%), respectively, in decision modelling.

Single ratios such as systolic/diastolic (S/D) ratio, albumin/creatinine (A/C) ratio and notch index

The review of diagnostic accuracy of single ratios such as S/D ratio, A/C ratio and notch index included three studies (659 women) for S/D ratio, four studies (1335 women) for A/C ratio and one study (625 women) for notch index (see Appendix 7). The quality of the studies is shown in *Figure 42* and Appendix 8. Sensitivities and specificities are shown in *Figure 43*. *Table 10* shows the results of subgroup analysis. The ROC space is shown in *Figure 44*. The subgroup sensitivities and specificities with their 95% CIs are for the S/D ratio 49% (30 to 69%) and 80% (60 to 92%), for the A/C ratio 71% (55 to 83%) and 82% (72 to 89%) and for notch index 12% (2 to 46%) and 78% (61 to 88%), respectively. We used pooled sensitivities and specificities of 55% (95% CI 37 to 72%) and 80% (95% CI 73 to 86%), respectively, in decision modelling.

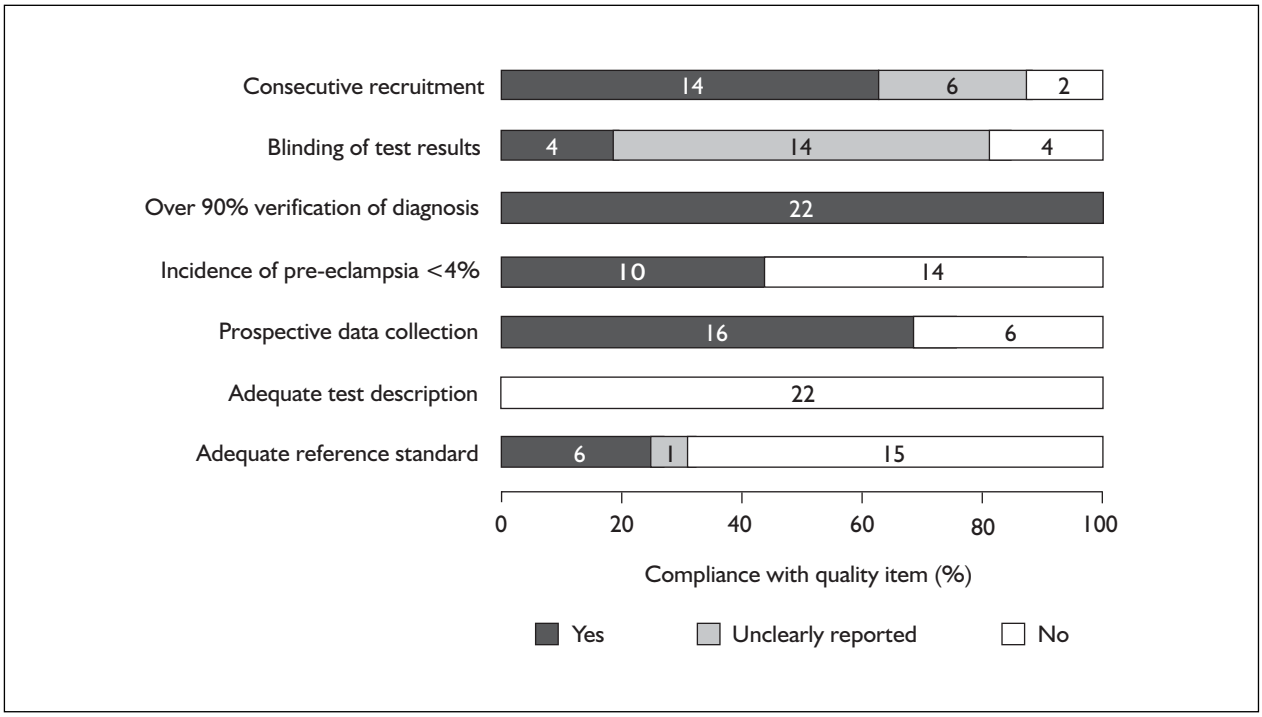


FIGURE 39 *Quality and reporting assessment of studies on Doppler bilateral notching*

TABLE 9 *Subgroup analysis (significance level p < 0.10) for bilateral notching of the main uterine arteries*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no. of studies)	48 (34 to 62)		92 (87 to 95)	
Incidence		0.864		0.096
<4% (9)	47 (28 to 68)		95 (89 to 97)	
≥4% (14)	45 (27 to 63)		89 (80 to 94)	

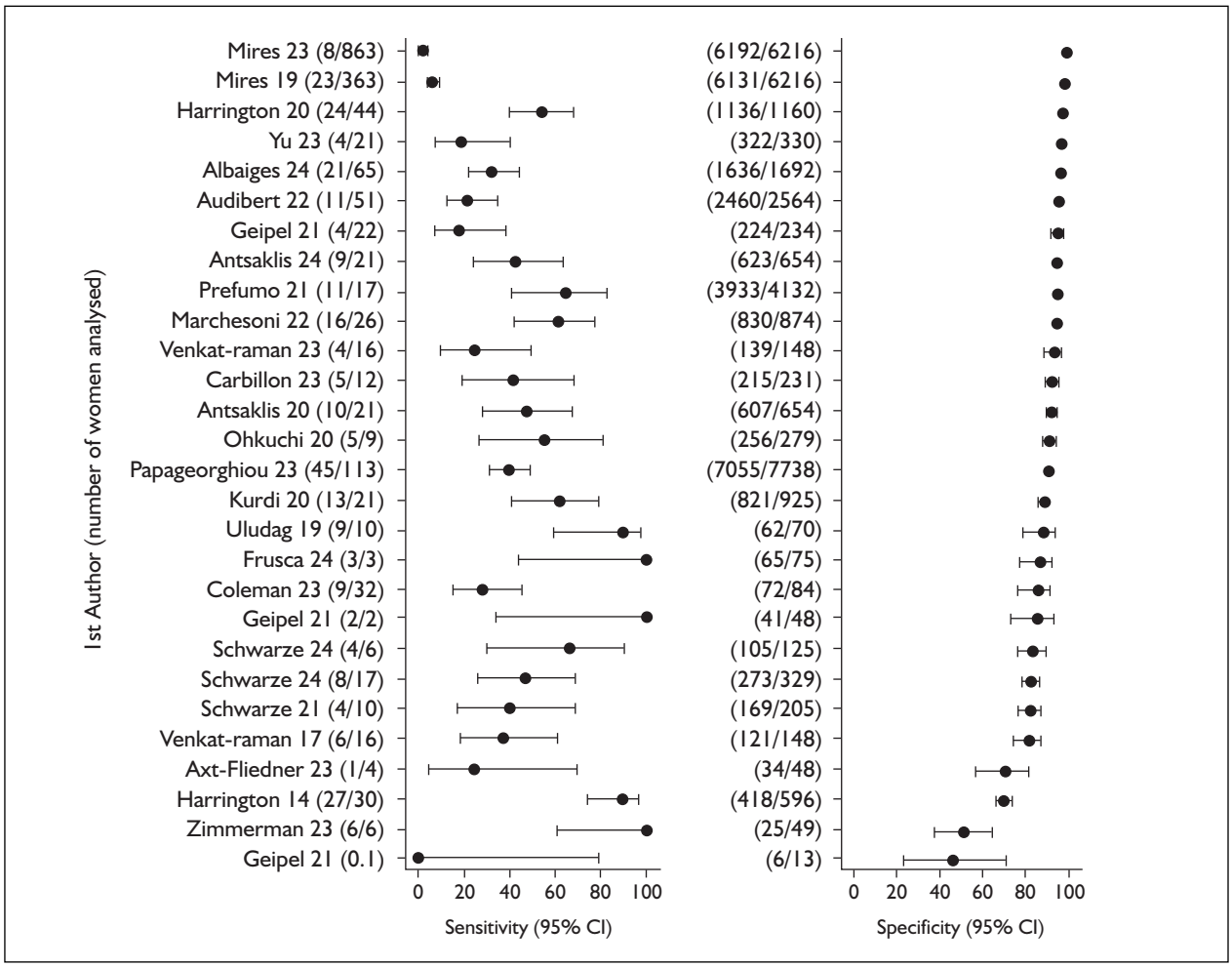


FIGURE 40 *Doppler bilateral notching of the main uterine arteries: sensitivities, specificities and 95% CIs. Numbers to the right of first author's name are average gestational ages (weeks) for time of testing. Note that some authors reported on several gestational ages.*

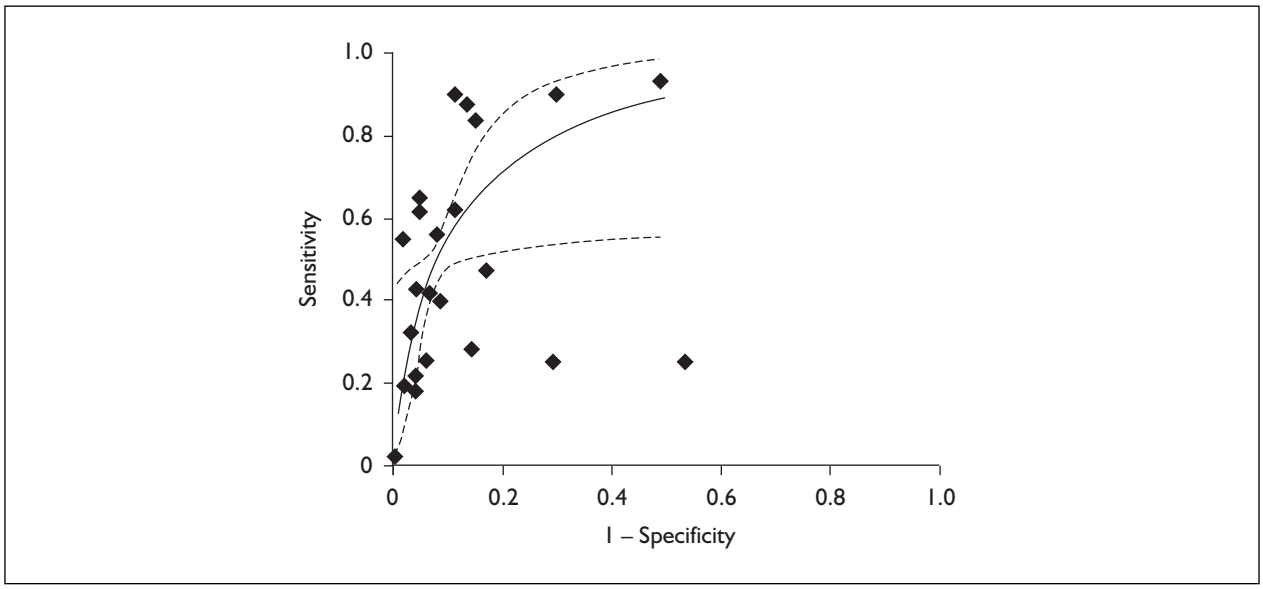


FIGURE 41 *Doppler bilateral notching plotted in ROC space. The ROC space has a solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

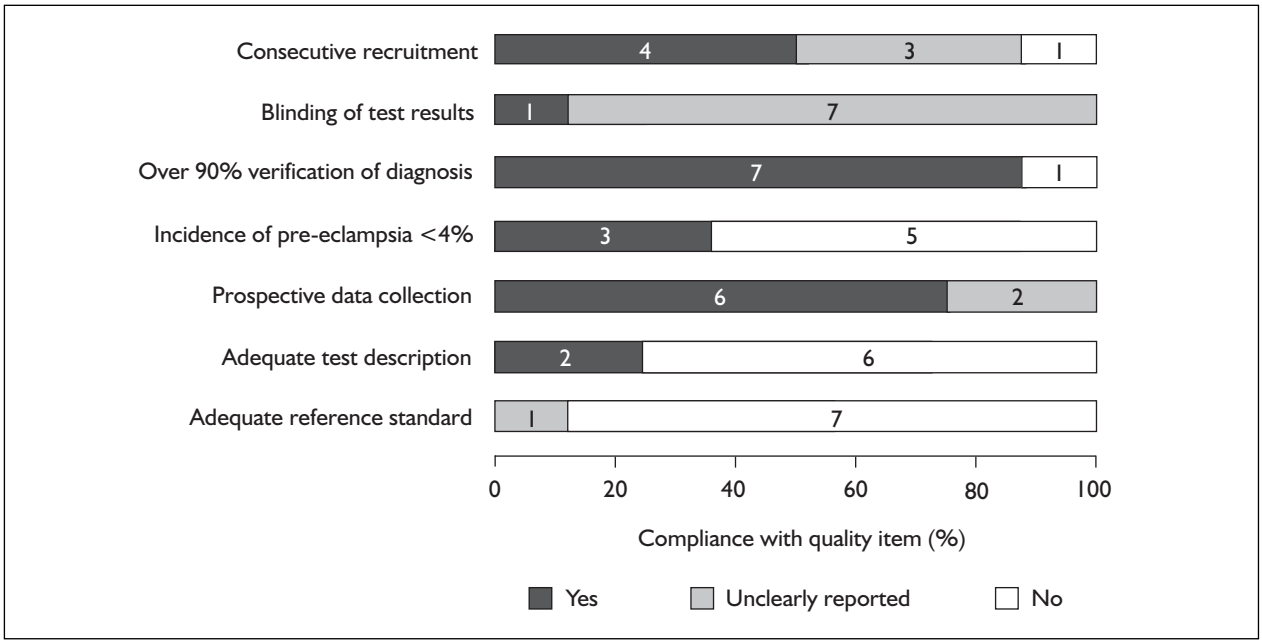


FIGURE 42 *Quality and reporting assessment of Doppler single ratios*

TABLE 10 *Subgroup analysis (significance level p < 0.10) for single ratios of the uterine artery. Aquilina's A/B ratio was not used in calculating pooled estimates to avoid duplicate inclusion of numbers of women*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no. of studies)	55 (37 to 72)		80 (73 to 86)	
Type of ratio		*0.095*		0.861
S/D (3)	49 (30 to 69)		80 (60 to 92)	
A/C (4)	71 (55 to 83)		82 (72 to 89)	
Notch index (2)	12 (2 to 46)		78 (61 to 88)	
Incidence		0.934		0.215
<4% (3)	53 (21 to 83)		84 (75 to 90)	
⩾4% (6)	55 (31 to 77)		77 (66 to 84)	

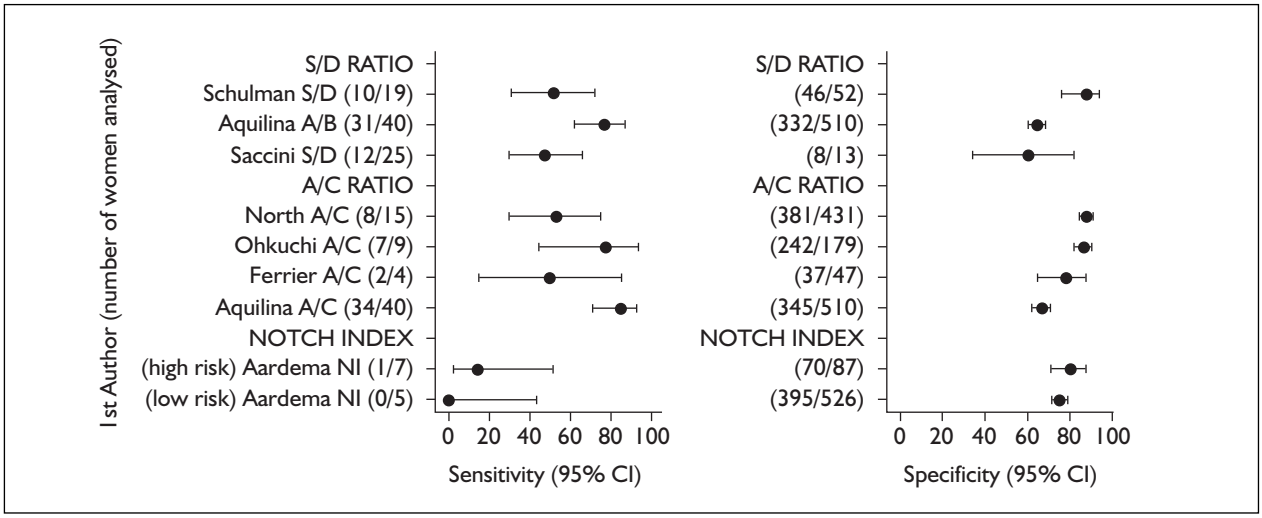


FIGURE 43 *Doppler single ratios: sensitivities, specificities and 95% CIs. Aquilina is one paper with two indices (AB and AC ratio).*

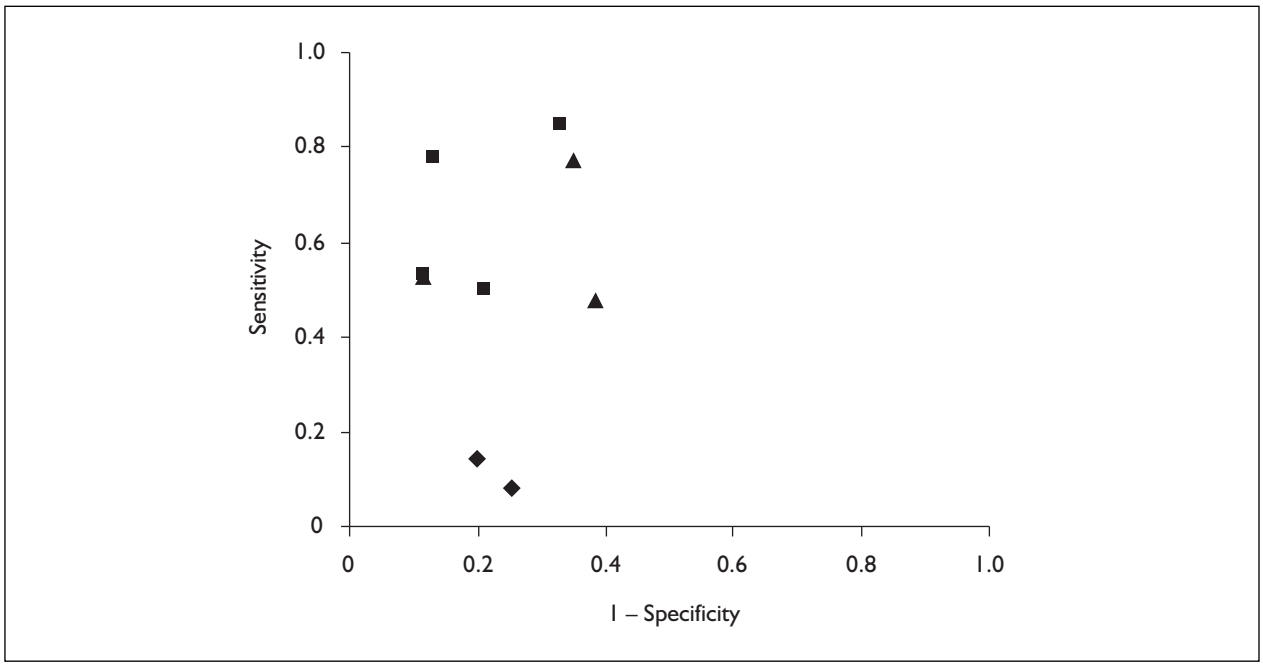


FIGURE 44 *Doppler single ratios plotted in ROC space*

Doppler uterine artery – pulsatility index

The review of test accuracy studies of Doppler pulsatility index included nine studies (reported in eight papers) (14,697 women) (see Appendix 7). The quality of the studies is shown in *Figure 45* and Appendix 8. Sensitivities and specificities are shown in *Figure 46*. *Table 11* shows the results of subgroup analysis. The ROC space is shown in *Figure 47*, where the solid line represents the sROC curve and dashed lines represent 95% CIs. Studies with several measurements are represented only once. We used pooled estimates of sensitivity and specificity of 48% (95% CI 29 to 69%) and 87% (95% CI 75 to 94%), respectively, in decision modelling.

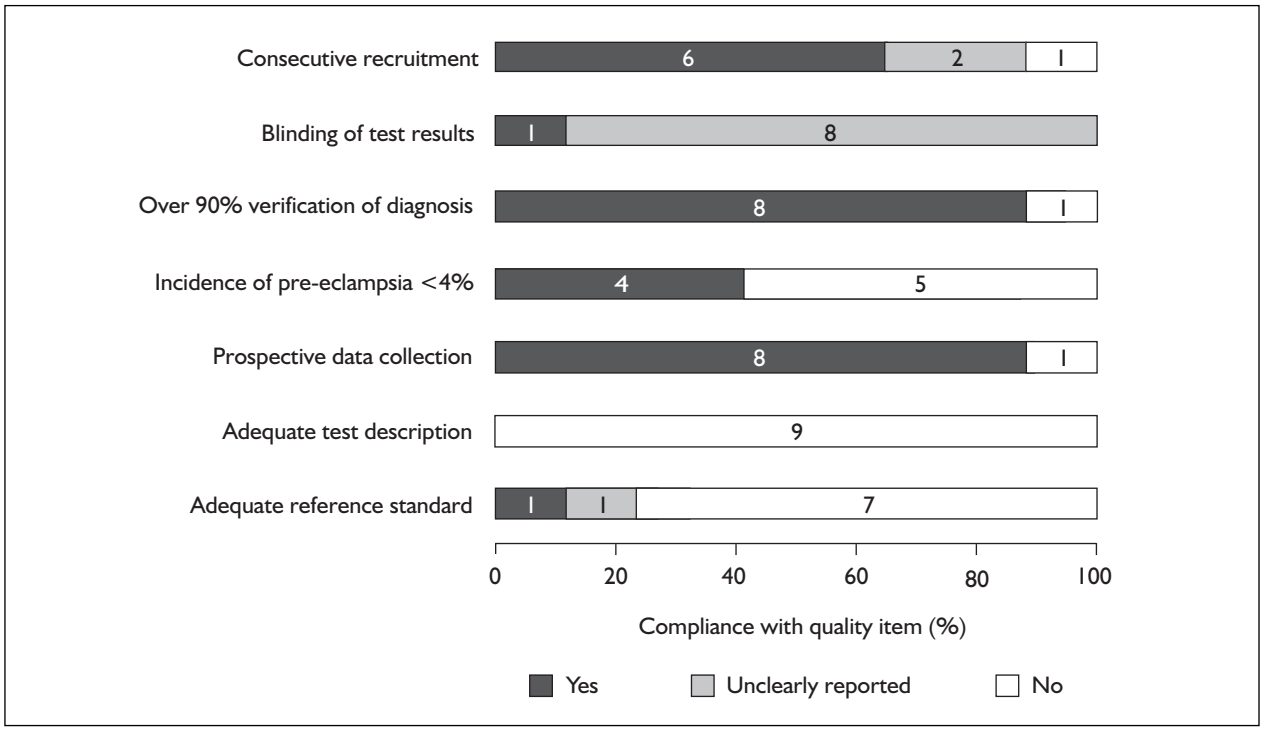


FIGURE 45 *Quality and reporting assessment of pulsatility index of the main uterine artery*

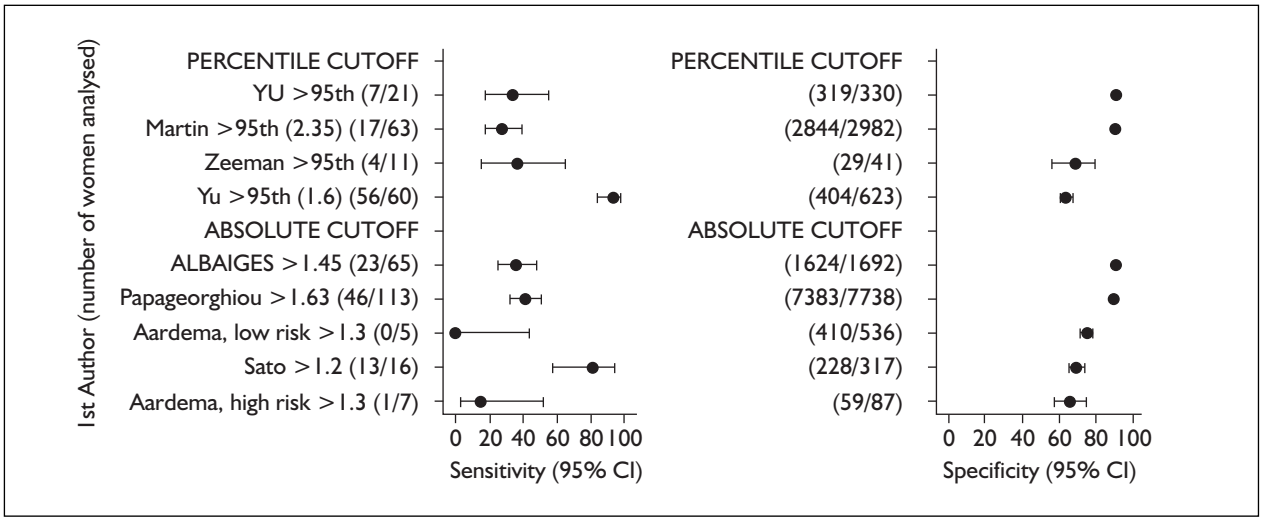


FIGURE 46 *Doppler pulsatility index of the main uterine artery: sensitivities, specificities and 95% CIs. Studies are classified by (1) early (cut-off 16 weeks, Martin and colleagues) versus late gestational age and (2) cut-off level [95th centile versus absolute values (bottom five)].*

TABLE 11 *Subgroup analysis (significance level* p < *0.10) for pulsatility index*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no. of studies)	48 (26 to 69)		87 (75 to 94)	
Incidence		0.185		*0.057*
< 4% (4)	31 (12 to 62)		93 (83 to 97)	
⩾4% (5)	59 (31 to 82)		79 (59 to 90)	

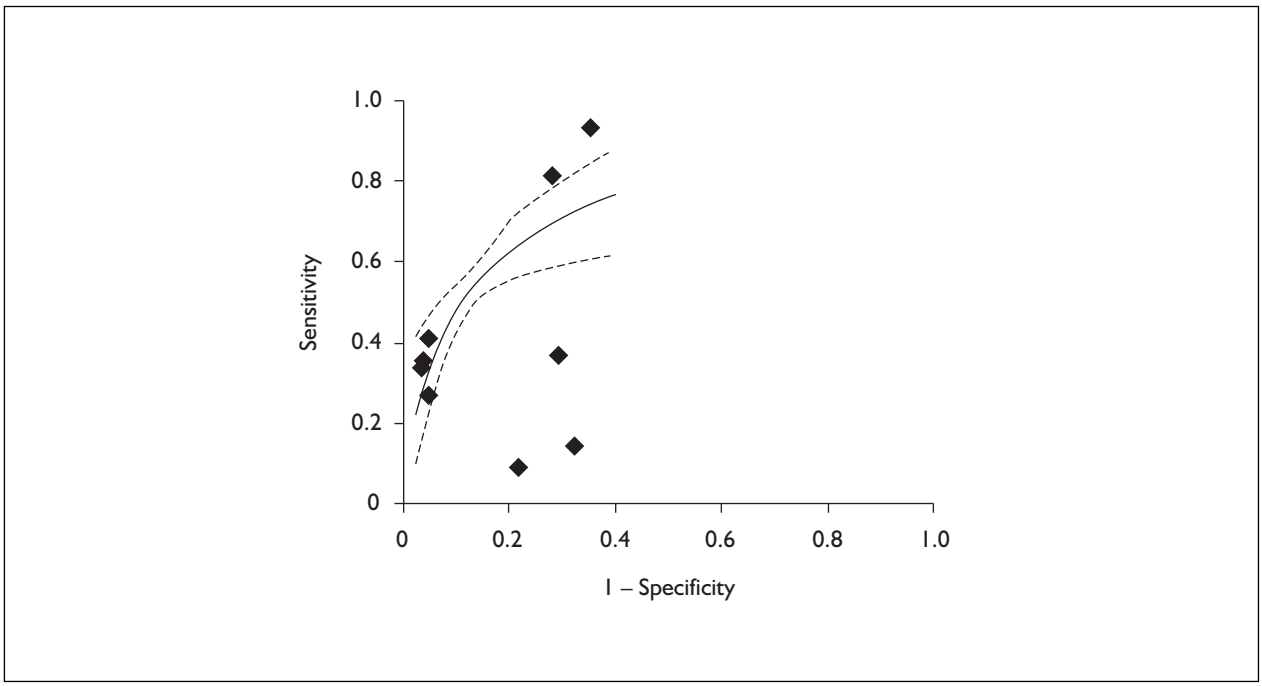


FIGURE 47 *Doppler pulsatility index of the main uterine artery plotted in ROC space. The ROC space has a solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

Doppler uterine artery – resistance index

The review of test accuracy studies of Doppler resistance index of the main uterine artery included 26 studies (reported in 25 papers) (5761 women) (see Appendix 7). The quality of the studies is shown in *Figure 48* and Appendix 8. (Note: one study recorded low- and high-risk women separately and has been counted as two studies in the quality diagrams.) Sensitivities and specificities are shown in *Figure 49*. *Table 12* shows the results of subgroup analysis. The ROC space is shown in *Figure 50*, where the solid line represents sROC curve and dashed lines represent the 95% CI of the sROC curve. Studies with data for several cut-off values were included only once. We used pooled estimates of sensitivity and specificity of 66% (95% CI 54 to 76%) and 80% (95% CI 74 to 85%), respectively in decision modelling.

Combinations of flow velocity waveforms

The review of diagnostic accuracy of combinations of notching and resistance index, notching and pulsatility index, notching and other ratios included 18 studies (11,778 women) for resistance

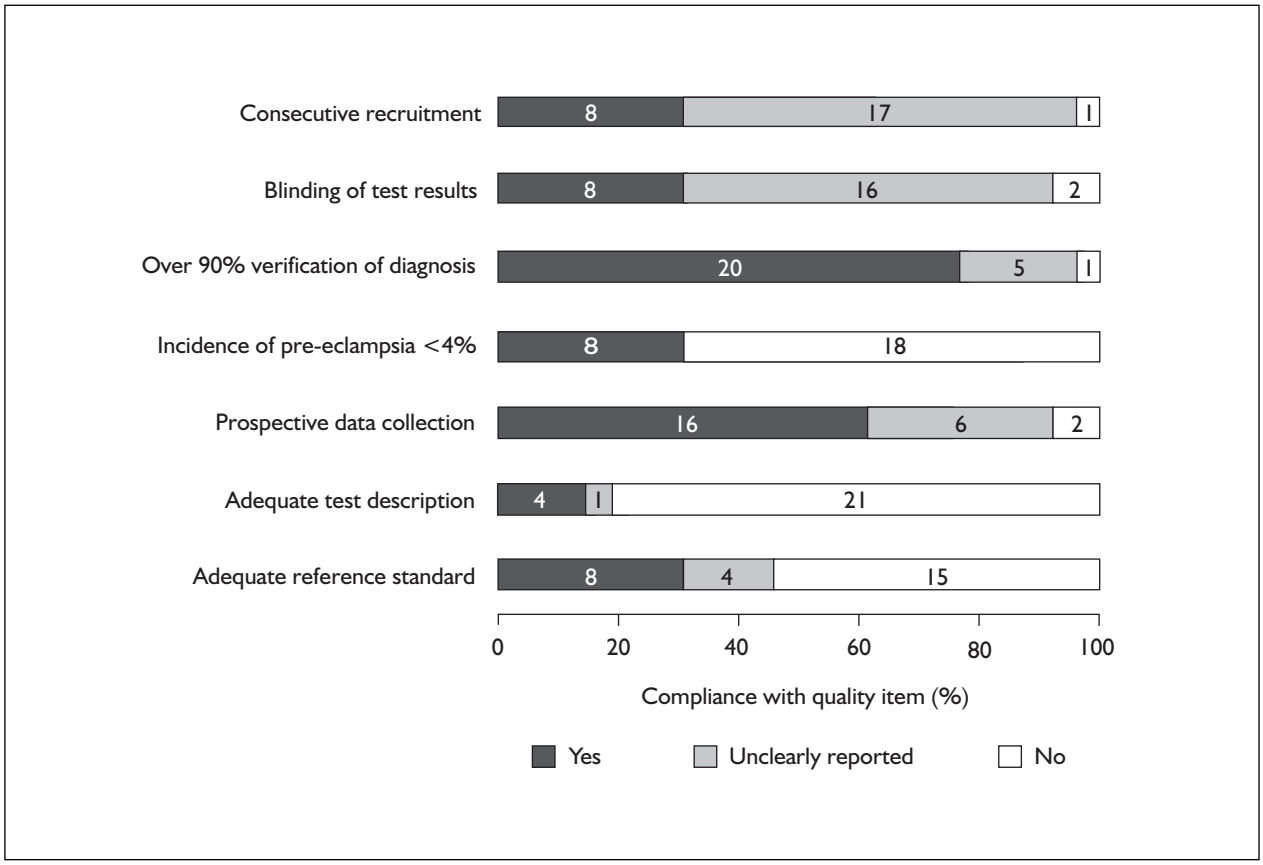


FIGURE 48 *Quality and reporting assessment of resistance index of the main uterine artery*

TABLE 12 *Subgroup analysis (significance level p < 0.10) for resistance index of the main uterine artery*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no. of studies)	66 (54 to 76)		80 (74 to 85)	
Definition of pre-eclampsia		0.902		0.499
Internationally accepted (8)	62 (39 to 80)		84 (73 to 91)	
Other variations (14)	60 (45 to 74)		80 (72 to 86)	
Unclearly/not reported (4)	74 (42 to 92)		85 (69 to 93)	
Incidence		0.371		0.472
<4% (8)	70 (49 to 85)		84 (75 to 90)	
⩾4% (18)	59 (45 to 71)		80 (73 to 86)	

[a] The category 'Not reported' was not used in calculating *p*-values.

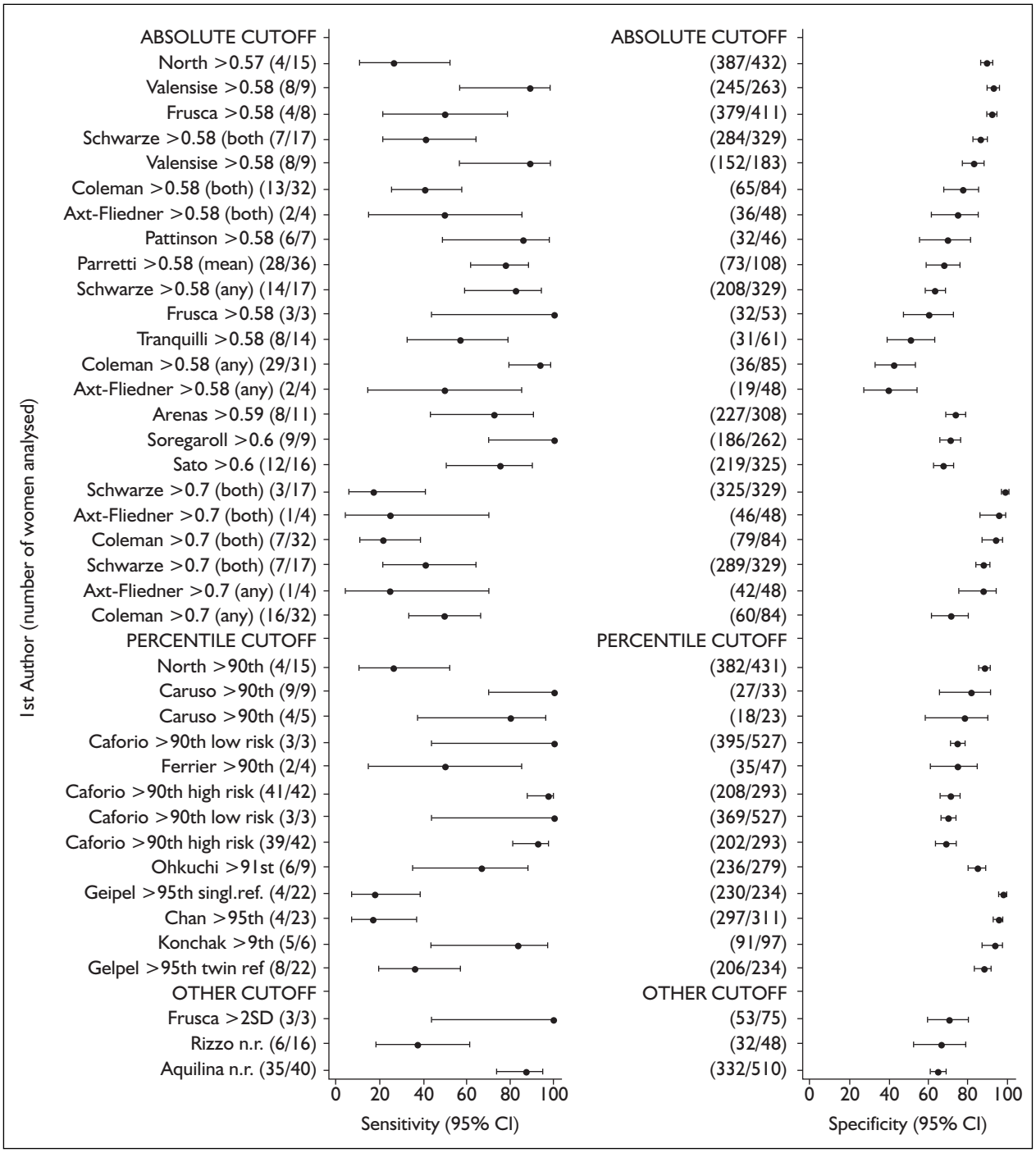


FIGURE 49 *Doppler resistance index of the main uterine artery: sensitivities, specificities and 95% CIs. Studies are classified by increasing cut-off value (absolute versus percentile versus other), which is stated to the right of the first author's name.*

index and/or notching, three studies (9959 women) for pulsatility index and/or notching and four studies (1159 women) for S/D ratio and/or notching (see Appendix 7). The quality of the studies is shown in *Figure 51* and Appendix 8. Sensitivities and specificities are shown in *Figure 52*. *Table 13* shows the results of subgroup analysis. The ROC space is shown in *Figure 53*. All studies are represented only once in the analysis. The sensitivities and specificities with their 95% CIs for notching and resistance index were 67% (56 to 77%) and 86% (82 to 90%), for notching and pulsatility index 38% (17 to 65%) and 95% (88 to 98%) and for notching and other ratios 60% (30 to 84%) and 79% (62 and 89%), respectively. We used pooled sensitivities and specificities of 64% (95% CI 54 to 74%) and 86% (95% CI 82 to 90%), respectively, in decision modelling.

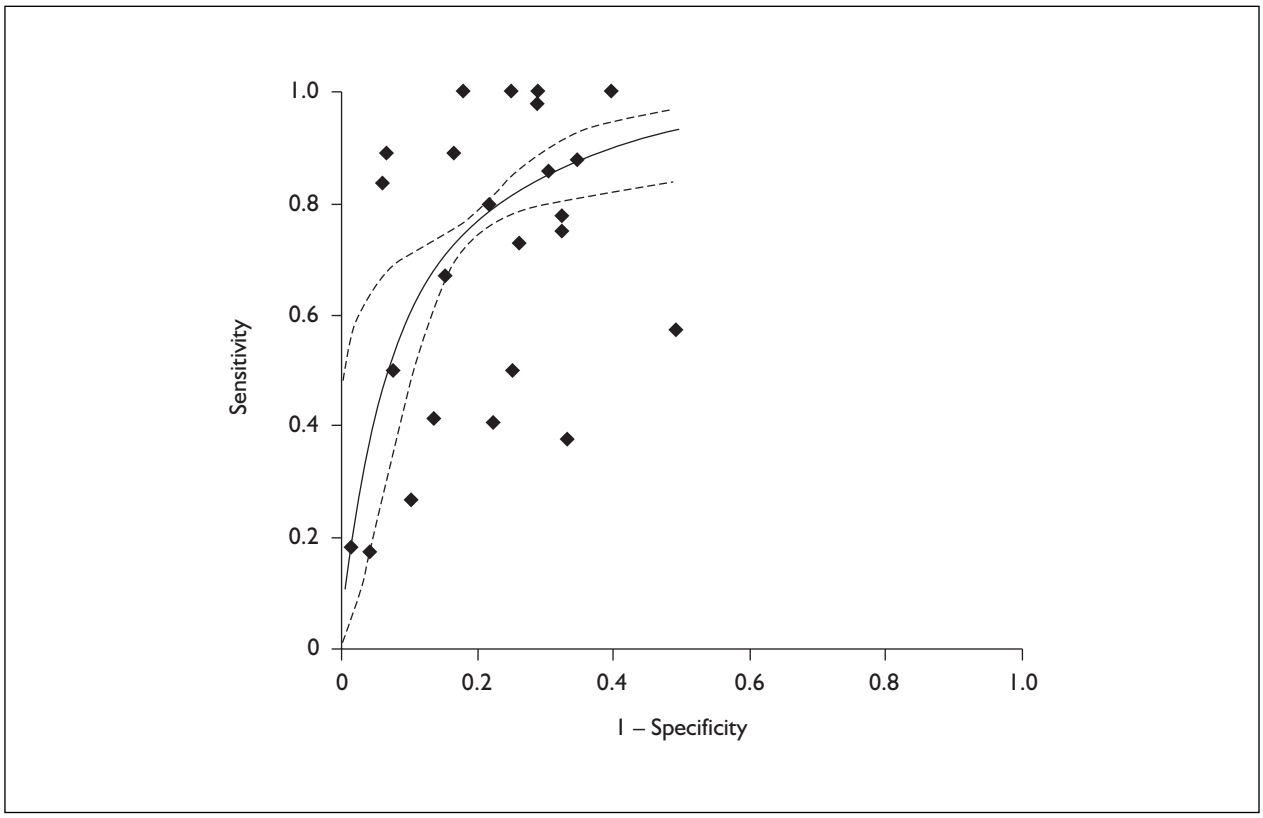


FIGURE 50 *Doppler resistance index plotted in ROC space. The ROC space has solid line representing the sROC curve and dashed lines representing the 95% CI of the sROC curve.*

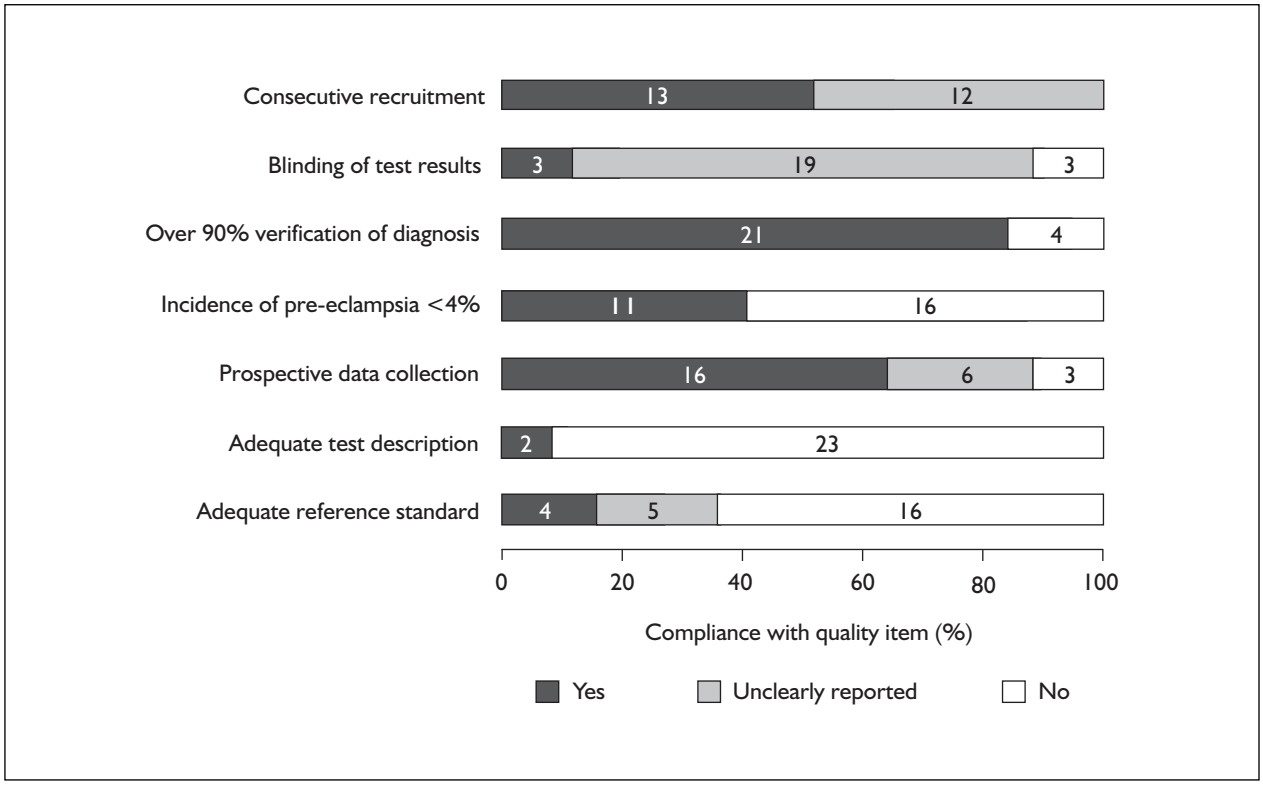


FIGURE 51 *Quality and reporting assessment of Doppler combinations of flow velocity waveforms*

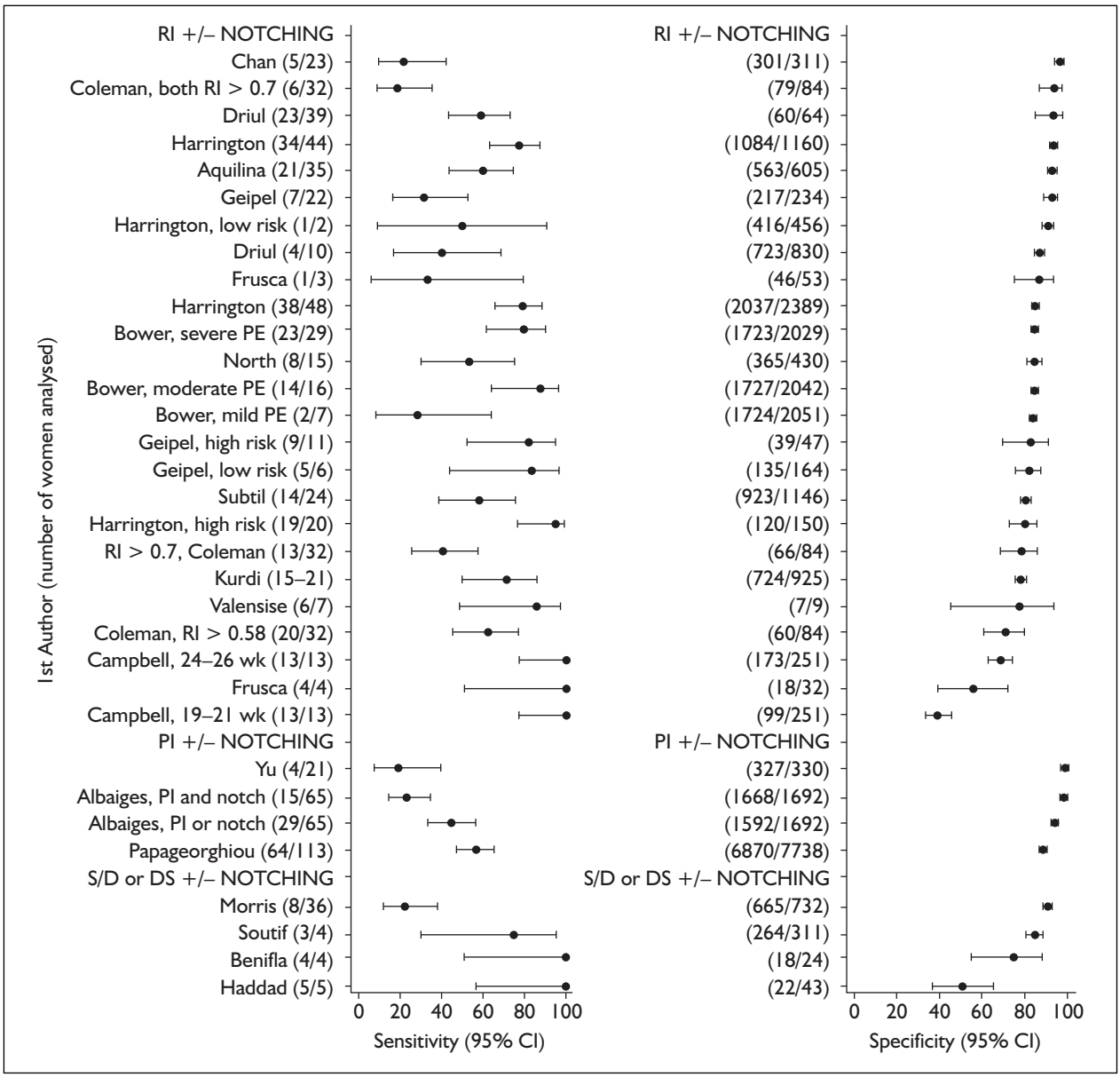


FIGURE 52 *Doppler combinations of flow velocity waveforms of the main uterine artery: sensitivities, specificities and 95% CIs. Studies are classified by (1) resistance index and/or notching, (2) pulsatility index and/or notching, (3) S/D or D/S ratio and/or notching. Note that some studies reported data for several subgroups (e.g. resistance index cut-off value; severity of pre-eclampsia; high- or low-risk population; gestational age), which in these cases is stated to the right of the first author's name.*

TABLE 13 *Subgroup analysis (significance level* p < *0.10) for combinations of flow velocity waveforms of the main uterine artery. All studies are represented only once in the analysis*

Covariate	Sensitivity (%) (95% CI)	*p*-Value	Specificity (%) (95% CI)	*p*-Value
Pooled estimates (no of studies)	64 (54 to 74)		86 (82 to 90)	
Combination of FVW		0.136		0.024
RI and/or notching (20)	67 (56 to 77)		86 (81 to 90)	
PI and/or notching (3)	38 (17 to 65)		95 (88 to 98)	
S/D or D/S and/or notching (4)	60 (30 to 84)		79 (62 to 89)	
Incidence		0.799		0.683
<4% (12)	65 (50 to 78)		87 (81 to 92)	
⩾4% (15)	63 (48 to 76)		85 (79 to 90)	

FVW, flow velocity waveform; PI, pulsatility index; RI, resistance index.

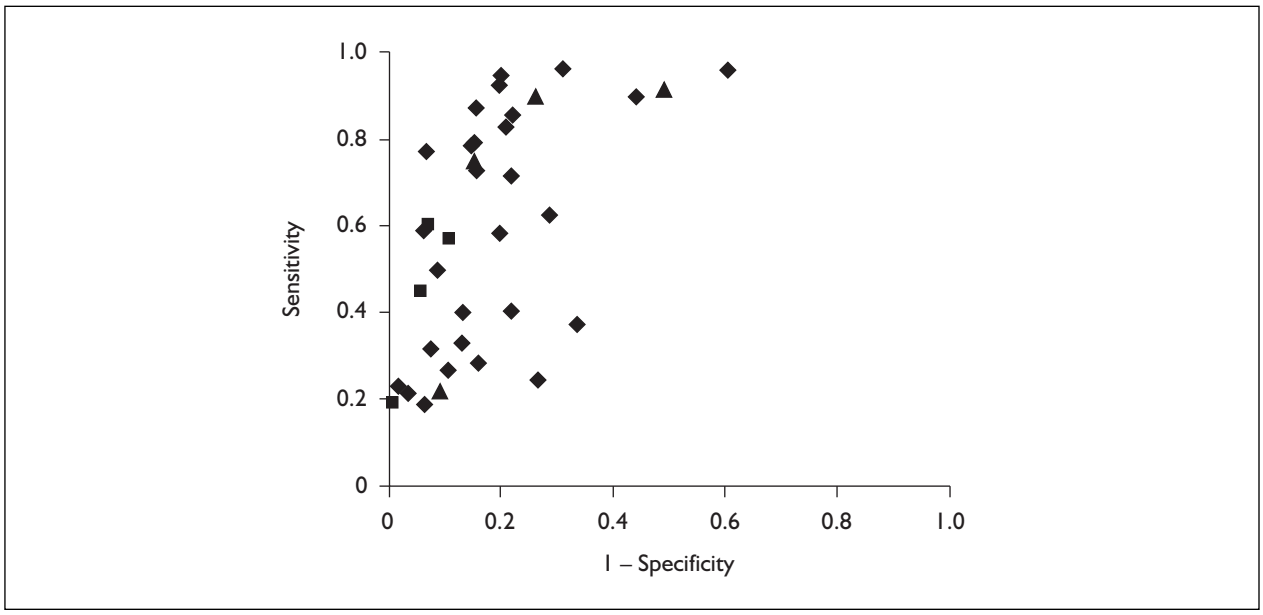


FIGURE 53 *Doppler combinations of flow velocity waveforms and/or early diastolic notching plotted in ROC space. Diamonds represent resistance index and/or notching, squares represent pulsatility index and/or notching and triangles represent S/D ratios and/or notching.*

Discussion of test accuracy

Summary of test accuracy findings

The main results are summarised in *Figures 54* and *55*. The results indicate that the quality of studies and accuracy of tests were generally poor. Some tests have high specificity, but sensitivities tend to be low. Over 90% of studies were published in English.

The total number of women included in the reviews ranged from 135 (cellular FN) to 452,615 (BMI), with a median of 4388 women (proteinuria). The number of women included per test accuracy study ranged from 14 (FN) to 287,213 (BMI). The number of studies per test that were meta-analysed was generally small with a median of seven (range 2–25) (see *Table 5*). Uterine artery Doppler was a notable exception, with a total of 63 studies on its evaluation. However, only coherent Doppler subgroups were meta-analysed, based on the many different indices used for interpretation of Doppler, and these groups were smaller (range 7–25). In the evaluation of many tests, including total FN, fDNA, haemoglobin/haematocrit, oestriol, SUA, urinary calcium excretion and many types of proteinuria, the limited number of studies and the limited number of cases with pre-eclampsia per study seriously constrained conclusions.

The overall quality of studies within reviews was variable. There were deficiencies in many areas of methodology (see *Figure 54*). No test had universally high-quality data. The interpretations of the accuracy data on all tests were negatively affected by poor reporting and potential threats to validity identified in assessment of study quality. In particular, studies suffered in blinding, test description and reference standard adequacy. Thus, when assessing results, we often could not be confident about the reported predictive ability of tests. Many studies included patients across the clinical risk spectrum, but did not provide separate results for specific parts of the spectrum, such as women without any particular risk factors. On the other hand, over half of the studies had pre-eclampsia incidences greater than 4%. Consequently, the material we studied sometimes gave an opportunity to study variation of test accuracy between low and high(er) incidence populations.

For most of the tests evaluated, results were pooled using the (random effects) bivariate method. This method accounts for statistical heterogeneity left unexplained after attempts, where feasible, to identify its sources in clinical subgroups, diagnostic modality variations and/ or quality items. However, in the case of fibronectin we deemed meta-analysis misleading in the light of extreme variations in test thresholds within studies and resultant heterogeneity in the estimation of accuracy. Here, only results of individual studies could be considered useful for clinical application. *Figure 55* is the forest plot of sensitivity and specificity that we believe to be suitably valid for consideration in clinical decision-making

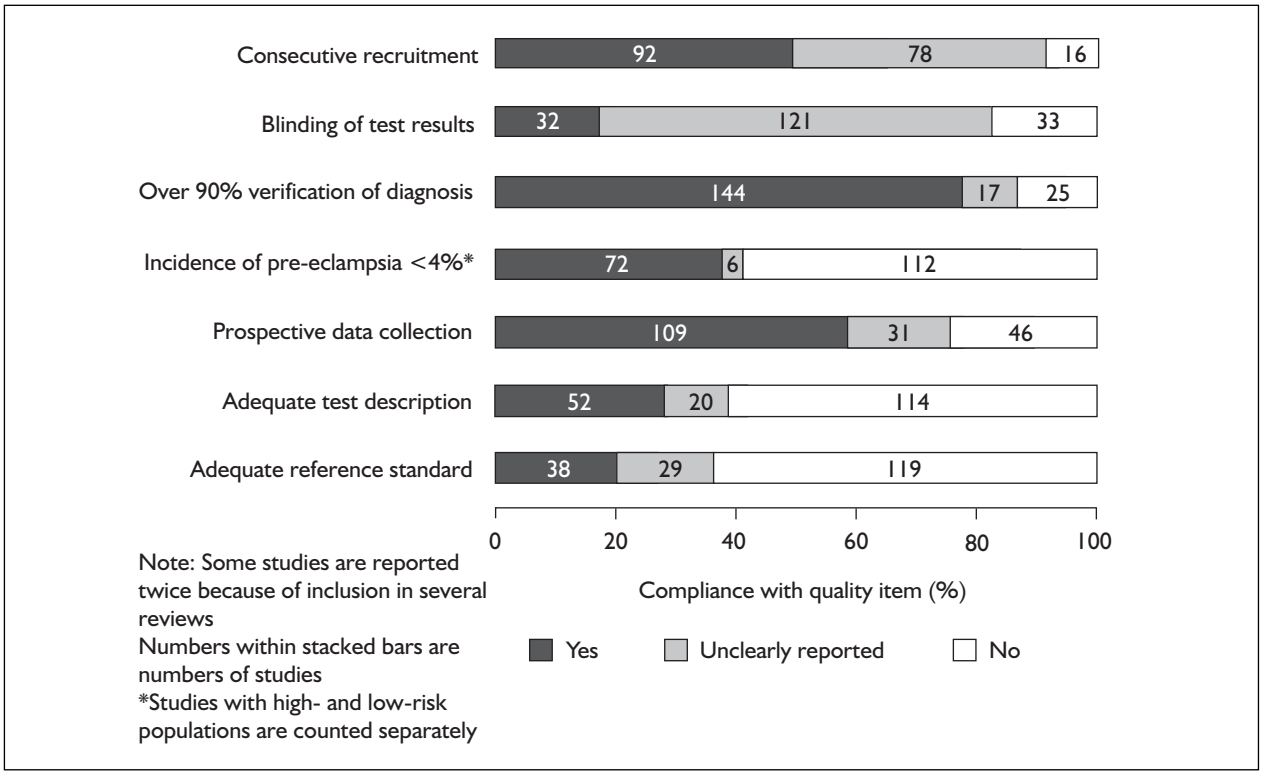


FIGURE 54 *Quality of all tests reviewed for prediction of pre-eclampsia*

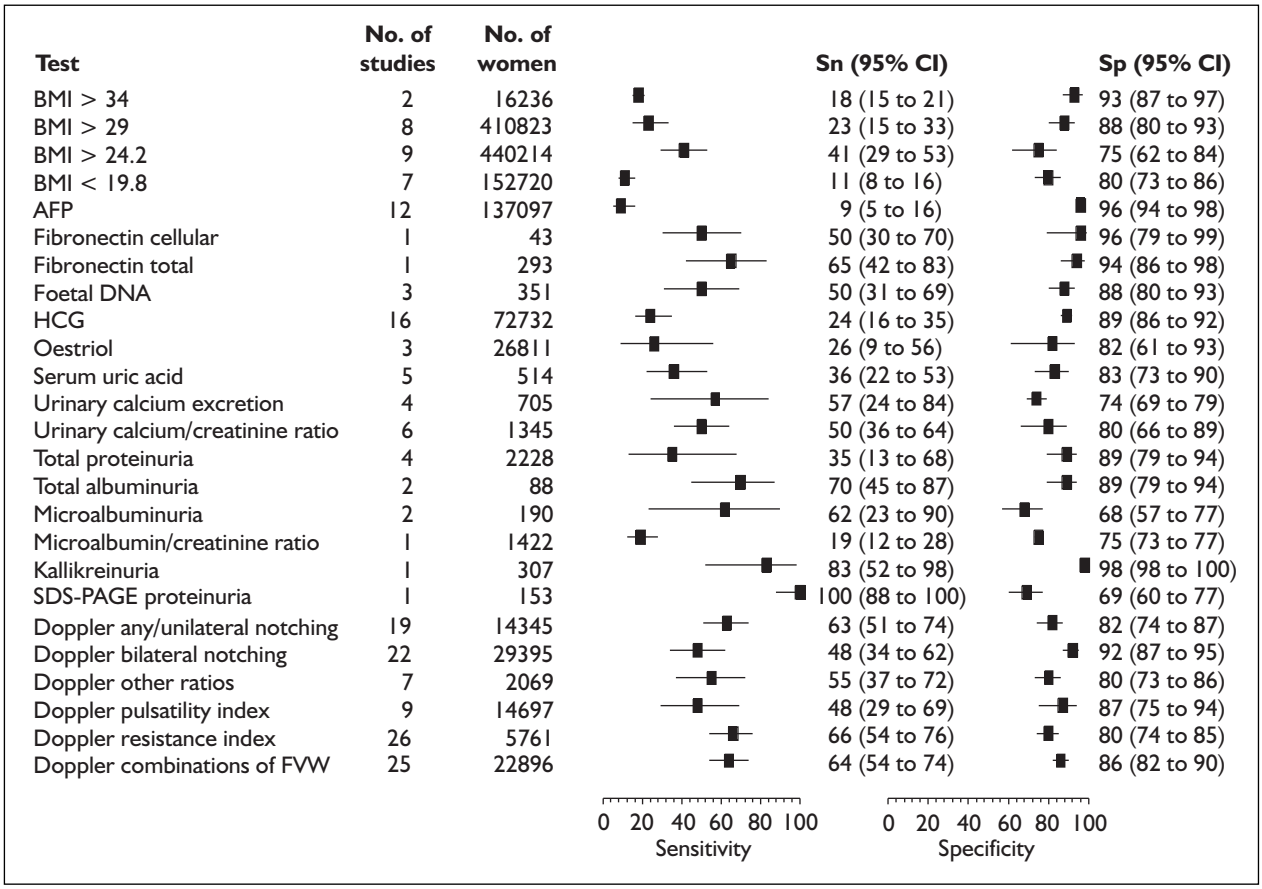


FIGURE 55 *Forest plot of accuracy estimates put forward for decision analysis*

of each of the tests reviewed. These results have been put forward for decision-analytic modelling.

In general, tests in early pregnancy for predicting later development of pre-eclampsia tended to have better specificity than sensitivity, although the precision of estimation varied considerably. Specificity (true negative rate) of a test is the proportion of those women who did not develop pre-eclampsia later who were initially identified as such. A highly specific test has a very low proportion of false positive results. Thus, when such a test produces a positive result it tends to rule in later development of disease (if sensitivity is moderate and prevalence is not too high). Sensitivity (true positive rate) of a test is the proportion of those women who really developed pre-eclampsia later in pregnancy who are initially identified as such. A highly sensitive test has a very low proportion of false negative results. Thus, when such a test produces a negative result it tends to rule out later development of pre-eclampsia (if specificity is moderate and prevalence is not too low).

Screening typically involves use of a confirmatory test after initial testing, prior to the institution of therapy. In this project, this use of confirmatory tests is not the case as testing is used to identify a risk group in which preventative interventions (both intensive monitoring and treatments) will be employed directly after test results are known. In this situation, for a test to serve as a good tool for screening, it should perform well in both sensitivity and specificity. However, there often tends to be a trade-off between sensitivity and specificity and the preferable balance depends largely on the outcomes of disease and morbidity and costs associated with the intervention. Given also the consequences of false positive results (both costs of intensive monitoring and treatment-associated morbidity among normal women), it is important that test specificity is suitably high. This is because erroneously providing interventions to women falsely labelled as positive leads to unwarranted inconvenience, expense and morbidity when pre-eclampsia would not have developed later in pregnancy anyway. Given the consequences of false negative results (both costs and morbidity of cases left untreated), it is important that the test sensitivity is suitably high. This is because erroneously withholding effective interventions from women falsely labelled as negative leads to excessive morbidity and expense when disease develops later in pregnancy. If available effective interventions are convenient, inexpensive, and without adverse effects (to both mother and child), it is better to have the accuracy trade-off in favour of sensitivity than specificity.

Figure 55 demonstrates that when considering the point estimates and imprecision in their estimation, most tests perform either poorly or the level of their performance is uncertain. Only a few tests reached specificity above 90%. These were BMI >34, AFP, FN (cellular and total), kallikrein and uterine artery Doppler (bilateral notching). Concerning Doppler sensitivity, only Doppler (any/unilateral notching, resistance index and combinations) were over 60% sensitive. Kallikreinuria and SDS-PAGE proteinuria seemed to offer the promise of high sensitivity at over 80%, without compromising specificity, but would require further investigation because these findings are based on results from single studies only. Depending on the level of effectiveness of various interventions (Chapter 4) and their associated inconvenience, costs and morbidity, a threshold analysis (Chapter 5) will be required to determine what levels of sensitivity and specificity are required to make testing cost-effective in the prevention of pre-eclampsia.

Provisos/limitations arising from problems with primary data

The interpretations of the accuracy data on tests are affected by threats to validity identified in assessment of study quality. There was no test that had universally high-quality data. The overall quality of studies within reviews was variable, with deficiencies in many areas of methodology (see *Figure 54*). Association between design quality components and diagnostic performance has been studied empirically.[81,91] A rationalistic approach is that study design (and execution) issues require their proper (honest) reporting before any measures of diagnostic performance (whatever their magnitude) count as scientific evidence.

Studies often did not conform to the standards of reporting for diagnostic studies.[82] In particular, they suffered in blinding, test description and reference standard adequacy. The extent to which these deficiencies have impacted on accuracy estimates depends on a number of factors. There is a 15–26-week time separation between predictive testing and its verification by the reference standard in pre-eclampsia. In this situation, blinded assessment of the reference standard may not be as major an issue if the predictive test results were collected for an unrelated purpose, for example Down's syndrome screening, and were forgotten by the time pre-eclampsia appeared in the course of pregnancy. This problem would be

further diminished if, during the study, healthcare providers did not employ the hypothesis that the test result carried information on the occurrence of pre-eclampsia. We would have liked to see sufficient information for others to be able to replicate tests and for us to be able to categorise patients according to new disease classifications for hypertensive disorders of pregnancy. This was often not possible. Our expectations of the level of detail that should be provided about test and reference standard in the primary studies were perhaps unrealistic given that initiatives to improve reporting are recent phenomena.

It was often not possible to be certain about the definition of pre-eclampsia used in studies. There was a lack of information on the exact technique of blood pressure measurement and Korotkoff threshold for abnormality or whether the proteinuria was in the absence of urinary tract infection and pre-existing renal disease or whether there was normalisation of blood pressure within 6 weeks of giving birth. Moreover, there was generally no specification of clinically important details of pre-eclampsia such as whether it was early or late and severe or non-severe. We had planned to perform subgroup analyses according to time of onset and severity of pre-eclampsia, wherever possible (see the section 'Methods for test accuracy reviews', p. 11) but lack of data precluded this for most of the diagnostic tests reviewed. The poverty of reporting also impacted on assessment for the risk of treatment paradox: i.e. giving effective treatments to test positive patients may lead to potential non-occurrence of pre-eclampsia, making an otherwise reasonable test appear inaccurate. However, the treatments that exist are mostly of not proven effectiveness (see Chapter 4).

Spectrum bias refers to the possibility that a test's sensitivity and/or specificity vary between groups of patients with different illness severity[92,93] In other words, spectrum bias refers to variation across subgroups (or, to use the technical term, effect measure modification). However, the issue of diagnostic confounding by other diagnostic test information has so far been overlooked. (Confounding here refers to when one or more diagnostic tests have predictive abilities that are related to each other and to the outcome so that it is difficult to assess the independent prediction (the added value of one, given the other) from each of the tests on the diagnosis of the outcome). Unfortunately, the issue of diagnostic confounding may only be dealt with by multivariable analysis of the primary study data or individual patient data (IPD) meta-analyses.[94] Interestingly, the latter approach was taken increasingly in Doppler studies after 2004. The tests could have been studied using IPD meta-analysis but this would have required access to raw data from studies, which was not within the scope of our work and would have required considerable additional resources. Such multivariable analysis would generate probabilities of pre-eclampsia for a series of patient characteristics (a predictive profile) that incorporate test results. If no multivariable analysis is planned, such confounding may be counteracted by the selection of patient groups that are homogeneous as to their other diagnostic characteristics (patient history and obstetric risk profile in multiparous women). However, such an approach is difficult given the large number of pieces of diagnostic information that usually exist (such as age, parity, co-morbidities and BMI).

Strikingly, there was a virtual absence of correlation between strictness of patient entry criteria and the incidence of pre-eclampsia between studies. This could be because entry criteria were haphazard such that the intended population was different to the sample enrolled. This could also be because of geographical, genetic, nutritional and other variations that predispose women to pre-eclampsia. To be practical, we therefore defined subgroups according to a 4% incidence threshold (see the section 'Methods for test accuracy reviews', p. 12), but studies often did not provide separate results for the low-risk subgroup. Over half of the studies had pre-eclampsia incidence of greater than 4%. Consequently, to some extent, the material that we studied gave an opportunity to study test accuracy in low- and high(er)-incidence populations. The results did not always provide information concerning prediction in purely low-risk groups.

Provisos/limitations arising from review methods

The selection of tests for review of their accuracy was based largely on the opinion of the research team, including practising obstetricians, also with advice from a small external group. To add scientific validity to the selection process, a Delphic survey of practice might have been more appropriate. The reviews were carried out using a comprehensive search strategy so as to minimise the risk of missing studies. Nevertheless, the amount of research identified per test was often insufficient to produce precise estimates of accuracy. With the exception of the Doppler test, the evaluation of many tests, particularly total FN,

fDNA, haemoglobin/haematocrit, oestriol, SUA, urinary calcium excretion and many types of proteinuria, was limited due to imprecision. In particular, the estimate that suffered most in this respect was sensitivity, as its precise estimation requires large absolute numbers of pre-eclampsia cases.[94] Thus, when assessing their results we could not always be confident about the range of reported predictive ability of tests.

Our review made explicit the deficiencies in the quality of studies.[81,82,91] We would have liked to have based our inferences on high-quality studies but often numbers of studies per test were too small or reporting was too unclear to achieve this. We had planned subgroup analyses according to study quality, population clinical risk level, disease severity and possible variations in test (sub)modalities used, for example different assay techniques for the same test. Ideally we would have liked to obtain estimates of accuracy for clinically relevant subgroups or test modalities adjusted for study quality. Our experience that this is very difficult has recently been formally acknowledged.[95] Due to the low number of included studies, subgroup analyses (either clinical or quality based) were often not possible or would have had low power to identify differences. Subgroup analyses on severe pre-eclampsia in the AFP and HCG reviews did not appear to make any difference in the pooled estimates.

Due to variations in test thresholds for determining abnormality, generating summaries of findings was not straightforward. The bivariate method deals with this by estimating the correlation between sensitivity and specificity. When information is scarce, however, such estimations may be imprecise. For some tests, and uterine artery Doppler in particular, the same study provided estimates of more than one diagnostic indicator (e.g. resistance index and notching). This precluded valid statistical comparison of these indices due to violation of the principle that the compared study samples are statistically independent. Recently, this issue was addressed in the literature, but the solution was based on the use of odds ratios, which has other drawbacks.[96] We made a systematic attempt (see the section 'Methods for test accuracy reviews', starting on p. 9) at translating results in a summary ROC space into clinically relevant information. For pooling test results, the bivariate method was particularly suitable as it takes into account the relationship between sensitivity and specificity that may exist due to threshold effects. Since it also uses a random effects approach, unexplained statistical heterogeneity was formally taken into account. We could not explore reasons for heterogeneity in detail largely because poor reporting and the small number of studies per test would have rendered the use of statistical methods such as meta-regression underpowered. As most pooled results amalgamated heterogeneous individual estimates, these should be interpreted with caution. Given also the uncertain impact of study design issues on the magnitudes of sensitivity and specificity,[91] our view is that the summaries that we generated provide the best available results for clinical interpretation at the time of completing our work.

Provisos/limitations arising from things not done

For some tests, we found so few studies that no meaningful analyses could be carried out (such as haemoglobin and haematocrit). Where studies were available, absence of primary data in key areas and limitations of reviews including few, generally poor studies limited our ability to explore the information collated as completely as we would have liked. As an example, incomplete analyses when repeated measurement of index tests had been performed (such as for proteinuria) precluded the possibility of taking a monitoring perspective which is critical in antenatal care, particularly among high-risk cases. Some studies reported mean ± SD for non-Gaussian distributions of index test results and did not provide 2 × 2 tables. Such information had to be excluded from our reviews. One of the key conclusions is that better quality primary studies, especially in new evaluations of new tests, are required.

It has already been highlighted above how reviews could have benefited from the use of advanced techniques such as meta-regression analysis and IPD meta-analysis had more (better reported) studies per test or more resources been available. Despite these deficiencies, in comparison with previous comprehensive work by the WHO[90] reviewing tests for pre-eclampsia, this review covered more tests and found more studies. The results here are more precise than in the previous work cited and currently provide the best available evidence for clinical interpretation.

Findings in the light of limitations

Screening typically involves use of a confirmatory test after initial testing, prior to institution of therapy. In our project, this is not the case as testing is used to identify a risk group in which preventative interventions (both intensive

monitoring and treatments) will be employed directly after test results are known. Given the quality, level and precision of the accuracy evidence, no single test has emerged as a front runner in the quest to predict and prevent pre-eclampsia. The test that seems to offer the promise of both high sensitivity and high specificity is kallikreinuria but it would require further investigation. Tests that offer high specificity, such as BMI >34, AFP, fibronectin and uterine artery Doppler (bilateral notching), have the potential to minimise unwarranted inconvenience, expense and morbidity associated with false positive results when disease would not have developed later in pregnancy anyway. Tests with high sensitivity, such as Doppler (resistance index and combinations), have the potential to reduce costs and morbidity of cases left untreated associated with false negative results.

Ramifications for the economic model

How accuracy results are incorporated into the model includes dealing with challenges relating to the systematic review process (covered above) and patient preferences. One of the key issues concerning screening or predictive tests in this project is that, if available, effective interventions are convenient, inexpensive and without particular risk of harm or side-effects (to both mother and child); high sensitivity is more important than high specificity. It is worth speculating that in preventing pre-eclampsia, it is difficult from a clinical and patient perspective to distinguish between false positive and false negative test results and so from this perspective the optimal test will be one which minimises both false positive (high specificity) and false negative (high sensitivity) results. As we have observed that tests tend to have higher specificity than sensitivity, they are unlikely to improve cost-effectiveness when used in combination with inexpensive, safe and effective treatments (e.g. aspirin). Doppler testing for predicting and preventing pre-eclampsia is particularly badly affected by cost-effectiveness analysis incorporating the costs and effects of treatment, when its perceived value depends on also predicting other things (growth restriction and perinatal mortality). There is a small risk of overlooking potentially cost-effective test accuracy results compatible with the included data, particularly maximised sensitivity, which may have been overlooked by focusing on summaries produced by bivariate analyses. For example, if we plot the sensitivity and specificity input into the model on the relevant ROC spaces for uterine artery Doppler (resistance index), the values do not appear to be completely representative of the data actually obtained from the included studies. This is largely because populations and test thresholds vary. We have only put forward data in *Figure 55* for decision-analytic modelling, which we believe provide the most robust estimates. Ultimately, the threshold analysis (Chapter 5) shows what levels of sensitivity and specificity will be required to make testing cost-effective in prevention of pre-eclampsia.

Recommendations for practice

Given the generally low sensitivities of the tests evaluated, a practical recommendation for clinicians for prevention of pre-eclampsia is to consider refraining from testing, but to initiate preventative treatment.

Recommendations for research

- The development of new tests or markers should be followed by new, more robustly designed test accuracy studies with sufficient power to estimate test sensitivity.
- Such studies should preferably evaluate the added value of new tests using statistical analyses that incorporate information which physicians document through the clinical history (risk profile).
- Power and validation of so-developed predictive models (mathematical risk functions) may involve (prospective) IPD diagnostic meta-analyses.
- The choice of tests for systematic review may be guided by a Delphic survey of practice.
- Combinations not evaluated, such as blood pressure and proteinuria, should be evaluated.
- Any new evaluations must be undertaken in the setting in which they will be applied.

Conclusions of test accuracy reviews

The quality of studies and accuracy of tests were generally poor (*Figure 54*). Some tests appear to have high specificity, but at the expense of compromised sensitivity. Only a few tests reached a pooled specificity above 90%. These were BMI >34, AFP and uterine artery Doppler (bilateral notching). Concerning Doppler sensitivity, only Doppler (resistance index and combinations) was over 60% sensitive. Cellular and total FN and kallikreinuria were found to have a specificity above 90% based on single estimates. A few tests not commonly found in routine practice, such as kallikreinuria and SDS-PAGE proteinuria, seemed to offer the promise of high sensitivity, without compromising specificity, but would require further investigation.

Chapter 4

Clinical effectiveness reviews

Study selection

Overall, of 1803 citations identified as potentially eligible for the Cochrane reviews (see *Figure 56* and *Table 14*), 315 RCTs were incorporated into reviews (see *Tables 15–17*).

Presentation of results

The Cochrane systematic reviews are grouped by interventions based on Antenatal care, Lifestyle, Dietary and Pharmacological interventions. The characteristics of included studies, methodological quality of included studies, results and input to the decision analysis-based economic model are described for each review. The primary outcome was pre-eclampsia and this was the input to the economic model. The pre-eclampsia complications also reported here are death of the baby, preterm birth and the baby being small for gestational age. These outcomes could not be incorporated into the economic model at the current stage of its development. Other outcomes including safety/side-effects/adverse events reviewed but not included in this report can be found in the Cochrane Library. Similarly, excluded studies for each review can be found in the Cochrane Library.

Antenatal care interventions

Ambulatory versus conventional methods for monitoring blood pressure during pregnancy

Blood pressure measurement plays a central role in the screening and management of hypertension during pregnancy. In recent years, the validity of conventional (clinic) blood pressure measurement has been questioned and it has been suggested that ambulatory automated devices, providing multiple measurements usually over a 24-hour period, might be more reliable.

The review of ambulatory versus conventional methods for monitoring blood pressure[97] did not identify any RCTs.

Lifestyle interventions

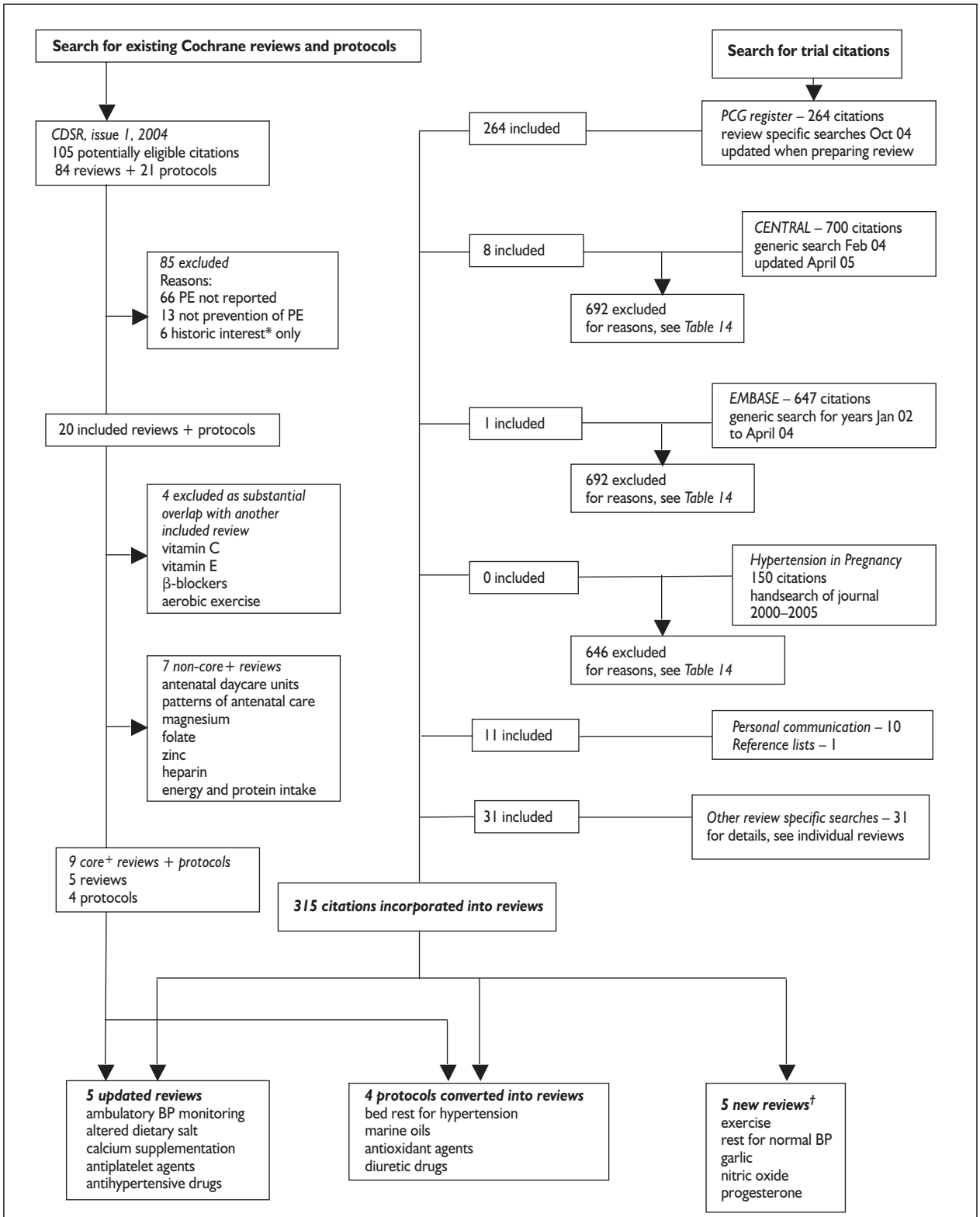
Bed rest with or without hospitalisation for hypertension during pregnancy

Women with high blood pressure are often advised to rest in bed either at home or in hospital. It is suggested that this might help to reduce the mother's blood pressure and so provide benefits for the baby. However, there may be adverse

TABLE 14 *Generic search: reasons for excluding potentially eligible citations*

Source	Not eligible			Excluded after further assessment								Full trial reports retrieved for detailed evaluation
	Total citations	Not HDP	Not RCT	Not prevention of PE	Duplicates (PCG register/other electronic database)	Not RCT	Not HDP	Not prevention of PE	Inappropriate intervention	Not human	Not women	Unable to trace	
CENTRAL	**700**	173	93	261	44	64	3	5	1	–	1	2	8
EMBASE	**647**	54	461	98	15	17	–	1	–	–	1	–	1
Hypertension in Pregnancy[a]	**150**	5	121	–	1	16	–	–	–	7	–	–	0

HDP, hypertensive disorders of pregnancy; PCG, Pregnancy and Childcare Group; PE, pre-eclampsia.
[a] Handsearch.



* Interventions not currently used clinically, or reviews which have been withdrawn and replaced by modified versions.
+ Core reviews/protocols were updated or completed within the project. Non-core reviews/protocols were included in the search strategy and updated where possible.
† New reviews conducted using methods outlined in the Generic Protocol
BP, blood pressure; CDSR, Cochrane Database of Systematic Reviews; PE, pre-eclampsia

FIGURE 56 *Search strategy for effectiveness reviews*

TABLE 15 *How the 315 citations were incorporated into each review for new reviews*

Intervention	Full papers retrieved for evaluation					Excluded						Included[a]	
						Reason for exclusion							
	Total citations	PCG register	Generic electronic searches	Review specific searches	Others: reference lists/personal communications	*Total citations*	Not RCT/inadequate randomisation[a]	More than 20% not analysed	Intervention not appropriate (nature/dose/duration)	Participants not appropriate (women with PE usually)	No relevant outcomes reported	*Total citations*	Total no. of trials[a]
Nitric oxide donors and precursors	**13**	10	2	1	–	*7*	–	–	2	3	2	*6*	6
Exercise	**14**	7	–	6	1	*11*	9	–	–	–	2	*3*	3
Garlic	**2**	1	–	–	1	*1*	–	1	–	–	–	*1*	1
Rest at home	**15**	14	–	1	–	*13*	–	1	–	12	–	*2*	2
Progesterone	**10**	6	–	3	1	*5*	4	–	–	–	1	*5*	2
Total citations	**54**					*37*						*17*	

[a] Includes trials that are completed, ongoing and those that are awaiting further clarification from authors regarding inclusion into the review.

TABLE 16 *How the 315 citations were incorporated into each review for protocols converted into reviews*

Intervention	Papers retrieved for evaluation					Excluded						Included[a]	
						Reason for exclusion							
	Total citations	PCG register	Generic electronic searches	Review specific searches	Others: reference lists/personal communications	*Total citations*	Not RCT/inadequate randomisation[a]	More than 20% not analysed	Intervention not appropriate (nature/dose/duration)	Participants not appropriate (women with PE usually)	No relevant outcomes reported	*Total citations*	No. of trials[a]
Antioxidant agents	**36**	25	1	10	–	*15*	2	2	3	6	2	*21*	15
Marine oils	**41**	37	–	4	–	*20*	2	6	6	3	3	*21*	10
Bedrest for women with hypertension	**14**	14	–	–	–	*9*	–	1	6	2	–	*5*	4
Total citations	**125**					*72*						*53*	

[a] Includes trials that are completed, ongoing and those that are awaiting further clarification from authors regarding inclusion into the review.

TABLE 17 *How the 315 citations were incorporated into each review for updated reviews*

Intervention	Trials already in review		New papers retrieved for evaluation					Excluded						Included[a]		
									Reason for exclusion							
	Included	Excluded (for reasons, see each review)	*Total citations*	PCG register	Generic electronic searches	Review specific searches	Others: reference lists/personal comm.)	*Total citations*	Not RCT/inadequate randomisation[b]	More than 20% not analysed	Intervention not appropriate (nature/dose/duration)	Participants not appropriate (women with PE usually)	No relevant outcomes reported	*Total citations*	Citations to new trials (no. of trials)	Additional citations to included trials
Calcium supplementation	11	18	*14*	13	–	–	1	*6*	–	–	1	–	5	*8*	4 (3)	4
Altered dietary salt	2	5	*6*	6	–	–	–	*1*	–	–	–	–	1	*5*	–	5
Antiplatelet drugs	51	51	*39*	26	5	1	7	*19*	9	1	5	2	2	*20*	8 (7)	12
Antihypertensive drugs	40	35	*77*	76	1											
Ambulatory BP monitoring	–	–	*0*	–	–	–	–	*0*	–	–	–	–	–	*0*	–	–
Total citations			***136***													

[a] Includes trials that are completed, ongoing and those that are awaiting further clarification from authors regarding inclusion into the review.

effects; for example, some women may find it stressful, it may contribute to blood clots in the legs and it can put a burden on the woman's family.

The Cochrane review of bed rest with or without hospitalisation in the secondary prevention of pre-eclampsia[98] included four RCTs (449 women) (see Appendix 9, *Table 83*). Two of these included women with hypertension but no proteinuria[99,100] and two included women with unspecified proteinuric hypertension[101,102] (which were not directly relevant to this project).

All participants were women with a singleton pregnancy between 26 and 38 weeks' gestation at trial entry. Two trials recruited both primigravid and multigravid women,[99,100] and the other two did not report on parity. The women had diastolic blood pressure between 90 and 110 mmHg. One trial also specified systolic pressure of at least 140 mmHg. No trials reported on whether women were using antihypertensive therapy at trial entry. Two trials compared strict bed rest in hospital with some rest in hospital[101,102] and the other two compared some bed rest in hospital with normal activity at home.[99,100] Characteristics of the studies can be seen in Appendix 9.

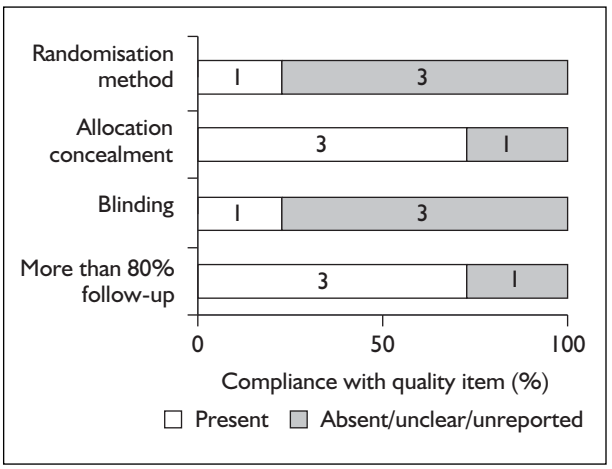


FIGURE 57 *Quality of RCTs of bed rest in the secondary prevention of pre-eclampsia*

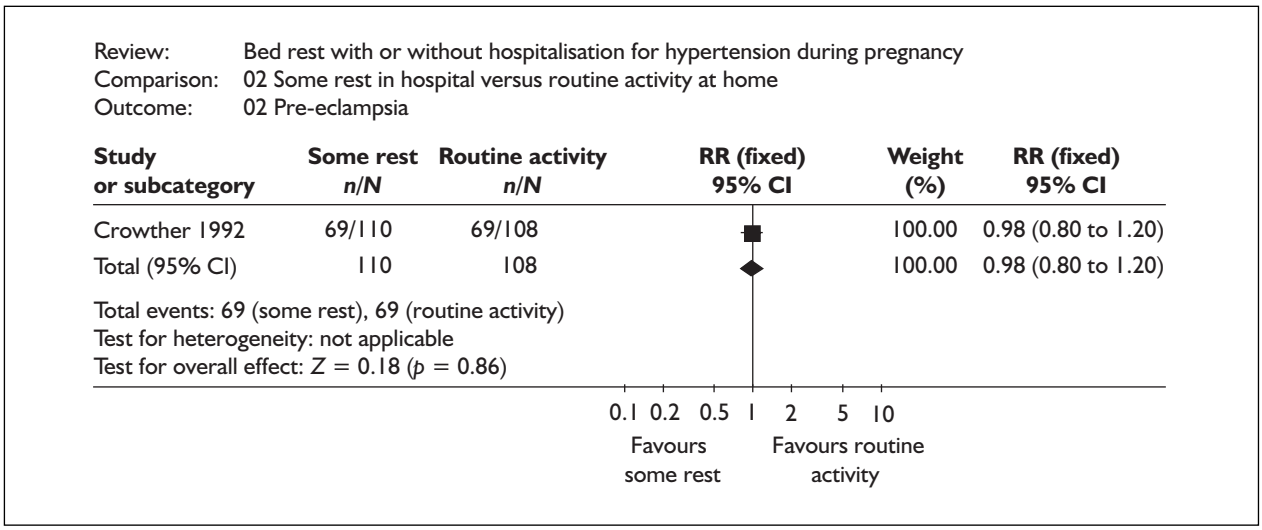


FIGURE 58 *Forest plot of the effects of bed rest in the secondary prevention of pre-eclampsia*

TABLE 18 *Effects of bed rest on perinatal outcomes*

Outcome	No. of trials	Rest *n/N*	Activity *n/N*	RR	95% CI	I^2 (%)
Death of baby	1	2/110	1/108	1.96	0.18 to 21.34	NA
Preterm birth (<37 weeks)	1	13/110	24/108	0.53	0.29 to 0.99	NA
Small for gestational age	1	15/110	15/108	0.98	0.51 to 1.91	NA

NA, not applicable.

The quality of the four studies is shown in *Figure 57*. Allocation concealment was adequate in three trials[99–101] but unclear in the fourth.[102] One trial stated that only the assessment of baby outcomes was blinded.[99] Blinding was not mentioned in the other reports, although blinding of participants would not have been possible. Two trials reported no losses to follow-up[99,101] and another[102] excluded 13% of women from the analysis. Reasons for exclusion included women not complying with their allocated treatment. The fourth trial[100] excluded 26% of women.

There was no clear effect of bed rest compared with normal activity at home in the secondary prevention of pre-eclampsia with an RR 0.98 (95% CI 0.80 to 1.20) (*Figure 58*). The perinatal outcome results are shown in *Table 18*. Bed rest was not used in decision analysis as the review is on secondary rather than primary prevention of pre-eclampsia.

Exercise or other physical activity for preventing pre-eclampsia and its complications

The belief that women should remain physically active during pregnancy is prevalent in many cultures, and can be traced back to ancient times. In the late twentieth century, as more women were comfortably off, and with the spread of labour-saving machines to do household tasks, the concept of antenatal exercises developed. These exercises aim to prepare the woman for the birth. With changes in lifestyle in modern times, sport and exercise have also become major leisure activities for women. In addition, women increasingly have paid employment outside the home that may include physical activity. When they become pregnant, women are often anxious about the safety to themselves and their unborn child of continuing these activities. Although there is a range of possible effects of exercise and other physical activity during pregnancy, this review deals primarily with those related to prevention of pre-eclampsia and its consequences.

The review of exercise or other physical activity for preventing pre-eclampsia and its complications[103] included two RCTs (45 women). In one,[104] women had gestational diabetes, in the other[105] they had either mild hypertension or a previous personal or family history of hypertension. All women were randomised between 18 and 34 weeks' gestation to moderate/high-intensity aerobic exercise or

normal activity. The exercise was moderate- to high-intensity walking or cycling for 30–45 minutes 3–4 times per week for 10 weeks or until delivery. Characteristics of the studies can be seen in Appendix 9.

The quality of the studies is shown in *Figure 59*. One study[105] was high quality, with adequate allocation concealment, blinding of outcome assessment and no losses to follow-up. The other[104] had adequate concealment of allocation, but with no blinding of outcome assessment and 12% of participants excluded from the analysis.

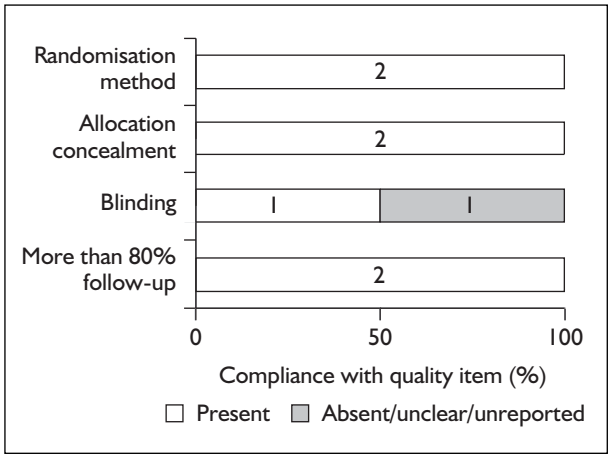


FIGURE 59 *Quality of RCTs of exercise for preventing pre-eclampsia and its complications*

Exercise (aerobic exercise) had a trend towards being more effective than normal activity in preventing pre-eclampsia with an RR of 0.31 (95% CI 0.01 to 7.09), but these findings could have been accounted for by chance alone (*Figure 60*). Because of the wide CIs, the effect of aerobic exercise relative to normal activity is highly uncertain. This result is compatible with both increased and decreased incidence of pre-eclampsia being associated with aerobic exercise. The perinatal outcome results are shown in *Table 19*. Exercise was not used in decision analysis as the results are based on small numbers with only one participant having the outcome of interest and because the trials were in women at higher risk of pre-eclampsia.

Rest for preventing pre-eclampsia and its complications in women with normal blood pressure

Restriction of activity and rest have traditionally been advocated during pregnancy for a variety of

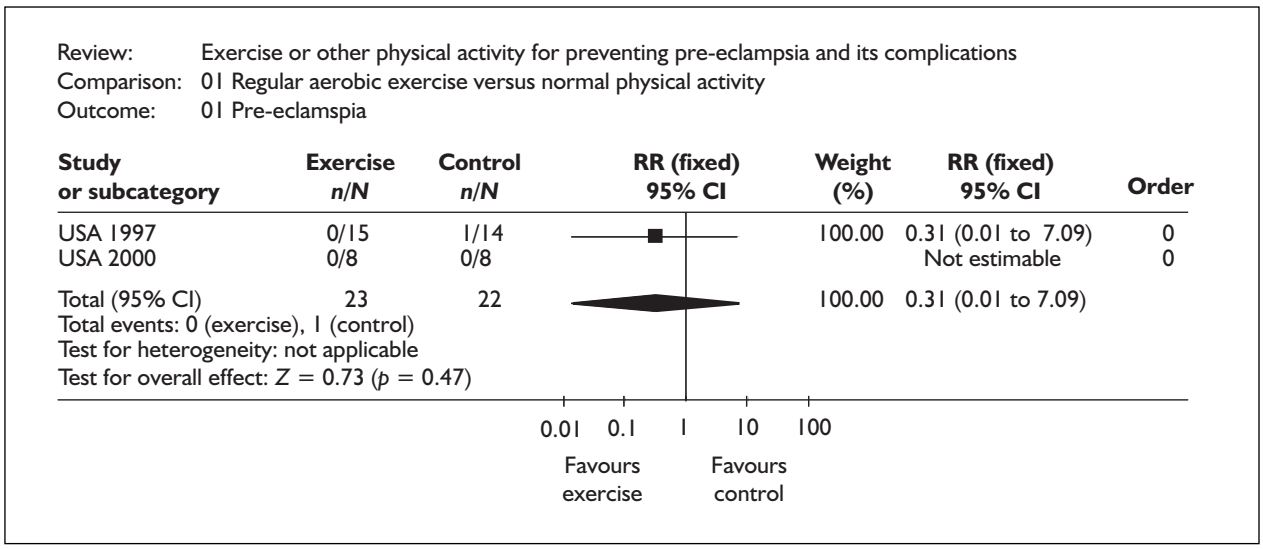


FIGURE 60 *Forest plot of the effects of exercise for preventing pre-eclampsia and its complications*

TABLE 19 *Effects of exercise on perinatal outcomes*

Outcome	No. of trials	Exercise *n/N*	Normal activity *n/N*	RR	95% CI	I^2 (%)
Death of baby	1	0/8	0/8	–	–	
Preterm birth	2	1/23	1/22	1.00	0.07 to 13.37	NA
Small for gestational age	1	1/8	1/8	3.00	0.14 to 64.26	NA

NA, not applicable.

indications, including prevention and treatment of hypertension. Surveys conducted in Canada and the USA on obstetrician and physician management of hypertensive disorders in pregnancy suggest that advice to stop work and/or to rest more is common when blood pressure is raised. This advice is based largely on findings from case–control studies and the observation that when women are walking or moving about they have a higher systolic blood pressure than when they have been sitting for some time.

The review of rest for preventing pre-eclampsia and its complications in women with normal blood pressure[106] included two RCTs (106 women). One compared rest alone with unrestricted activity where rest was in the left lateral recumbent position for 4 hours daily until delivery. If mean arterial pressure increased by at least 9 mmHg, the duration of rest was increased to 6 hours per day. The other trial compared rest plus nutritional supplementation (soy protein, calcium and linoleic acid) with unrestricted activity plus placebo (iron tablets) where rest was in the left lateral position for 15 minutes twice daily until delivery. All participants were at moderate risk of pre-eclampsia. Women were enrolled between 28 and 32 weeks' gestation. Neither study reported baseline activity of the women at trial entry: in one,[107] some participants were in paid employment, but the physical activity in this employment is not stated; in the other,[108] the only information is that women in the control group did not have regular daytime rest. One trial compared 4 hours per day of rest with unrestricted activity.[107] For both trials, rest was lying in the left lateral position at home, but not necessarily in bed. Neither required women to stop working. Neither trial reported compliance with the advice to rest. Although in one study[107] participants were visited by nurses to ensure compliance with rest, what the nurses observed during these visits is not reported. Characteristics of the studies can be seen in Appendix 9.

The quality of the two studies is shown in *Figure 61*. Clearly, blinding of participants to rest was not possible, although the caregivers were blinded in one trial. Neither study reported whether the outcome assessment was blinded.

On average, rest was more effective than unrestricted activity in preventing pre-eclampsia (*Figure 62* overleaf). We used RR 0.05 (95% CI 0.00 to 0.83) (rest alone) and RR 0.13 (95% CI 0.03 to 0.51) (rest combined with other nutrient supplements) for primary prevention of pre-eclampsia in decision analysis. No results were available for perinatal outcomes (see *Table 20* overleaf).

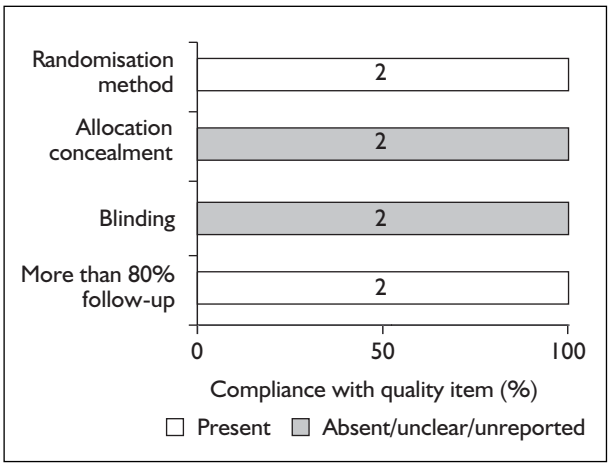


FIGURE 61 *Quality of RCTs of rest for preventing pre-eclampsia and its complications in women with normal blood pressure*

Nutrition and dietary interventions

Altered dietary salt for preventing pre-eclampsia and its complications

In the early part of the twentieth century, a low salt diet was often recommended as treatment for oedema, in both pregnant and non-pregnant people. At that time oedema was included in the definition of pre-eclampsia, although it is now recognised to be part of normal pregnancy as it affects 80% of pregnant women. This led to the idea that restricting salt intake might treat, and also prevent, pre-eclampsia. By the 1940s, a low salt diet was widely recommended during pregnancy, particularly for women with pre-eclampsia. In the late 1950s and early 1960s, this practice began to be questioned, and it was even suggested that a high salt intake might prevent or treat pre-eclampsia. Subsequently, interest in salt consumption during pregnancy has largely faded away. In most parts of the world women are no longer advised by clinicians to alter their salt intake during pregnancy. A notable exception is in The Netherlands where, until relatively recently, this practice remained widespread. Nevertheless, some lay literature aimed at pregnant women continues to advocate salt restriction during pregnancy.

The review of altering dietary salt in the primary prevention of pre-eclampsia[109] included two RCTs (631 women). Women in these trials were nulliparous. In one all women were normotensive[110] and in the other they had a diastolic blood pressure of at least 85 mmHg at

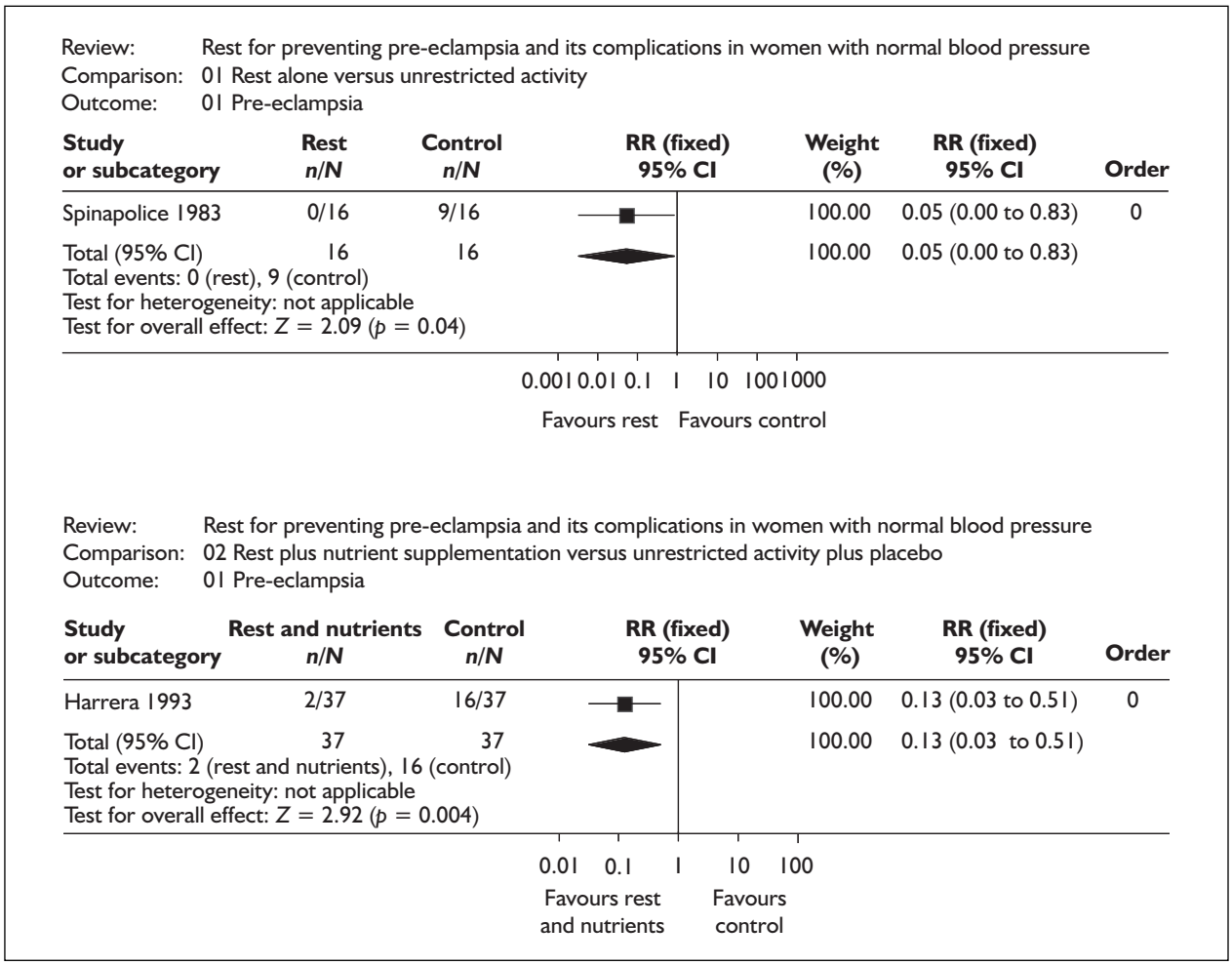


FIGURE 62 *Forest plot of the effects of rest in the primary prevention of pre-eclampsia*

TABLE 20 *Effects of rest on perinatal outcomes*

Outcome	No. of trials	Rest *n/N*	Unrestricted activity *n/N*	RR	95% CI	I^2 (%)
Death of baby	0					
Preterm birth	0					
Small for gestational age	0					

trial entry.[111] Both studies compared advice to restrict dietary salt (to 20 or 50 mmol/day) with advice to continue normal dietary salt. Compliance was assessed by checking urinary sodium excretion. Although this was higher than the target level for the low-sodium group, sodium excretion was still lower than for the normal diet group. Characteristics of the studies can be seen in Appendix 9.

The quality of these studies is shown in *Figure 63*. Follow-up was complete in one study, in the other 10% of women were excluded primarily from the low-salt group as women did not want to use the recommended diet. Blinding of participants was

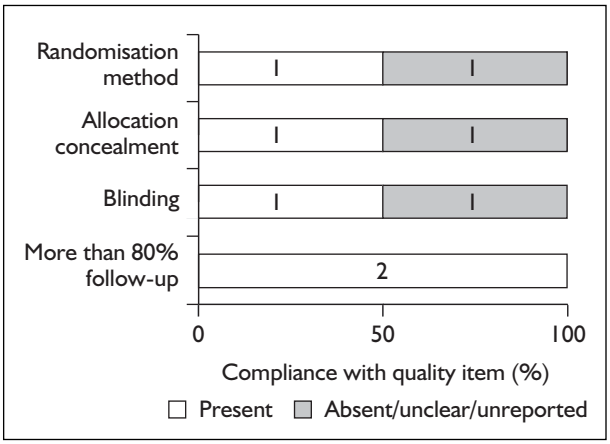


FIGURE 63 *Quality of RCTs of altering dietary salt in the primary prevention of pre-eclampsia*

not possible. In one study, the caregiver was blinded to urinary sodium concentration measurements.

Advice to restrict dietary salt had a trend towards being less effective than advice to continue normal dietary salt in preventing pre-eclampsia, but these findings could have been accounted for by chance alone. Because of the wide CIs, the effect of altered dietary salt relative to normal diet is highly uncertain. This result is compatible with both increased and decreased incidence of pre-eclampsia being associated with advice to restrict dietary salt. We used RR 1.11 (95% CI 0.46 to 2.66) for primary prevention of pre-eclampsia in decision analysis (*Figure 64*). The perinatal outcome results are shown in *Table 21*.

Antioxidants for preventing pre-eclampsia

Antioxidants are loosely defined as any substance that, when present in low concentrations compared with that of an oxidisable substrate, significantly delays or inhibits oxidation of that substrate. Antioxidants protect proteins and enzymes from oxidation and destruction by free radicals, and help to maintain cellular membrane integrity. Recently, the observation that women with pre-eclampsia have decreased plasma and placental concentrations of antioxidants has led to the proposal that placental underperfusion may mediate a state of oxidative stress.

The review of vitamin (vitamin C, vitamin E and β-carotene), mineral (selenium) and non-vitamin antioxidants (glutathione peroxidase, catalase, superoxide dismutase)[112] included seven RCTs (6082 women). [Since this report was finished, two large trials have been published. The recently updated Cochrane Antioxidant review also excludes the quasi-randomised trial. The updated review included 10 RCTs (nine for the pre-eclampsia outcome, RR = 0.73 (95% CI 0.51 to 1.06).] Most women (5572, 95%) were at moderate/low risk at trial entry. Two trials (351 women) recruited women before 20 weeks' gestation,[113,114] and another reported recruiting women "during late pregnancy", which probably meant after 20 weeks' gestation.[115] The remaining studies all recruited women both before and after 20 weeks' gestation; one specified 16–22 weeks' gestation,[116] while others merely stated below 24 weeks', below 26 weeks' or below 29 weeks' gestation. One or more vitamins were the antioxidant most commonly evaluated (5982 women). The vitamins evaluated were vitamin C only (one trial),[117] vitamins C plus E only (two trials),[113,116] vitamin C plus multivitamin and iron, calcium, iodine, manganese, copper, vitamin A, B and D (one trial)[118] and vitamins C and E with fish oil and aspirin (one trial).[119] The other two

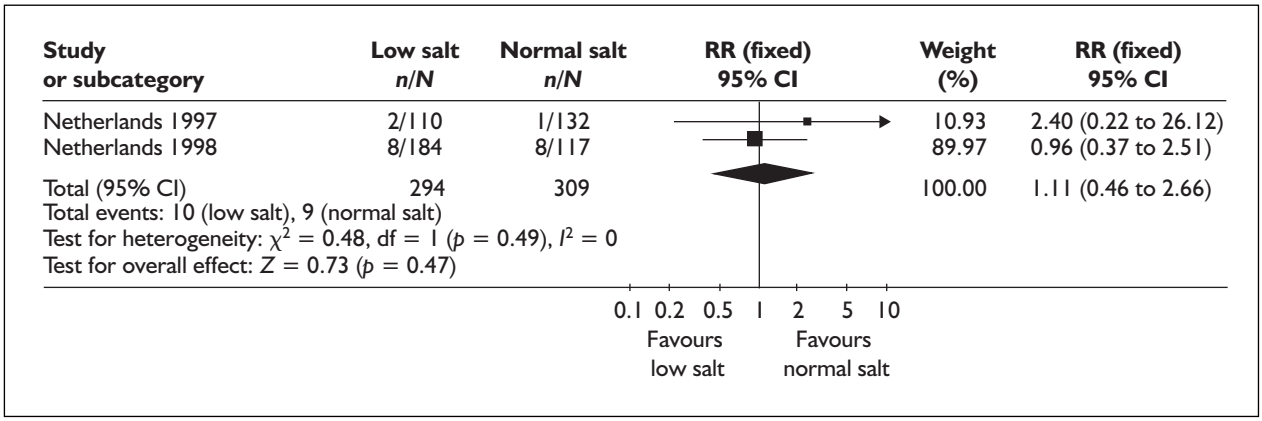


FIGURE 64 *Forest plot of the effects of altering dietary salt in the primary prevention of pre-eclampsia*

TABLE 21 *Effects of altering dietary salt on perinatal outcomes*

Outcome	No. of trials	Low salt *n/N*	Normal salt *n/N*	RR	95% CI	I^2 (%)
Death of baby	2	2/206	1/203	1.92	0.18 to 21.03	NA
Preterm birth	1	9/110	10/132	1.08	0.46 to 2.56	NA
Small for gestational age	1	15/110	12/132	1.50	0.73 to 3.07	NA

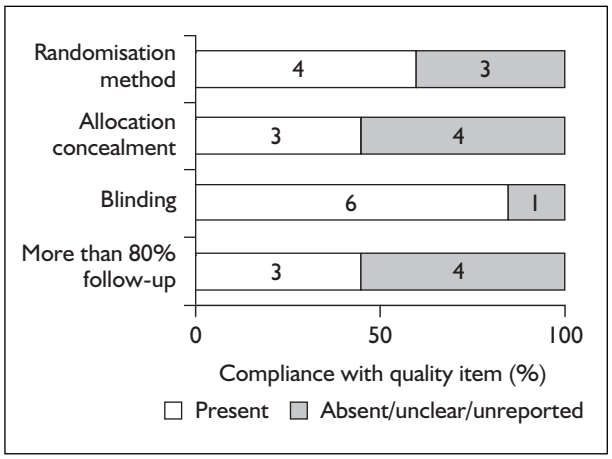


FIGURE 65 *Quality of RCTs of antioxidants in the primary prevention of pre-eclampsia*

antioxidants were the mineral selenium[115] and the non-vitamin antioxidant lycopene.[114] Seven trials reported pre-eclampsia as an outcome, although three did not say how they defined pre-eclampsia. One study reported "toxaemia" and defined this as "hypertension occurring with albuminuria".[118] Characteristics of the studies can be seen in Appendix 9.

The quality of these studies is shown in *Figure 65*. One study was quasi-randomised, with women allocated treatments according to alternate lists; allocation concealment was therefore inadequate.[118] Two trials reported outcome for all women according to treatment allocation, and another three did not mention any losses to follow-up. In the two remaining trials, losses to follow-up were 8 and 11%. For three trials women, caregivers and researchers were blinded to the intervention. Another trial stated it was "double-blind" in the text, and a fourth used the term "triple-blind". Blinding was not mentioned in reports of the remaining two trials. The six properly randomised trials used a placebo control. The quasi-random study did not use a placebo.

On average, antioxidants were more effective than placebo in preventing pre-eclampsia (*Figure 66*).

Review: Antioxidants for preventing pre-eclampsia
Comparison: 01 Any antioxidants versus control or placebo
Outcome: 01 Pre-eclampsia (subgroups by whether random or quasi-random allocation)

Study or subcategory	Antioxidant(s) n/N	Control n/N	RR (fixed) 95% CI	Weight (%)	RR (fixed) 95% CI
01 Studies with random allocation					
Beazley 2002	9/52	9/48		4.25	0.92 (0.40 to 2.13)
Chappell 1999	11/141	24/142		10.87	0.46 (0.24 to 0.91)
Han 1994	0/52	4/48		2.13	0.10 (0.01 to 1.86)
Rivas 2000	1/63	14/64		6.31	0.07 (0.01 to 0.54)
Sharma 2003	10/116	24/135		10.08	0.48 (0.24 to 0.97)
Steyn 2002	3/100	3/100		1.36	1.00 (0.21 to 4.84)
Subtotal (95% CI)	524	537		35.01	0.45 (0.31 to 0.66)
Total events: 34 [antioxidant(s)], 78 (control)					
Test for heterogeneity: $\chi^2 = 8.02$, df = 5 ($p = 0.16$), $I^2 = 37.6\%$					
Test for overall effect: $Z = 4.08$ ($p < 0.0001$)					
02 Studies with quasi-random allocation					
People's League 1942	100/2510	143/2511		64.99	0.70 (0.55 to 0.90)
Subtotal (95% CI)	2510	2511		64.99	0.70 (0.55 to 0.90)
Total events: 100 [antioxidant(s)], 143 (control)					
Test for heterogeneity: not applicable					
Test for overall effect: $Z = 2.81$ ($p = 0.005$)					
Total (95% CI)	3034	3048		100.00	0.61 (0.50 to 0.75)
Total events: 134 [antioxidant(s)], 221 (control)					
Test for heterogeneity: $\chi^2 = 9.32$, df = 6 ($p = 0.16$), $I^2 = 35.6\%$					
Test for overall effect: $Z = 4.62$ ($p < 0.00001$)					

FIGURE 66 *Forest plot of the effects of antioxidants in the primary prevention of pre-eclampsia*

TABLE 22 *Effects of antioxidants on perinatal outcomes*

Outcome	No. of trials	Antioxidant *n/N*	Control *n/N*	RR	95% CI	I^2 (%)	*p*-Value
Neonatal death	2	36/2542	27/2534	1.33	0.81 to 2.19	0	0.45
Preterm birth (<37 weeks)	3	76/293	54/290	1.38	1.04 to 1.82	0	0.94
Small for gestational age	3	49/309	81/325	0.64	0.47 to 0.87	0	0.52

We used RR 0.61 (95% CI 0.50 to 0.75) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 22*.

Calcium supplementation during pregnancy

An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980, based on epidemiological and clinical studies, and led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high blood pressure and pre-eclampsia among women with low calcium intake. Low calcium intake may cause high blood pressure by stimulating either parathyroid hormone or renin release, thereby increasing intracellular calcium in vascular smooth muscle and leading to vasoconstriction. A possible mode of action for calcium supplementation is that it reduces parathyroid release and intracellular calcium, and so reduces smooth muscle contractility. By a similar mechanism, calcium supplementation could also reduce uterine smooth muscle contractility and prevent preterm labour and delivery. Calcium might also have an indirect effect on smooth muscle function by increasing magnesium levels. A theoretical risk of increased renal tract stone formation with calcium has not been substantiated and no other adverse effects of calcium supplementation have been documented.

The review of calcium supplementation in the primary prevention of pre-eclampsia[71] included 12 RCTs (15,206 women). About one-third of the women had adequate calcium intake whereas the remainder had low calcium intake (5275 adequate, 10,253 low calcium intake). Most of the information was from two large trials.[120,121] Most women were low risk at trial entry (14,923 low risk, 605 high risk). The dose of calcium evaluated was primarily 1.5–2 g as calcium carbonate (eight trials),[121–128] gluconate (one trial)[129] or elemental calcium (three trials),[130–132] treatment was started at anywhere between 20 and 32 weeks until delivery and this was compared with placebo.

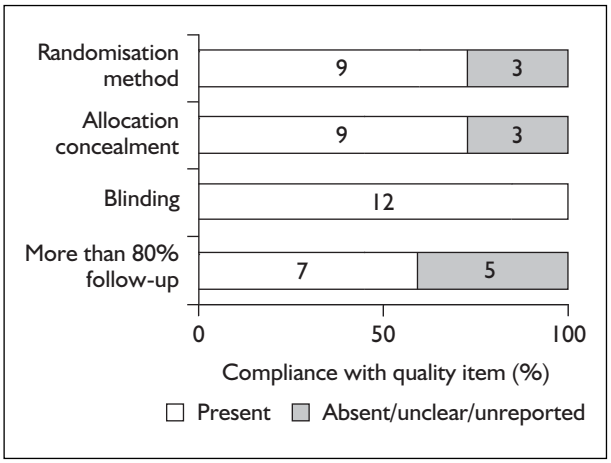


FIGURE 67 *Quality of RCTs of calcium supplementation during pregnancy*

Characteristics of the studies can be seen in Appendix 9.

The quality of the studies is shown in *Figure 67*. Overall, these trials were high quality, with the two large trials being well conducted. For one small study there is a large discrepancy in the size of the two allocated groups,[129] the reason for which is unclear.

Calcium supplementation was more effective than placebo in preventing pre-eclampsia and these findings are unlikely to be accounted for by chance alone (*Figure 68* overleaf). There was significant heterogeneity so a random effects model was used in meta-analysis. We used RR 0.48 (95% CI 0.33 to 0.69) in decision analysis. The perinatal outcome results are shown in *Table 23* overleaf.

Energy and protein intake in pregnancy

Observational studies have reported that both gestational weight gain and energy intake are strongly and positively associated with foetal growth, and possibly associated with a reduced risk of preterm birth. Moreover, these associations are stronger in undernourished women, that is, those with low prepregnancy weight-for-height. The Dutch Famine Study found a clear reduction in foetal growth, but no effect on gestational

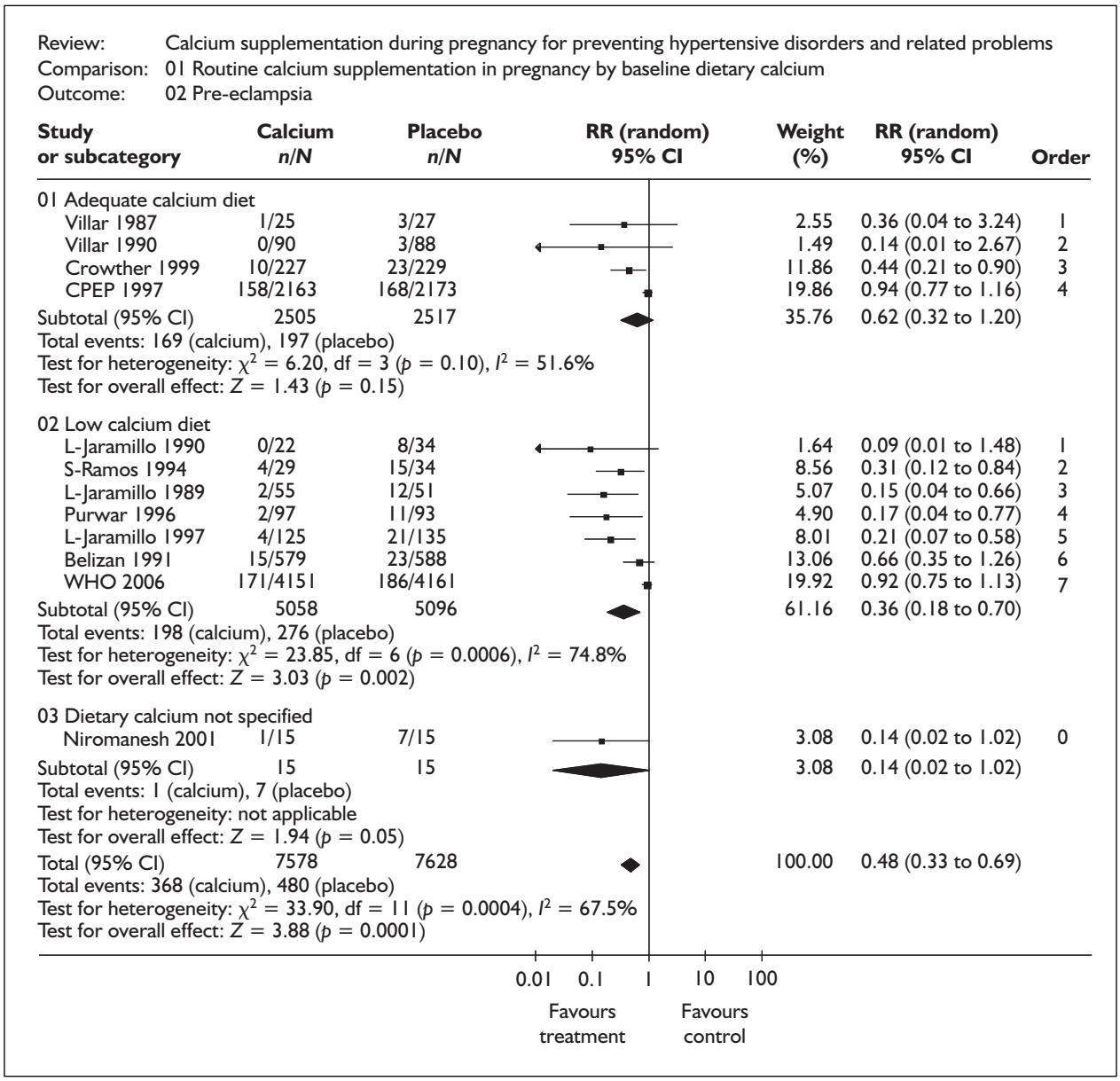


FIGURE 68 *Forest plot of the effects of calcium supplementation in the primary prevention of pre-eclampsia*

TABLE 23 *Effects of calcium supplementation on perinatal outcomes*

Outcome	No. of trials	Calcium n/N	Placebo n/N	RR	95% CI	I^2 (%)	p-Value
Death of the baby	10	177/7548	200/7593	0.89	0.73 to 1.09	0	
Preterm birth (<37 weeks)[a]	10	703/7347	763/7404	0.81	0.64 to 1.03[a]	57.2	0.02
Small for gestational age	3	164/6543	149/6548	1.10	0.88 to 1.37	0	

[a] Random effects model, as I^2 57%.

duration when pregnant women were forced by the Germans in 1944 and 1945 to reduce their energy intake during the third trimester. Non-randomised trials of 'balanced' energy/protein supplementation (i.e. supplements in which protein provides less than 25% of the total energy content) have reported beneficial effects on foetal growth, although the evidence from properly randomised trials suggests more modest benefits. Trials of interventions to increase foetal growth have taken on greater interest in light of recent evidence that higher

birth weight for gestational age is associated with reduced risks for type 2 diabetes, hypertension and coronary heart disease in late adulthood. High-protein dietary supplementation (i.e. supplementation in which the protein provides at least 25% of its total energy content) may adversely affect pregnancy outcome. Isocaloric protein supplementation denotes a supplement in which the protein content is 'balanced', that is, provides less than 25% of its total energy content, but replaces an equivalent amount of energy in the diet. Before 1970, clinicians frequently counselled pregnant women to restrict their food intake in an attempt to prevent pre-eclampsia, despite the absence of evidence that such advice was beneficial. Moreover, evidence from observational studies (including the Dutch Famine Study) strongly suggests that such restriction (among non-obese women, at least) is associated with impairment in foetal growth. No evidence points to specific effects of protein (as opposed to energy) restriction, although prescription of a well-balanced diet that restricts energy intake will also lead to a reduction in protein intake.

The review of energy and protein intake in pregnancy looked at five related interventions – nutritional advice during pregnancy (five trials, 1134 women), balanced protein/energy supplementation in pregnancy (13 trials, 4665 women), high protein supplementation in pregnancy (two trials, 1076 women), isocaloric balanced protein supplementation in pregnancy (three trials, 966 women) and energy/protein restriction in pregnant women with high weight-for-height or weight gain (three trials, 384 women) and included 23 trials in total.[133] (Since this report was finished, the Cochrane Energy and Protein review has been updated; there were no new included studies so the results have not changed for the pre-eclampsia outcome.) The trials of high protein supplementation in pregnancy did not report pre-eclampsia. Participants varied in the trials between well nourished women and those who were nutritionally vulnerable. The interventions within each category varied considerably. Controls were mainly no intervention except for eight trials where some form of placebo was used.[134–141] Characteristics of the studies can be seen in Appendix 9.

The quality of the 23 studies is shown in *Figure 69*. Alternate allocation or quasi-random methods of allocation were used in six trials.[137,142–146] No details on follow-up were given in this systematic review.

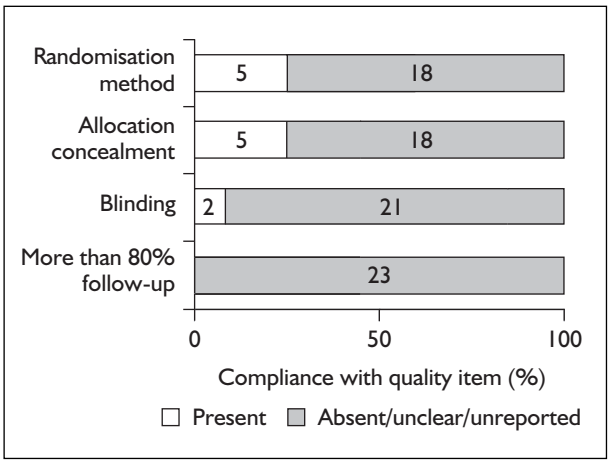


FIGURE 69 *Quality of RCTs of energy and protein intake in pregnancy*

Nutritional advice had a trend towards being more effective than no advice but these findings could have been accounted for by chance alone, RR 0.89 (95% CI 0.42 to 1.88). Isocaloric balanced protein supplementation was as effective as control, RR 1.00 (95% CI 0.57 to 1.75). Balanced protein/energy intake had a trend towards being less effective than control but these findings could have been accounted for by chance alone, RR 1.20 (95% CI 0.77 to 1.89). Energy/protein restriction also had a trend towards being less effective than normal diet but these findings could have been accounted for by chance alone, RR 1.13 (95% CI 0.59 to 2.18) (*Figures 70–73*). The perinatal outcome results are shown in *Tables 24–27*. Because of the wide CIs, the effect of energy and protein intake relative to comparator is highly uncertain. These results are compatible with both increased and decreased incidence of pre-eclampsia being associated with energy and protein intake interventions. Energy and protein intake review results were not used in decision analysis because of the possibility of harm from two of the interventions, one showing no apparent effect and the remaining result based on one trial only.

Garlic for preventing pre-eclampsia and its complications

Garlic (*Allium sativum*) is part of the *Allium*, or onion, family and is used in both traditional Chinese and Ayurvedic medicine. The traditional medicinal uses of garlic include prevention of infection and treatment of colds, influenza, bronchitis, whooping cough, gastroenteritis, dysentery and skin problems. More recently, it has been suggested that garlic may have lipid-lowering properties which may be beneficial for the treatment of arteriosclerosis and diabetes and for the prevention of myocardial infarction. The

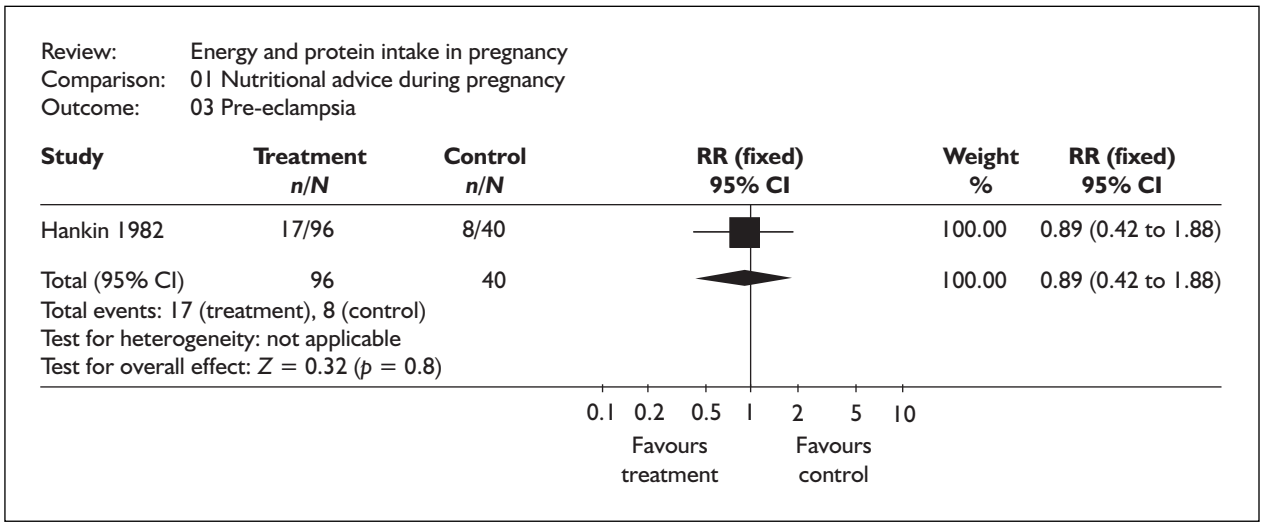


FIGURE 70 *Forest plot of the effect of nutritional advice during pregnancy to prevent pre-eclampsia*

TABLE 24 *Effects of nutritional advice on perinatal outcomes*

Outcome	No. of trials	Nutritional advice *n/N*	Placebo *n/N*	RR	95% CI	I^2 (%)	*p*-Value
Neonatal death	1	5/221	4/227	1.28	0.35 to 4.72	NA	
Preterm birth (<37 weeks)	2	9/238	18/211	0.46	0.21 to 0.98		0.83
Small for gestational age	1	12/205	12/199	0.97	0.45 to 2.11	NA	

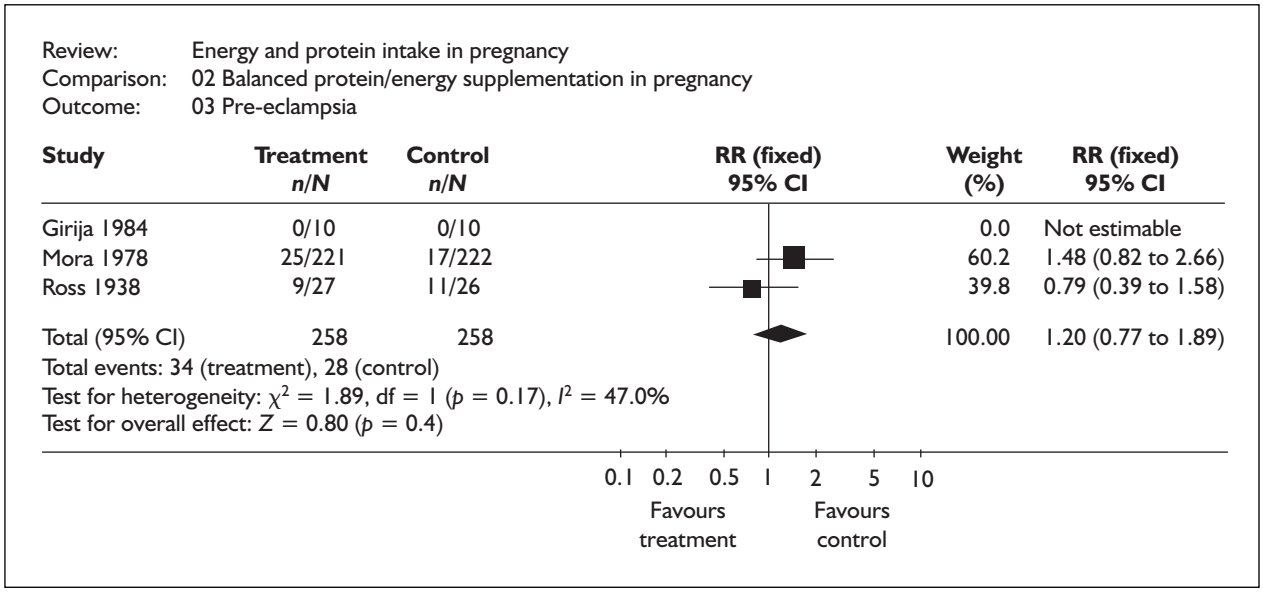


FIGURE 71 *Forest plot of balanced protein and energy supplementation in pregnancy to prevent pre-eclampsia*

TABLE 25 *Effects of balanced energy and protein supplementation on perinatal outcomes*

Outcome	No. of trials	Balanced energy/protein *n/N*	Placebo *n/N*	RR	95% CI	I^2 (%)	*p*-Value
Neonatal death	4	23/1153	33/1053	0.62	0.37 to 1.05		0.81
Preterm birth (<37 weeks)	5	97/1225	118/1211	0.83	0.65 to 1.06		0.94
Small for gestational age	6	142/1757	193/1639	0.68	0.56 to 0.84		0.66

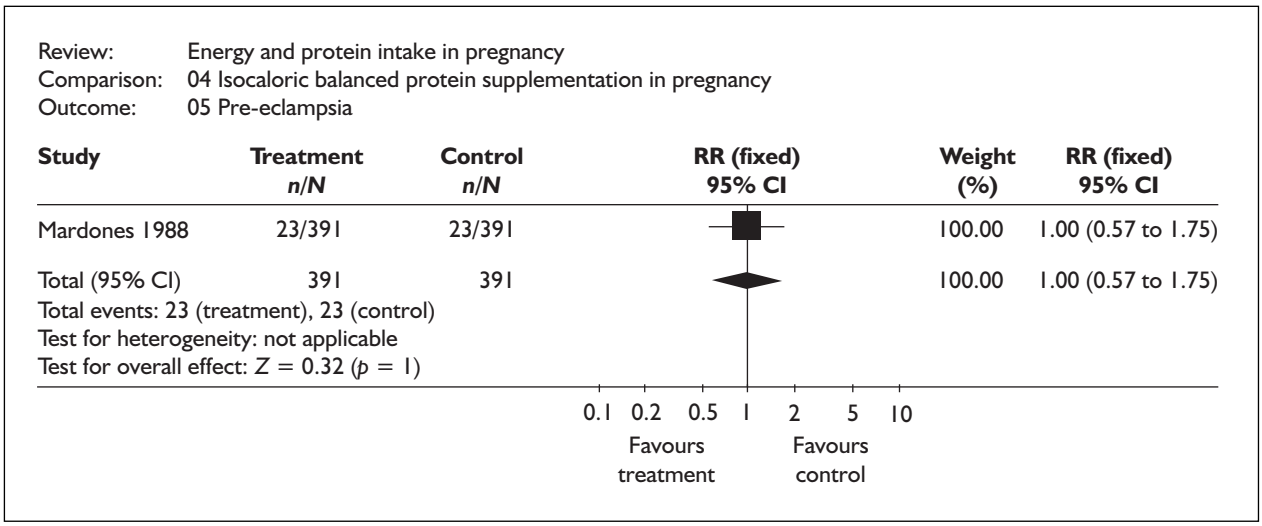


FIGURE 72 *Forest plot of isocaloric balanced protein supplementation in pregnancy to prevent pre-eclampsia*

TABLE 26 *Effects of isocaloric protein supplementation on perinatal outcomes*

Outcome	No. of trials	Isocaloric protein *n/N*	Placebo *n/N*	RR	95% CI	I^2 (%)
Neonatal death	1	1/391	2/391	0.50	0.05 to 5.49	NA
Preterm birth (<37 weeks)	1	40/391	38/391	1.05	0.69 to 1.60	NA
Small for gestational age	1	171/391	127/391	1.35	1.12 to 1.61	NA

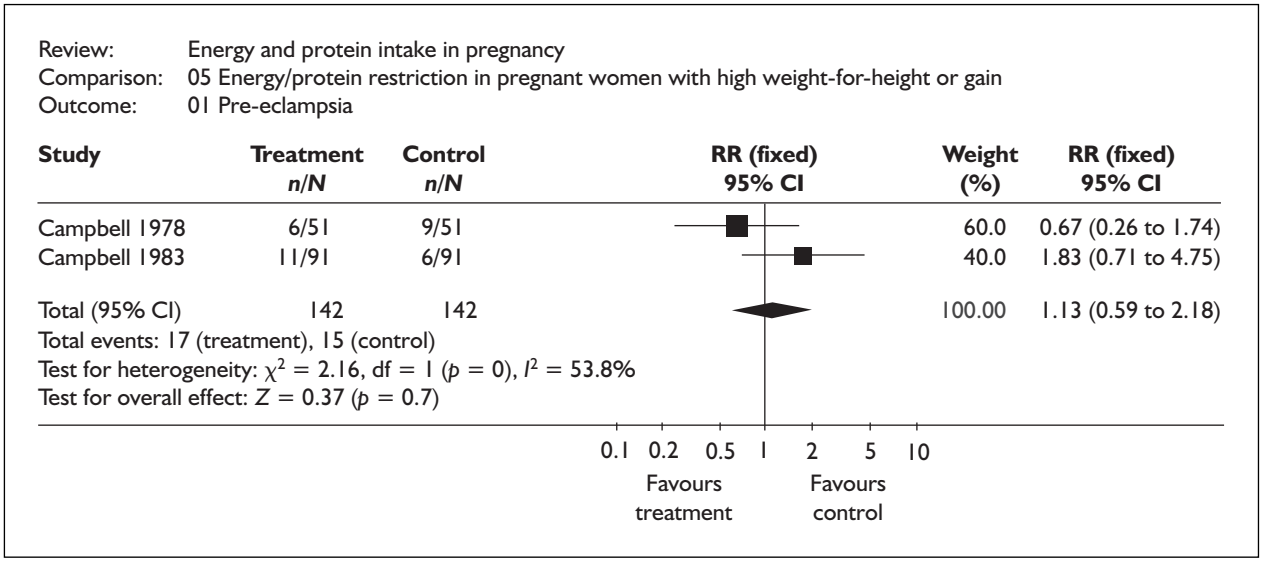


FIGURE 73 *Forest plot of energy and protein restriction in high weight for height or weight gain during pregnancy to prevent pre-eclampsia*

TABLE 27 *Effects of energy and protein restriction on perinatal outcomes*

Outcome	No. of trials	Energy/protein restriction *n/N*	Placebo *n/N*	RR	95% CI	I^2 (%)
Death of the baby	0					
Preterm birth (<37 weeks)	1	2/91	4/91	0.50	0.09 to 2.66	NA
Small for gestational age	0					

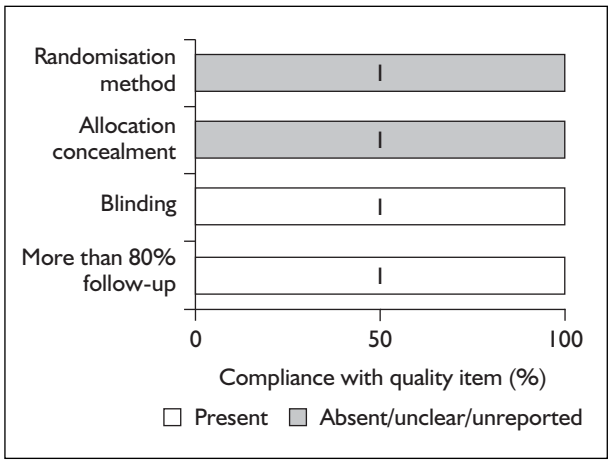


FIGURE 74 *Quality of RCTs of garlic for preventing pre-eclampsia and its complications*

suggestions that garlic may lower blood pressure, reduce oxidative stress and/or inhibit platelet aggregation have led to the hypothesis that garlic may have a role in the prevention of pre-eclampsia. Many commercial preparations of garlic are available but garlic's active compound allicin is unstable, so the bioavailability of allicin remains uncertain.

The review of garlic for preventing pre-eclampsia and its complications[147] included one RCT (100 women).[148] This study included primigravid women at 28–32 weeks at moderate risk of pre-eclampsia, was conducted in Iran and evaluated garlic in tablet form. Characteristics of the study can be seen in Appendix 9.

The quality of the study is shown in *Figure 74*. There is no information about how the randomisation sequence was prepared or the allocation concealed. Follow-up was reported for all women. A placebo was used, although garlic odour was reported by one-third of the women in the active group. There was no other blinding.

Garlic had a trend towards being more effective than placebo in preventing pre-eclampsia, but these findings could have been accounted for by chance alone (*Figure 75*). We used RR 0.78 (95% CI 0.31 to 1.93) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 28*.

Magnesium supplementation in pregnancy

Magnesium is one of the essential minerals needed by humans in relatively large amounts. It works with many enzymes to regulate body temperature and synthesise proteins, in addition to maintaining electrical potentials in nerves and muscle membranes. Magnesium occurs widely in many foods; dairy products, breads and cereals, vegetables and meats are all good sources. It is therefore not surprising that frank magnesium

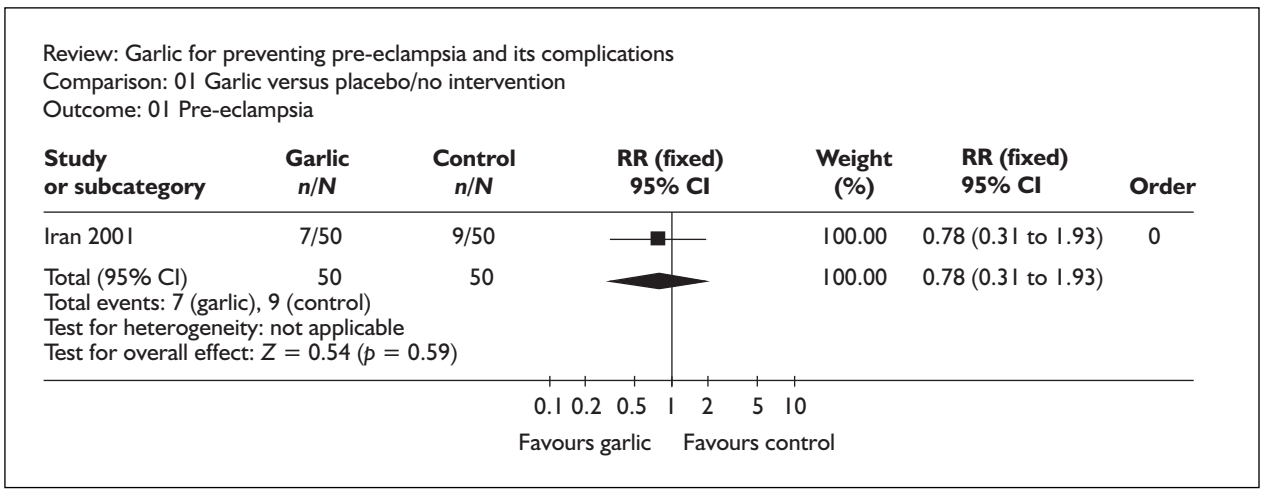


FIGURE 75 *Forest plot of the effects of garlic for preventing pre-eclampsia and its complications*

TABLE 28 *Effects of garlic on perinatal outcomes*

Outcome	No. of trials	Rest *n/N*	Activity *n/N*	RR	95% CI	I^2 (%)
Death of the baby	1	0/50	0/50	–	–	–
Preterm birth (<37 weeks)	1	NA	NA	–	–	–
Small for gestational age	1	NA	NA	–	–	–

deficiency has never been reported to occur in healthy individuals who eat varied diets. Dietary intake studies during pregnancy consistently demonstrate that many women, especially those from disadvantaged backgrounds, have intakes of magnesium below recommended levels. It has been reported that magnesium supplementation during pregnancy was associated with a reduced risk of foetal growth retardation and pre-eclampsia. Higher magnesium intake is associated with increased birth weight.

The review of magnesium supplementation in pregnancy included seven RCTs (2689 women). Participants were a mixture of women with high- and low-risk pregnancies and at high and low risk of having a low magnesium diet. The magnesium was given as oxide,[149] citrate,[150] gluconate (two RCTs)[151,152] and aspartate (three RCTs)[153–155] with a variety of doses that may or may not be comparable. Comparator was either placebo (six RCTs) or no treatment (one RCT).[150] Characteristics of the studies can be seen in Appendix 9.

The quality of the studies is shown in *Figure 76*. The largest trial was a cluster randomised trial that did not take intra-cluster correlation effects into account in the statistical analysis.[153] Another was a quasi-randomised trial in that participants were allocated to groups by using their date of birth.[155]

Magnesium supplementation had a trend towards being more effective than comparator in preventing pre-eclampsia but these findings could have been accounted for by chance alone (*Figure 77*). We used RR 0.87 (95% CI 0.57 to 1.32) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 29*.

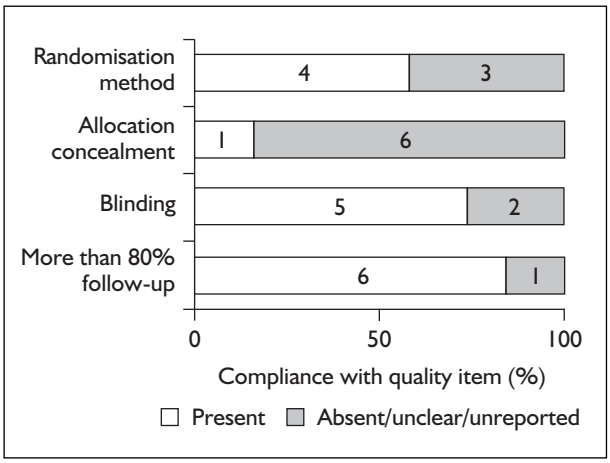


FIGURE 76 *Quality of RCTs of magnesium supplementation in pregnancy*

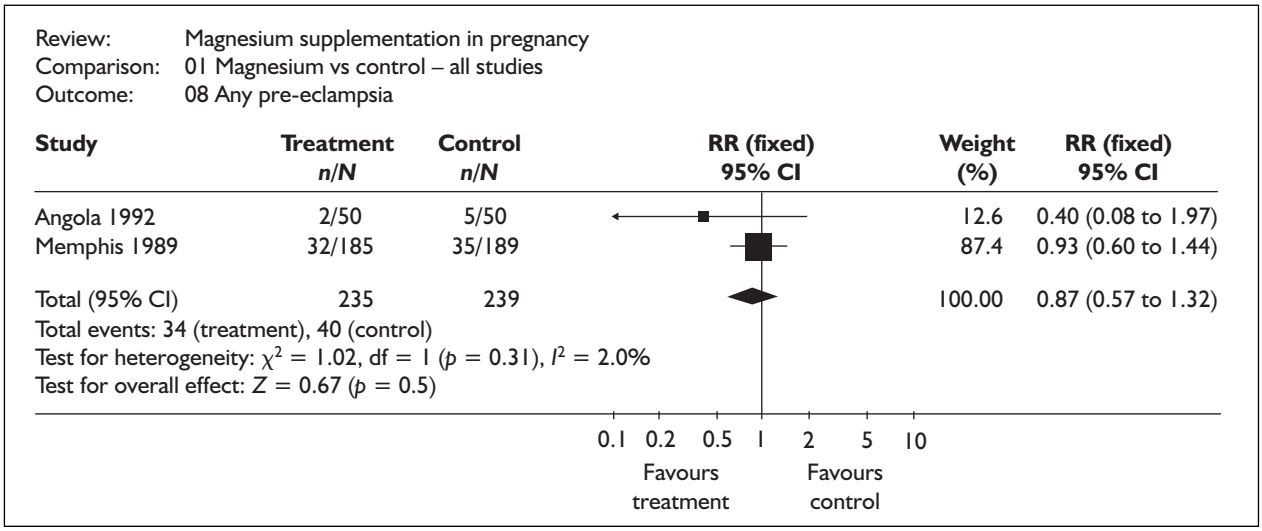


FIGURE 77 *Forest plot of the effects of magnesium in the primary prevention of pre-eclampsia*

TABLE 29 *Effects of magnesium supplementation on perinatal outcomes*

Outcome	No. of trials	Magnesium *n/N*	Control *n/N*	RR	95% CI	I^2 (%)	*p*-Value
Death of baby prior to discharge	3	5/893	3/908	1.59	0.42 to 6.05	0	
Preterm birth (<37 weeks)	5	86/1125	121/1150	0.73	0.57 to 0.94	56.5	0.06
Small for gestational age	3	72/865	104/876	0.70	0.53 to 0.93	32.6	0.23

Marine oil and other prostaglandin precursor supplementation during pregnancy

The use of fish oil supplements during the second half of pregnancy has been proposed as a possible strategy to prevent pre-eclampsia and preterm birth and to increase birthweight. Marine oils are a rich source of the *n*-3 long-chain polyunsaturated fatty acids (omega-3 fatty acids). These are precursors to the 3-series prostaglandins and have been shown to modulate inflammatory and vascular effects. Since pre-eclampsia is associated with vasoconstriction and endothelial damage, it is plausible that marine oil fatty acids can down-regulate these responses through direct competition with the thromboxane A2 precursor arachidonic acid. Other agents, such as evening primrose oil, contain the fatty acid called γ-linolenic acid, which is a precursor to the 1-series prostaglandins. These prostaglandins have a similar hypothesis for their mode action to those derived from *n*-3 (marine oil) fatty acids. They are therefore included in this review.

The review of marine oil and other prostaglandin precursor supplements[156] included six RCTs (2783 women). All six compared a supplement, or food containing marine fatty acids, with either placebo or no supplement. Four trials used oil derived from fish[157–160] and another used a combination of evening primrose oil and fish oil.[149] The sixth assessed consumption of eggs enriched with docosahexaenoic acid, by feeding an algal oil to egg-laying hens.[161] Most trials started supplementation after 16 weeks' gestation. Three included women with high-risk pregnancies.[158–160] Characteristics of the studies can be seen in Appendix 9.

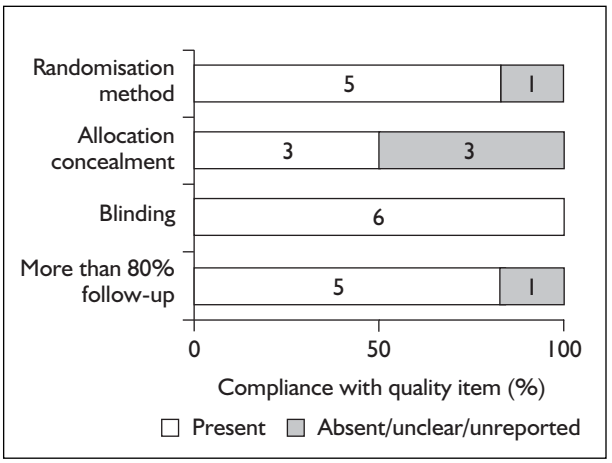


FIGURE 78 *Quality of RCTs of marine oil and other prostaglandin precursor supplements in the primary prevention of pre-eclampsia*

The quality of these studies is shown in *Figure 78*. Only one study did not use a placebo for the control group.[149] Trials that assessed the success of blinding indicate that the majority of women taking marine oil could guess their group allocation, largely because of belching and an unpleasant taste associated with taking the fish oil supplements.

Marine oil and other prostaglandin precursor supplements show a trend towards being more

Review: Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction (Editorial process 310106)
Comparison: 01 Prostagladin precursor supplementation versus none or placebo – all women
Outcome: 02 Pre-eclampsia (hypertension with proteinuria)

Study or subcategory	Marine oil n/N	Control n/N	RR (fixed) 95% CI	Weight (%)	RR (fixed) 95% CI
Angola 1992	2/50	5/50		9.92	0.40 (0.08 to 1.97)
Denmark 1992	0/266	5/267		10.89	0.09 (0.01 to 1.64)
England 1995	15/113	18/119		34.79	0.88 (0.47 to 1.66)
Europe 2000	25/398	23/420		44.40	1.15 (0.66 to 1.99)
Total (95% CI) 827	856			100.00	0.86 (0.5 to 1.27)

Total events: 42 (marine oil), 51 (control)
Test for heterogeneity: $\chi^2 = 4.25$, df = 3 ($p = 0.24$), $I^2 = 29.3\%$
Test for overall effect: $Z = 0.74$ ($p = 0.46$)

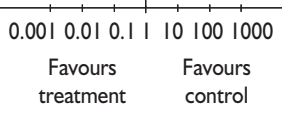


FIGURE 79 *Forest plot of the effects of marine oil and other prostaglandin precursor supplements in the primary prevention of pre-eclampsia*

TABLE 30 *Effects of marine oil and other prostaglandin precursor supplements on perinatal outcomes*

Outcome	No. of trials	Marine oil *n/N*	Control *n/N*	RR	95% CI	I^2 (%)
Neonatal death	3	7/1136	6/1167	1.17	0.41 to 3.29	0
Preterm birth (<37 weeks)	5	205/947	228/969	0.92	0.79 to 1.07	0
Small for gestational age	1	208/685	185/689	1.13	0.96 to 1.34	NA

effective than placebo or no supplement in preventing pre-eclampsia but these findings could have been accounted for by chance alone (*Figure 79*). We used RR 0.86 (95% CI 0.59 to 1.27) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 30*.

Pharmacological interventions

Antihypertensive drug therapy for mild to moderate hypertension during pregnancy

During the early weeks of normal pregnancy blood pressure falls, climbing slowly in later pregnancy to reach pre-pregnancy levels at term. This complicates the diagnosis of hypertension during pregnancy. The role of antihypertensive therapy for pregnant women with mild to moderate hypertension is unclear. As there is no immediate need to lower blood pressure, the rationale for treatment is that it will prevent or delay progression to more severe disease, thereby benefiting the woman and/or her baby and reducing consumption of health service resources. In addition to reducing blood pressure, the belief has been that these drugs reduce the risk of preterm delivery and placental abruption and improve foetal growth. A wide variety of drugs have been advocated, and each group has different potential side-effects and adverse events.

The review of antihypertensive drugs for mild to moderate hypertension in pregnancy[76] included 40 RCTs (3797 women). [Since this report was finished, a new version of the Cochrane Antihypertensives review has been published. This included 46 RCTs, 28 compared with placebo/no treatment (22 for the pre-eclampsia outcome). The results were RR = 0.97 (95% CI 0.81 to 1.13).] Twenty-two RCTs (2815 women) compared antihypertensive with placebo/no antihypertensive and 17 RCTs (1182 women) compared one antihypertensive drug with another; these are not discussed further here. The dose for several agents varied considerably between studies, in both amount and duration of therapy. Most studies recruited women during the second or third trimester of pregnancy. Characteristics of the studies can be seen in Appendix 9.

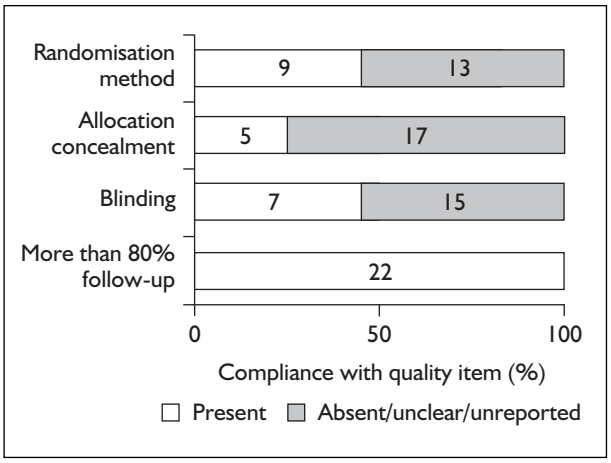


FIGURE 80 *Quality of RCTs of antihypertensive drug therapy for mild to moderate hypertension for prevention of pre-eclampsia*

The quality of the studies is shown in *Figure 80* (note that RCTs' percentage follow-up was not given in the review). Concealment of allocation was reported as adequate for just five of the trials.[162–166] None of the trials comparing drug with no treatment mentioned blinding in the assessment of outcome.

There was no clear effect of antihypertensive drugs compared with placebo/no treatment in preventing proteinuria/pre-eclampsia (*Figure 81*). We used RR 0.99 (95% CI 0.84 to 1.18) for prevention of pre-eclampsia in decision analysis. The perinatal outcome results when compared with placebo/no treatment are shown in *Table 31*.

Antiplatelet agents for preventing pre-eclampsia and its complications

It is thought that activation of platelets and the clotting system may occur early in the course of pre-eclampsia, before clinical symptoms develop. Deficient intravascular production of prostacyclin, a vasodilator, with excessive production of thromboxane, a platelet-derived vasoconstrictor and stimulant of platelet aggregation have also been demonstrated to occur in pre-eclampsia.

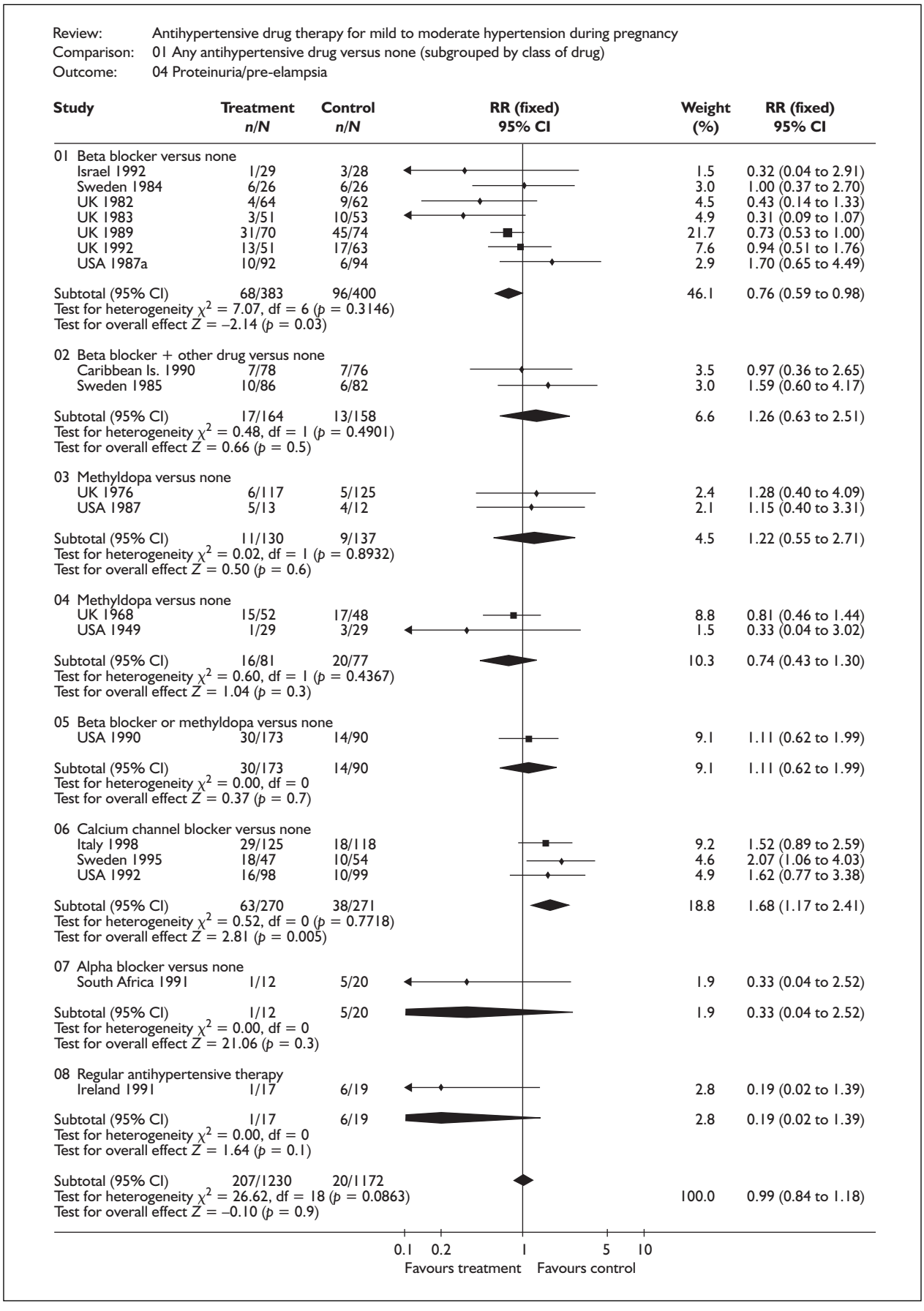


FIGURE 81 *Forest plot of antihypertensive drug therapy compared with placebo/no treatment for mild to moderate hypertension*

TABLE 31 *Effects of antihypertensive drug therapy compared with placebo/no treatment on perinatal outcomes*

Outcome	No of trials	Anti-hypertensive *n/N*	Placebo/no treatment *n/N*	RR	95%CI	I^2 (%)
Foetal or neonatal deaths	23	30/1409	44/1318	0.71	0.46 to 1.09	NA
Preterm birth (<37 weeks)	12	252/912	241/826	1.00	0.87 to 1.15	NA
Small for gestational age	17	147/1124	118/1035	1.13	0.91 to 1.42	NA

These observations led to the hypotheses that antiplatelet agents, and low-dose aspirin in particular, might prevent or delay the development of pre-eclampsia and that, for women who already have the disorder, the risk of adverse events might be reduced.

The review of antiplatelet agents for the primary prevention of pre-eclampsia[74] included 51 RCTs (36,500 women). [Since this report was finished, the Cochrane Antiplatelet review has been updated. This included 59 trials, 46 for the pre-eclampsia outcome RR = 0.83 (95% CI 0.77 to 0.89).] The antiplatelets were mostly aspirin at a dose of between 50 and 150 mg/day (mostly either 60–100 mg/day). In four trials aspirin was given with dipyridamole[167–170] and in one it was given with vitamin C and E.[171] One trial gave dipyridamole with heparin[172] and one gave ozagrel hydrochloride.[173] Treatments were started at anywhere between 12 and 34 weeks and were continued until between 34 weeks and delivery (where specified). Comparator was placebo mostly, but one-fifth of the trials used no treatment. Characteristics of the studies can be seen in Appendix 9.

The quality of the studies is shown in *Figure 82*. On average, antiplatelet agents were more effective than placebo or no antiplatelet agent in preventing pre-eclampsia and these results are unlikely to be accounted for by chance alone (*Figure 83* overleaf). We used RR 0.81 (95% CI 0.75 to 0.88) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 32* on p. 75.

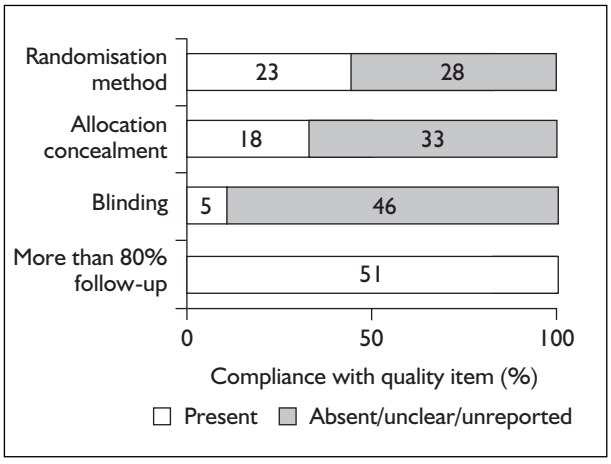


FIGURE 82 *Quality of RCTs of antiplatelet agents in the primary prevention of pre-eclampsia*

Diuretics for preventing pre-eclampsia

Diuretics are commonly used to treat hypertension in non-pregnant individuals. They were also formerly used in pregnancy to treat high blood pressure and delay or prevent pre-eclampsia onset. As diuretics promote excretion of sodium and decrease oedema and blood pressure in non-pregnant people, it was assumed that they would be beneficial in preventing pre-eclampsia. The sustained blood pressure-lowering effect of thiazide diuretics is thought to involve mobilisation of excess sodium from the arteriolar wall, with widening of the vessel lumen. This might theoretically be of benefit in the pathological vasoconstriction which is an important characteristic of pre-eclampsia. The use of diuretics in pregnancy became controversial, with increasing evidence of the reduction of plasma volume in pre-eclampsia. There have also been case reports of maternal side-effects of diuretics in pregnancy including low potassium and sodium levels, decreased carbohydrate tolerance (increased tendency to diabetes) and pancreatitis.

The review of diuretics for preventing pre-eclampsia[174] included five RCTs (1836 women). Participants were both primiparous and multiparous women and were randomised from the first to the third trimester. Two trials included women with normal blood pressure only[175,176] one included women with chronic hypertension only[177] and two did not report on blood pressure at trial entry.[178,179] Two trials stated they excluded women with proteinuria.[175,176] One trial included women based on presence of excessive weight gain or oedema.[176] Thiazide diuretics were evaluated in all trials: chlorothiazide (three studies)[176,178,179] hydrochlorothiazide (one study)[175] and unspecified thiazide diuretics (one study).[177] These were compared with placebo in four studies and against no treatment in one study.[177] Restricted

Review: Antiplatelet agents for preventing pre-eclampsia and its complications
Comparison: 01 Antiplatelet agents versus placebo/no antiplatelet (subgrouped by maternal risk)
Outcome: 02 Proteinuric pre-eclampsia

Study	Antiplatelet agent *n/N*	Control *n/N*	RR (fixed) 95% CI	Weight (%)	RR (fixed) 95% CI
01 Moderate-risk women					
Australia 1993	1/55	5/55		0.4	0.20 (0.02 to 1.66)
Australia 1996a	4/52	7/50		0.6	0.55 (0.17 to 1.76)
Australia 1992	0/22	6/19		0.5	0.07 (0.00 to 1.11)
Barbados 1998	40/1819	46/1822		3.6	0.87 (0.57 to 1.32)
Brazil 1996	32/476	30/494		2.3	1.11 (0.68 to 1.79)
China 1996	4/40	12/44		0.9	0.37 (0.13 to 1.05)
China 1999	3/118	7/75		0.7	0.27 (0.07 to 1.02)
CLASP 1994	267/3992	302/3982		23.6	0.88 (0.75 to 1.03)
Colrado 1993	6/48	9/42		0.7	0.58 (0.23 to 1.50)
EPREDA 1993	5/156	8/73		0.9	0.29 (0.10 to 0.86)
ERASME 2003	28/1632	26/1637		2.0	1.08 (0.64 to 1.83)
Finland 1997	4/13	2/13		0.2	2.00 (0.44 to 9.08)
Israel 1994	0/24	2/23		0.2	0.19 (0.01 to 3.80)
Italy 1993	12/497	9/423		0.8	1.13 (0.48 to 2.67)
Jamaica 1998	215/3023	189/3028		14.7	1.14 (0.94 to 1.38)
Netherlands 1986	0/23	7/23		0.6	0.07 (0.00 to 1.10)
S Africa 1988	4/30	4/14		0.4	0.47 (0.14 to 1.60)
Spain 1997	3/50	7/50		0.5	0.43 (0.12 to 1.56)
Tanzania 1995	0/64	6/63		0.5	0.08 (0.00 to 1.32)
Thailand 1996	9/651	19/697		1.4	0.51 (0.23 to 1.11)
UK 1990	1/48	10/52		0.7	0.11 (0.01 to 0.81)
UK 1995	5/58	7/60		0.5	0.74 (0.25 to 2.20)
USA 1993	5/302	17/302		1.3	0.29 (0.11 to 0.79)
USA 1993a	69/1485	94/1500		7.3	0.74 (0.55 to 1.00)
Subtotal (95% CI)	14678	14539		65.4	0.85 (0.77 to 0.94)
Total events: 717 (antiplatelet agents), 831 (control)					
Test for heterogeneity $\chi^2 = 47.94$, df = 23 ($p = 0.003$) $I^2 = 52.0\%$					
Test for overall effect $Z = 3.24$ ($p = 0.001$)					
02 High-risk women					
Australia 1995a	0/9	6/11		0.5	0.09 (0.01 to 1.45)
Australia 1996	1/27	1/25		0.1	0.93 (0.06 to 14.03)
Australia 1997	5/58	5/50		0.4	0.86 (0.26 to 2.81)
Finland 1993	9/97	11/100		0.8	0.84 (0.37 to 1.95)
Finland 2002	2/43	10/43		0.8	0.20 (0.05 to 0.86)
France 1985	0/48	6/45		0.5	0.07 (0.00 to 1.25)
France 1990	1/46	4/45		0.3	0.24 (0.03 to 2.10)
Germany 2000	3/22	2/21		0.2	1.43 (0.27 to 7.73)
India 1994	6/46	19/48		1.5	0.33 (0.14 to 0.75)
India 1999	14/79	36/81		2.8	0.40 (0.23 to 0.68)
Israel 1989	1/34	7/31		0.6	0.13 (0.02 to 1.00)
Israel 1990	6/23	6/24		0.5	1.04 (0.39 to 2.77)
Italy 1999	18/103	21/104		1.6	0.87 (0.49 to 1.53)
Japan 1999	5/20	12/20		0.9	0.42 (0.18 to 0.96)
Netherlands 1989	0/5	1/5		0.1	0.33 (0.02 to 6.65)
USA 1994	3/24	5/25		0.4	0.63 (0.17 to 2.33)
USA 1998	231/1254	254/1249		19.9	0.91 (0.77 to 1.06)
Venezeula 2000	1/63	14/64		1.1	0.07 (0.01 to 0.54)
Zimbabwe 1998	17/113	23/117		1.8	0.77 (0.43 to 1.35)
Subtotal (95% CI)	2114	2108		34.6	0.73 (0.64 to 0.83)
Total events: 323 (antiplatelet agents), 443 (control)					
Test for heterogeneity $\chi^2 = 35.78$, df = 18 ($p = 0.008$) $I^2 = 49.7\%$					
Test for overall effect $Z = 4.74$ ($p < 0.00001$)					
Total (95% CI)	16792	16647		100.0	0.81 (0.75 to 0.88)
Total events: 1040 (antiplatelet agents), 1274 (control)					
Test for heterogeneity $\chi^2 = 85.59$, df = 42 ($p = <0.0001$) $I^2 = 50.9\%$					
Test for overall effect $Z = 5.31$ ($p < 0.00001$)					

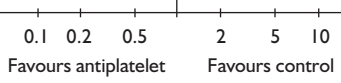


FIGURE 83 *Forest plot of the effects of antiplatelet agents in the primary prevention of pre-eclampsia*

TABLE 32 *Effects of antiplatelet agents on perinatal outcomes*

Outcome	No. of trials	Antiplatelets *n/N*	Control *n/N*	RR	95% CI	I^2 (%)	*p*-Value
Foetal and neonatal deaths	38	401/17040	470/16970	0.84	0.74 to 0.96	0	0.63
Preterm birth (<37 weeks)	28	2574/15950	2743/15895	0.93	0.89 to 0.98	0	0.64
Small for gestational age	32	978/12211	1041/12099	0.92	0.85 to 1.00	27.3	0.08

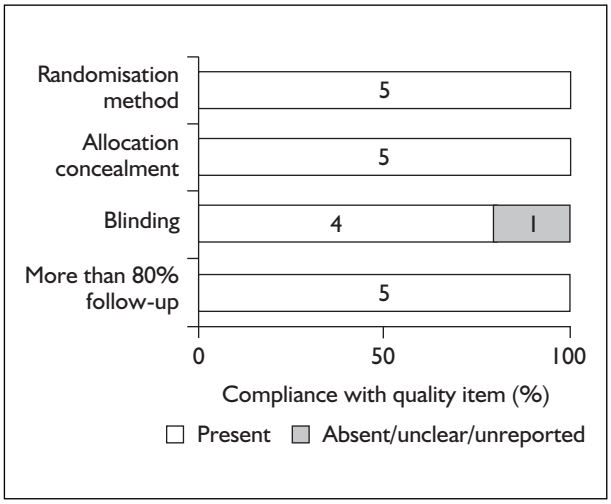


FIGURE 84 *Quality of RCTs of diuretics for preventing pre-eclampsia*

salt intake was advised in all five studies, although there was a wide range (salt intake of 1.8–5 g/day). Characteristics of the studies can be seen in Appendix 9.

The quality of the studies is shown in *Figure 84*. Four studies were double blinded and one was not blinded.[177] Follow-up for two studies was complete,[176,177] but the remaining three studies had losses to follow-up ranging from 8 to 14%.

Diuretics had a trend towards being more effective than placebo/no treatment in preventing pre-eclampsia, but these findings could have been accounted for by chance alone (*Figure 85*). We used RR 0.68 (95% CI 0.45 to 1.03) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 33*.

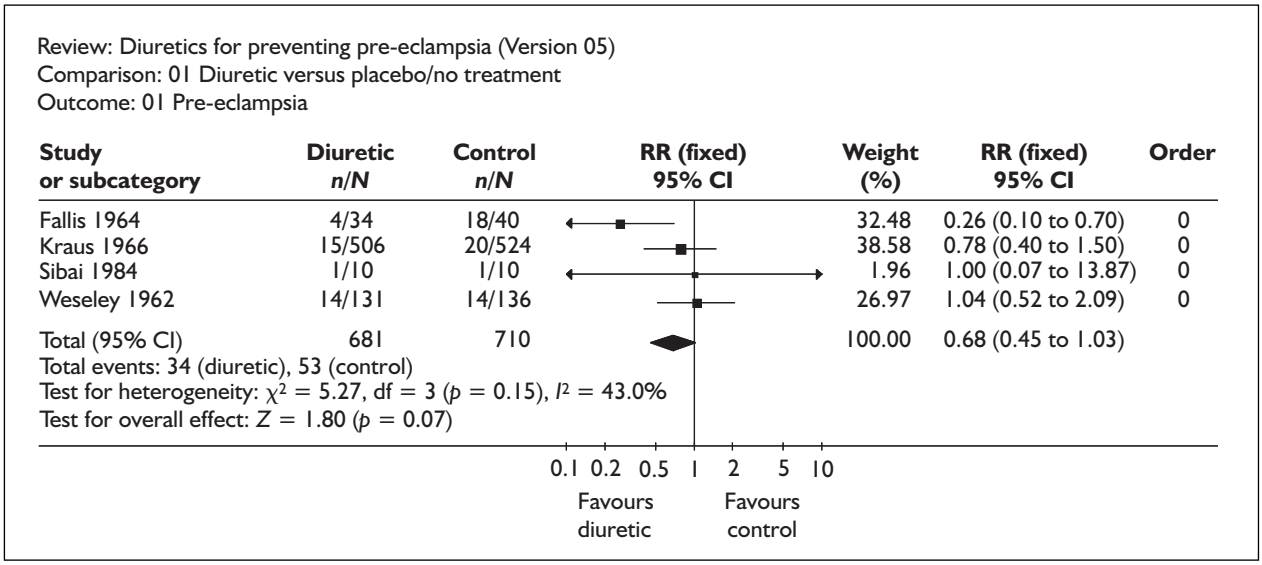


FIGURE 85 *Forest plot of the effects of diuretics for preventing pre-eclampsia*

TABLE 33 *Effects of diuretics on perinatal outcomes*

Outcome	No. of trials	Diuretics *n/N*	Control *n/N*	RR	95% CI	I^2 (%)	*p*-Value
Perinatal death	5	22/1016	26/820	0.72	0.40 to 1.27	0	
Premature birth	2	17/345	9/120	0.67	0.32 to 1.41	2.1	0.31
Small for gestational age	1	0/10	0/10	Not estimable	–	–	–

Nitric oxide donors and precursors for preventing pre-eclampsia and its complications

In 1987, nitric oxide was first identified as an endothelium-derived factor associated with vascular relaxation. Although it is now known to have a wide range of biological functions, interest in its possible role in pre-eclampsia has been generated largely because nitric oxide mediates many functions of the endothelium, including vasodilatation and inhibition of platelet aggregation. Nitric oxide is believed to contribute, at least in part, to the physiological vascular adaptations of normal pregnancy. Therefore, reduced availability of nitric oxide may have a role in the pathophysiology of pre-eclampsia. Drugs that can be converted by the body into nitric oxide (known as nitric oxide donors) are widely available, and have been used for years as therapeutic agents in cardiovascular diseases such as angina and hypertension. Commonly used nitric oxide donors include glyceryl trinitrate, isosorbide mononitrate, isosorbide dinitrate, *S*-nitroglutathione and sodium nitroprusside. They may be taken in a range of ways such as oral or sublingual tablets, aerosol spray under the tongue, skin patches or by intravenous injection.

The review of nitric oxide donors and precursors for preventing pre-eclampsia and its complications[180] included six RCTs (310 women). Four small trials (198 women) compared nitric oxide donors or precursors with placebo or no intervention and two trials compared nitric oxide donors or precursors with alternative agents (nifedipine,[181] antiplatelet agents[182]) and are not discussed further here. The four trials included women at moderate to high risk of developing pre-eclampsia: one trial each of gestational hypertension,[183] either gestational hypertension or pre-eclampsia,[184] chronic hypertension and a past history of early onset pre-eclampsia[185] or foetal growth restriction and normal blood pressure and an abnormal Doppler scan.[186] Gestation at randomisation was less than 16 weeks in one trial,[185] more than 24 weeks in two trials[184,186] and not reported for one trial.[183] Three trials evaluated glyceryl trinitrate transdermal patches and one evaluated the nitric oxide precursor L-arginine.[184] Characteristics of the studies can be seen in Appendix 9.

The quality of the studies is shown in *Figure 86*. Patients and caregivers were blinded to the intervention in two studies, only the caregiver was blinded in one study[183] and blinding was not mentioned in the remainder.[185] Follow-up was complete in two studies, 8% of the women were excluded from analysis in one study[184] and the other did not report completeness of follow-up.[185]

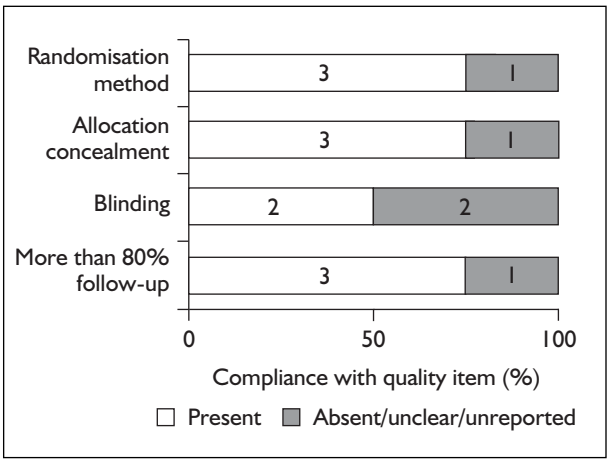


FIGURE 86 *Quality of RCTs of nitric oxide for preventing pre-eclampsia and its complications*

Nitric oxide had a trend towards being more effective than placebo or no intervention in preventing pre-eclampsia, but these findings could have been accounted for by chance alone (*Figure 87*). We used RR 0.83 (95% CI 0.49 to 1.41) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 34*.

Progesterone for preventing pre-eclampsia and its complications

Progesterone is a hormone which plays an essential role in reproduction, both in the regulation of the menstrual cycle and in the maintenance of pregnancy. It is used for a range of gynaecological problems such as heavy uterine bleeding, fertility control and postmenopausal hormone replacement. In addition, it has been suggested that progesterone may have a role in the treatment of premenstrual syndrome (PMS), threatened miscarriage and preterm birth. In the past, administration of progesterone has been suggested for prevention and treatment of pre-eclampsia. The hypothesis that progesterone reduced the risk of pre-eclampsia was tested but the use of progesterone for prevention of pre-eclampsia has never become widespread in clinical practice.

The review of progesterone for preventing pre-eclampsia and its complications[187] included one RCT (128 women).[188] This RCT had women with normal blood pressure at 16–28 weeks' gestation. Progesterone 100 mg was given daily or on alternate days for 1 week by intramuscular

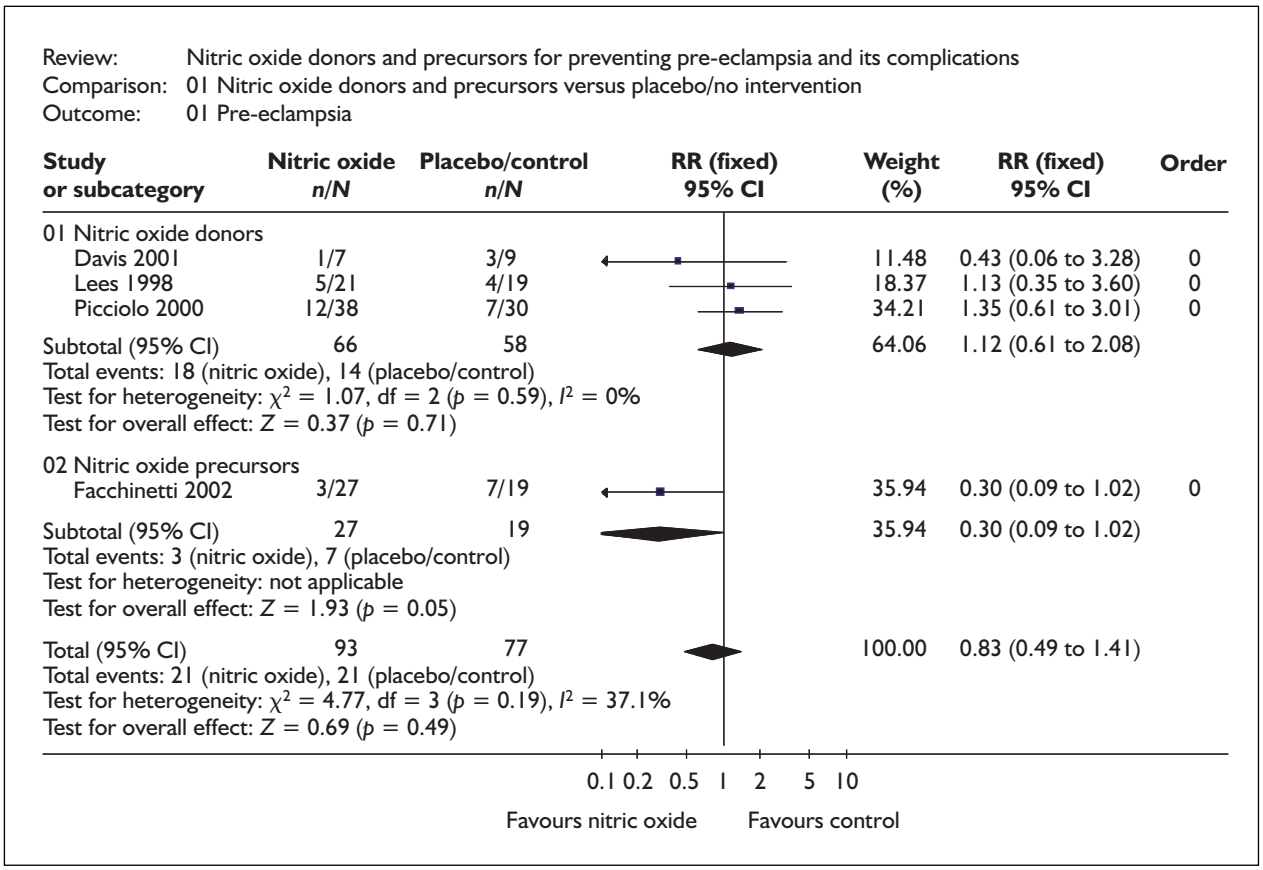


FIGURE 87 *Forest plot of the effects of nitric oxide for preventing pre-eclampsia and its complications*

TABLE 34 *Effects of nitric oxide on perinatal outcomes*

Outcome	No. of trials	Nitric oxide *n/N*	Control *n/N*	RR	95% CI	I^2 (%)	*p*-Value
Death of the baby	2	0/65	2/49	0.25	0.03 to 2.34	0	0.23
Preterm birth	3	5/86	13/68	0.48	0.21 to 1.07	0	0.07
Small for gestational age	2	9/59	10/49	0.78	0.36 to 1.70	0	0.53

injection, with the subsequent dosage (between 50 mg alternate days and 300 mg daily) depending on changes in intensity of "toxaemic" symptoms of tiredness, depression, nausea, irritability and headache. Women in the control group were offered simple treatments such as alkalis, analgesics, sedatives and antihistamines for the relief of their "toxaemic" symptoms. How many women needed these is not reported. Characteristics of the studies can be seen in Appendix 9.

The quality of the study is shown in *Figure 88*. Twenty-two participants (15%) were excluded from the analyses.

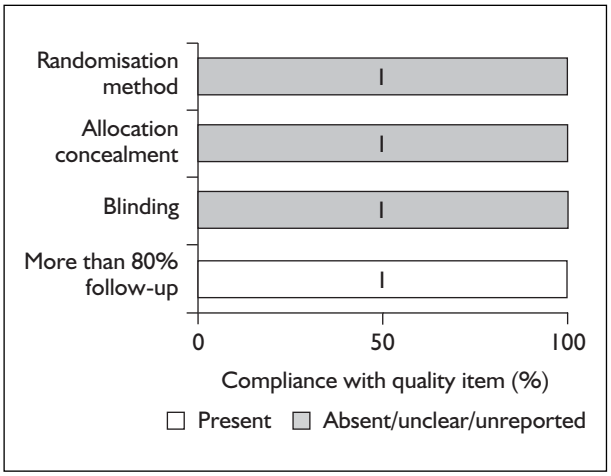


FIGURE 88 *Quality of RCTs of progesterone for preventing pre-eclampsia and its complications*

Progesterone had a trend towards being more effective than placebo in preventing pre-eclampsia

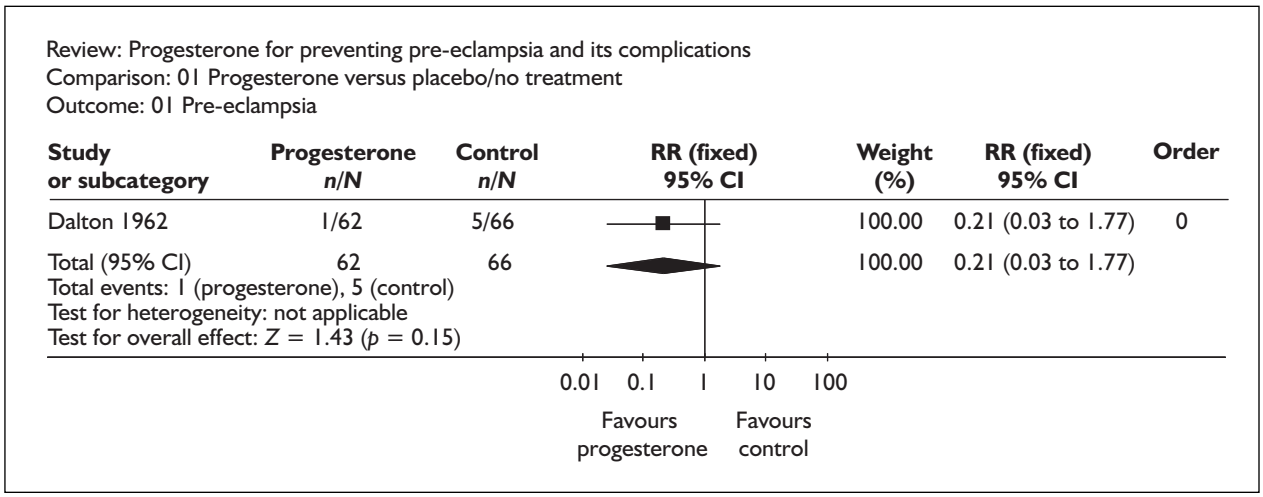


FIGURE 89 *Forest plot of the effects of progesterone for preventing pre-eclampsia and its complications*

TABLE 35 *Effects of progesterone on perinatal outcomes*

Outcome	No. of trials	Progesterone *n/N*	Control *n/N*	RR	95% CI	I^2 (%)
Perinatal death	1	1/62	3/66	0.35	0.04 to 3.32	NA
Preterm birth	0					
Small for gestational age	0					

but these findings could have been accounted for by chance alone (*Figure 89*). We used RR 0.21 (95% CI 0.03 to 1.77) for primary prevention of pre-eclampsia in decision analysis. The perinatal outcome results are shown in *Table 35*.

Discussion of results of clinical effectiveness reviews

Summary of effectiveness findings

Overall, the study quality for these trials (*Figure 90*) was variable or poorly reported. As the large trials tended to be of higher quality, however, high-quality results were available for the majority of women in the small number of reviews with these trials. There were deficiencies in the four main quality areas investigated here and no intervention had universally high-quality data. The number of trials included in the meta-analyses was relatively small – for 11 of the 15 reviews there were fewer than 10 trials and eight had five trials or fewer. The review of antiplatelet agents was a notable exception with 51 trials. As in the summary of test accuracy reviews, in the evaluation of many interventions, including exercise, advice to rest, advice to restrict dietary salt, garlic supplementation and progesterone treatment, the limited number of studies and the limited number of women with pre-eclampsia per study were limiting factors. The difficulties with study quality and small sample sizes in many of them meant that interpretation of effectiveness results was often difficult.

The effect on the RR of pre-eclampsia across the reviews is presented in *Figure 91*. Only four interventions showed a statistically significant reduction: rest at home, antioxidant agents, calcium supplementations and antiplatelet agents. For rest at home for women with normal blood pressure, the 95% CIs are wide and there are no results on outcomes for the baby (death, preterm birth or small for gestational age). For antioxidants, the findings presented here indicate that they are effective in preventing pre-eclampsia (although the updated Cochrane review, which included two large, recently published trials, reported a smaller effect size that was no longer statistically significant). Calcium supplementation was effective at preventing pre-eclampsia, but without any clear impact on perinatal outcomes. Antiplatelet agents, primarily low-dose aspirin, are associated with a modest reduction in pre-eclampsia, which is reflected in similar modest reductions in adverse outcomes for the baby.

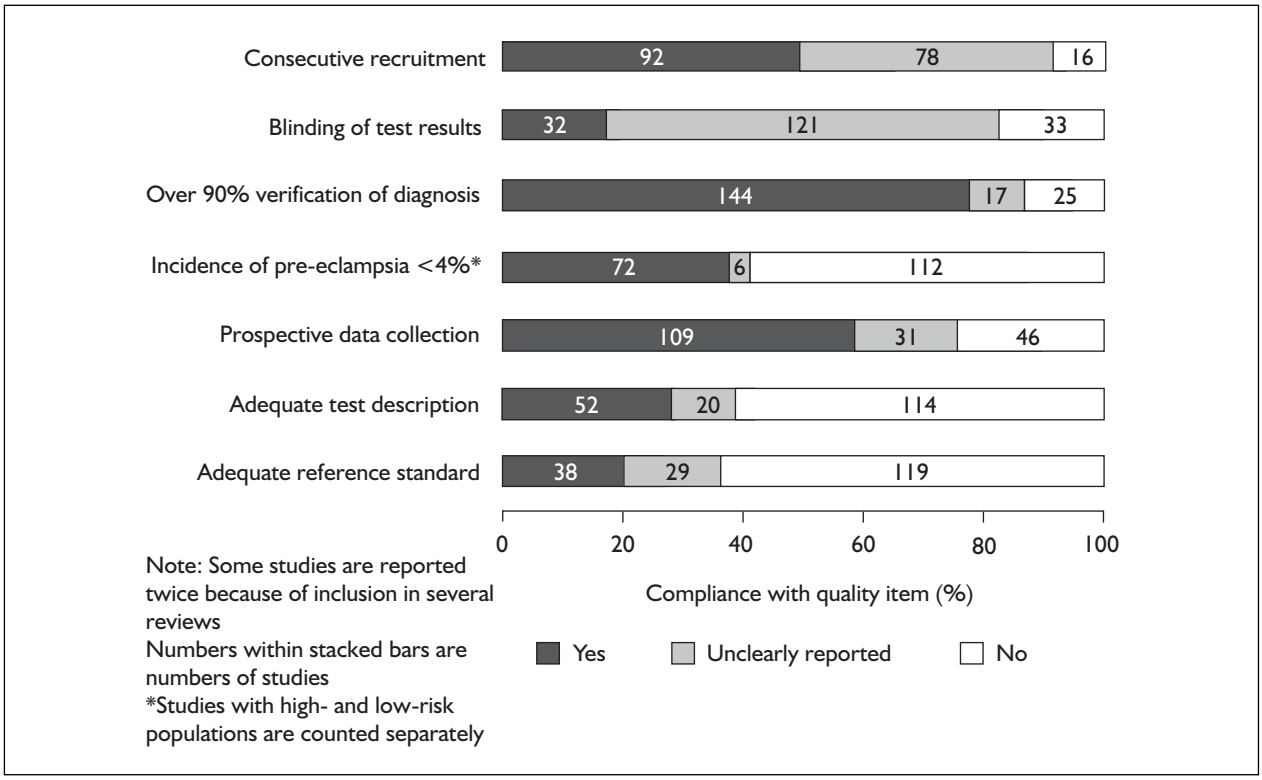


FIGURE 90 *Quality of all effectiveness review included studies*

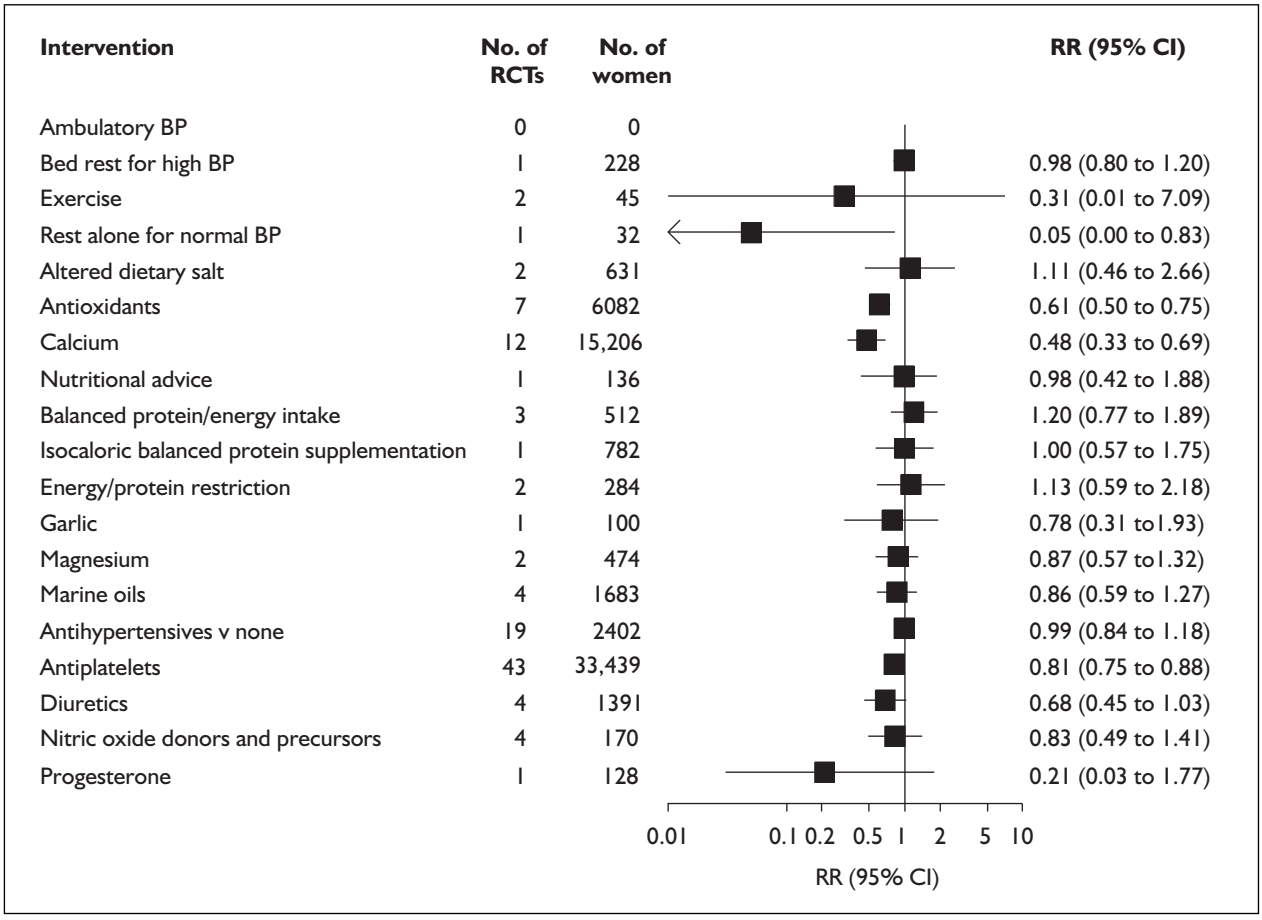


FIGURE 91 *Forest plot of summary of results of clinical effectiveness reviews*

The best pattern of antenatal care for higher-risk pregnancy is a frequently asked question from women at risk of pre-eclampsia (see *Table 2*, p. 7), yet there were no systematic reviews on most aspects of antenatal care. The single review looking at alternative strategies for assessing blood pressure during pregnancy found no trials.

Lifestyle issues, such as how much to rest or exercise, are usually a matter for personal choice. Whether to rest or give up work are common concerns for women at risk of pre-eclampsia (see *Table 2*, p. 7). For women with normal blood pressure who are at moderate risk, it remains unclear whether advice to rest, from 28 weeks' gestation onwards, with or without nutrient supplementation, is beneficial overall. For women with gestational hypertension, rest in hospital seems to be associated with a reduction in the RR of severe hypertension and perhaps also of preterm birth. Nevertheless, these findings need confirmation in larger studies, along with more reliable information about other potential benefits and hazards. In addition, there is little reliable information about the potential effects of exercise, whether recreational, domestic or occupational, for women at risk of pre-eclampsia. In the absence of such evidence, women should be reassured that they can make their own choice about how much to rest or exercise during pregnancy.

A range of dietary interventions have been suggested as possibly having a role in the prevention of pre-eclampsia. There is no clear evidence that advice to alter salt intake during pregnancy has any beneficial effect in prevention of pre-eclampsia or its consequences. Salt consumption during pregnancy should therefore remain a matter of personal preference. The initial optimism that antioxidants, particularly the combination of vitamin C and E, would reduce the risk of pre-eclampsia has, so far, not been confirmed by two recent large trials. Results of further ongoing trials are awaited. In the meantime, these agents cannot be recommended for clinical practice. Calcium supplementation is associated with a reduction in pre-eclampsia, although this was not reflected in reductions in perinatal outcomes. Nevertheless, calcium supplementation is probably worthwhile, particularly for women with low dietary intake. Dietary advice, protein/energy supplementation or restriction could not be supported, based on current evidence. There is insufficient evidence for any reliable conclusions about the potential benefits or harms of garlic. The review of magnesium supplementation also found not enough high-quality evidence to recommend this intervention. For marine oil, and other prostaglandin precursor supplements during pregnancy, large reductions in the risk of pre-eclampsia, preterm birth, low birth weight or small-for-gestational age are unlikely, although more moderate reductions have not been excluded.

Various pharmacological agents have also been advocated for women at risk of pre-eclampsia. For women with mild to moderate hypertension during pregnancy, it remains unclear whether lowering blood pressure with antihypertensive drug therapy is overall worthwhile. Whether the reduction in the risk of severe hypertension is considered sufficient to warrant treatment is a decision that should be made by women in consultation with their obstetrician. Antiplatelet agents, primarily low-dose aspirin, are associated with moderate–small reductions in the RR of pre-eclampsia and the main outcomes for the baby; namely death before discharge, preterm birth and being small for gestational age. Low-dose aspirin appears to be reasonably safe. Women at high risk should be offered low-dose aspirin. From a public health perspective, it may also be worth considering for more widespread use, should this be found to be cost-effective. It is unclear whether diuretics prevent pre-eclampsia. There is insufficient evidence for reliable conclusions about whether nitric oxide donors and precursors prevent pre-eclampsia and its complications. Some nitric oxide donors also have a high risk of headache. Similarly, it remains unclear whether progesterone prevents pre-eclampsia. None of these agents can therefore be recommended for clinical practice.

In the summary diagram forest plot (*Figure 91*) all of the clinical effectiveness results that were included in this report are presented. Twelve of these were used in decision analysis-based economic modelling (see *Table 37*, p. 88) and the remainder not used for a variety of reasons (see *Table 47*, p. 105).

Provisos/limitations arising from problems with primary data

The overall quality in the four main areas investigated were relatively poor and no intervention had universally high-quality data. Also, the number of trials that were meta-analysed was relatively small – for 11 of the 15 reviews there were fewer than 10 trials and eight had five trials or fewer. The reviews of calcium and antiplatelet agents were notable exceptions. As in the summary

of test accuracy reviews, in the evaluation of many interventions, including exercise, rest at home, advice to restrict dietary salt, garlic supplementation and progesterone treatment, the small number of studies and the low number of cases with pre-eclampsia per study were limiting factors. The sample size needed to demonstrate clinically meaningful differences for detecting modest effects was often inadequate as studies had been sized using over-optimistic estimates of possible effects of interventions on pre-eclampsia. In general, due to the limitations in quality and reliability (small numbers of studies and women) of the data reviewed, often there was a lack of evidence to assess effectiveness rather than good evidence of lack of effect.

Only four interventions were associated with a statistically significant decrease in pre-eclampsia cases. As discussed above, there are problems with the reviews of all of these interventions:

- The review of rest at home included only two small trials of poor quality, so at least some of the reported effect on pre-eclampsia may reflect bias and/or random errors, rather than a true effect of rest at home. Also, such a large reduction in risk associated with rest at home from 28 weeks' gestation onwards seems implausible. In order to interpret the results for women, information on compliance with rest at home and on the women's baseline activity level, is needed. Information about other substantive outcomes, including potential hazards, is also required before there can be any certainty about the overall benefits and harms. Although physical activity is inevitably reduced, some women may find the experience stressful and disruptive. Rest may also have financial implications for the women, their families and for society, particularly if it means leaving paid employment earlier than expected
- The review of antioxidants included a mixture of interventions – vitamin antioxidants such as vitamins C and E, mineral antioxidants such as selenium and non-vitamin antioxidants such as lycopene. It is conceivable that these interventions may have differing effects. Most of the results, however, refer to a combination of vitamins C and E. The meta-analysis results for pre-eclampsia did show some heterogeneity, but the I^2 value was not above 50%. However, tests for heterogeneity do not have high power, so the results should be viewed with some caution. Importantly, the antioxidant review reported here is now out of date as two large trials evaluating vitamin C and E were published in 2006 and have now been incorporated into the updated Cochrane review which became available after the economic modelling was completed. The additional trials had the effect of reducing the point estimate of effectiveness of antioxidants and the results are no longer statistically significant.
- Calcium supplementation appears effective for prevention of pre-eclampsia, but to date the evidence as to whether this is reflected in improvement in substantive outcome for the baby is inconclusive. The heterogeneity in results of the calcium trials seems to be largely associated with study size, with the small studies having the most positive results. As the small studies tended to recruit high-risk women, at least some of the heterogeneity may be explained by calcium having a greater effect for high-risk women. An alternative explanation may be publication bias. No small 'negative' studies have been identified, which is surprising as at least some would be expected, and tends to support the hypothesis of publication bias. However, there are probably still too few studies to establish whether publication bias is happening. Over 15,000 women have been recruited to trials evaluating calcium supplementation. Allocation to at least 1 g calcium was associated with a halving of the RR of pre-eclampsia. However, women with an adequate dietary intake of calcium were the only subgroup for which this did not achieve statistical significance. The greatest reduction in risk was for women at high risk and for those with low baseline dietary calcium intake. This suggests that calcium supplementation may be of more benefit for women with an inadequate diet, as found more frequently in economically poorer countries. Where women are generally well nourished, as in the UK, calcium supplementation may have a more limited role.
- For the antiplatelet review, there were very few trials in low-risk populations (event rate in control arm less than 2.5%). When a sensitivity analysis was done on this, the lowest risk group had a slightly smaller effect size. Funnel plots for this review have consistently been asymmetric, suggesting that small negative trials may be missing. Most small positive trials were published in the 1980s and early 1990s. It remains possible that small negative trials conducted at that time have still not been published. Interestingly, the more recent small studies are also largely positive. The funnel plot for pre-eclampsia therefore continues to be asymmetric. However, the funnel plot for data on stillbirths and neonatal deaths is more

symmetrical. Also, publication bias is not the only cause of funnel plot asymmetry, as it can be due to differences in maternal characteristics in small compared with large trials.

Provisos/limitations arising from review methods

The main strength of this report is that all of the included systematic reviews are Cochrane reviews, which follow a rigorous methodology. The strengths of this approach include a comprehensive search strategy, restriction to randomised (or for some reviews randomised and quasi-randomised) trials, peer reviewed and published protocol, peer-reviewed reviews, regular updating and a system for feedback. The Cochrane Pregnancy and Childbirth Group editorial process includes internal and external peer review, statistical review and review by a consumer panel. Because of time constraints, for four of the current reviews, the currently available version was used for the economic modelling because the updated results were not available. These were energy and protein, antioxidants, antihypertensives and antiplatelets. For three of these reviews, the updated results differed very little from the previous results and so the update would not have had any effect on the result of the subsequent economic evaluation. For the antioxidant review, the new update substantially changed the results and this has been flagged up throughout this report. The effect of this would have been to alter the results of any economic evaluation away from a recommendation to suggest antioxidants as a cost effective option.

- The systematic review of energy and protein intake was originally published in 2003. The updated version did not include any extra trials.
- The systematic review on antioxidants was originally published in 2005. The updated version had three extra trials (with 4385 women). The addition of these trials shifted the estimate of RR from 0.61 (95% CI 0.50 to 0.75) to 0.73 (95% CI 0.51 to 1.06).
- The systematic review of antihypertensives included in this report was originally published in 2000. The updated version had six extra trials for the comparison of any hypertensive versus placebo/no treatment. The addition of these trials had little impact on the estimate of RR of pre-eclampsia, which in the 2000 review was 0.99 (95% CI 0.84 to 1.18) and in the 2006 update was 0.97 (95% CI 0.83 to 1.13).
- The systematic review on antiplatelet agents included in this review was originally published in 2003. The updated version had seven extra trials. The addition of these trials had little impact on the estimate of RR of pre-eclampsia, which in the 2003 review was 0.81 (95% CI 0.75 to 0.88) and the 2006 update was 0.83 (95 %CI 0.77 to 0.89).

As Cochrane reviews are regularly updated, the search strategy for this report did not start from a single time-point. This made the construction of the QUOROM-style diagram complex, particularly for numbers of excluded studies, as shown in *Figure 56*, p. 54. Also, the updating process means that versions of the Cochrane reviews referred to in this report may quickly change and no longer be available in the public domain as the updates are published. Therefore, an archive of the versions used in this report has been kept, whereas the most up-to-date versions of the Cochrane reviews will be available in the Cochrane Library.

Several of the Cochrane reviews reported here include a range of similar interventions within a single review, rather than reporting each intervention separately. Where there might be potential differences in the effects of the different interventions, the Cochrane reviews have dealt with this by using subgroup analyses to investigate heterogeneity. Some of these subgroups have been shown in the forest plots presented in the report, for example with antihypertensives. Cochrane review authors judged it reasonable to combine results across subgroups where there was no clear evidence of statistical heterogeneity, as in the antioxidant and antiplatelet reviews.

In this report, we have presented the quality of the included trials within each review as a single diagram. Inevitably, this results in loss of detail regarding quality aspects of each trial. However, the quality of included trials is fully reported within each review in the Cochrane Library. Individual trial quality assessment is most useful within a review for indicating studies which may be more open to bias than others and less well adapted to indicating parameters which may be underpinned by relatively weak evidence. It was the latter, however, which was more important in this project.

Provisos/limitations arising from things not done

The original project plan included a wide list of potential interventions that could have been systematically reviewed (see *Table 49*, p. 140). We also asked a consumer group for information about the questions that women were asking of their help line (see *Table 2*, p. 7). As this

information was not available until late in the project, it was not feasible to use it to prioritise topics for review. Such an approach would have been of considerable benefit to both women and clinicians and should be considered in the future. A key limitation of this report is that we did not have space to report on a wide variety of other relevant outcomes including those on adverse events or side-effects of treatments included in the Cochrane reviews. There is potential for some of the treatments reviewed to have serious side-effects that could outweigh the advantages if they prevented pre-eclampsia. We did not include all Cochrane reviews that reported pre-eclampsia as an outcome because some are subsets of other Cochrane reviews, such as the review on beta-blockers in pregnancy,[189] which is also reported in the antihypertensives review.

Findings in the light of limitations

The quality assessment of the trials included in this report suggested that trials of good methodology have been done and many of these are large, but in general most trials have important deficiencies in terms of both methodology and small sample size. These limitations have hampered the search for effective treatments to prevent pre-eclampsia. We have good evidence on the effectiveness of a few interventions that aim to reduce pre-eclampsia. However, the limitations introduce considerable uncertainty on other interventions. This arises from lack of evidence about the effect on pre-eclampsia or because of differing effects on outcomes beyond pre-eclampsia and because of variability in the size of effect between studies.

Ramifications for the economic model

The implications of the finding on effectiveness for the economic evaluation are multiple. The reviews with apparently the most beneficial effects were entered into the model. However, concerns about the quality and sparcity of the data (particularly for interventions such as rest at home) need to be considered when interpreting the model results. This is discussed in greater detail at the end of Chapter 5.

Recommendations for practice

Anti-platelet agents, particularly low-dose aspirin, produce moderate but consistent and important reductions in pre-eclampsia and its consequences for the baby. This information should be discussed with women at risk of pre-eclampsia to help them make informed decisions about their antenatal care. Potential side-effects of this treatment have not been addressed here. Further details are available in the Cochrane review on antiplatelet agents. There is a possibility that calcium supplementation should be offered to women, particularly with low dietary calcium intake. Otherwise there are few recommendations for practice.

Recommendations for research

There needs to be a closer match between the interests and clinical needs of pregnant women about the questions they would like answered (see *Table 2*, p. 7) and the clinical trials and systematic reviews currently being undertaken.

As calcium supplementation appears to be effective for the prevention of pre-eclampsia, the most effective and acceptable methods of dietary calcium fortification could be investigated.

Until the cause of pre-eclampsia is fully understood, developing potentially effective interventions to prevent this important condition remains problematic. As pre-eclampsia is a multi-system disorder, effectiveness also needs to be assessed by the impact on other outcomes for both the woman and the child. These include the three neonatal outcomes included in the effectiveness section, neonatal deaths, preterm births and small for gestational age, but also other measures of serious morbidity for the mother and the long-term outcome for mother and child.

The lifestyle interventions such as rest for normotensive women and exercise are of considerable interest to women. These merit good-quality, adequately powered RCTs which measure all relevant clinical outcomes, side-effects, costs and acceptability to women.

Given the difficulty with the variable quality of RCTs, what may be required are subgroup analyses of the highest quality studies. This is particularly possible for the antiplatelet intervention where there are sufficient studies to be able to attempt IPD meta-analysis or meta-regression.[190] An IPD analysis of the antiplatelet trials has been completed and is due to be published shortly.

Conclusions of effectiveness reviews

Sixteen systematic reviews of interventions were presented in this report, of which 15 provided estimates of effectiveness in pre-eclampsia. However, the overall quality of studies was variable and few interventions have been shown to reduce the risk of pre-eclampsia. The largest systematic review included 51 trials and investigated the effectiveness of antiplatelet agents, principally

aspirin, to prevent pre-eclampsia. This was the only review where the intervention was shown to reduce the RR of pre-eclampsia and its consequences for the baby. Calcium supplementation also appears to reduce pre-eclampsia but without any clear benefit to the baby. Antioxidants, primarily the combination of vitamin C and E and rest at home, also appear to reduce the risk of pre-eclampsia, but again there are limitations with these results.

Chapter 5

Economic evaluation

Methods for economic evaluation

Introduction

The objective of the economic evaluation in this study was to collate the data from the reviews on the accuracy of the tests with the data on the effectiveness of the interventions and to explore the relative cost-effectiveness of a range of different testing and treatment options. Whereas the accuracy and effectiveness reviews considered tests or interventions applied to both normal women at no predetermined risk of pre-eclampsia and to women considered at risk or high risk, the main focus of the economic analysis was on test and interventions that are applied to normal women who have no prior history to suggest they are at risk of pre-eclampsia. Although results from 12 interventions were modelled, just the tests and/or interventions that are shown to be of significant interest are presented in more detail. The final output of the modelling exercise is in terms of the dominating strategies (those achieving greater effectiveness at reduced cost) and the relative incremental cost-effectiveness ratios (ICERs) for the better test and treatment options. The results are in terms of cost per case of pre-eclampsia avoided. The perspective adopted for the economic evaluation was that of the NHS. Private out-of-pocket costs to women are not included in the analysis.

Model structure

The appropriate model for this study was a decision tree. This was constructed in DATA Treeage. Space constraints do not allow the full diagram of the model to be presented as it comprises 538 alternative strategies combining all 21 tests and 12 interventions and a branch with a no test, no treatment option [NB: the reason for 538 branches rather than $(21 \times 12 \times 4) + 1$ branches is because where a branch looks at no test and treatment for all, only 12 branches are required rather than 21×12 branches and where a branch is test all and no treatment, only 21 branches are required rather than 21×12 branches]. To illustrate the approach for each test/treatment pairing we present a subset of the model for one test [Doppler: any unilateral notching (AUN)] and one intervention (calcium). This is presented in *Figure 92*.

In this diagram, each branch to the right of the chance node (round symbol) indicates one way in which the test under consideration (Doppler AUN) and treatment (calcium) can be brought together. All the ways in which test and treatment could in theory be used together are considered for completeness, although not all of these may have direct clinical relevance (see below for further explanation). Thus the model considers for each test and treatment combination the number of cases of pre-eclampsia and the associated cost for:

1. No test and no intervention ("No test/no treatment").
2. Intervention, calcium, given to all with no preceding testing ("No test/calcium_all").
3. Test, Doppler AUN, applied to all, but no subsequent intervention ["Doppler (AUN)/no treatment"].
4. Test, Doppler AUN, applied to all, followed by the intervention, calcium, being given just to those testing positive (having the characteristic indicated, i.e. AUN or a test value above a stated value) ["Doppler (AUN)/calcium_positive"].
5. Test, Doppler AUN, applied to all followed by the intervention, calcium to all (regardless of test result) ["Doppler (AUN)/calcium_all"].

Branch 1, the no test, no intervention option, represents the comparison group for all the other branches 2–5, and indeed is the common comparator for all modules of the model for each test and treatment pairing considered. It indicates the number of cases of pre-eclampsia and the associated costs in "normal practice", assuming that there is currently no systematic testing and treatment of those deemed at high risk on the basis of the test. This assumption is unlikely to be true in the NHS, which is why normal practice appears in parentheses. Despite this, it still represents the most informative baseline against which to consider alternative strategies.

Branches 2 and 4 represent the chief clinically relevant alternative strategies for test and treatment pairings. Branch 2 considers the benefits and costs of treating all mothers, an

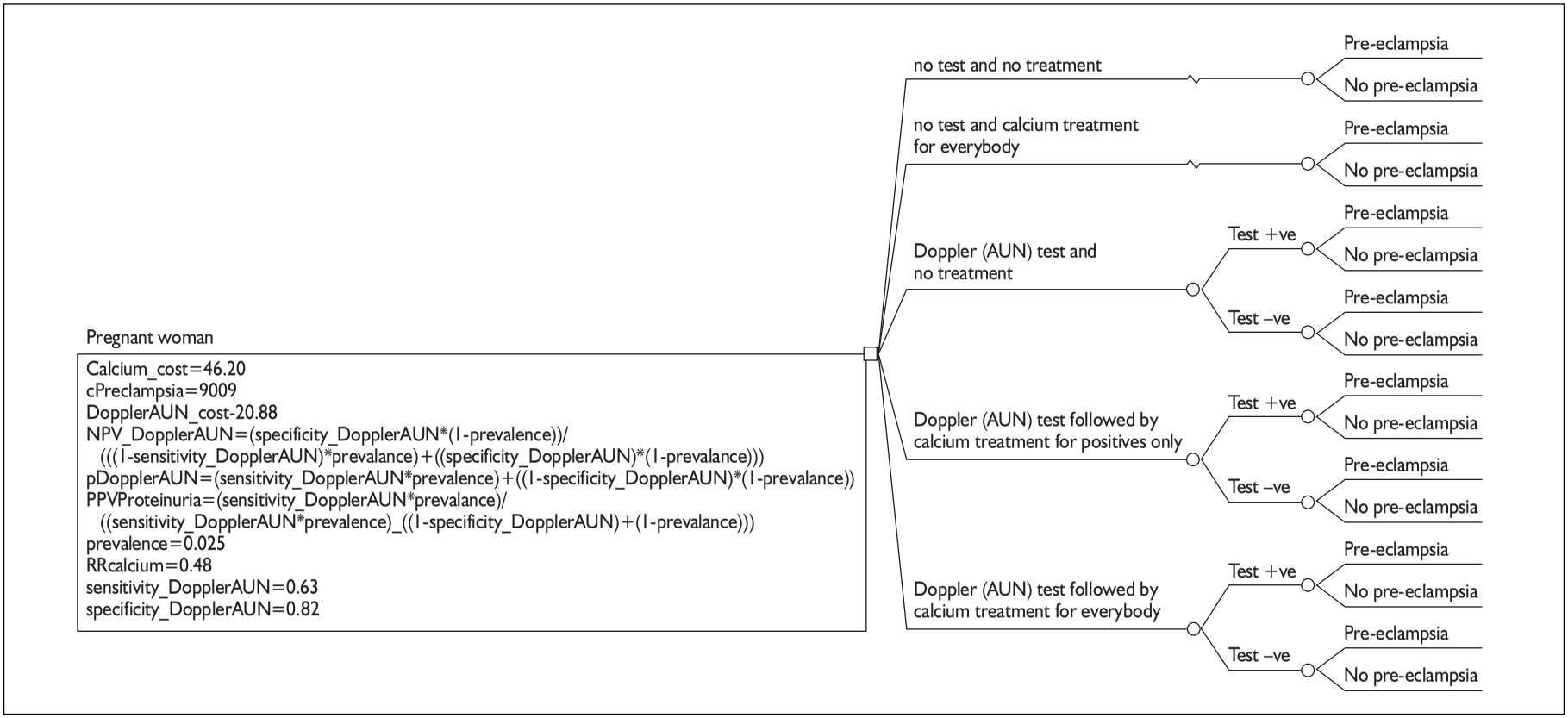


FIGURE 92 *Model structure*

TABLE 36 *Diagnostic test sensitivity and specificity results for each test provided by the project's systematic reviews of test accuracy – inputs to model*

Accuracy	Sensitivity	95% CI	Specificity	95% CI	PPV[a]	NPV[a]
Maternal serum AFP	9	5 to 16	96	94 to 98	5	98
Maternal serum HCG	24	16 to 35	89	86 to 92	5	98
Serum unconjugated oestriol	26	9 to 56	82	61 to 93	4	98
Cellular fibronectin	50	30 to 70	96	79 to 99	24	99
Total fibronectin	65	42 to 83	94	86 to 98	22	99
SUA	36	22 to 53	83	73 to 90	5	98
fDNA	50	31 to 69	88	80 to 93	10	99
Urinary calcium excretion	57	24 to 84	74	69 to 79	5	98
Urinary calcium/creatinine ratio	50	36 to 64	80	66 to 89	6	98
Total proteinura[b]	35	13 to 68	89	79 to 94	8	98
Total albuminuria	70	45 to 87	89	79 to 94	14	99
Microalbuminura	62	23 to 90	68	57 to 77	5	99
Microalbumin/creatinine ratio	19	12 to 28	75	73 to 77	2	97
Doppler uterine artery: pulsatility index	48	29 to 69	87	75 to 94	9	98
Doppler uterine artery: any unilateral notching	63	51 to 74	82	74 to 87	8	99
Doppler uterine artery: bilateral notching	48	34 to 62	92	87 to 95	13	99
Doppler uterine artery: resistance index	66	54 to 76	80	74 to 85	8	99
Doppler uterine artery: combination of abnormal waveforms	64	54 to 74	86	82 to 90	10	99
Doppler: other ratios	55	37 to 72	80	73 to 86	7	99
BMI ⩾34	18	15 to 21	93	87 to 97	6	98
BMI >29	23	15 to 33	88	80 to 93	5	98

[a] Positive and negative predictive values (PPV and NPV), rounded to nearest integer, associated with given sensitivity and specificity in population with prevalence of pre-eclampsia of 2.5%.

[b] Test accuracy of kallikreinuria also considered. Sensitivity and specificity were apparently good (83% and 99%, respectively, for thresholds of <100 or <200 inactive urinary kallikrein to creatinine ratio) but it was evaluated in a study with only 12 cases of proteinuric pre-eclampsia. Hence although noting this to be a test worthy of further evaluation, the results were not modelled, a reinforcing concern being clinical advice that the test is not routinely available. This concern also applies to SDS-PAGE proteinuria.

important scenario to investigate if there is doubt about the accuracy of the available tests. Branch 4 considers the approach which attempts to focus the intervention on those indicated by the test to be at highest risk, and so avoid any adverse effects of the intervention in those thought unlikely to gain benefit, because their risk of developing pre-eclampsia is so low.

Branches 3 and 5 represent theoretical combinations which have no direct clinical relevance, but are nonetheless important for a complete understanding of the relationship between benefits, disbenefits and costs. Branch 3 provides an opportunity to scrutinise the costs and direct effects of testing independently of any effect of treatment. Branch 5 indicates the worst-case scenario with respect to cost, including both test and treatment costs applied to all. However, it also includes the highest level of benefit and disbenefit that might conceivably be achieved too, as all mothers receive the treatment under consideration.

In *Figure 92*, the right-hand side of the diagram indicates the outcomes considered in measuring which of branches 1–5 in this and other modules is optimal. As already indicated, the main outcome is cases of pre-eclampsia relative to cases without pre-eclampsia. In branches where a test result is obtained, the model considers separately the number of cases of pre-eclampsia occurring in those testing positive and those testing negative. Although this is shown as being a feature of the way the model works in branches 3–5, it is only strictly necessary in branch 4, as this is the only option where treatment is truly contingent on the test result. The box beneath the population of interest, pregnant women, on the far left of the diagram, indicates the model parameters being used. Thus "Calcium_cost=46.20" indicates that the cost of calcium supplementation over the course of pregnancy is £46.20 and "sensitivity_DopplerAUN=0.63" that the sensitivity estimate being used in this module of the model is 63%. These parameters will differ depending on the module. They will also vary if

TABLE 37 *Effectiveness RR of pre-eclampsia for each intervention provided by the project's systematic reviews of effectiveness – inputs to model*

Group	Treatment	RR	95% CI	Revised RR[a]	95% CI
Group 1[b]	Rest for normotensive women vs unrestricted activity	0.05	0.0 to 0.83	No subgroup analyses	
	Antioxidants vs placebo/no antioxidants	0.61	0.50 to 0.75	0.45[d]	0.31 to 0.66
	Calcium supplement vs placebo	0.48	0.33 to 0.69	0.62[e]	0.32 to 1.20
	Antiplatelets vs placebo/no intervention	0.81	0.75 to 0.88	0.85[f]	0.77 to 0.94
Group 2[c]	Progesterone vs no progesterone	0.21	0.03 to 1.77	NA	
	Diuretics vs placebo/no diuretics	0.68	0.45 to 1.03	NA	
	Garlic vs placebo	0.78	0.31 to 1.93	NA	
	Nitric oxide donors or precursors vs placebo/no intervention	0.83	0.49 to 1.41	NA	
	Marine/fish oils vs placebo/no treatment	0.86	0.59 to 1.27	NA	
	Magnesium vs placebo/no treatment	0.87	0.57 to 1.32	NA	
	Antihypertensives vs placebo/no treatment	0.99	0.84 to 1.18	NA	
	Advice to reduce dietary salt vs advice to continue normal diet	1.11	0.46 to 2.66	NA	

[a] RRs based on subgroup analyses, defined in detail in the text, and used as parameters in sensitivity analyses.
[b] Group 1 are those treatments with an RR whose upper 95% CI is <1.0.
[c] Group 2 are those treatments with an RR whose 95% CI include a value compatible with worsened outcome.
[d] Subgroup excluding the single large quasi-randomised trial.
[e] Subgroup of trials carried out in populations with an adequate calcium diet.
[f] Subgroup of trials carried out in populations with mothers at 'moderate risk' of pre-eclampsia rather than both 'moderate-' and 'high-risk' combined.

the sensitivity of the model to variation in a particular parameter is being tested.

Inputs to model

Test accuracy and effectiveness inputs

The results from the systematic reviews assessing the accuracy of all the tests reviewed as part of this project, reported in Chapter 3, were the source of the sensitivity and specificity model parameters. The forms used for data collection are shown in Appendix 10. The actual values used were generally based on pooled sensitivities and specificities using the bivariate method of meta-analysis described in the section 'Methods for test accuracy reviews' (p. 13). These values and their associated 95% CIs are given in *Table 36*. Similarly the results from the systematic reviews of the effectiveness, reported in Chapter 4, were the source of model parameters concerning the effect of various treatments on the number of cases of pre-eclampsia. The values used, generally the summary RR from the meta-analyses, along with their 95% CIs, are summarised in *Table 37*. There are two groups of treatments differentiated because they are dealt with slightly differently by the model (see below). In group 1, the 95% CIs for the RR do not include values >1.0, indicating that a true value of the RR compatible with increased numbers of pre-eclampsia cases (i.e. worsened outcome) is unlikely. Conversely, in group 2, the 95% CIs for RR do include values >1.0, that is, a possible worsened outcome. *Table 37* also gives values for the RR values obtained from important subgroup analyses (for group 1 treatments only) which were used in sensitivity analyses (see below). Some of the Cochrane review update results became available too late to be incorporated into the economic model. These have been reported in Chapter 4 but are not referred to in this section.

Cost inputs

A systematic review of the economic literature to search for costs was not undertaken as part of this project. A systematic review of the economic literature on antenatal ultrasound screening[191] and antenatal screening[192] were carried out by one of the present authors (TR) and were published during the life of the current study. Any relevant information identified in the two systematic reviews mentioned above was used in the current analysis. The cost of each test and each intervention was estimated from different sources described in more detail below. All costs are presented in UK£, 2005–06 prices.

Test accuracy costs

Costs for the tests came from two main sources, the Birmingham Women's Hospital (*Table 38*,

TABLE 38 *Estimated costs of diagnostic tests*

Test	Nature of test	Unit cost from Birmingham Women's Hospital (£)	Costs from literature (UK£ 2005)	
			Unit cost (upper and lower estimates)	Source
BMI measurements	Measurement of weight and height		5.00	Estimate based on 5 minutes of nursing time and an of estimate fixed costs
Maternal serum AFP	Venous blood test 2.5 ml	16	44.41 (38.25–50.56)	Literature[191]
Cellular FN	Venous blood test 5 ml	5[a]	44.41 (38.25–50.56)	Proxy based on literature for AFP[191]
Total FN	Venous blood test 5 ml	5[a]	44.41 (38.25–50.56)	Proxy based on literature for AFP[191]
fDNA	Venous blood test 5 ml	5[a]	44.41 (38.25 to 50.56)	Proxy based on literature for AFP[191]
Maternal serum HCG	Venous blood test 2.5 ml	16	44.41 (38.25 to 50.56)	Proxy based on literature for AFP[191]
Serum unconjugated oestriol	Venous blood test 2.5 ml	16	44.41 (38.25 to 50.56)	Proxy based on literature for AFP[191]
SUA	Venous blood test 5 ml	5	44.41 (38.25 to 50.56)	Proxy based on literature for AFP[191]
Urinary calcium excretion	24-hour urine collection (home or hospital)	6.6	7.56	Proxy based on literature for PCR tests[195]
Urinary calcium creatinine ratio	24-hour urine collection (home or hospital)	6.6	7.56	Proxy based on literature for PCR test[195]
Total proteinuria	24-hour urine collection (home or hospital)	6.5	7.56	Proxy based on literature for PCR test[195]
Albuminuria	24-hour urine collection (home or hospital)	7.85	7.56	Proxy based on literature for PCR test[195]
Microalbuminuria	24 hour urine collection (home or hospital)	7.85	7.56	Proxy based on literature for PCR test[195]
Albumin/creatinine ratio	24 hour urine collection (home or hospital)	7.85	7.56	Proxy based on literature for PCR test[195]
Doppler examinations	Ultrasound scan lasting 10 minutes	NA (used literature reference)	20.86 (18.11–23.63)	Literature[191]

NA, not applicable; PCR, polymerase chain reaction.
[a] These costs were not provided by the Birmingham Women's Hospital and so cost of SUA was used as a proxy; chosen because it was inexpensive and would not disadvantage the test. This will be discussed in case 4.

column 3) and the literature (*Table 38*, columns 4 and 5). The costs for most of the tests, with the exception of Doppler, were available from the Birmingham Women's Hospital (Coles N; personal communication, April 2006). The costs provided are the costs applied within the hospital for the named test. However, if the test was carried out on behalf of another hospital, an additional cost (charge) would be applied.

An alternative set of literature-based test costs was available from a previous study evaluating antenatal tests that had been carried out by one of the members of the economic and modelling team. The costs determined as part of that study are based on average estimates from an inclusive review of international literature that, at the time, were considered the best available published estimates. Consequently, the estimated

average costs are somewhat higher than local estimates.

A cost estimate for AFP was identified in a review of the economic antenatal literature carried out by one of the present authors some years previously.[191] This was inflated to 2005–6 prices using the hospital and community health services pay and price inflation index[193] and International Monetary Fund website exchange rates.[194] A literature estimate of cost was not identified for any of the other blood tests and so in the absence of more accurate data, the cost of the AFP blood test was used as a proxy for these other blood tests.

The accuracy reviews indicated that the six ultrasound scans all comprised Doppler examinations lasting approximately 10 minutes that would cost the same. The cost of a Doppler examination had been estimated previously[191] and was inflated to current prices as described above. The Doppler scan, deemed most analogous to the 10-minute scans reported by the accuracy reviews, was the second trimester anomaly scan. This cost was applied as a proxy for all six Doppler examination tests identified by the accuracy reviews.

The cost of the BMI tests, which comprised measurement of weight and height, was assumed to take approximately 5 minutes, but costs were estimated for 10 minutes of an antenatal appointment with midwife or nurse practitioner at the general practice, the cost of which was estimated from standard reference costs.[193] Although the time taken to do the test would be only a few minutes, extra time was included in the cost to allow for rapport building and administration. The 24-hour urine tests were all assumed (based on expert advice from within the current study) to be performed on a urine collection carried out by the patients at home and not as inpatients, with negligible costs for urine collection receptacles provided by the hospital. Thus the required cost is for the test and administration time of this only. No estimate of the costs of the alternative urine tests was found in any recently published reviews, so the cost of a urine test estimated as part of a different study,[195] but carried out by some of this project's health economics and modelling team (TR and PB), was used as a proxy for the cost of a urine test here.

Treatment costs

The systematic reviews on intervention effectiveness indicated the dose and duration of treatment used in the included RCTs. These are summarised in *Table 39*. It was assumed that each intervention therapy would be prescribed in an appointment with the clinician and the cost of this appointment was not included in the analysis as it should be approximately the same for all interventions. However, in some cases the prescribed intervention has no direct cost to the health service, such as the advice to reduce salt in the diet or advice to take rest. For other interventions, where a dose range was presented, the costs of the upper and the lower limit of the dose were used. The treatment dose (if appropriate) and duration were applied to the treatment unit costs to give the total cost. For drugs, the unit costs were taken from the British National Formulary (BNF) (Volume 51, 2006).[196] The unit costs for the vitamin or herbal supplements such as fish oils and garlic were obtained from the Holland and Barrett website (a commercial health food shop).[197]

Pre-eclampsia outcome costs

We used the most recently available estimate for the cost of pre-eclampsia[198] (*Table 39*) In that study, the cost of a case of pre-eclampsia, without eclampsia occurring, was estimated to be $12760.32 (US$ 2001) in high-income countries. These costs were estimated in a regression analysis as part of the economic evaluation of the Magpie Trial[198] [Simon J, University of Oxford Health Economics Research Centre (HERC): personal communication, March 2006]. The estimate includes all hospital costs (even those not directly related to pre-eclampsia, i.e. delivery costs, etc.) for both mother and baby. The cost translated to £10,074 in UK£ when converted and inflated as appropriate to the price year 2005–6.[193,194] The cost of a normal delivery was removed from this estimate of pre-eclampsia for use in the model. The cost of normal delivery was estimated to be between £1227 and £903 with and without concomitant complications, respectively.[199]

The resulting cost for pre-eclampsia of £9009 was considered to be the best available estimate despite including other costs. The reason for excluding the cost of birth from the estimate was that the cost of birth was not being included in any of the comparator arms of the model.

Source of other model parameter

The prevalence of pre-eclampsia that was used in the model was estimated by using the Cochrane Review on antiplatelet agents for preventing pre-eclampsia and its complications.[74] We inspected the list of trials and their inclusion criteria to find trials with low-, medium- and high-risk women

TABLE 39 *Estimated costs of interventions and outcomes*

Treatment	Nature and dose	Duration	Total cost (UK£ 2005)	Bases for cost estimate (comment)	Source of unit
Advice to reduce dietary salt	Advice to reduce dietary salt	None	0	Advice to reduce dietary salt incurs no direct cost to the NHS	
Antioxidants	Vitamin C and E (often combined). Vitamin C 100–1000 mg/day. Vitamin E 400 IU/day. Selenium 100 μg/day and lycopene 4 mg/day	20 weeks (range 18–24 weeks)	54.45	Lycopene (10 mg), pack of 50 tablets = £10.49 – 3 packs required Vitamin C and E (500 mg), 100 capsules = £11.49 – 2 packs required	Holland and Barrett[197] (unavailable in BNF)
Calcium	Calcium tablets 1.5–2 g/day were used	20 weeks	46.20	Assumed to be calcium gluconate effervescent tablets 1 g; 28 tablets in pack @ £4.62 each. Assume 10 packs required	BNF[196]
Garlic	One capsule/day	20 weeks	9.98	100 capsules (500 mg) @ £4.99 – 2 packs required	Holland and Barrett[197]
Magnesium	Magnesium tablets 300 mg/day	20 weeks	29.90	30 tablets in pack @ £2.99, assume 10 packs required	Holland and Barrett[197]
Marine/fish oils	1 capsule/day	24 weeks	16.99	250 capsules @ £16.99	Holland and Barrett[197] (not reported in BNF)
Antihypertensives	25–50 mg/day for β-blocker such as atenolol	20 weeks	4.90 [4.20 (50 mg) – 5.60 (25 mg)]	Atenolol assumed – 25 mg pack of 28 tablets = £1.12; 50 mg, 28 tablets = £0.84; 5 packs required	BNF[196]
Antiplatelets (principally aspirin)	75–150 mg/day	20 weeks	2.69 [1.54 (75mg) – 3.08 (150 mg)]	Aspirin 75 mg; 20 tablets @ £0.22; 7 packs needed for 140 days. For 150 g per day, 14 packs required	BNF[196]
Diuretics	Hydrochlorothiazide 50–75 mg/day	20 weeks	10.25 [8.20 (50 mg) – 12.30 (75 mg)]	50 mg Hygroton 28 tablets pack = £1.64. 5 packs required for 140 days = 140 tablets	BNF[196]
Nitric oxide donors or precursors	GTN patches 5 or 10 mg intermittently. Assume 1 patch/day	20 weeks	61.20 (58.1–64.35)	Patches of 5 mg/24 hours. Pack of 30 = £11.62; 10 mg/24 hours pack of 30 = £12.87. 5 packs required	BNF[196]

continued

TABLE 39 *Estimated costs of interventions and outcomes (cont'd)*

Treatment	Nature and dose	Duration	Total cost (UK£ 2005)	Bases for cost estimate (comment)	Source of unit
Progesterone	300 mg i.m. injection daily to 50 mg i.m. injection on alternate days	Given for 1 week and then offered again at subsequent visits (therefore cost is 7–14 days of progesterone), stopped if symptoms disappeared or labour started	54.10 [45.70 (50 mg)–62.50 (300 mg)]	50 mg/ml in 1-ml ampoule = £0.57; 2-ml ampoule (100 mg) = £0.75. Assume 10 days for all. Cost includes the cost of injection at outpatients/clinic for 10 days plus the cost of the drug for 10 days. Cost varies depending on dose. Cost of drug £5.70 (50 mg)–£22.50 (300 mg)	BNF[196]
				10 minutes of practice nurse time assumed to administer injection. Hourly rate of practice nurse is £24/hour. Thus 10 minutes = £4.00, for 10 days = £40.00	Curtis and Netten[193]
Cost of pre-eclampsia	The cost which will be saved for each case of pre-eclampsia avoided by applying a test and treatment combination		9,009[a] (average of 8847 and 9171)	Cost from Simon *et al.*,[198] has been converted from US$ 2001 to UK£ inflated to 2004–5 costs Cost of delivery taken from HRG costs	Magpie study

GTN, glyceryl trinitrate; HRG, healthcare resource group.
[a] Calculated as cost of pre-eclampsia from Simon *et al.*,[198] minus cost of normal birth with and without complications.
£10,074 includes cost of delivery – normal delivery £903 without complications and £1227 with complications.

with pre-eclampsia. For studies with over 100 participants there was one study that had unselected pregnant women – low risk; there were five studies with primiparous women only – medium risk; and six studies with high-risk women (e.g. previous pre-eclampsia, diabetes or hypertension). We then calculated the pre-test prevalence and 95% CIs of pre-eclampsia in the control groups using MetaDisc software. For unselected women the prevalence of pre-eclampsia in the control groups was 2.5% (95% CI 1.9 to 3.4), for primiparous, medium-risk women it was 4.7% (95% CI 4.3 to 5.3) and for high-risk women it was 10% (95% CI 9.3 to 10.8).

Analysis

Various alternative analyses were carried out.

In the base-case analyses, referred to as case 1, the point estimates of the key parameters for each test were combined with the point estimates of the key parameters for interventions where the 95% CIs for the RR did not include 1.0 referred to as group 1 interventions in *Table 2*, p. 7. As already indicated, this group of interventions is distinct because the true value of the RR is unlikely to be compatible with worsening of the outcome of frequency of pre-eclampsia, in contrast to other interventions where the 95% CI for the RR includes values >1.0. The cost-effectiveness relative to 'no test/no treatment' of each alternative combination of test and treatment pairing were estimated by the model in a deterministic analysis. The results, the ICERs, were expressed as the additional cost for each additional case of pre-eclampsia avoided. In case 1, the average unit cost was applied to tests and interventions as appropriate. The costs of tests used in case 1 were those provided by the Birmingham Women's Hospital. The prevalence of pre-eclampsia was set at 2.5%, a value compatible with a population of mothers at low risk of developing pre-eclampsia.

In case 2, a probabilistic sensitivity analysis (PSA) of case 1 was carried out to explore the effects on the ICERs of the uncertainty in the model input data, as implied by the 95% CI of RR of developing pre-eclampsia with any particular intervention. In PSA, each model parameter is assigned a distribution reflecting the amount and pattern of its variation and cost-effectiveness results are calculated by simultaneously selecting random values from each distribution. The process is repeated many times in a Monte Carlo simulation of the model to give an indication of how variation in the model parameters leads to variation in the ICERs for a given combination of a test and treatment pairing. The appropriate distribution for the data on test accuracy (sensitivity and specificity) is either a beta or normal distribution depending on the statistical characteristics of the parameters. The appropriate distribution for data on intervention effectiveness (RR of developing pre-eclampsia) was a log-normal distribution.

Unit cost uncertainty is excluded from the PSA because any variations that might exist for unit costs are of a different nature from the data-driven uncertainty in the patient flow parameters. Further additional analyses were conducted using different cost estimates, and also more detailed analysis of the significant results (sensitivity analyses). In summary, the complete set of analyses were:

- *Case 1, base case* (already detailed). A deterministic analysis using data for all the tests combined with group 1 treatments/interventions with costs from the Birmingham Women's Hospital in a low-risk population.
- *Case 2* (already detailed). A PSA of case 1.
- *Sensitivity analyses* were carried out for cases 1 and 2 in which the cost of pre-eclampsia is reduced.
- *Case 3*. A further PSA using alternative RRs for group 1 interventions suggested by subgroup analyses undertaken as part of the effectiveness meta-analyses – see *Table 2*, p. 7. However, the impact of the subgroup RR for calcium was not actually examined because the 95% CI extended beyond 1.0 (rationale for exclusion, the same as for separation of interventions into group 1 and 2). The case 3 PSA was further repeated for prevalence estimates that applied to women at moderate risk (4.5%) and high risk (10%) of pre-eclampsia. The costs are the same as in case 1.
- *Case 4*. A threshold analysis to explore what test accuracy and cost parameters would be required to optimise cost-effectiveness using the PSA presented in case 3 as the starting point. The costs are the same as in case 1.

Results from cases 1–4 are presented below in the main report. Two further sets of analyses were also carried out.

- *Case 5*. A deterministic analysis similar to case 1 but using literature estimates for the costs of tests, rather than those provided by the Birmingham Women's Hospital. Results not presented.
- *Case 6*. A deterministic analysis similar to case 1 but using data for the full range of the

interventions/treatments whether the RR 95% CI included 1.0 or not (i.e. both group 1 **and** group 2 interventions). The results of case 6 are presented in Appendix 11

Results of economic evaluation

Main result

The results of the effectiveness reviews showed that advice to take rest for women was the most effective option for reducing the risk of pre-eclampsia in normal women. The point estimate for the RR was 0.05 (95% CI 0 to 0.83). This very high level of effectiveness in reducing pre-eclampsia (although subject to uncertainty due to the small sample size and other factors, the implications of which are discussed later) associated with negligible cost to the health service (also subject to uncertainty, the implications of which are also discussed later) combine to make advising rest for all women apparently the most cost-effective option. When this intervention, applied to all women without preceding testing, was initially included in the case 1 deterministic model, it was shown to dominate (be more effective at reduced cost) all other combinations of all other test and treatment pairings. It was excluded from the subsequent deterministic analysis so that determination of the second best intervention could be estimated. However, all further results need to be preceded by repetition of the finding that a highly effective, near zero cost intervention, an example of which appears to be advice to take rest, applied to all women without preceding testing, has already been indicated to be the most cost-effective option.

Case 1: base case

In *Table 40*, the results of both a partial and complete analysis are presented for case 1 with 'rest for normotensive women' excluded from the model (see above for explanation). A partial analysis was carried out first, which excluded the costs of pre-eclampsia in the comparator arm of the model. In this partial analysis, the no test/no treatment option is shown to cost nothing in monetary terms but has considerable cost in terms of effectiveness since doing nothing does not have a zero cost if it results in more cases of pre-eclampsia. Removing the cost of pre-eclampsia in the partial analysis provides a comparator against which additional costs of testing and treating can be gauged, but overlooks the fact that substantial cost is associated with cases of pre-eclampsia and that this cost can be reduced by reducing the number of cases of pre-eclampsia. This is the additional factor which is captured in the complete analysis.

In the partial analysis only, the strategy of providing 'no test/antiplatelets_all' is the most cost-effective strategy. The intervention of antiplatelets is relatively cheap at an average cost of £2.69 per woman treated and the strategy saves nearly five cases of pre-eclampsia per 1000 women, a number-needed-to-treat (NNT) of 208. There is an additional cost of £566 per case of pre-eclampsia averted compared with 'no test/no treatment'. The next most effective option after antiplatelets in this partial analysis is to use the total fibronectin test and provide calcium to all who tested positive ('total fibronectin test/calcium_positive'). The results are presented incrementally compared with the previous best option. Therefore, 'total fibronectin test/calcium_positive' avoids nearly four more cases of pre-eclampsia in 1000 women than 'no test/antiplatelet_all', but costs £5.80 more, giving an ICER of £1557 of additional test and treatment cost per additional case of pre-eclampsia averted.

When the model comparator arm included the full cost of pre-eclampsia, it penalised the treatments that missed the most cases of pre-eclampsia. For instance, the additional cost of providing calcium to all compared with the cost of antiplatelets was overwhelmed by the costs saved by avoiding more cases of pre-eclampsia. Hence, as calcium is more effective, 'no test/calcium_all' becomes the dominant strategy in terms of relative cost-effectiveness. Therefore, the complete analysis shows that the dominant strategy, out of those strategies included in the model, is to provide calcium treatment to all without any preceding test. Alternatively stated, of the strategies considered, 'no test/calcium_all' is the least costly option, because it is the option which avoids most cases of pre-eclampsia. The next strategy presented in the complete analysis section of *Table 40* indicates that applying the Doppler (AUN) test to all before providing calcium to all leads to increased costs, without change in overall effectiveness.

In *Figure 93*, the results shown for the complete case in *Table 40* are presented diagrammatically alongside all the cost-effectiveness estimates produced by the case 1, base-case model. Each point represents one of the options for each test/treatment pairing considered in the model. The nearer the bottom right corner of the graph a point is, the greater is its effectiveness and the less its cost. Most of the points represent dominated

TABLE 40 *Case 1, base-case results: costs, effects and ICERs for most cost-effective combinations of test and treatment pairs from any test combined with a group 1 intervention*

Test/treatment combination[a]	Mean cost per woman (UK£ 2005)	Difference in costs (UK£ 2005)	Effectiveness[b]	Absolute risk reduction	ICER[c]	NNT
Partial analysis: excludes the cost of pre-eclampsia in the comparator arm of the model						
No test/no treatment	0		0.975			
No test/antiplatelets_all	2.7	2.7	0.980	0.005	566	208
Total fibronectin test/calcium_positive	8.5	5.8	0.983	0.004	1557	270
Albuminuria/calcium_positive	13.6	5.2	0.984	0.001	7938	1428
No test/calcium_all	46.20	32.6	0.988	0.004	8355	256
Doppler(AUN) test/calcium_all[d]	67.1	20.9	0.988	0	This (and the rest) are dominated by no test/calcium_all	
Complete analysis: includes the cost of pre-eclampsia in the comparator arm of model						
No test/calcium_all	154		0.988		Dominant	
Doppler (AUN)/calcium_all[d]	174.8	20.9	0.988	0	These are all dominated by no test/calcium_all	
Doppler (RI)/calcium_all[d]	174.8	0	0.988	0		
Doppler (BN)/calcium_all[d]	174.8	0	0.988	0		

The no test_rest option is the most effective option, achieved at zero additional cost, and is thus self-evidently the most cost-effective approach. It was therefore not incorporated into the model whose results are reported in this table, which primarily explores the second most cost-effective option after the no test/rest_all option.

[a] No test/rest_all dominates all options below.

[b] Effectiveness is defined as the proportion of women remaining free of pre-eclampsia. Therefore, the difference in effectiveness between two strategies is the absolute risk reduction.

[c] ICER: incremental cost-effectiveness ratio expressed as the additional cost per additional case of pre-eclampsia prevented.

[d] These "test all/treat all" strategies were included in the model for completeness (elaborated in more detail in the economic methods section). Each is more costly and no more effective than a strategy of treating all women without testing.

options, where greater effectiveness can be achieved at lower cost by an alternative. *Figure 93* thus reaffirms that, when the costs of pre-eclampsia are included in the analysis the option 'no test/calcium_all' dominates all other options, being nearest to the south-east extremity of the cost-effectiveness plane. However, it should again be noted that the 'no test/rest_all' option would appear below and to the right of all the options on *Figure 93* were it to have been included in the model.

Case 2: probabilistic sensitivity analysis of case 1

The results of case 2 are presented in *Table 41*. The results reaffirm that 'no test/rest_all' is the dominant option at all values of willingness to pay.

When 'rest for normotensive women' is removed from the model to explore the second most cost-effective option, the results show that 'no test/calcium_all' is the dominant option at all values of willingness to pay. For example, at a given threshold of say £30,000, which means that a policy maker would be willing to pay £30,000 per case of pre-eclampsia avoided, there is an 87% chance that 'no test/calcium_all' is the preferred option with respect to its cost-effectiveness. At the same threshold there is only a 10% chance that an alternative option of 'no test/antioxidant_all' is the preferred option and less than a 1% chance of preference for all other options such as 'total fibronenctin/antioxidants_positive' and 'total fibronenctin/calcium_positive'. If the willingness to pay threshold was increased to £100,000 per case of pre-eclampsia avoided, then there is still an 87% chance that 'no test/calcium_all' is the preferred option whilst the chance of 'no test/antioxidant_all' being the preferred option rises slightly to 11%. This shows that the results, particularly concerning the second preference for the 'no test/calcium_all' option, are robust for all thresholds of willingness to pay. The results are presented diagrammatically in *Figure 94*, a cost-effectiveness acceptability curve (CEAC). It should be noted that the curves for most of the options

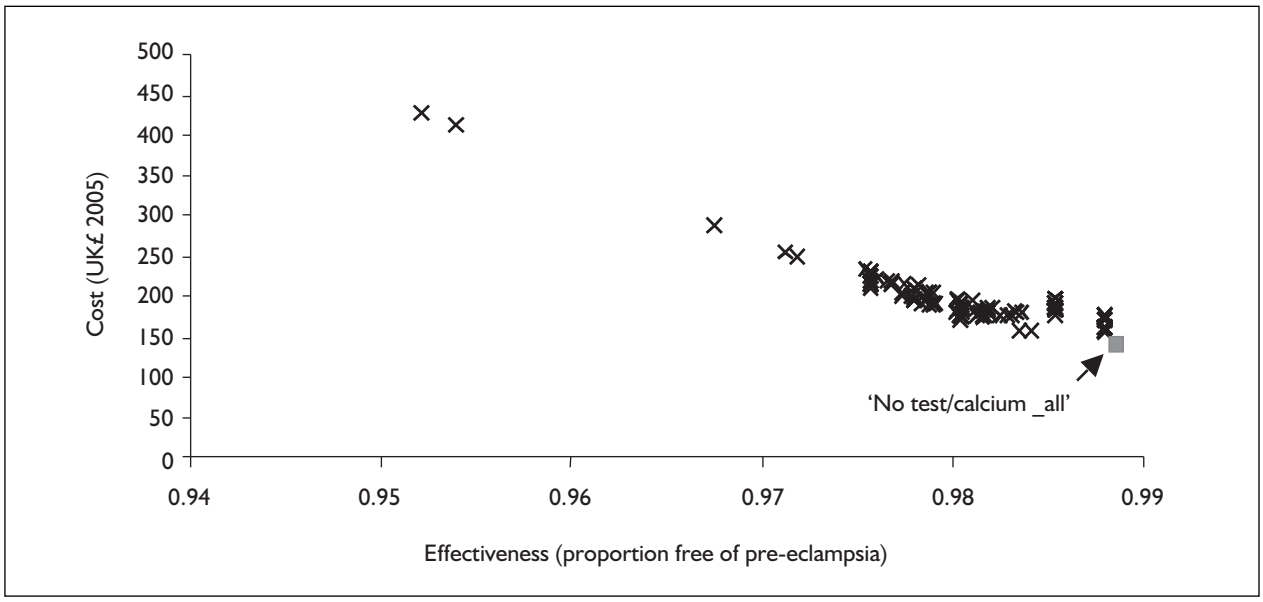


FIGURE 93 *Case 1, base-case results: costs, effects and ICERs on cost-effectiveness plane for all combinations of test and treatment pairs from any test combined with a group 1 intervention (complete analysis)*

examined are indistinguishable, because they are coincident with the horizontal axis of the graph. Additional analyses were carried to examine the effect of altering estimated eventual prevalence of pre-eclampsia in the target populations from low-risk groups (2.5% as in the base case) to 4.7% representing moderate-risk groups and 10% representing high risk-groups. The results show that the higher the prevalence, the higher is the probability that an intervention of 'no test/calcium_all' was the preferred option at any willingness to pay threshold.

Sensitivity analysis for case 1 and case 2

The costs of pre-eclampsia used in the current study were obtained from one published study and were the only available estimate for this condition. Clearly there is some doubt about this estimate, but in the absence of any other information we subjected this cost to sensitivity analysis. The high estimated cost for pre-eclampsia will severely penalise any cases of pre-eclampsia missed by any of the test and treat options.

Table 42 gives the results of the sensitivity analysis for case 1, in which the costs of pre-eclampsia are reduced from the £9009 level used in the base-case deterministic analysis. The partial analysis, presented in *Table 40*, which excluded the costs of pre-eclampsia totally, highlighted which test and treatment options could be considered more cost-effective than 'no test/calcium all' if the costs of pre-eclampsia were reduced from the £9009 to zero. The results in *Table 42* show that if the cost of pre-eclampsia was £8300, the albuminuria test and treating only the positives would be slightly cheaper and slightly more effective than 'no test/calcium_all' and would have been considered more cost-effective in the deterministic analysis. If the cost of pre-eclampsia was reduced further to £7900, the 'total fibronectin test/calcium_positive' becomes a more cost-effective option than 'no test/calcium_all' and would be considered cost-effective. When the cost is reduced to £1500, no test/antiplatelets_all becomes the most cost-effective option.

However, the deterministic analysis is based only on the point estimates of the sensitivity and specificity of the tests and RRs from the reviews. *Table 43* shows that when the uncertainty around these point estimates is included in the analysis, even if the cost of pre-eclampsia was as low as £1000, 'no test/calcium_all' has the highest percentage of being the preferred option at all values of willingness to pay, thus showing that despite the uncertainty surrounding the costs of pre-eclampsia used in the current study, the biggest driver in the results is the fact that the tests have very poor sensitivity and specificity and the RRs of treatments such as 'no test/rest_all' (for which the result would also remain unchanged although not shown) and 'no test/calcium_all' remain the preferred option because these are the tests shown to be most effective.

TABLE 41 *Case 2, PSA of case 1, results: probability that stated options are the most cost-effective option at different levels of willingness to pay for a case of pre-eclampsia avoided*

	Willingness to pay (UK£ 2005/6)[a]					
	0	**10,000**	**30,000**	**50,000**	**80,000**	**100,000**
Test/treatment option						
No test/rest_all	0.953	0.951	0.949	0.948	0.947	0.944
Secondary analysis excluding 'no test/rest_all' from the model[b] (prevalence 2.5%)						
No test/calcium_all	0.268	0.815	0.871	0.870	0.869	0.868
No test/antioxidants_all	0.003	0.060	0.098	0.107	0.110	0.110
Total fibronectin/antioxidants_positive	0.041	0.009	0.001	0	0	0
Total fibronectin /calcium_positive	0.232	0.017	0.001	0	0	0
No test/no treatment	0	0	0	0	0	0
Sensitivity analysis for different prevalence rates						
No test/calcium_all (prevalence 4.7%)	0.818	0.885	0.882	0.880	0.879	0.879
No test/calcium_all (prevalence 10%)	0.891	0.885	0.881	0.879	0.879	0.879

[a] Per case of pre-eclampsia avoided.
[b] Explores the next most preferred option after 'no test/rest_all'.

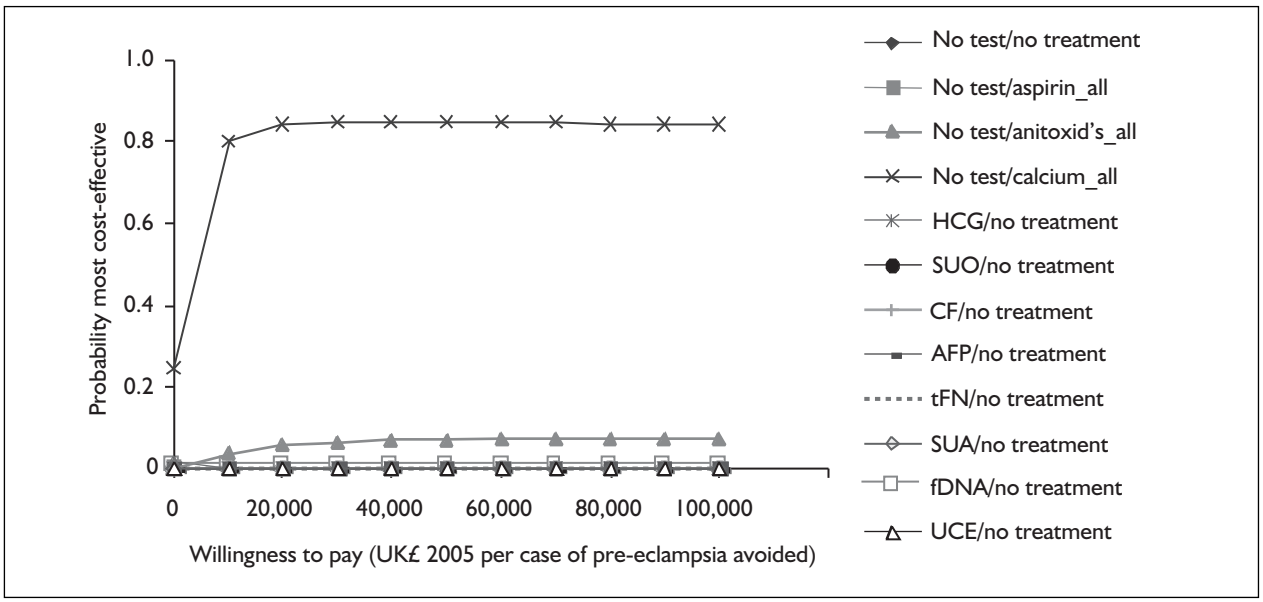


FIGURE 94 *Case 2, PSA of case 1, results ('no test/rest all' option not included)*

Case 3: additional sensitivity analyses

In this version of the model, further PSAs were carried out using revised data, based first on important subgroup analysis results emerging from the systematic reviews of effectiveness and associated meta-analyses of the four group 1 interventions. The revised results used for this analysis were presented in the last two columns of *Table 37*, p. 88. There was no relevant subgroup analysis for the intervention of advising rest, and the subgroup result for calcium had a 95% CI which exceeded 1.0, and so could not be included in the model. The subgroup estimate (excluding a quasi-randomised trial) for the effectiveness of antioxidants improved the estimate of effectiveness; the subgroup estimate for antiplatelets, restricting to trials which were in 'moderate' as opposed to 'moderate' and 'high' risk populations combined, slightly worsened the effectiveness. The results for case 3 are presented in *Table 44* and show that providing antioxidants to all with no preceding test ('no

TABLE 42 *Sensitivity analysis for case 1: deterministic analysis for case 1 when the cost of pre-eclampsia is reduced from the base-case level of £9009*

Strategy	Mean cost per woman (UK£ 2005)	Difference in costs (UK£ 2005)	Effectiveness	Absolute risk reduction	ICER	NNT
Cost of pre-eclampsia £8300						
Albuminuria test/calcium_positive	145.6		0.9841			
No test/calcium_all	145.8	0.2	0.988	0.0039	55.53	256
Cost of pre-eclampsia £7900						
Total fibronectin test/calcium_positive	139.2		0.9834			
Albuminuria test/calcium_positive	139.2	0	0.9841	0.0007	38.46	1428
No test/calcium_all	141	1.8	0.988	0.0039	455.53	256
Cost of pre-eclampsia £1500						
No test/antiplatelets	33.1		0.9797			
Total fibronectin test/calcium_positive	33.3	0.2	0.9834	0.0037	57.69	270
Albuminuria test/calcium_positive	37.5	4.2	0.9841	0.0007	6438.46	1428
No test/calcium_all	64.2	26.7	0.988	0.0039	6855.53	256

TABLE 43 *Sensitivity analysis for case 2: PSA for case 1 when the cost of pre-eclampsia is reduced from the base-case level of £9009*

	Willingness to pay (UK£ 2005)					
Strategy	**0**	**10,000**	**30,000**	**50,000**	**80,000**	**100,000**
Cost of pre-eclampsia = £2000						
Nothing/calcium_all	0	0.568	0.867	0.875	0.875	0.875
Nothing/antioxidants_all	0	0.015	0.085	0.091	0.1	0.102
Nothing/antiplatelets_all	0.282	0.004	0	0	0	0
Cost of pre-eclampsia = £1000						
Nothing/calcium_all	0	0.493	0.88	0.886	0.883	0.884
Nothing/antioxidants_all	0	0.014	0.08	0.089	0.095	0.095
Nothing/antiplatelets_all	0.773	0.006	0	0	0	0

test/antioxidants_all') becomes the preferred option from a cost-effectiveness perspective at any willingness to pay threshold. It should again be remembered that this does not overturn the main result concerning dominance of the option 'no test/rest_all'. It indicates that in a best-case scenario for the effectiveness of antioxidants (but nonetheless still compatible with the results of the systematic review), 'no test/antioxidant_all' becomes the second most preferred option instead of 'no test/calcium_all'.

The second set of additional sensitivity analyses in case 3 examined the effect of altering the estimated eventual prevalence of pre-eclampsia in the target populations from low risk (2.5%, as in the base case) to 4.7%, representing moderate-risk groups, and 10%, representing high-risk groups. The results show that the higher the prevalence, the higher was the probability that an intervention of 'no test/antioxidants_all' was the preferred option at any willingness to pay threshold.

Case 4: threshold analysis for potentially cost-effective test parameters

The absence of any options involving prior testing from those indicated as preferred from a cost-effectiveness perspective in the prior analyses prompted this analysis. We used the model presented in case 3 to explore what the test characteristics would need to be for a test to be worth doing prior to providing an intervention. The intervention used in combination with the hypothetical test was antioxidants supplementation, hence the test whose cost-effectiveness was being considered could be referred to as 'hypothetical test/antioxidants_positive'. The majority of tests were shown to have relatively poor sensitivity but the specificity was generally slightly better. The

TABLE 44 *Case 3, further PSA results based on important effectiveness subgroup analysis results from systematic reviews of effectiveness for group 1 interventions (especially antioxidants): probability that stated options are the most cost-effective option at different levels of willingness to pay for a case of pre-eclampsia avoided*

	Willingness to pay UK£ (2005/6)[a]					
	0	**10,000**	**30,000**	**50,000**	**80,000**	**100,000**
Test/treatment option						
No test/antioxidants_all[b] Prevalence 2.5%	0	0.811	0.964	0.974	0.977	0.978
Sensitivity analysis for different prevalence rates						
No test/antioxidants_all Prevalence 4.7%	0.813	0.982	0.986	0.988	0.989	0.989
No test/antioxidants_all Prevalence 10%	0.991	0.996	0.977	0.997	0.997	0.997

[a] Per case of pre-eclampsia avoided.
[b] This is equivalent to the secondary analysis in case 2, excluding 'no test/rest_all' from the model, and so explores the next most preferred option after 'no test/rest_all'.

starting characteristics for the hypothetical test were therefore based, in part, on a test which had a relatively good specificity, such as Doppler (bilateral notching) with a specificity of 92% and a cost of approximately £20 or either of the two fibronectin tests, cellular fibronectin, or total fibronectin which have specificities of 96 and 94%, respectively.

In *Tables 45* and *46*, the results of the analysis are presented. The model was first run with a hypothetical test that was 99% sensitive and specific. If this hypothetical test cost £20, then there was almost a 100% chance that the preferred option would be 'hypothetical test/antioxidants_positive' for all values of willingness to pay. Holding the costs at £20, as the sensitivity and specificity were adjusted, modest changes in these characteristics, such as a specificity of 96% and a sensitivity of 90%, resulted in a switch back in favour of 'no test/antioxidants_all' for thresholds above

TABLE 45 *Case 4a, threshold analysis on characteristics of a test that would be cost-effective when combined with the intervention antioxidants ('hypothetical test/antioxidants_positive')*

Necessary characteristics of test	**Test/treatment option**	**Probability of being most cost-effective option at different levels of willingness to pay for a case of pre-eclampsia averted (UK£ 2005/6)**				
		0	**10,000**	**30,000**	**50,000**	**100,000**
Sensitivity = 0.99 Specificity = 0.99 Cost = £20.00	Test and treat all positives with antioxidants	0.986	0.996	0.997	0.997	0.997
Sensitivity = 0.90 Specificity = 0.96 Cost = £20.00	Test and treat all positives with antioxidants	0.806	0.729	0.025	0.0	0.0
Sensitivity = 0.95 Specificity = 0.96 Cost = £20.00	Test and treat all positives with antioxidants	0.934	0.991	0.761	0.178	0.0
Sensitivity = 0.95[a] Specificity = 0.92 Cost = £20.00	Test and treat all positives with antioxidants	0.873	0.992	0.629	0.125	0.0

[a] Level of sensitivity needing to be achieved in order to make 'hypothetical test/antioxidants_positive' the preferred cost-effective option in the majority of willingness to pay thresholds examined, assuming levels of cost and specificity actually obtained for Doppler (bilateral notching).

TABLE 46 *Case 4b, threshold analysis on characteristics of a test that would be cost-effective when combined with the intervention antioxidants ('hypothetical test/antioxidants_positive'): characteristics of hypothetical test based on cellular fibronectin*

Necessary characteristics of test	Test/treatment option	Probability of being most cost-effective option at different levels of willingness to pay for a case of pre-eclampsia averted (UK £ 2005/6)				
		0	10,000	30,000	50,000	100,000
Sensitivity = 0.91[a] Specificity = 0.96 Cost = £5.00	Test and treat all positives with antioxidants	0.994	0.987	0.456	0.045	0.0
Sensitivity = 0.92[a] Specificity = 0.96 Cost = £5.00	Test and treat all positives with antioxidants	0.993	0.981	0.637	0.114	0.0
Sensitivity = 0.95[a] Specificity = 0.96 Cost = £5.00	Test and treat all positives with antioxidants	0.998	0.993	0.985	0.705	0.001

[a] Level of sensitivity needing to be achieved in order to make 'hypothetical test/antioxidants_positive' the preferred cost-effective option in the majority of willingness to pay thresholds examined, assuming levels of cost and specificity actually obtained for cellular and total FN. Although the cost of the FN test at £5 was used in the model, this was a proxy estimate based on another test as a more accurate estimate for the cost of an FN test was unavailable.

£10,000 (82% chance of being the preferred option at the £20,000 threshold). Only at the lower thresholds did 'hypothetical test/antioxidants_positive' remain preferred (73% chance of being the preferred option at a threshold of £10,000).

When the model was run with two of the characteristics of the Doppler (bilateral notching) test, namely the cost of £20.00 and a specificity of 92%, the analysis showed that the test would be required to have a sensitivity of at least 95%, in order to have a 63% chance of 'hypothetical test/antioxidants_positive' being the preferred option at the willingness to pay threshold of £30,000.

A similar analysis was carried out using the characteristic of a relatively cheaper test such as cellular FN. It must be emphasised that the cost of this test was a proxy based on the cost of the SUA test and the true costs of a cellular FN test might be in excess of £5. However, if we assume that the hypothetical test had the same specificity as cellular FN 96% (95% CI 79 to 99) and cost approximately £5, the analysis showed that the test would be required to have a sensitivity of at least 92% in order to have a 64% chance of 'hypothetical test/antioxidants_positive' being the preferred option at the willingness to pay threshold of £30,000. After that threshold, a switch back in favour of 'no test/antioxidants_all' occurred.

Case 5

The results using the literature-based costs for the tests were no different to the results presented in case 1 and are therefore not presented.

Case 6

The results are presented in Appendix 11 for completeness. However, they provide very limited additional insights into the cost-effectiveness of alternative combinations of the test and treatment pairings and are not considered further. The only possible exception is the predictable emergence of progesterone treatment ('no test/progesterone_all') as a potentially cost-effective additional option. The finding is in keeping with the general observation that effective, low-cost interventions, applied without prior testing, emerge as preferred from a cost-effectiveness perspective (RR = 0.21, 95% CI 0.03 to 1.77; cost £54.10). However, progesterone needs to be approached with some caution as a specific example of such an intervention for pre-eclampsia given the age and size of the single RCT on which the effectiveness evidence is based (see the text on pp. 76–8 for further details).

Discussion of results of economic evaluation

Main findings

The key results, not already highlighted from preceding parts of the project, emerging from the

health economic and modelling evaluations were as follows:

1. The cost of most of the tests examined in this project with potential to improve identification of pre-eclampsia was modest. It ranged from £5 for blood tests such as SUA to approximately £20 for Doppler examination.
2. Similarly, the cost of most interventions examined with potential to reduce the number of cases of pre-eclampsia was also modest. Treatment duration was generally for 20 weeks and treatment costs to cover this period ranged from:
   (a) virtually zero, but open to question as to whether true cost would actually be zero, for example, advice to take rest in normal pregnancy and advice to reduce salt intake
   (b) likely low cost, for example, antiplatelet agents, particularly aspirin (£3) or antihypertensives (atenolol) (£5)
   (c) upper range, but still modest, for example, calcium supplementation (£46), antioxidants (£54) and progesterone intramuscular injection (10 days) (£54).
3. In contrast, the best estimate of the additional average cost associated with a case of pre-eclampsia is high at approximately £9000. This was reduced to £1000 in the PSA and still did not change the result.
4. The main finding of the economic modelling is that advice to all women with a normal pregnancy ('no test/rest_all'), without any initial testing is the most cost-effective 'test/treatment' combination, delivering the greatest reduction in number of cases of pre-eclampsia at virtually zero additional cost.
5. The economic modelling suggests that the second most cost-effective option is giving calcium supplementation to all women, without any initial testing ('no test/calcium_all'). The model indicates that for every 1000 mothers treated there will be approximately 13 fewer cases of pre-eclampsia. The costs averted as a result of this reduction in cases of pre-eclampsia greatly exceed the cost of the calcium supplementation.
6. The third most cost-effective option suggested by the economic modelling is antioxidant supplementation to all women without initial testing ('no test/antioxidants_all'). The sensitivity analysis suggested that with an optimistic, yet plausible assumption about effectiveness, 'no test/antioxidants all' might actually become the second most cost-effective option ahead of 'no test/calcium_all'.
7. All three main predictions of the economic model are affected by uncertainty, discussed in detail below.
8. However, within the constraints of the model, an important general finding is that effective treatments (RR < 0.7) with modest costs (<£50) applied to all women without prior testing are likely to be preferred from the perspective of cost-effectiveness.
9. Prior testing, particularly with the test accuracy levels identified, appears to have little to offer as a way of improving cost-effectiveness. The threshold analyses conducted in the economic model suggest that tests with costs in the upper range of those identified would need substantially improved sensitivities (assuming that the best level of specificity achieved in any test was maintained). Tests with costs in the lower range of those examined would need less marked improvements (again assuming that the best level of specificity achieved in any test was maintained). However, such levels of sensitivity have rarely been achieved. There have been particularly high hopes that Doppler examinations might have useful predictive ability for pre-eclampsia. The economic model provides little support that any form of Doppler testing has sufficiently high sensitivity and specificity to be cost-effective for the early identification of pre-eclampsia and in isolation from other objectives it might achieve.
10. The economic model also suggests that the pattern of cost-effectiveness is no different in higher-risk mothers than the low-risk mothers considered in the base case. The cost-effectiveness of particular strategies is enhanced in high-risk populations (more cases of pre-eclampsia avoided for given cost). However, 'no test/treat_all' strategies remain the most cost-effective options. It should be noted that the model assumes that the test accuracy and RR of treatments remains constant with risk, there being no evidence that these parameters differ depending on risk level.
11. The economic model showed that the costs applied to the tests and the treatments were largely irrelevant to the overall final results. Key drivers in the analysis included the poor sensitivities and specificities of all the tests which meant that none of them would be recommended as worth doing as part of a 'test/treat_positives' strategy. For the treatments, the key driver in the results was their RR, which led to the treatment which

had the lowest RR being recommended. The cost of pre-eclampsia used in the analysis was high at approximately £9000. Thus the combination of poor test accuracy and relatively cheap effective interventions led to a 'no test/treat_all' strategy dominating the results because pre-eclampsia is a serious and costly condition. Furthermore, even when the cost of pre-eclampsia was reduced to as low as £1000, the main results were unchanged.

Strengths of the economic evaluation

The economic analyses and model use data on accuracy of tests and effectiveness of the interventions from the most recently available systematic reviews and meta-analyses of the evidence. The model itself was developed by an experienced health economic and modelling team with clinical and methodological input at all stages, from the original design of the model, through its execution, to the final interpretation of its results. Although there are some important limitations, we believe that the model is structurally sound, with key features such as PSA to help deal with the ever present challenges arising from uncertainty. As far as we are aware, there have been no previous attempts to model combined test-treatment options for the prevention of pre-eclampsia, particularly as part of a project which simultaneously attempts to summarise the best available evidence on all potentially relevant tests and treatments. In this situation, we cannot compare our approach with others to judge relative merits.

Limitations of the economic evaluation

There are two main sources. The first arises from constraints arising from the way in which the model itself was designed and structured, and include:

1. The model considers only single test results; combinations of tests or combinations of treatments may offer opportunities which are more cost-effective and these could not have been incorporated into the model as conceived unless data were available for combined tests or treatments (which they were not).
2. The existing model focuses on the outcome pre-eclampsia, and so may overlook the impact of test/treatment combinations on other outcomes, particularly to the infant such as intra-uterine growth retardation and perinatal death. This is especially problematic if the effect on these other outcomes is not experienced to the same degree as the impact on the number of cases of pre-eclampsia. Antioxidants provide a difficult example of this problem where although there is a reduction in risk of pre-eclampsia, which is captured by the model, there is an increase in risk of preterm birth, which is not captured. However, fortunately, as can be seen in the results of the systematic review of effectiveness, the direction of effect concerning pre-eclampsia usually mirrors the effect on infant outcomes. Even so, there is a possibility that the model systematically underestimates the effect of test/treatment combinations because benefits attributable to reduction in outcomes like perinatal death, preterm birth and small for gestational age are not fully accounted for.
3. Similarly, the existing model assumes that side-effects of tests and treatments are negligible. This seems a reasonable assumption given the available data for aspirin and calcium.[200] However, it must be acknowledged that this information is limited in many cases. This may be particularly important where the universal use of interventions without prior testing is being speculated on; confirmation of absence of adverse events particularly to the baby may require detailed investigation and high levels of scrutiny. It should also be noted that apparent absence of adverse events associated with treatments is a contributor to the observed superiority of 'no test/treat_all' strategies; if there were associated adverse events there would be added value from avoiding false positives such as would be achieved by a predictive test for pre-eclampsia with high specificity.
4. The model assumes that the comparator for all test/treatment pairings is 'no test/no treatment'. Although the only practical choice for the model, this may not be the best reflection of current practice in that some testing and treatment may already occur. It therefore needs to be considered that the benefits and costs for all test/treatment combinations considered are likely to overestimate those that can actually be achieved, to a degree which will vary depending on existing implementation. It also reminds us that there may be opportunities for avoiding costs associated with test/treatment activity is likely to be ineffective or inefficient.
5. Finally, care is required in the interpretation of some of the combinations of test/treatment pairs examined in the model. Antihypertensive therapy provides a good example. In applying antihypertensive therapy to the reduction of pre-eclampsia, blood pressure measurement is the trigger for starting therapy and is thus 'the test'. There were, however, no data for the

sensitivity and specificity for a given level of blood pressure indicating need for antihypertensives. Further combining antihypertensive treatment with any of the other tests is inappropriate as it is unlikely that test positive results of, say, Doppler examination would be given antihypertensives irrespective of actual blood pressure. In the event, the inappropriateness of the model in dealing with the actual options for antihypertensive therapy is mitigated by the fact that antihypertensives have very limited effectiveness in reducing cases of pre-eclampsia (RR 0.99, 95% CI 0.84 to 1.18), making it implausible that it would be a potentially cost-effective option in any circumstances despite the low cost of the drugs which might be used, such as atenolol (£5).

The restriction of the economic model to an NHS perspective could also be considered a potential limitation. The main counter argument is that because most assessments of cost-effectiveness are done from the perspective of the healthcare payer, doing the economic model from the NHS perspective remains most relevant in order to facilitate comparison with other uses of healthcare resources. Ideally, cost-effectiveness taking into account societal and individual costs would be worth exploring; however, experience suggests that data to do this accurately are rarely routinely available and would require primary data collection, which was outside the original agreed protocol. It must be acknowledged that limiting the analysis to the NHS perspective may lead to underestimation of certain costs, particularly for interventions such as advice to rest in normal pregnancy, where the onus is placed on the individual, their family and society to achieve implementation. In the absence of versions of the model from an individual and societal perspective, such considerations can only be incorporated into the conclusions qualitatively.

The second main source of limitations is the data used to provide the model parameters. Again, there are a number of specific issues:

1. There is marked stochastic variation in many of the parameters, manifest in wide 95% CIs. The effect of this on conclusions of the economic modelling is explored using the PSAs, and the main findings appear to be robust. However, the implications of the 95% CI do still need to be considered, particularly where the 95% CI includes values of RR > 1.0, implying that the intervention causing increased numbers of cases of pre-eclampsia remains a possibility based on the available data. This was the rationale for separating group 1 interventions, where 'harm' was unlikely to be a possibility, from group 2 interventions, where it was. Progesterone is an example of an intervention which, applied universally without prior testing, may be a relatively high preference from the perspective of cost-effectiveness. However, caution does need to be exercised through the observation that the 95% CI for RR (0.03 to 1.77) includes the possibility of increasing the number of cases of pre-eclampsia.
2. In addition to chance, there is uncertainty arising from systematic variation, including operation of bias. Provisos therefore sometimes need to be added concerning the fact that there may be threats to validity. Parameters based on single, small studies with very small numbers of outcomes raise not just concerns about effect of chance (reflected in the 95% CI) but also susceptibility to bias. This was an important consideration in:
   (a) effectiveness of advice on rest in normal pregnancy [RR 0.05 (95% CI 0.0 to 0.83) based on one small RCT (n = 32), with nine outcome events, with lack of clarity about method of randomisation and completeness of follow-up]
   (b) effectiveness of progesterone [RR 0.21 (95% CI 0.03 to 1.77) based on a single RCT published in 1962 (n = 122) with six outcome events, with limited reporting on method of randomisation]
   (c) effectiveness of exercise [RR 0.31 (95% CI 0.01 to 7.09) based on one outcome event in two small RCTs (n = 29 and 16)].

   In the last case, the concern was so great that the result was not actually included in the modelling exercise at all.
3. There is sometimes further uncertainty arising where estimates of accuracy or effectiveness are based on several primary studies and there is heterogeneity between the results (more variation than can be accounted for by chance alone). If the cause of this heterogeneity cannot be isolated, there may be concern about use of a summary measure from a meta-analysis. This is a theoretically important issue for virtually all estimates of test accuracy, and for effectiveness estimates for interventions like calcium (RR 0.48, χ^2 33.9, 11 degrees of freedom) and antiplatelets (RR 0.81, χ^2 85.6, 42 degrees of freedom). Sometimes plausible subgroup effects can be identified and, where these occurred in the group 1 interventions, the impact on the conclusions of the economic model were

investigated with further sensitivity analyses. Of particular importance was that for antioxidants, where a subgroup estimate excluding the results of a large quasi-randomised RCT led to an improved estimate of effectiveness [base-case RR 0.61 (95% CI 0.5 to 0.75); sensitivity analysis, RR 0.45 (95% CI 0.31 to 0.66)].

4. There is general concern about the cost estimates used for the tests and treatments and this is common throughout economic evaluation. However, in the present study, the tests were not sensitive enough for their costs to be worth investigating in any more detail than presented. If a test had been shown to be worth doing in a 'test/treatment_positives' result, by the economic model, and none were, then it would be important to be sure that the cost information leading to that recommendation was accurate. But when the tests are shown to be generally insensitive, accurate costs are less relevant. If the test was improved (i.e. more effort was made to make it of higher sensitivity), the appropriate cost would also change. In the main analysis (cases 1–4) the costs provided by the Birmingham Women's Hospital were applied. These were far less expensive than those suggested in the literature (which were used in case 5). There is some certainty that test costs of £5 applied to the total FN test, for example, which appears to show potential in the deterministic analysis, are probably lower than would be viable in practice. We have, therefore, not disadvantaged the tests with these low costs. This is confirmed in the PSA, in which it is shown that the uncertainty associated with the estimates of sensitivity and specificity leads any potential recommendations in favour of these tests to be ruled out, despite basing the evaluation on very favourable cost estimates.
   A similar argument holds for the cost of treatments used in the model. The costs used are considered reasonable estimates and based on the BNF. There are only four treatments in group 1 that were used in the model. The order of the results presented in case 2 is based wholly on the order of the estimate for the RR, despite antiplatelets being estimated to cost just £2.69. The costs of these treatments would have to be considerably and unrealistically higher for their cost to influence the results. This is highlighted by case 3, when the priorities for calcium and antioxidants switch in line with their RR in the subgroup analysis.
5. There was absence or effective absence of information on certain key parameters. Hence there may be new or established tests or interventions which have not yet been fully evaluated. Kallikreinuria is a test which falls into this category. Although the single small evaluation identified in the systematic review suggested potentially useful sensitivity and specificity, the result was not modelled because of the limited number of evaluations and the reported rare use of the test in practice by clinical members of the project team. Interventions such as exercise, discussed above, could also fall into this category, in that initial evaluations indicate potential, but require further confirmatory results. In addition, there may well also be tests and treatments under development that do not appear in the literature at all, of which we would be unaware. Finally, some systematic review results, or updates thereof, arrived after the modelling had been completed. There were also other pre-eclampsia results that were not incorporated into the economic modelling for a variety of reasons. These are indicated in *Table 47*, which is a modified version of *Table 37* that gave the effectiveness parameters actually used in the modelling. As can be seen from *Table 47* the effectiveness results which were not incorporated into the model were extremely unlikely to lead to changes in the main findings.

Recommendations for practice

The findings of the health economic evaluation are insufficient on their own to dictate changes in practice. However, the results do suggest that universal application of a number of potentially effective treatments requires consideration. Some interventions such as exercise, advice to rest and progesterone need further evaluation of their effect on pre-eclampsia. For others, evidence on effectiveness may already be sufficient to consider assessing feasibility, checking acceptability to mothers/healthcare staff and developing pilot schemes for further evaluation.

Recommendations for research

As already indicated, the development and evaluation of pilot programmes applying effective, low-cost interventions, such as calcium supplementation, without prior testing to mothers at low risk of pre-eclampsia would be the next logical step from the findings of the economic analysis. Obtaining reassurance about adverse events would be very important, as would confirmation about costs.

RCTs providing further evidence about the effectiveness of interventions such as rest, exercise

TABLE 47 *Data on all RR of pre-eclampsia estimates provided by the project's systematic reviews of effectiveness*

	Treatment	RR	95% CI	Revised RR[a]	95% CI
Group 1[b]	Rest for normotensive women vs unrestricted activity	0.05	0.0 to 0.83	No subgroup analyses	
	Antioxidants vs placebo/no antioxidants	0.61	0.50 to 0.75	0.45[d]	0.31 to 0.66
	Calcium supplement vs placebo	0.48	0.33 to 0.69	0.62[e]	0.32 to 1.20
	Antiplatelets vs placebo/no intervention	0.81	0.75 to 0.88	0.85[f]	0.77 to 0.94
Group 2[c]	Progesterone vs no progesterone	0.21	0.03 to 1.77	NA	
	Diuretics vs placebo/no diuretics	0.68	0.45 to 1.03	NA	
	Garlic vs placebo	0.78	0.31 to 1.93	NA	
	Nitric oxide donors or precursors vs placebo/no intervention	0.83	0.49 to 1.41	NA	
	Marine/fish oils vs placebo/no treatment	0.86	0.59 to 1.27	NA	
	Antihypertensives vs placebo/no treatment	0.99	0.84 to 1.18	NA	
	Advice to reduce dietary salt vs advice to continue normal diet	1.11	0.46 to 2.66	NA	
				Comments	
RRs not used in the models	**Updated review** Antiplatelets vs placebo/no intervention	0.83	0.77 to 0.89	Results virtually identical with older version of review results used in the model	
	Updated review Antihypertensives vs placebo/no treatment	0.97	0.83 to 1.13		
	Exercise	0.31	0.01 to 7.09	Results based on one outcome in 2 small RCTs (n = 16 and 29)	
	Bed rest for hypertension during pregnancy	0.98	0.80 to 1.20	Inappropriate population	
	Nutritional advice during pregnancy	0.89	0.42 to 1.88	Results based on 1 RCT	
	Balanced energy/protein supplementation	1.20	0.77 to 1.89	Risk of harm	
	Isocaloric protein supplementation	1.00	0.57 to 1.75	Results based on 1 RCT	
	Energy/protein restriction	1.13	0.59 to 2.18	Risk of harm	

[a] RRs based on subgroup analyses, defined in detail in the text, and used as parameters in sensitivity analyses.
[b] Group 1 are those treatments with an RR whose upper 95% CI is <1.0.
[c] Group 2 are those treatments with an RR whose 95% CI includes a value compatible with worsened outcome.
[d] Subgroup excluding the single large quasi-randomised trial.
[e] Subgroup of trials carried out in populations with an adequate calcium diet.
[f] Subgroup of trials carried out in populations with mothers at 'moderate risk' of pre-eclampsia rather than both 'moderate' and 'high risk' combined.

and progesterone on pre-eclampsia are also priorities as they appear on preliminary RCT findings to be sufficiently effective and low cost to be cost-effective also. New effective, low-cost interventions may also continue to emerge, and these too should be priorities for rigorous evaluation.

There are also opportunities for further research that may precede or accompany these main recommendations. The first might be to develop a more comprehensive economic model which deals simultaneously with the multiple outcomes which may contribute to effectiveness and cost-effectiveness across the board. As a minimum this would need to consider the infant outcomes identified, that is, preterm birth, and consider not just tests and interventions thought to have an impact on pre-eclampsia, but those primarily targeting these other outcomes also. The complexity of such a model would be great, particularly if it attempted to explore whether combinations of tests or combinations of treatments might be more cost-effective. Any new modelling should include the opportunity to do primary data collection on costs, the absence of which was a limitation in this analysis. Second, there should also be some continuing commitment to improving estimates of test accuracy. Newly developed or emerging tests predicting development of pre-eclampsia with modest costs that have very high levels of test accuracy should continue to be sought and evaluated. Kallikreinuria is such a test, an initial

evaluation of which suggests that its sensitivity and specificity may be at a level where it offers the possibility of contributing to a cost-effective test/treatment pairing.

Conclusions from the economic evaluation

The observed limitations do impinge on the initially stated main findings of the economic evaluation, particularly the specific interventions emerging as potentially preferred from a cost-effectiveness perspective. Thus for the 'no test/rest_all' option there are concerns about the robustness of the estimate of effect and the assumption of near zero cost to the NHS; for 'no test/calcium_all' there may be concern that when the effectiveness results are restricted to just those RCTs in populations with an adequate calcium diet, the 95% CI for the RR extends beyond 1.0 and that there may be also uncertainty about adverse events associated with widespread use of calcium in a low-risk population; finally, for 'no test/antioxidants all' there may again be concern about lack of data on adverse events and the observation that there is a disadvantageous effect on preterm birth <37 weeks (RR 1.38, 95% CI 1.04 to 1.82).

However, the general finding that the most cost-effective option is likely to be effective treatments (RR < 0.7) with modest costs (<£50) applied to all women without prior testing would seem to be robust. The three interventions indicated would clearly be those of greatest potential, provided that the uncertainties identified were resolved. However, other interventions such as progesterone and exercise were also highlighted, which with further evaluation might emerge as equally cost-effective options. Similarly, the need to investigate combinations of interventions should also not be overlooked.

Concerning the pessimistic findings about the lack of contribution to predictive testing to a preferred option from the point of view of cost-effectiveness, there seems little in the limitations to challenge this initial finding. As already stated, this situation principally arises because there are effective, relatively cheap interventions which appear to be free of adverse effects. Little would seem to threaten this, with the exception that adverse events might emerge when the interventions in question are widely used. The threshold analysis indicates the levels of accuracy that a test might need to achieve to become cost-effective. Generally, such levels of sensitivity and specificity have not been achieved. However, there are some preliminary results for kallikreinuria suggesting that the there may be tests which can achieve the very high levels of test accuracy demanded, provided that the cost remains modest. Hence the search for potentially useful tests should not be completely abandoned, and kallikreinuria certainly deserves further evaluation.

Chapter 6
Conclusions

Introduction

Overall this review hoped to identify combinations of tests and treatments that would lead to reduction in pre-eclampsia, which is an important threat to public health in both developed and developing countries. This project completed three distinct pieces of work to contribute to this goal:

- series of systematic reviews of test accuracy of the prediction of pre-eclampsia
- series of systematic reviews of effectiveness of interventions with potential to reduce cases of pre-eclampsia
- health economic evaluation, including an economic model, of the combined effect of tests and treatments on pre-eclampsia.

Each of these components has been described in detail, its main findings reported and the conclusions discussed in the light of any limitations identified at the end of each of the three preceding chapters. This chapter attempts to focus on the key findings and limitations emerging from all the previous sections as a whole. It is **not** a comprehensive summary of all the issues raised in each of the earlier chapters.

Main findings

- The accuracy of virtually all tests purported to be of value in prediction of pre-eclampsia was disappointing. Sensitivity, that is, the ability to predict all mothers who will develop pre-eclampsia, was particularly poor.
- The effectiveness of several interventions which might reduce the number of cases of pre-eclampsia was, in contrast, more promising. In addition to well-known interventions such as antiplatelet agents, the review has focused attention on other less frequently cited interventions, such as rest, exercise and calcium supplementation.
- By the standard of many healthcare interventions, those indicated to be potentially useful in avoiding pre-eclampsia were noted to be affordable (costs generally less than £50 for the whole of pregnancy, often substantially so).
- From the perspective of cost-effectiveness, providing effective treatment without prior testing is likely to be preferred to using a test followed by treating those who are positive. The provisos are that the true costs remain modest, that any effect on pre-eclampsia is not offset by contrary effects on important infant outcomes and that there are no serious adverse events associated with widespread use of the interventions in low-risk mothers.

Strengths of the report

There have been no previous attempts to assess systematically the potential cost-effectiveness of different combinations of tests and treatments for pre-eclampsia as a whole. We believe that the particular strength of this report is that it combines the results from a wide range of test accuracy systematic reviews with a wide range of different types of interventions in one economic model. The aim is to give clinicians and researchers a much more comprehensive overview of the current state of knowledge in this area than would be gained from single studies on diagnostic tests and interventions to prevent pre-eclampsia.

Limitations of the project

- It is acknowledged that not all possibly relevant tests have been included in this report (possible missing candidates include sFlt1) and that not all possibly relevant interventions were included.
- The systematic reviews of test accuracy encountered several challenges (see Chapter 3). However, none of these seriously threatened the validity of the main finding that the accuracy of virtually all tests was disappointing. Better reviews and more primary research on those tests examined are unlikely to change this picture.
- It is possible that there are new tests which have not been fully evaluated or have not reached evaluation. Kallikreinuria is a possible example of a test which in early evaluation appears to combine good sensitivity and specificity.
- One of the main limitations of the accuracy

reviews was that combinations of tests could not be assessed. This will require new prospective primary studies or IPD meta-analysis.
- The main limitation with the systematic reviews of effectiveness (see Chapter 4) is the paucity of data for several promising interventions, particularly rest at home and exercise, and also for the lack of universal high-quality data for some other interventions.
- Antiplatelet agents and calcium supplementation reduce the risk of pre-eclampsia. For antiplatelet agents this is reflected in reductions in perinatal outcomes of death, preterm birth and having a small for gestational age baby. However, for calcium supplementation there are no clear differences in baby outcomes. Also, for antioxidants, although the review presented here shows a reduction in the risk of pre-eclampsia, this is no longer statistically significant in the updated review.
- Another limitation of the effectiveness reviews was that combinations of interventions could not be assessed. This will require new prospective primary studies.
- One limitation of this project with respect to effectiveness reviews is that results of Cochrane reviews updated after the economic evaluation was performed (particularly antioxidants, where two new large trials were published late on in this project) could not be included in the final report.
- Pre-eclampsia has limitations as an outcome. Its full impact needs to be assessed by looking at a range of other outcomes for the woman and baby. It is the consequences of pre-eclampsia that we really need to assess. Interventions may influence the diagnosis of pre-eclampsia (by altering blood pressure, for example, without actually influencing the underlying pathological process). The consequences of pre-eclampsia, rather than the diagnosis itself, that are most important.
- There are some limitations to the economic model used, arising from the quality of the data (see above) and the availability of appropriate data both on effectiveness and side-effects. Pre-eclampsia was the only outcome used and the model did not assess side-effects. It is virtually self-evident that an effective, affordable and safe intervention is unlikely to be improved upon by applying a test with poor accuracy. Furthermore, with a condition as serious and costly as pre-eclampsia, correct identification of those who will develop pre-eclampsia will be more important than correct categorisation of those who will not develop pre-eclampsia. In this respect, it is important that the compromised sensitivity is the aspect of test accuracy where all the potential tests are particularly deficient.
- The small amount of information on adverse events associated with interventions, particularly in the longer term and to the child, is an important limitation, as is the lack of information on side effects of the tests.
- Another limitation is the lack of quality information concerning costs.

Overall conclusion

The main findings of this review appear largely unaffected by the limitations identified. Of these findings, we believe that the main driver of future practice and research is the likelihood that an effective intervention applied to all mothers without preceding testing will be the most cost-effective approach to reducing pre-eclampsia. We have identified several candidates for an appropriate intervention. Some, such as rest and exercise, require further evidence on effectiveness; others, such as calcium supplementation, need confirmation of absence of adverse events and reasonable cost.

Recommendations for practice

With regard to effectiveness results, low-dose aspirin could be offered to women at risk of pre-eclampsia and calcium supplementation could be considered for those with low dietary calcium intake. With regard to the economic modelling, the most cost-effective approach to reducing pre-eclampsia is likely to be the provision of an effective, affordable and safe intervention applied to all mothers without prior testing to assess levels of risk. However, we believe that it is probably premature to suggest the implementation of a treat-all intervention strategy such as advice to rest, low-dose aspirin or calcium supplementation on cost-effectiveness grounds at present. Some consideration needs to be given as to whether we should continue to do certain tests reviewed in this report whose main perceived value up to now has been to help identify pre-eclampsia.

Recommendations for research

- There is a need for systematic reviews to map the aetiopathogenesis of pre-eclampsia in order to better develop new tests and treatments.
- Similarly, there is a need for systematic reviews

to evaluate prognostic/predictive features that are associated with maternal and foetal complications once pre-eclampsia has started (see *Figure 1*, p. 6).

- Researchers may wish to consult more widely to ensure that all relevant diagnostic tests and interventions are considered for review in future projects. It is important to involve consumers in priority setting for research. Consensus conferences and Delphic surveys may be useful to define important questions and designs for the future.
- There is a need for RCTs that investigate whether lifestyle interventions such as rest at home and exercise are actually effective in reducing pre-eclampsia.
- Those who design future trials should do this in a way that facilitates meta-analysis and IPD analysis, for example by using similar protocols whenever possible, by collecting information about women's risk status at trial entry and standardising the definitions of outcome measures.
- Evaluation of pilot schemes for universal treatment of mothers with effective pharmacological interventions such as calcium supplementation or aspirin should be considered. Such evaluation should include investigation of adverse events and actual costs.
- There is a need for IPD meta-analysis of effectiveness literature where it has not already been done and where there is sufficient research to warrant this approach in order to delineate subgroup effects powerfully.
- Rigorous evaluation is required of tests with modest cost whose initial assessments suggest that they may have high levels of both sensitivity and specificity. Kallikreinuria may fall into this category, but there may be other contenders in development which would need further investigation.
- Diagnostic IPD meta-analyses are required for delineating the added value of tests and for studying the value of test combinations in light of the interdependence that exists between tests.
- Multiple (direct and indirect) comparisons considering all the tests and interventions may help delineate their rank. Methodological research is needed to assess if this could produce outputs suitable for decision analysis.
- There is a need for the development of an economic model which considers not just pre-eclampsia, but also other related outcomes, particularly those relevant to the infant such as perinatal death, preterm birth and small for gestational age. This would help to enable the development of comprehensive care pathways. Such a modelling project should make provision for primary data collection on costs.

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Contribution of authors

Pelham Barton (Senior Lecturer) was modelling advisor to the project. He advised on the model structure and provided advice throughout both the analysis and interpretation of the results. He commented on the draft economic section of the report. Jeltsje Cnossen (Research Fellow) did systematic reviews of diagnostic tests (all except proteinuria), statistical analysis, project management of diagnostic accuracy work stream and drafting of methods and results of diagnostic accuracy parts of the final report. Lelia Duley (Professor of Obstetric Epidemiology) was co-applicant on the grant application to obtain funding, undertook project management of effectiveness systematic reviews and development of the generic protocol for effectiveness reviews, conducted new effectiveness reviews and updated existing reviews in collaboration with Cochrane review authors. She also contributed to the background, systematic reviews of effectiveness studies and discussion sections of the final report. Janesh Gupta (Professor of Obstetrics and Gynaecology) was co-applicant on the grant application to obtain funding and undertook project management and editing and revisions of manuscript. Chris Hyde (Reader in Evidence Synthesis in Health Care) was co-applicant on the grant application to obtain funding and undertook development of protocol, assistance with test accuracy review on proteinuria, assistance with the economic model, particularly interpretation and presentation, and drafting and editing of the final report. Ariadna Juarez-Garcia (Research Fellow) helped to collate the data from the clinical reviews, constructed the model using Data TreeAge software and carried out the main analyses for the economic evaluation using the model and probabilistic sensitivity analysis. She helped to interpret the results and commented on the draft economic section of the report. Khalid Khan (Professor of Obstetrics-Gynaecology and Clinical Epidemiology) was the main applicant on the grant application to obtain funding and undertook development of protocol, project management and drafting and editing of the final report. Mariska Leeflang (Research Fellow) did systematic reviews of diagnostic accuracy studies. Catherine Meads (Lecturer) did project management, organised meetings and took minutes, conducted one test accuracy review, constructed abstracts of accuracy and effectiveness reviews, assisted with drafting of the background, methods section of accuracy and effectiveness reviews and economics sections, drafted part of the effectiveness discussion and overall discussion, finished the report and liaised with NCCHTA. Shireen Meher (Research Fellow) did systematic reviews of effectiveness, developed the generic protocol for effectiveness reviews, coordinated input from Cochrane review authors, conducted new effectiveness reviews and updated existing reviews in collaboration with Cochrane review authors. She also contributed to drafting of the background and effectiveness sections of the final report. Ben Willem Mol (Consultant in Obstetrics and Gynaecology) and Joris van der Post (Professor in Obstetrics) did systematic reviews of diagnostic accuracy studies. Gerben ter Riet (Associate Professor) developed the the protocol and undertook project management of diagnostic accuracy systematic reviews, statistical analysis and drafting of the diagnostic accuracy methods section in the final report. Tracy Roberts (Senior Lecturer) was co-applicant on the grant application to obtain funding and was responsible for overseeing the economic evaluation component of the project. She collated data from the clinical reviews, collected the cost data used in the model, helped design the model structure and co-analysed the results. She wrote the main draft of the economics section of the report.

Papers published in other peer-reviewed journals relating to this research project

Cnossen JS, de Ruyter-Hanhijärvi H, van der Post JAM, Mol BWJ, Khan KS, ter Riet G. Accuracy of serum uric acid determination in predicting pre-eclampsia: a systematic review. *Acta Obstet Gynecol Scand* 2006;**85**: 519–25.

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Appendix 1

Protocol for the effectiveness reviews

The effectiveness reviews were to be conducted in collaboration with the Cochrane Pregnancy and Childbirth Group. The review process for this project therefore needed to be nested within the existing framework of Cochrane reviews. It also needed to comply with the editorial and peer review processes of this review group. Key issues in developing a strategy for the effectiveness reviews were to invite all existing Cochrane review authors to collaborate, to ensure that their work was properly acknowledged and to agree a single generic protocol within this collaborative group for these reviews.

Protocol development followed the following steps:

1. Identifying published reviews and protocols, and registered titles for reviews, that were relevant to prevention of pre-eclampsia.
2. Inviting the contact review author for each of these reviews, protocols and titles to join a collaborative group to agree a generic protocol laying out a standard set of methods for the Cochrane reviews of prevention of pre-eclampsia.
3. Requesting review authors of published reviews and protocols, and of registered titles, to allow us to work with them to update as many reviews as possible within the time frame of the project.
4. Dividing topics into 'core reviews' which had a primary focus on prevention of pre-eclampsia and would be completed or updated within the time frame of this project, and 'non-core' reviews which had a broader focus. Review authors for both 'core' and 'non-core' review were encouraged to use the generic protocol as the basis for their reviews, and the search strategy included topics relevant to both categories.
5. Submitting the generic protocol, which had been agreed by the Prevention of Pre-eclampsia Cochrane Review authors, to the editorial and peer review process of the Cochrane Pregnancy and Childbirth Group.

The generic protocol is published within the Cochrane Database of Systematic Reviews.[79] It was used for conducting all new reviews. Review authors of reviews and protocols already published at the start of this project were also encouraged to comply with these agreed standardised methods when updating their reviews or protocols.

Advantages of working within the Cochrane group were not only having access to the trial register maintained by the group, but also that the generic protocol and each review were passed through the full editorial process. This process included peer review by an editor and a review author within the Cochrane Pregnancy and Childbirth Group, by the Group's consumer panel, by the Group's statistician and by an expert outside the Group.

Appendix 2

Test accuracy search strategy

MEDLINE

1. preeclamp* OR eclamp* OR pre-eclamp* OR (pre AND eclamp*) OR (pregnan* AND hypertens*)
2. ("Eclampsia"[MeSH] OR "Gestosis, EPH"[MeSH] OR ("Hypertension"[MeSH] AND "Pregnancy"[MeSH]))
3. "Sensitivity and Specificity"[MeSH] OR predict* OR diagnose* OR diagnosi* OR diagnost* OR accura*

Diagnosis: (1 OR 2) AND 3

4. ((((("cohort studies"[mh] OR "case-control studies"[MeSH Terms]) OR "risk"[mh]) OR "epidemiologic factors"[MeSH Terms]) OR ("odds"[tw] AND "ratio*"[tw])) OR ("relative"[tw] AND "risk"[tw])) OR ("case"[tw] AND "control*"[tw]))

Aetiology: (1 OR 2) AND 4

EMBASE

1. exp "ECLAMPSIA AND PREECLAMPSIA"/
2. exp PREGNANCY/
3. exp hypertension/
4. 2 and 3
5. 1 or 4
6. (preeclamp$ or eclamp$ or pre-eclamp$ or (pre and eclamp$) or (pregnan$ and hypertens$)).mp.
7. (sensitiv$ or detect$ or accura$ or specific$ or reliab$ or positive or negative or diagnos$).mp. or di.fs.
8. 5 or 6
9. 7 and 8 (*diagnosis*)
10. cohort analysis/
11. exp risk/
12. (odds$ adj ratio$).mp.
13. (relative adj risk).mp.
14. case control study/
15. (case$ adj control$).mp.
16. (causa$ or predispos$).mp.
17. or/10-16
18. 5 or 6
19. 17 and 18 (*aetiology*)

Appendix 3

Data extraction form

1. RefID Original Study: RefIDPP	PP/ RL	2. Assessor: AssOr	☐1	Jeltsje Cnossen	☐5	Mariska Leeflang
			☐2	Gerben ter Riet	☐6	.....
			☐3	Joris van der Post	☐7	.....
			☐4	Ben Willem Mol	☐8	Other, ...

3. ID of corresponding systematic review: IdSR State abbreviation of test under review	88	4. RefID within corresponding systematic review: RefIDSR	
5. First author: Author	88	6. Publication year: PubYear	

7a. Setting: SetCare ☐1 primary care *GP, midwifery* ☐2 secondary/ tertiary care *hospital* ☐3 mixed care ☐55 other ☐66 not reported

7b. Number of participating centers: Centers 88

7c. Country of investigation: Country 88

8. Eligibility/ in-/ exclusion criteria	**NB: if "no", state numbers if mentioned: e.g. # patients normotensive <20wk**			
8a. Were all patients normotensive before 20th week of pregnancy (or 6 weeks after birth)? SelNormo	☐1 yes	☐2 no	...../.....	☐66 not reported
8b. Were all patients non proteinuric before 20th week of gestation? SelProt	☐1 yes	☐2 no	...../.....	☐66 not reported
8c. Did all patients have singleton pregnancies? SelSingl	☐1 yes	☐2 no	...../.....	☐66 not reported
8d. Were all patients primigravid? SelPrimi	☐1 yes	☐2 no	...../.....	☐66 not reported
8e. Were patients with pre-eclampsia in previous pregnancies excluded/not included? SelPE	☐1 yes, or not applicable	☐2 no		☐66 not reported
8f. Were patients with the following major systemic disorders excluded/not included?				
8f1. Insulin dependent diabetes mellitus: SelIDDM	☐1 yes	☐2 no		☐66 not reported
8f2. Chronic renal disease: SelRenal	☐1 yes	☐2 no		☐66 not reported
8f3. Systemic lupus erythemathodes: SelSLE	☐1 yes	☐2 no		☐66 not reported

8f4. Antiphospholipid syndrome: SelAPLS ☐ 1 yes ☐ 2 no ☐ 66 not reported

8f5. Chronic hypertension: SelChrRR ☐ 1 yes ☐ 2 no ☐ 66 not reported

8f6. Foetal chromosomal or structural abnormalities: SelFtGen ☐ 1 yes ☐ 2 no ☐ 66 not reported

8g. Other eligibility/in-/exclusion criteria: SelOth

` ☐ 66 not reported

88

9. Study population: describe age (mean ± SD or median (range)): PopAge
Describe for whole group! If only data can be described for subgroups, describe for subgroups

☐ 66 not reported

88

10. Start inclusion patients (year): InclStrt ☐ 66 not reported

11. End inclusion patients (year): InclEnd ☐ 66 not reported

12a. Study design: StuDes ☐ 1 cohort ☐ 2 case control ☐ 3 rct/ cct ☐ 4 cross sectional ☐ 55 other

12b1. Case control design: CCDes ☐ 1 nested in cohort ☐ 2 matched ☐ 3 both, nested and matched ☐ 55 other ☐ 66 not reported ☐ 77 not applicable

12b2. How was the case group composed? CaseGrp ☐ 1 incident cases *occurrence of pre-eclampsia in group of pregnant women* ☐ 2 prevalent cases *presence of pre-eclampsia in group of women* ☐ 3 both ☐ 66 not reported ☐ 77 not applicable

12b3. Severity of the disease in pre-eclamptic patients: SevPE ☐ 1 representative sample of population with the disease ☐ 2 sample of more severe cases ☐ 3 sample of less severe cases ☐ 66 not reported

12b4.How was the control group composed? ContrGrp ☐ 1 differential diagnosis sample ☐ 2 convenience sample ☐ 3 healthy controls sample ☐ 66 not reported ☐ 77 not applicable

13a. Consecutive series of patients (*selection*): ConsPts ☐ 1 yes ☐ 2 no, random sample ☐ 3 no, neither consecutive, nor random sample *(e.g. matched cohort)* ☐ 66 not reported

13b. If "no" at item 13a, number(s) of patients missed: ConsMiss ☐ 66 not reported

14. Details of Index test measurement
Index test under review: IndDet Fibronectin 88

14a. Fibronectin: FNmeas ☐ 1 total ☐ 2 cellular ☐ 3 both ☐ 66 not reported

14b. Manufacturer: Manuf ☐ 66 not reported 88

14c. Description Index test: DetMeth 88

15. Details of Reference test

15a. Blood pressure (*Korotkoff*): RefKor ☐ 1 K4 ☐ 2 K5 ☐ 3 both ☐ 66 not reported

15b. Blood pressure measurement (*instrument*): RefInstr ☐ 1 mercury sphygmo-manometer ☐ 2 ambulatory ☐ 3 automated 55 other, ... ☐ 66 not reported

15c. Blood pressure (*position*): RefPos ☐ 1 seated ☐ 2 supine ☐ 3 lateral ☐ 66 not reported

15d1. Blood pressure measurement (*mmHg diastolic, repetitive, hours apart*): RefDBP ☐ 1 ⩾90 mmHg twice ⩾4 hrs apart ☐ 2 ⩾110 mmHg at least once ☐ 3 both (1+2) ☐ 55 other ☐ 66 not reported

15d2. If "other" at 15d1. report details (*mmHg diastolic, repetitive, hours apart*): RefBlood 88

15e1. Increase in blood pressure (state *quantity*): RefIncr ☐ 1 yes ..... (Syst) /..... (Diast) ☐ 2 no ☐ 66 not reported

15f.Proteinuria (*dipstick*): RefDip ☐ 1 ⩾1+ ☐ 2 ⩾2+ ☐ 3 ⩾3+ ☐ 55 other ☐ 66 not reported

15g. Proteinuria (state *quantity threshold*): RefProt ☐ 1 g/ 24 hrs ☐ 2 g/ L ☐ 55 other, ... ☐ 66 not reported

15h. Oedema (*presence*): RefOed ☐ 1 yes ☐ 2 no

15i. Other details of Reference test (e.g. elevated serum uric acid): RefOth 88

16. Flow, index test executed first: Indfirst ☐ 1 yes, or not applicable ☐ 2 no, reference test first ☐ 3 no, at random ☐ 4 no, mixed ☐ 66 not reported

17. Prospective data collection: TimeData ☐ 1 yes ☐ 2 no, retrospective ☐ 3 no, ambispective ☐ 66 not reported

18. Were pregnant women treated before occurrence of pre-eclampsia? Treat PE ☐ 1 yes treatment 88 ☐ 2 no ☐ 66 not reported

19. Index test blind for reference test results: IndBlind ☐ 1 yes, or not applicable ☐ 2 no ☐ 66 not reported

20. Reference test blind for index test results: RefBlind ☐ 1 yes, or not applicable ☐ 2 no ☐ 66 not reported

21. Index test blind for clinical information: IndCli ☐ 1 yes ☐ 2 no ☐ 66 not reported

22. Reference test blind for clinical information: RefCli ☐ 1 yes ☐ 2 no ☐ 66 not reported

23. Training of assessors: TraiAss ☐ 1 yes ☐ 2 no ☐ 66 not reported

24. Number of assessors: NrAss ☐ 66 not reported

25a. Absence or existence of not interpretable, indeterminate, intermediate results reported: NonInt ☐ 1 yes ☐ 2 no

25b. Number of not interpretable, indeterminate, intermediate index test results: IndMes index test

25c. Number of not interpretable, indeterminate, intermediate reference test results: RefMes reference test

25d. Number of not interpretable, indeterminate, intermediate test results overall: TotMes overall

25e. Is reported, whether former results were included or excluded when indexes of accuracy were calculated: FormRes ☐ 1 yes ☐ 2 no ☐ 77 not applicable

25f. Are drop-outs reported: Dropout ☐ 1 yes ☐ 2 no
Drop-outs should not have been scored at any previous item!

25g. If 'yes' at item 25f, state number of drop-out: NrDrop ☐ 66 not reported

25h. Total number of patients **excluded**: NrDrop ☐ 66 not reported

26. Prespecified cut-off for **Index test** positivity or variation (Δ) reported: CutRep ☐ 1 yes ☐ 2 no

27. Cut-off value(s) **Index test**: CutVal Threshold / Δ ☐ 66 not reported

28. Units of measurement for **Index test** (e.g. MoM, mg/dL): UnMeas 88

29a. Gestational age(s) of patients at time(s) of index test measurement(s): GestAge 88 ☐ 66 not reported

29b. Onset of pre-eclampsia in study population: OnsetPE ☐1 < 32 wks ☐2 > 32 wks ☐3 both (1+2) ☐4 other: </> .....wks ☐ 66 not reported

30. Prevalence of pre-eclampsia in study population (%): PrevPE ☐ 66 not reported

31. True Positives: TP

32. False Positives: FP

33. False Negatives: FN

34. True Negatives: TN

35a. Measures of statistical uncertainty presented (e.g. confidence interval): CIRep ☐ 1 yes ☐ 2 no

35b. State measures of statistical uncertainty: CIMeas		88
36. If reported, describe data for reproducibility of 2x2 data table: ReprTab (e.g. mean, median, SD, SE, CI, distribution)		88
37. Correlation coefficients between tests (state coefficients and tests): CorrCo		88

38. Financial support of industry: Conflict ☐ 1 yes ☐ 2 no ☐ 66 not reported

Appendix 4

Effectiveness reviews generic search strategy

CENTRAL (The Cochrane Library)

1. pregnan
2. *pregnancy*ME
3. pregnancy-complications*ME
4. hypertension*ME
5. hypertens*
6. blood press*
7. ((#1 or #2 or #3) and (#4 or #5 or #6))
8. PIH
9. toxaemi* near pregnan*
10. toxemi* near pregnan*
11. pre-eclampsia*ME
12. pre-eclamp*
13. preeclamp*
14. pre next eclamp*
15. #7 or #8 or #9 or #10
16. #15 or #11 or #12 or #13 or #14

EMBASE (2002 to current)

1. randomization/
2. double blind procedure/
3. crossover procedure/
4. intermethod comparison/
5. single blind procedure/
6. clinical study/
7. controlled study/
8. randomized controlled trial/
9. (clin$ adj2 trial$).tw.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).tw.
11. exp clinical trial/
12. placebo/
13. placebo$.tw.
14. random$.tw.
15. comparison/
16. drug comparison/
17. follow up/
18. evaluation.mp. and follow up/
19. "evaluation and follow up"/
20. exp "drug control"/
21. drug screening/
22. prospective study/
23. major clinical study/
24. (control$ or prospectiv$ or volunteer$).tw.
25. or/1-17
26. or/19-24
27. 25 or 26
28. exp Eclampsia and Pre-eclampsia/
29. (pre-eclamp$ or preeclamp$ or pre adj eclamp$).tw.
30. (toxemi$ or toxaemi$) adj3 pregnan$).tw.
31. (hypertens$ adj3 pregnan$).tw.
32. pih.ti,ab
33. 28 or 29 or 30 or 31 or 32
34. 33 and 27
35. limit 34 to human

Appendix 5

Cochrane review subgroup categorisation and list of outcomes

Population subgroups

Whenever possible, and relevant, women were grouped on the basis of their risk status at trial entry as follows.

For normotensive women

- High risk: defined as having one or more of the following: diabetes, renal disease, thrombophilia, autoimmune disease, previous severe or early-onset pre-eclampsia, or multiple pregnancy.
- Moderate risk: defined as none of the above, but having either previous pre-eclampsia that was not severe or early onset (or severity unspecified), or a first pregnancy and at least one of the following: teenager or over 35 years age, family history of pre-eclampsia, obesity (BMI $\geq$ 30), increased sensitivity to angiotensin II, positive roll-over test, abnormal uterine artery Doppler scan.
- Low risk: defined as pregnancy that did not qualify as either high or moderate risk.
- Undefined risk: when the risk was unclear or not specified.

For hypertensive women, without proteinuria

These women are all at high risk of developing pre-eclampsia. They were classified into two groups:

- Gestational hypertension: hypertension detected for the first time after 20 weeks' gestation, in the absence of proteinuria.
- Chronic hypertension: essential or secondary hypertension detected prior to pregnancy or before 20 weeks' gestation. Some women with chronic hypertension may have long-standing proteinuria due to their underlying disease. These women were included, as their proteinuria was not due to pre-eclampsia.

If a trial included women with pre-eclampsia in addition to those with non-proteinuric hypertension (gestational or chronic), where possible only the women with non-proteinuric hypertension alone were included in the review. Trials that do not report results separately for the two categories could be included in the review but, if so, were presented as a separate subgroup.

For women with undefined blood pressure

This category was used for women for whom it was unclear, or not specified, whether or not they had hypertension at trial entry.

Cochrane review list of outcomes

Outcomes for the woman

1. Pre-eclampsia: defined where possible as hypertension (blood pressure $\geq$140 mmHg systolic or $\geq$90 mmHg diastolic) with proteinuria ($\geq$300 mg protein in a 24-hour urine collection or $\geq$30 mg/dl in a single sample or $\geq$1+ on dipstick or $\geq$30 mg/mmol urine protein/creatinine ratio). For a woman with chronic hypertension and proteinuria at trial entry, pre-eclampsia was defined as sudden worsening of proteinuria and/or hypertension, or other signs and symptoms of pre-eclampsia after 20 weeks' gestation.
2. Severe hypertension was used as a main outcome for reviews which included women with hypertension during pregnancy defined where possible as blood pressure $\geq$160 mmHg systolic or $\geq$110 mmHg diastolic.
3. Death: during pregnancy or up to 42 days after end of pregnancy.
4. Severe morbidity: including eclampsia, liver or renal failure, haemolysis, elevated liver enzymes and low platelets syndrome, disseminated intravascular coagulation, stroke and pulmonary oedema. These outcomes were reported individually, and as a composite measure where the information was available.
5. Severe pre-eclampsia: there is no widely accepted definition of severe pre-eclampsia. The following are generally regarded as features of severe disease: severe hypertension (blood pressure $\geq$160 mmHg systolic or 110 mmHg diastolic), severe proteinuria [usually at least 3 g (range 2–5 g) protein in 24 hours, or >3 on dipstick), reduced urinary volume (<400–500 in 24 hours), neurological

disturbances such as headache, visual disturbances and exaggerated tendon reflexes, upper abdominal pain, pulmonary oedema, impaired liver function tests, high serum creatinine, low platelets, intrauterine growth restriction or reduced liquor volume.
6. Early onset of pre-eclampsia: defined where possible as pre-eclampsia before 33 completed weeks.
7. Gestational hypertension: defined where possible as hypertension (blood pressure ⩾140 mmHg systolic or ⩾90 mmHg diastolic) after 20 weeks' gestation.
8. Use of antihypertensive drugs or need for additional antihypertensive drugs.
9. Abruption of the placenta or antepartum haemorrhage.
10. Elective delivery: induction of labour or Caesarean section.
11. Caesarean section: emergency and elective.
12. Postpartum haemorrhage: defined as blood loss of 500 ml or more.
13. Side-effects: any side-effects or adverse events related to the intervention, intervention stopped due to side-effects.
14. Use of hospital resources: visit to day care unit, antenatal hospital admission, intensive care (admission to intensive care unit, length of stay) ventilation, dialysis.
15. Women's experiences and views of the interventions: childbirth experience, physical and psychological trauma, postnatal depression, breastfeeding, mother–infant interaction and attachment.

Outcomes for the child

1. Death: including all deaths before birth and up to discharge from hospital.
2. Preterm birth: defined as birth before 37 completed weeks' gestation.
3. Small for gestational age: defined as growth below the third centile, or the lowest centile reported.
4. Death, classified by timing of death: miscarriage (foetal loss up to 19 completed weeks' gestation or however defined in the study), stillbirth (death *in utero* at or after 20 weeks' gestation), perinatal death (stillbirth or death in the first 7 days of life), neonatal death (death in the first 28 days after birth), infant death (death in the first year of life).
5. Severity of preterm birth: very preterm birth (before 33 completed weeks) and extremely preterm birth (before 27 completed weeks).
6. Apgar score at 5 minutes: low (⩽7) and very low (⩽4) or lowest reported.
7. Endotracheal intubation or use of mechanical ventilation.
8. Neonatal morbidity: respiratory distress syndrome, chronic lung disease, sepsis, necrotising enterocolitis, retinopathy of prematurity and intraventricular haemorrhage.
9. Long-term growth and development: blindness, deafness, seizures, poor growth, neurodevelopmental delay and cerebral palsy.
10. Side-effects associated with the intervention.
11. Use of hospital resources: admission to neonatal intensive care unit, duration of hospital stay after delivery.

Economic outcomes

1. Costs to health service resources: short term and long term for both mother and baby.
2. Costs to the woman, her family, and society associated with the intervention.

Subgroups investigated in Cochrane reviews

The following subgroup analyses are included in the generic protocol:

1. By maternal risk of pre-eclampsia at trial entry: women at high risk, moderate risk, low risk or undefined risk. Women with gestational hypertension and chronic hypertension were either analysed as a separate group to normotensive women or within the high-risk group, depending on the focus of the individual review.
2. By type of hypertension at trial entry: gestational hypertension or chronic hypertension. Reviews with trials where results for women with non-proteinuric hypertension and pre-eclampsia had not been reported separately were presented as a separate subgroup (as discussed above).
3. By gestation at trial entry: before 19 completed weeks, after 19 completed weeks or gestation unclear/not specified.
4. By baseline level of the intervention of interest at trial entry: adequate or inadequate (for example, low or normal/high calcium intake) or unknown.
5. By type of intervention: type of drug or supplement.
6. By dosage regimens of intervention: the cut-off for each subgroup was explained and prespecified.

As not all subgroup analyses were relevant to each review, and as multiple analyses increase the risk of being misled by the play of chance, review authors prespecified which subgroups to include in their review. Thus the number of subgroups for each review was minimised. Only the main outcomes listed above were included in the subgroup analyses.

Details of which subgroup analyses were conducted for each review are available in the published Cochrane reviews. Subgroup analyses prespecified for a review might not have been conducted if there were insufficient data.

Sensitivity analyses were also conducted, where necessary, to explore the effects of trial quality on the summary statistic as follows:

- excluding trials with clearly inadequate allocation concealment (rated C)
- excluding trials with no intervention for the control group (no placebo)
- excluding quasi-randomised studies.

Details of which sensitivity analyses were conducted for each review are available in the published Cochrane reviews.

Appendix 6

Comparison between proposed diagnostic and screening tests and treatments for pre-eclampsia to be systematically reviewed and final systematic reviews completed

TABLE 48 *Proposed and final diagnostic and screening tests for pre-eclampsia*

	Proposed list of diagnostic and screening tests	**Final list of diagnostic and screening tests systematically reviewed (see *Table 3*)**
History	Risk factors, e.g. nulliparity, new partner, hypertension on oral contraceptives, pre-existing diabetes, renal disease, chronic hypertension parity	(Review available[78])
Examination	Blood pressure (systolic and diastolic and mean arterial pressure), peripheral oedema, BMI, waist circumference, hip/waist ratio	BMI
Investigations		
Biochemical	SUA, urinary calcium excretion, urinary albumin creatinine and calcium creatinine ratios, microalbuminuria, FN, spot proteinuria, 24-hour urinary protein levels	SUA, urinary calcium excretion, urinary calcium creatinine ratio, plasma cellular FN, plasma total FN, 24-hour urinary protein, urinary albumin creatinine ratio, microalbuminuria, spot proteinuria
Haemodymanic	Pressor response to various forms of stimuli, e.g., supine 'roll-over', isometric exercise, passive tilting, uterine artery Doppler (update existing review)	Uterine artery Doppler
Haematological	Antithrombin III, platelet count, haemoglobin, haematocrit, fibrinogen	Haemoglobin, haematocrit
Other tests	Thrombomodulin, endothelin-1, plasminogen activator inhibitor, free fatty acids, atrial natriuretic peptide, angiotensin II infusion, platelet angiotensin II binding site density, HCG, AFP, fasting insulin levels	HCG, AFP
Additional tests		Serum unconjugated oestriol (uE3) fDNA

TABLE 49 *Proposed and final list of treatments for pre-eclampsia*

Proposed list of treatments	**Final list of treatments systematically reviewed (see *Table 4*)**
Antiplatelet agents for preventing and treating pre-eclampsia	Antiplatelet agents for preventing pre-eclampsia
Abdominal decompression for suspected foetal compromise/ pre-eclampsia	–
Abdominal decompression in normal pregnancy	–
Balanced protein/energy supplementation in pregnancy	–
Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems	Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems
Magnesium supplementation in pregnancy	–
Reduced salt intake compared with normal dietary salt, or high intake, in pregnancy	Reduced salt intake compared with normal dietary salt, or high intake, in pregnancy
Routine Doppler ultrasound in pregnancy	–
Zinc supplementation in pregnancy	–
Ambulatory versus conventional methods for monitoring blood pressure during pregnancy	Ambulatory versus conventional methods for monitoring blood pressure during pregnancy
Antenatal oestrogens for preventing adverse foetal outcome	–
Fish oil and other prostaglandin precursor supplementation during pregnancy for reducing pre-eclampsia	Marine oil and other prostaglandin precursor supplementation during pregnancy for reducing pre-eclampsia
Vitamins during pregnancy	Antioxidants
Bed rest for prevention	Bed rest for hypertension in pregnancy Rest for preventing pre-eclampsia and its complications in women with normal blood pressure
Diet for prevention	Energy and protein intake in pregnancy
Dietary advice for preventing pre-eclampsia	–
Diuretics for preventing pre-eclampsia	Diuretics for preventing pre-eclampsia
Self blood pressure monitoring versus conventional or ambulatory blood pressure monitoring during pregnancy	–
Drugs for prevention – normotensive women at risk of hypertension/pre-eclampsia	Antihypertensives
Exercise for prevention of hypertension	Exercise for prevention of hypertension
Additional treatments	Nitric oxide Garlic Progesterone

Appendix 7

Test accuracy tables of methodological and reporting characteristics of included studies

TABLE 50 *Methodological and reporting characteristics of studies on BMI*

Study	Population Age Country (study design[a])	No. of women analysed	Incidence of PE (%)	Reference standard	BMI cut-off
Sibai, 1997	IN: healthy nulliparae (CPEP trial). EX: medical, obstetric or known foetal complications Any age USA (RCT)	4,310	7.6	DBP ⩾90 mmHg twice 4–168 h apart, proteinuria ⩾0.3 g/24 h or + dipstick twice or protein/creatinine ratio ⩾0.35 once or ++ dipstick once	⩾34 ⩾30 ⩾26 <20
Baeten, 2001	IN: singleton pregnancies, nulliparae Any age USA	96,384	6.8	NR	⩾30 ⩾25 <20
Bianco, 1998	IN: singleton pregnancies, age 20–34 years, EX: BMI 27–34 USA	11,926	3.7	NR	⩾35 vs 19–27
Bowers, 1999	EX: <37 weeks of delivery, multiple pregnancies, pre-existing chronic maternal illness Any age (mean 22.2 years) USA	281	5.0	Rise RR >30/15 mmHg or RR >140/90 mmHg twice 6 h apart, proteinuria not specified	>29 >26
Knuist, 1998	IN: nulliparae, singleton pregnancies, EX: pre-existing disease, obstetric abnormality Any age The Netherlands	2,080	1.4	DBP ⩾90 mmHg twice 4 h apart, proteinuria ++ dipstick twice 4 h apart, no UTI	>26.0 <19.8
Lee, 2000	EX: chronic hypertension, foetal anomalies 29.9 ± 4.1 years Taiwan	29,735	1.4	DBP ⩾90 mmHg twice 4 h apart, proteinuria >0.3 g/24 h or >++ dipstick twice 4 h apart	>24.2 <19.8
Ogunyemi, 1998	IN: black, low-income women, singleton pregnancies, >37 weeks Any age USA	582	7.9	New onset hypertension and proteinuria	>29 >26 <19.8
Ros, 1998	IN: nulliparae, age <34 years Sweden	2,418	5.4	RR ⩾140/90 mmHg or rise 30/15 mmHg twice 6 h apart, proteinuria + dipstick twice or ⩾0.3 g/24 h	>29 >26 <19.8
Sebire, 2001	Unselected population 28.5 ± 5.2 years UK	28,7213	0.9	NR	⩾30 ⩾25
Steinfeld, 2000	IN: singleton pregnancies Any age USA	2,424	5.3	ACOG criteria	⩾29

continued

TABLE 50 *Methodological and reporting characteristics of studies on BMI (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Incidence of PE (%)	Reference standard	BMI cut-off
Thadhani, 1999	EX: chronic hypertension 25–42 years USA	15,262	0.5	Baseline SBP <140 and rise of 30 mmHg twice, baseline DBP <90 and rise of 15 mmHg twice, proteinuria ++ dipstick or ⩾0.3 g/24 h	⩾30 ⩾25 <21

ACOG, American College of Obstetricians and Gynecologists; CPEP, Calcium for Pre-eclampsia Prevention Trial; DBP, diastolic blood pressure; EX, excluded; IN, included; NR, not reported; PE, pre-eclampsia; SBP, systolic blood pressure; UTI, urinary tract infection.
[a] Studies were cohort designs unless stated otherwise.
Primary studies were extracted once and were derived from O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of pre-eclampsia: a systematic overview. *Epidemiology* 2003;**14**:368–74.

TABLE 51 *Methodological and reporting characteristics of studies on AFP*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Morssink, 1997	IN: singleton pregnancies EX: diabetes, structural or chromosomal anomalies 28 years The Netherlands	2,008	15–20	2.0	Diastolic rise >15 mmHg; Proteinuria ⩾300 mg/24 h; Davey and MacGillivray, 1988	Method NR 2.5 MoM
Yaron, 1999	EX: structural or chromosomal anomalies Age NR USA	60,040	14–22	3.2	SBP ⩾140 mmHg or DBP ⩾90 mmHg; presence of proteinuria	Competitive RIA (Sanofi Diagnostics) 2.5 MoM
Wenstrom, 1996	EX: multiple pregnancies, foetal malformation or aneuploidy, AF blood contamination, positive AF acetylcholinesterase Age NR USA	4,614	2nd trimester	1.1	NR	RIA (Sanofi Pasteur) 2.5 MoM
Jauniaux, 1996	IN: all singleton pregnancies with abnormal uterine artery Doppler; past history of PE (n = 11) Age NR UK	41	20–24	26.8	RR ⩾140/90 mmHg persistent; proteinuria ⩾100 mg/l	FEIA (Hybritech) 2.5 MoM
Different cut-off value						
Leung, 1999	IN: singleton pregnancies 30.8 ± 4.9 years China	1,015	18.1 ± 1.3	2.1	DBP ⩾90 mmHg 2× 4 h or ⩾110 mmHg 1×; proteinuria ⩾2+ 2× 4 h apart or 300 mg/24 h	MEIA (IMx Abbott) 2.0 MoM
Pouta, 1998	IN: nulliparas EX: multiple pregnancies, foetal defects 27.7 ± 4.5 years Finland	637	15–19	5.3	RR ⩾140/90 mmHg 2× 6 h apart or rise 30/15 mmHg; proteinuria ⩾300 mg/24 h	Time-resolved FIA (Wallac) 2.0 MoM

continued

TABLE 51 *Methodological and reporting characteristics of studies on AFP (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Milunsky, 1989	EX: multiple pregnancies 20–34 years (90%) USA	13,486	15–20	1.7	NR	RIA (Clinical Assays) 2.0 MoM
Waller, 1996	IN: singleton pregnancies EX: foetal malformations 27 years (mean) USA	51,008	15–19	1.3	NR	EIA (Abbott) 2.0 MoM
Capeless, 1992	Screening programme Age NR USA	358	16–20	2.0	NR	Method NR 2.0 MoM
Simpson, 1995	EX: multiple pregnancies, foetal malformations Age NR USA	650	15–20	1.0	SBP ⩾140 mmHg or DBP ⩾90 mmHg 2×; proteinuria ⩾1+ 2× or ⩾300 mg/24 h	EIA (Hybritech Tandem ERA, Abbott) 2.0 MoM
Severe PE						
Raty, 1999	Matching of delivery and screening databases 26.9 ± 3.6 years Finland	1,242	15.9 ± 1.2	0.8	**Severe PE:** RR ⩾160/110 mmHg; proteinuria ⩾5.0 g/l; oliguria; subjective symptoms	Time resolved IFMA (Wallac) 2.0 MoM
Stamilio, 2000	IN: non-smoking, mild PE in control group EX: multiple pregnancies, foetal anomalies 25.7 ± 0.3 years USA	1,998	15–19	2.5	**Severe PE:** SBP ⩾160 mmHg or DBP ⩾110 mmHg; proteinuria ⩾3+ or ⩾5.0 g/24 h (oliguria/ symptoms)	Method NR 2.0 MoM

AF, amniotic fluid; EIA, enzyme immunoassay; FEIA, fluoroenzyme immunoassay; FIA, fluoroimmunoassay; IFMA, immunofluorescence microassay enzyme immunoassay; MEIA, microenzyme immunoassay; RIA, radioimmunoassay.
[a] All studies were cohort studies, often from foetal screening programmes. Most studies included singleton pregnancies only.

TABLE 52 *Methodological and reporting characteristics of studies on cellular and total fibronectin*

Study	Population Age Country (study design)	No. of women analysed[a]	Gestational age at test (trimester)	Incidence of PE (%)	Reference standard	Index test Cut-off (μg/ml)
Chavarria, 2002	IN: normotensive and non-proteinuric <20 weeks EX: IDDM, CTD, APLS, SLE, miscarriages, multiple pregnancies, essential hypertension, aspirin therapy, gest/transient hypertension, gest. DM, oligohydramnion, stillbirth, preterm delivery 28.2 ± 5.7 years Mexico (nested matched case–control)	78	2nd	33.3	RR ⩾140/90 mmHg or rise of SBP 30 and/or DBP 15 mmHg, 2× 6 h apart; proteinuria >0.3 g/24 h or >1+ dipstick and oedema >1+ after bedrest	ED-B (EIA, Adeza Biomedical) 2.7; 3.6; 4.5

continued

TABLE 52 *Methodological and reporting characteristics of studies on cellular and total fibronectin (cont'd)*

Study	Population Age Country (study design)	No. of women analysed[a]	Gestational age at test (trimester)	Incidence of PE (%)	Reference standard	Index test Cut-off (μg/ml)
Lockwood, 1990	IN: singleton pregnancies, normotensive <20 weeks EX: IDDM, CH, abruptio placentae and infections, history of previous PE Mean 20.2 years USA (nested matched case–control)	14*	1st	45.6	RR 140/90 mmHg, rise of SBP 30 or DBP 15 mmHg; proteinuria 1 g/l; 2× > 6 h apart	ED 1+ (dual ELISA) 2.8; 3.2; 4.0
		43**	2nd			ED 1+ 3.2; 4.2; 5.8
Total FN						
Lockwood, 1990	IN: singleton pregnancies, normotensive <20 weeks EX: IDDM, CH, abruptio placentae and infections, history of previous PE Mean 20.2 years USA (nested matched case–control)	14*	1st			Total FN (dual ELISA) 347; 370; 393; 415
		43**	2nd			Total FN 230; 350; 380; 400
Soltan, 1996	IN: normotensive and non-proteinuric <20 weeks gestation EX: IDDM, CTD, history of cardiovascular or renal disease, aspirin therapy, antiprostaglandins, calcium, albuminuria, 'any abnormality' (e.g. congenital malformations). 20.3 ± 2.6 years Egypt (cohort)	88	14–24 weeks	19.3	Rise of SBP ⩾30 mmHg or DBP ⩾15 mmHg proteinuria ⩾0.3 g/24 h (oedema)	Total FN (immuno-diffusion technique) 293
Paarlberg, 1998	IN: singleton pregnancies, nulliparous, normotensive <20 weeks EX: GH, DM, CTD, age <18 years; miscarriage <16 weeks; treatment; Crohn; idiopathic hyperglobulinuria; myomata uteri; uterine anomaly; sickle cell anaemia; trisomy-21 infant; twin pregnancy; congenital abnormalities 30.8 ± 0.4 years The Netherlands (cohort)	228*	1st	11.4	Rise of DBP ⩾15 mmHg and/or antenatal DBP ⩾90 mmHg in previously normotensive woman; proteinuria >0.3 g/24 h (ACOG)	Total FN (nephelo metric assay, Beckman Array Immuno-chemical System) 240
		228*	2nd			Total FN 230

APLS, antiphospholipid syndrome; CH, chronic hypertension; CTD, connective tissue disease; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; GH, gestational hypertension; IDDM, insulin-dependent diabetes mellitus; SLE, systemic lupus erythematosis.

[a] * and ** indicate the same patients within individual study.

TABLE 53 *Methodological and reporting characteristics of studies on fDNA*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Cotter, 2004	IN: normotensive non-proteinuric women, male foetuses EX: aneuploid foetuses 26.1 ± 5.9 years Ireland (nested and matched)	264	15.7 ± 3.6	NR	RR ⩾140/90 mmHg; proteinuria ⩾0.3 g/24 h or 1+/2+ dipstick (20/88 severe PE cases)	fDNA Real-time PCR TaqMan SRY <10,000 copies/ml <50,000 >50,000
Farina, 2004	IN: normotensive women Median 32 (PE) vs 29.5 (controls) years Japan (nested in cohort of 209 controls and 48 PE)	36	20.4 ± 2.1	18.7	SBP ⩾140 mmHg 2× or DBP ⩾90 mmHg 2×; proteinuria ⩾0.3 g/24 h	Cell free fDNA Real-time PCR DYS14 5; 10; 15; 20% FPR
Leung, 2001	IN: singleton pregnancies, male foetuses Age NR Hong Kong (nested and matched)	51	11–22	NR	DBP ⩾90 mmHg 2× ⩾4 h apart or DBP ⩾110 mmHg; proteinuria ⩾0.3 g/24 h or 2+ dipstick 2× ⩾4 h apart	fDNA Real-time PCR TaqMan SRY ⩾33.5 Geq/ml

PCR, polymerase chain reaction.
[a] Studies were case–control studies.

TABLE 54 *Methodological and reporting characteristics of studies on haemoglobin/haematocrit*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Goh, 1991	IN: singleton live deliveries in nulliparas Age NR Australia	546	⩽26	7.0	DBP ⩾90 mmHg twice proteinuria ⩾1+ dipstick	Haematocrit >34% ⩾41%
Heilmann, 1993	EX: tocolysis, haemodilution, multiple pregnancies 28 ± 5.7 years Germany	707	14–30	5.4	Hypertension with proteinuria, not quantified	Haemoglobin ⩾13 g/dl

[a] All studies are cohort studies.

TABLE 55 *Methodological and reporting characteristics of studies on HCG*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Yaron, 1999	EX: structural or chromosomal anomalies Age NR USA	45,565	14–22	3.0	SBP ⩾140 mmHg or DBP ⩾90 mmHg; presence of proteinuria	β-HCG IRMA 2.5 MoM
Morssink, 1997	IN: singleton pregnancies EX: diabetes, structural or chromosomal anomalies 28 years The Netherlands	2,008	15–20	2.0	Diastolic rise >15 mmHg; proteinuria ⩾300 mg/24 h; Davey and MacGillivray, 1988	HCG Method NR 2.5 MoM
Lambert-Messerlian, 2000	IN: singleton pregnancies EX: chronic hypertension, diabetes 26.9 ± 7.3 years USA (case–control)	359	15–21	16.7	RR >140/90 mmHg; proteinuria >300 mg/24 h or ⩾2+ dipstick	Total HCG (Serono MAIO Clone) 2.3 MoM
Heinonen, 1996	EX: multiple gestation, pregnancy loss <24 weeks, foetal chromosomal abnormalities, structural malformations Age <18 years (n = 30), 18–35 years (n = 4698). >35 years (n = 562) Finland	5,290	15	4.6	NR	Total β-HCG (IMx Abbott) 2.0 MoM
Lee,[b] 2000	IN: singleton deliveries >24 weeks' gestation 28.7 ± 4.2 years Taiwan (case–control)	1,052	15–20	9.0	RR ⩾140/90 mmHg 2× 6 h apart; proteinuria ⩾1+ dipstick	β-HCG MEIA (Abbott) 2.0 MoM
Aquilina, 2000	EX: multiple pregnancy, diabetic pregnancies, hypertension <20 weeks, chromosomal or structural abnormality Age NR UK	640	15–19	5.5	DBP ⩾90 mmHg 2× 4 h apart or DBP ⩾110 mmHg; proteinuria >300 mg/24 h or ⩾2+ dipstick 2× 4 h apart	Free β-HCG Sandwich magnetic ELISA 2.3 MoM
Muller, 1996	IN: normotensive, PIH, SGA neonates Age NR France	5,776	15–18	0.6	SBP ⩾140 mmHg or DBP ⩾90 mmHg 2× 10 min rest; proteinuria >300 mg/l	HCG EIA (SFRI) 2.0 MoM
Ashour, 1997	IN: singleton pregnancies EX: foetal/chromosomal abnormalities, diabetes, chronic hypertension 28.1 ± 5.3 years USA	6,138	15–22	3.2	SBP ⩾140 mmHg or DBP ⩾90 mmHg 2× 6 h apart; proteinuria >300 mg/24 h or ⩾1+ dipstick 2× 6 h apart	β-HCG (IMx Abbott) 2.0 MoM
Luckas, 1998	IN: primigravidas EX: multiple pregnancies, essential hypertension, diabetes, foetal abnormality Age NR UK	430	15–18	4.4	Gestational/chronic hypertension; proteinuria ⩾300 mg/24 h or ⩾2+ dipstick or with HELLP; Davey and MacGillivray, 1988	RIA (Amerlex-M) 2.0 MoM

continued

TABLE 55 *Methodological and reporting characteristics of studies on HCG (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Onderoglu, 1997	IN: non-diabetic, singleton pregnancies EX: MSAFP > 2.0 MoM 30.1 ± 5.2 years Turkey	562	15–20	2.7	RR rise 30/15 mmHg over 1st trimester values or persistent RR ⩾140/90 mmHg; proteinuria ⩾500 mg/l	HCG (Kodak) 2.0 MoM
Vaillant, 1996	EX: multiple pregnancies, Down syndrome, IVF 29 ± 5 years France	434	14–20	3.7	DBP ⩾90 mmHg 2× 4 h apart or DBP ⩾110 mmHg > 22 weeks; proteinuria >300 mg/24 h or ⩾2+ dipstick	β-HCG EIA 41,000 IU
Pouta, 1998	IN: nulliparas EX: multiple pregnancies, foetal defects 27.7 ± 4.5 years Finland	637	15–19	4.7	RR ⩾140/90 mmHg 2× 6 h apart or rise 30/15 mmHg; proteinuria ⩾300 mg/24 h	β-HCG FIA (Delfia Wallac) 2.0 MoM
Jauniaux, 1996	IN: all singleton pregnancies with abnormal uterine artery Doppler; past history of PE Age NR UK	41	20–24	26.8	⩾140/90 mmHg persistent; ⩾100 mg/l	Free β-HCG IRMA (BioMerieux) 2.5 MoM
Early test						
Haddad, 1999	IN: singleton IVF pregnancies 33.6 ± 4.2 years France	180	4–7	1.7	DBP >90 mmHg 2× 4 h apart; proteinuria ⩾300 mg/24 h or ⩾2+ dipstick 4 h apart	HCG (Amerlite HCG60) 90th centile
Yaron, 2002	IN: singleton pregnancies EX: chromosome aberrations, foetal anomalies 30.4 ± 4.3 years Israel	1,622	10–13	1.7	DBP ⩾110 mmHg 1× or ⩾90 mmHg 2× 4 h apart (no history of pre-existing hypertension or renal disease); proteinuria >300 mg/24 h or >1+ dipstick	Free β-HCG FIA (Delfia Wallac) 2.0 MoM
Severe PE						
Lee,[b] 2000	IN: singleton deliveries >24 weeks' gestation; 28.7 ± 4.2 years Taiwan (case–control)	1,052	15–20	5.3	**Severe PE:** SBP ⩾160 mmHg or DBP ⩾110 mmHg 2× 6 h apart; proteinuria ⩾3+ dipstick; oliguria <400 ml/24 h	β-HCG MEIA (Abbott) 2.0 MoM
Stamilio, 2000	IN: non-smoking, mild PE in control group EX: multiple pregnancies, foetal anomalies 25.7 ± 0.3 years USA	1,998	15–19	2.5	**Severe PE:** SBP ⩾160 mmHg or DBP ⩾110 mmHg; proteinuria ⩾3+ or ⩾5.0 g/24 h; (oliguria/symptoms)	HCG Method NR 2.0 MoM

IVF, *in vitro* fertilisation; MSAFP, maternal serum AFP; PIH, pregnancy-induced hypertension; SGA, small for gestational age.
[a] Studies were cohort studies unless stated otherwise, mostly from foetal screening programmes. Most studies included singleton pregnancies only.
[b] One reference reporting on different outcomes.

TABLE 56 *Methodological and reporting characteristics of studies on oestriol*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Yaron, 1999	Unselected Age: NR USA	24,504	14–22	3.2	SBP ⩾140 mmHg or DBP ⩾90 mmHg; presence of proteinuria	RIA (Sanofi Diagnostics) 0.5 MoM
Kowalczyk, 1998	EX: patients with HCG or AFP levels ⩾2.0 MoM, ⩾35 years, multiple pregnancies; Age: median 22 years (test-positives); 23 years (test-negatives) USA	309	15–21	4.2	SBP ⩾140 mmHg or DBP ⩾90 mmHg; proteinuria ⩾0.3 g/24 h or haemolysis, elevated liver enzymes, low platelets	RIA (Diagnostic Systems Lab.) 0.75 MoM
Severe PE						
Stamilio, 2000	EX: multiple pregnancies and foetal anomalies; Age: 25.7 ± 0.3 years USA	1,998	15–19	2.5	**Severe PE:** SBP ⩾160 mmHg or DBP ⩾110 mmHg; proteinuria ⩾3+ or ⩾5.0 g/24 h (and/or oliguria/subjective symptoms)	NR; 0.9 MoM

[a] All studies were cohort studies.

TABLE 57 *Methodological and reporting characteristics of studies on serum uric acid*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Jauniaux, 1996	IN: all singleton pregnancies with abnormal uterine artery Doppler; past history of PE (n = 11) Age NR UK	41	20–24	26.8	SBP >140/90 mmHg; proteinuria ⩾100 mg/l	Enzymatic (uricase) 0.24 mmol/l
Salako, 2003	Source: normotensive primigravidae EX: history of chronic hypertension, DM, renal disease, collagen vascular disease Age 28.0 ± 3.6 years Nigeria	21	<20	23.8	SBP ⩾140/90 mmHg; proteinuria >300 mg/l (1+ dipstick)	Alkaline phosphotung state method (sodium carbonate) 0.21 mmol/l
Conde-Agudelo, 1994	Source: nulliparous women EX: DM; renal disease; essential hypertension; proteinuria <20 weeks; other chronic diseases Control group in analysis: healthy (n = 335) + GH (n = 39) 23.8 ± 5.7 years Argentina	387	20	3.4	SBP ⩾140 mmHg or DBP ⩾90 mmHg; proteinuria ⩾300 mg/l	Enzymatic (uricase) 0.23 mmol/l

continued

TABLE 57 *Methodological and reporting characteristics of studies on serum uric acid (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Winocour, 1989	Source: IDDM Median 25 years (range 18–44) UK	22	2nd trimester	40.9	MAP >106 mmHg from 3 recordings, confirmed on 3 separate occasions; proteinuria >300 mg/24 h; oedema	Multichannel analyser 0.24 mmol/l
Different type of cut-off value						
Jacobson, 1990	Source: essential hypertension; history of PE; DM; renal disease; history of IUGR/stillbirth/abruption; other high-risk subjects Control group in analysis: healthy + GH (n = 7) + IUGR (n = 8) Age NR UK	43	24	9.3	DBP ⩾90 + rise of 25 mmHg in previously normotensive women or DBP rise of 15 mmHg in chronic hypertensive women; hyperuricaemia or proteinuria ⩾500 mg/24 h	Method NR Rise ⩾0.05 mmol/l above baseline

GH, gestational hypertension; IUGR, intrauterine growth restriction; MAP, mean arterial pressure.
[a] All studies were cohort studies.

TABLE 58 *Methodological and reporting characteristics of studies on urinary calcium excretion*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off
Sanchez-Ramos, 1991	IN: normotensive nulliparas EX: diabetes mellitus, renal disease, chronic hypertension, other chronic medical illnesses 18.7 ± 0.5 years USA	99	10–24	8.1	RR ⩾140/90 mmHg twice ⩾6 h apart or rise SBP ⩾30 mmHg or DBP ⩾15 mmHg; proteinuria ⩾0.3 g/24 h or ⩾1+ dipstick	Colorimetric/ colorimetric autoanalyser ⩽195 mg/24 h
Nisell, 1996	IN: hypertensive women 33.1 ± 1.7 years Sweden	37	11–13	29.7	RR ⩾140/90 mmHg proteinuria ⩾0.3 g/24 h	NR ⩽195 mg/24 h
		37	19–21			
Baker, 1994	IN: normotensive nulliparas EX: renal disease, chronic hypertension Median 27 years (range 24–31) UK	500	18–19	2.6	DBP ⩾90 mmHg twice ⩾4 h apart; proteinuria ⩾0.3 g/24 h	Perspective analyser (colorimetric)/ Monarch centrifugal analyser (kinetic) NR
Suarez, 1996	IN: primigravidas <25 years EX: malnutrition, chronic hypertension, renal disease, DM 19.6 ± 2.8 years Peru	69	17–20	21.7	Presence of gestational hypertension; proteinuria ⩾0.3 g/24 h or 0.03 g/dl on dipstick and/or hyperuricaemia ⩾5.5 mg/dl	Colorimetric (cresolphthalein)/ spectrophotometry ⩽192 mg/24 h

[a] All studies were cohort studies.

TABLE 59 *Methodological and reporting characteristics of studies on urinary calcium/creatinine ratio*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test Cut-off (ratio)
Soltan, 1996	IN: healthy normotensive primigravidas EX: cardiovascular or renal diseases 20.3 ± 2.6 years Egypt	88	14–24	19.3	Rise of SBP ⩾30 mmHg or DBP ⩾15 mmHg; proteinuria ⩾0.3 g/24 h (oedema)	NR NR
Rogers, 1994	IN: normotensive primigravidas, singleton pregnancies EX: congenital malformations 27.1 ± 3.8 years Hong Kong	199	18–26	4.0	RR ⩾140/90 mmHg ⩾twice; proteinuria ⩾0.3 g/l	Cresolphthalein method (American Monitor)/ Beckman Astra-8 analyser 0.3
Conde, 1994	IN: normotensive nulliparas, singleton pregnancies EX: DM, renal disease, proteinuria, chronic hypertension, other chronic medical illnesses 23.8 ± 5.7 years Argentina	387	20	3.4	SBP ⩾140 or DBP ⩾90 mmHg twice ⩾6 h apart; proteinuria ⩾0.3 g/l	Colorimetric (direct)/picrato alcalino method 0.07
Kazerooni, 2003	IN: nulliparas (18–35 years) EX: renal disease, DM, proteinuria, chronic hypertension, other chronic medical illnesses 22.8 ± 4.5 years Iran	102	20–24	7.8	RR ⩾140/90 mmHg or rise SBP ⩾30 mmHg or DBP ⩾15 mmHg twice ⩾6 h apart; proteinuria ⩾0.3 g/24 h or ⩾1+ dipstick	NR ⩽0.229 (mg/dl:mg/dl)
Suarez, 1996	IN: primigravidas <25 years EX: malnutrition, chronic hypertension, renal disease, DM 19.6 ± 2.8 years Peru	69	17–20	21.7	Presence of gestational hypertension; proteinuria ⩾0.3 g/24 h or 0.03 g/dl on dipstick and/or hyperuricaemia ⩾5.5 mg/dl	Colorimetric (cresolphthalein)/ spectropho tometry ⩽0.24 mg/mg
Baker, 1994	IN: normotensive nulliparas EX: renal disease, chronic hypertension Median 27 years (range 24–31) UK	500	18–19	2.6	DBP ⩾90 mmHg twice ⩾4 h apart; proteinuria ⩾0.3 g/ 24 h	Perspective analyser (colorimetric)/ Monarch centrifugal analyser (kinetic) NR

[a] All studies were cohort studies.

TABLE 60 *Methodological and reporting characteristics of studies on proteinuria*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Proteinuria cut-off
Total proteinuria						
Sibai 2, 2000	IN: pregestational diabetes and singleton pregnancy 25.9 years (SD 6.0 years) USA (RCT)	462	9.6 ± 4.1	NA	Development of hypertension (either SBP ⩾140 mmHg or DBP ⩾90 mmHg on ⩾2 occasions ⩾4 h apart, mercury sphygmomanometer, seated 5th Korotkoff sound) plus one of proteinuria (300 mg/24 h or 2+ twice, recorded ⩾4 h apart with no evidence of UTI), thrombocytopenia <100,000 cells/mm^3) or pulmonary oedema	⩾300 mg/24 h
Combs, 1993	Case. Pregestational diabetes, no UTI, creatinine excretion rate at least 10 mg/kg/day, pregnancy beyond 20 weeks. Hypertension not excluded Cont. no chronic hypertension 30.3 years (SD 5.4 years) for 113 participants, 26.2 years (SD 5.0 years) for 198 participants USA (case–control)	311	<20	NA	Either baseline MAP (SBP + [2× DBP]/3) >105 mmHg on ⩾2 occasions or an increase in MAP of 20 mmHg above baseline (BP taken in sitting or lateral decubitus position) plus proteinuria of ⩾300 mg/day	⩾300 mg/day
Sibai 1, 1998	IN: singleton pregnancies with chronic hypertension EX: diabetes 26.8% below 25 years, 27.9% between 26 and 30 years, 45.2% above 30 years USA (RCT)	763	13–26	NA	SBP ⩾140 mmHg, DBP ⩾90 mmHg, (mercury sphygmomanometer, seated, 5th Korotkoff sound) on ⩾2 occasions ⩾4 h apart plus proteinuria of ⩾300 mg/24 h. Where baseline proteinuria, PE defined as either raised serum alanine aminotransferase (>70 U/l) or worsening hypertension (DBP ⩾110 mmHg on ⩾2 occasions ⩾4 h apart no more than 1 week before delivery if hypertensive treatment, plus one of increasing proteinuria, persistent severe headaches or epigastric pain	⩾300 mg/24 h

continued

TABLE 60 *Methodological and reporting characteristics of studies on proteinuria (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Proteinuria cut-off
Delmis, 1993	IN: pregnant women with or without chronic hypertension. Hypertensives 29.2 years (SD 5.4). Control 26.9 (SD 4.8) Croatia	692	1st trimester	27.9	SBP ⩾140 mmHg, DBP ⩾90 mmHg, or increase in SBP of 30 mmHg, DBP 15 mmHg, plus proteinuria ⩾0.5 g/l	⩾0.5 g/l
Total albuminuria						
Ekbom 2, 1999	IN: pregestational diabetes (white ethnicity), before 17 weeks gestation EX: hypertension, diabetic nephropathy, abortions 33 years (SD 5 years) for 8 PE participants 30 years (SD 5 years) for 57 normal BP participants Denmark	65	<14	12.3	SBP ⩾140 mmHg, DBP ⩾90 mmHg and proteinuria ⩾0.3 g/24 h	>30 mg/24 h
Winocour, 1989	IN: Diabetic pregnant women. 25 years (range 18–44) UK	23	2nd trimester	39.1	Mean BP >106 mmHg (supine, resting, left lateral, mercury sphygmomanometer, average of at least three recordings); proteinuria >0.3 g/24 h with oedema	0.3 g/24 h
Microalbuminuria						
Gonzalez, 2003	IN: singleton pregnancies who all had risk factors for PE EX: diabetes, renal disease, collagenopathies, UTI, multiple pregnancy 26 years Spain	102	16–18	28.4	Diagnosis of PE according to criteria of 'la Norma Institucional del IMSS'. SBP ⩾140 mmHg or rise of 30 mmHg, DBP ⩾90 mmHg or rise of 15 mmHg and proteinuria >300 mg/l	>20 mg/l
Soltan, 1996	IN: primigravid women EX: cardiovascular disease, renal disease, gestational age 14–24 years, BP >140/90 mmHg 19.8 years (SD 1.6) for 17 with PE, 20.4 (SD 2.8) for 71 non-PE Egypt	88	14–24	19.3	SBP increased by 30 mmHg, DBP by 15 mmHg, proteinuria >300 mg/24 h or generalised oedema plus one or both BP increase or proteinuria	300 mg/24 h
Microalbuminuria/creatinine ratio						
Masse, 1993	IN: nulliparous women. EX: diabetes, cardiovascular disease, chronic hypertension, renal disease, more than 20 weeks pregnant 25.5 years (SD 4.3) for 109 PE, 26.2 (SD 4.2) for 1116 non-PE Canada	1422	8–14 15–24	7.1	ACOG criteria (include oedema) (BP seated, right arm, by Dinamap oscillometric sphygmomanometer); proteinuria >300 mg/24 h	0.39 mmg/mmol

continued

TABLE 60 *Methodological and reporting characteristics of studies on proteinuria (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Proteinuria cut-off
Kallikrein						
Millar, 1996	IN: healthy, normotensive, normal renal function EX: DM, taking drugs 25.6 years (SD 6.3) UK (cross-sectional)	307	16–20	3.9	DBP >90 mmHg or increase of 25 mmHg; proteinuria >1+ on dipstick	IUK:Cr ratio of 170
SDS-PAGE proteins						
Winkler, 1988	IN: asymptomatic EX: hypertension, diabetes, renal disease, SLE, antiphospholipid syndrome Age not given Germany	153	12–34	19.0	SBP >140 mmHg, DBP >90 mmHg and proteinuria >0.3 g/24 h	Cut-off not specified

IUK, inactive urinary kallikrein; NA, not applicable.
[a] All studies were cohort designs unless otherwise stated.

TABLE 61 *Methodological and reporting characteristics of studies on Doppler any/unilateral notching*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Geipel, 2002	IN: dichorionic twins EX: foetal malformation, PPROM, unclear chorionicity 31.5 ± 4.2 years Germany	256	18–24	8.6	RR ⩾140/90 mmHg repeated; proteinuria ⩾0.3 g/24 h	Any notch (twin) CD
Geipel, 2001	IN: ICSI patients and controls (low risk), twin pregnancies 32.5 years Germany	50	18–24	4.0	RR ⩾140/90 mmHg repeated; proteinuria ⩾0.5 g/24 h	CD
	IN: ICSI patients and controls (high risk), twin pregnancies: CH, DM, adiposity (BMI > 27), nulliparae ⩾35 years; multiparae with history of IUGR, PE, placental abruption, IUD	14	18–24	7.1		
Venkat-raman, 2001	IN: recurrent miscarriage and positive APL antibodies (no SLE or thromboembolic disease) 33 (21–43) years[b] UK	164	16–18 22–24	9.8	RR ⩾140/90 mmHg twice >4 h apart or DBP ⩾110 mmHg once; proteinuria ⩾0.3 g/24 h	Any notch CD

continued

TABLE 61 *Methodological and reporting characteristics of studies on Doppler any/unilateral notching (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Antsaklis, 2000	IN: all nulliparae EX: multiple pregnancies, cardiovascular or renal disease, DM, foetal abnormalities Age NR Greece	675	19–21 24	3.1	RR ⩾140/90 mmHg twice 6 h apart; proteinuria ⩾0.3 g/24 h	Any notch Unilateral notch CD + PW
Aardema, 2000	IN: singleton pregnancies, history of hypertensive disorders in previous pregnancy, no current pathology 31 (21–42) years[b] The Netherlands	94	21–22	7.5	DBP ⩾90 mmHg twice; proteinuria ++ dipstick	Any notch CD + PW
Ohkuchi, 2000	IN: unselected women with singleton pregnancies (healthy) 28.7 ± 4.0 years Japan	288	16–23.9	3.1	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick	Any notch CD + PW
Frusca, 1998	IN: chronic hypertension EX: multiple pregnancies, foetal anomalies Age NR Italy	78	24–25	3.9	Superimposed PE: aggravated hypertension (rise DBP >15 mmHg) and proteinuria >0.3 g/24 h	Any notch CD + PW
Harrington, 1997	IN: singleton pregnancies, unselected 15–49 years UK	626	12–16	4.8	SBP ⩾140 or DBP ⩾90 mmHg; proteinuria >0.3 g/24 h	Any notch CD + PW
Harrington, 1996	EX: multiple pregnancies, foetal abnormalities, PE and/or IUGR at 24 weeks Age NR UK	1204	18–21	3.7	Rise of RR ⩾30/25 mmHg twice 4 h apart or DBP ⩾110 mmHg; proteinuria >0.5 g/24 h	Unilateral notch CD + PW
Konchak, 1995	IN: MSAFP >2.0 MoM twice or >2.5 MoM once, singleton pregnancies, no foetal anomaly, normal amniotic fluid volume 27.1 ± 5.1 years USA	103	17–22	5.8	Not specified	Unilateral notch CD + PW
Bower, 1993	Unselected Age NR UK	2058 2026	18–22 24	2.2 2.2	Mild PE: rise RR <30/25 mmHg; proteinuria + Moderate PE: rise RR <30/25 mmHg; proteinuria ++ Severe PE: DBP ⩾110 mmHg and rise ⩾30/25 mmHg; proteinuria ⩾ ++ or ⩾0.5 g/24 h	Unilateral notch CW + CD

continued

TABLE 61 *Methodological and reporting characteristics of studies on Doppler any/unilateral notching (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Phupong, 2003	IN: healthy nulli- and multiparae EX: multiple pregnancies, renal and cardiovascular disease, DM, foetal anomalies 26.4 ± 4.8 years Thailand	322	22–28	5.9	RR >140/90 mmHg twice 6 h apart; proteinuria ⩾0.3 g/24 h or + dipstick (Severe PE: DBP ⩾110 mmHg, proteinuria 5.0 g/24 h or +++ dipstick)	Any notch CD + PW
Marchesoni, 2003	Unselected women 31.7 ± 5.3 years Italy	900	20, 24	2.9	RR >140/90 mmHg; proteinuria >0.3 g/24 h	Any notch CD
Frusca, 1996	IN: previous history of PE, normal blood pressure after that pregnancy Age NR Italy	56	24	5.4	DBP ⩾90 mmHg twice 4 h apart in 3rd trimester; proteinuria >0.3 g/24 h; no UTI	Any notch CD + PW
Coleman, 1993	IN: essential and secondary hypertension, renal disease, SLE, APL syndrome, previous PE or placental abruption EX: multiple pregnancies, foetal abnormalities 31 (19-43) years[b] New Zealand	116	22–24	27.6	RR ⩾140/90 mmHg with rise of DBP 15 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick, Superimposed PE: RR >140 mmHg with rise of ⩾30/15 mmHg with new proteinuria or doubling of existing proteinuria	Any notch CD
Prefumo, 2004	IN: all singleton live births from clinical database EX: foetal abnormalities 29.4 ± 5.9 years UK	4149	18–23	0.4	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h or + dipstick twice	Any notch CD + PW
Carbillon, 2004	Routine ultrasound screening 29.6 ± 6.2 years France	243	12–14	4.9	RR ⩾140/90 mmHg twice 4 h apart; proteinuria ⩾0.3 g/24 h or + dipstick	Any notch NR
Axt-Fliedner, 2005	IN: singleton pregnancies with history of PET, IUGR, IUD, placental abruption 32.8 (23–46) years[b] Germany	52	19–26	7.7	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h; no UTI	Any notch CD
Audibert, 2005	IN: AFP + HCG testing at 14–18 weeks and ultrasound screening 10–14 weeks EX: women with raised NT, delivery <24 weeks 30.9 ± 4.5 years France	2615	18–26	2.0	SBP ⩾140 or DBP ⩾90 mmHg twice; proteinuria >0.3 g/24 h or ++ dipstick	Unilateral notch NR

continued

TABLE 61 *Methodological and reporting characteristics of studies on Doppler any/unilateral notching (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Schwarze, 2005	EX: essential hypertension, DM, autoimmune disorders, history of PE, IUGR, IUD, placental abruption; multiple pregnancies, foetal anomalies 31.4 (17–46) years Germany	215	19–22	4.7	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h; no UTI	Any notch CD
		131	23–26	4.6		

APL, antiphospholipid syndrome; CD, colour Doppler; CW, continuous wave; ICSI, intracytoplasmic sperm injection; IUD, intra-uterine device; NT, nuchal translucency; PPROM, premature prelabour rupture of membranes; PW, pulsed wave.
[a] All studies were cohort designs.
[b] Median age.

TABLE 62 *Methodological and reporting characteristics of studies on Doppler bilateral notching*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test
Zimmerman, 1997	IN: family or personal history of PE, CH, IUGR or IUD 28.1 ± 3.8 years Finland	55	22–24	10.9	RR ⩾145/85 mmHg and dipstick testing not specified on ⩾2 occasions 24 h apart	CD + PW Aloka SSD 650
Geipel, 2002	IN: dichorionic twins EX: foetal malformation, PPROM, unclear chorionicity 31.5 ± 4.2 years Germany	256	18–24	8.6	RR ⩾140/90 mmHg repeated; proteinuria ⩾0.3 g/24 h	ATL HDI 5000, Acuson 128 XP 10
Yu, 2002	IN: twin pregnancies, 2 live foetuses, no foetal abnormality, no TTS 31.7 (18–46) years[b] UK	351	22–24	6.0	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ⩾2+ dipstick twice if no 24-h collection available	CD + PW transvaginal
Papageorghiou, 2001	IN: singleton pregnancies, routine antenatal care EX: foetal abnormalities 29.7 (16–47) years UK	7851	22–24	1.4	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ⩾2+ dipstick twice if no 24-h collection available	CD + PW, transvaginal Acuson SP-10, Aloka 5000, Aloka 17000, ATL HDI 3000, ATL HDI 3500, Hitachi, Toshiba, Siemens

continued

TABLE 62 *Methodological and reporting characteristics of studies on Doppler bilateral notching (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test
Venkat-Raman, 2001	IN: recurrent miscarriage and positive APL antibodies (no SLE or thromboembolic disease) 33 (21–43) years[b] UK	164	16–18 22–24	9.8	RR ⩾140/90 mmHg twice >4 h apart or single DBP ⩾110 mmHg; proteinuria ⩾0.3 g/24 h	CD Acuson 128 XP 10
Antsaklis, 2000	IN: nulliparae EX: multiple pregnancies, renal and cardiovascular disease, DM, foetal abnormalities Age NR Greece	675	19–21 24	3.1	RR ⩾140/90 mmHg twice 6 h apart; proteinuria ⩾0.3 g/24 h	CD + PW Ultramark 9 HDI
Ohkuchi, 2000	IN: singleton pregnancies (healthy) 28.7 ± 4.0 years Japan	288	16–23.9	3.1	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick	CD + PW EUB 165A
Albaiges, 2000	IN: singleton pregnancies, routine antenatal care 30 (18–44) years[b] UK	1757	22–25	3.7	RR ⩾140/90 mmHg twice >2 h apart; proteinuria ⩾0.3 g/24 h or dipstick 0.3 g/l	CD + PW Acuson Aspen or Aloka SSD 1700
Mires, 1998	All women with singleton pregnancies eligible 15–49 years Scotland	6579	18–20 18–20 and 22–24	5.5	ICD 9 classification	CD Acuson XP 10
Kurdi, 1998	EX: multiple pregnancies, foetal anomalies, women already on low-dose aspirin Age NR UK	946	19–21	2.2	Baseline DBP <90 mmHg and rise of 25 mmHg, baseline DBP ⩾90 mmHg and rise of 15 mmHg; proteinuria ⩾1+; no UTI	CD Acuson 128
Frusca, 1998	IN: chronic hypertension EX: multiple pregnancies, foetal anomalies Age NR Italy	78	24–25	3.9	Superimposed PE: aggravated hypertension (rise DBP >15 mmHg) and proteinuria >0.3 g/24 h	CD + PW Toshiba SSH 140A
Harrington, 1997	IN: singleton pregnancies, unselected 15–49 years UK	626	12–16	4.8	SBP ⩾140 or DBP ⩾90 mmHg; proteinuria >0.3 g/24 h	CD + PW, transvaginal Acuson 128
Harrington, 1996	EX: multiple pregnancies, foetal abnormalities, PE or IUGR <24 weeks Age NR UK	1204	18–21	3.7	Rise RR ⩾30/25 mmHg twice 4 h apart or DBP ⩾110 mmHg; proteinuria 0.5 g/24 h	CD + PW Acuson 128
Marchesoni, 2003	Unselected women 31.7 ± 5.3 years UK	900	(20) 24	2.9	RR >140/90 mmHg; proteinuria >0.3 g/24 h	CD Acuson Sequoia

continued

TABLE 62 *Methodological and reporting characteristics of studies on Doppler bilateral notching (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Index test
Uludag, 2002	IN: non-smokers EX: DM, foetal anomalies, multiple pregnancies 30.8 ± 6.1 years Turkey	80	18–20	12.5	RR >140/90 mmHg >24 weeks ± proteinuria >0.3 g/24 h	CD + PW HDL 3000
Coleman, 1993	IN: essential and secondary hypertension, renal disease, SLE, APLS, previous PE or placental abruption EX: multiple pregnancies, foetal abnormalities 31 (19–43) years[b] New Zealand	116	22–24	27.6	RR ⩾140/90 mmHg and rise of DBP 15 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick. Superimposed PE: RR >140 mmHg and rise of RR ⩾30/15 mmHg with new proteinuria or doubling of existing proteinuria	CD Toshiba 270 or Diasonics
Prefumo, 2004	IN: all singleton live births from clinical database EX: foetal abnormalities 29.4 ± 5.9 years UK	4149	18–23	0.4	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h or + dipstick twice if no 24 h collection available Outcome: PE with delivery <32 weeks	CD + PW
Carbillon, 2004	Routine USS 29.6 ± 6.2 years France	243	(12–14) 22–24	4.9	RR ⩾140/90 mmHg twice 4 h apart; proteinuria ⩾0.3 g/24 h or + dipstick	Toshiba Powervision 6000
Axt-Fliedner, 2005	IN: singleton pregnancies with history of PE, IUGR, IUD, abruption 32.8 (23–46) years[b] Germany	52	19–26	7.7	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h; no UTI	CD Elegra, Acuson 128 XP10
Audibert, 2005	IN: AFP and HCG testing at 14–18 weeks and USS EX: women without USS 10–14 weeks for dating, women with raised NT, delivery <24 weeks 30.9 ± 4.5 years France	2615	18–26	2.0	SBP ⩾140 or DBP ⩾90 mmHg twice; proteinuria >0.3 g/24 h or ++ dipstick	NR
Schwarze, 2005	EX: essential hypertension, DM, autoimmune disorders, history of PE, IUGR, IUD, placental abruption; multiple pregnancies, foetal abnormalities 31.4 (17–46) years Germany	215 131	19–22 23–26	4.9	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h; no UTI	CD Elegra (Siemens), Acuson 128 XP10

NT, Nuchal translucency; TTS, twin transfusion syndrome; USS, ultrasound screening.
[a] All studies were cohort designs.
[b] Median age.

TABLE 63 *Methodological and reporting characteristics of studies on Doppler combinations of flow velocity waveforms*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Resistance index and/or notching						
Aquilina, 2001	IN: unselected women with inhibin A measurement EX: multiple pregnancies, DM, CH, chromosome/ structural anomalies Age NR UK	640	18–22	5.5	DBP ⩾90 mmHg twice >4 h apart or DBP ⩾110 mmHg once; proteinuria ⩾0.3 g/24 h or ++ dipstick twice; no UTI	Mean RI ⩾0.55 and bilateral notching; or mean RI ⩾0.65 and unilateral notching CD + PW
Bower, 1993	Unselected EX: multiple pregnancies, foetal anomalies Age NR UK	2058	18–22	0.34	Mild PE: rise RR <30/25 mmHg; proteinuria + dipstick. Moderate PE: rise RR <30/25 mmHg; proteinuria ++ dipstick. Severe PE: DBP ⩾110 mmHg and rise RR ⩾30/25 mmHg; proteinuria ++ dipstick or ⩾0.5 g/24 h	RI >95th centile and/or any notching CW + CD
Campbell, 2000	Age NR UK	264	19–21 24–26	4.9	RR ⩾140/90 ⩾ twice 4 h apart; proteinuria ⩾0.3 g/24 h or + dipstick	RI >0.6 and/or any notching CW + CD
Chan, 1995	IN: high risk due to age >35 years, poor obstetric history, medical complications of pregnancy, low pre-pregnancy weight, single mother, smoker >10/day Age NR Hong Kong	334	20	6.9	RR ⩾140/90 mmHg twice 6 h apart; proteinuria >0.3 g/24 h or ++ dipstick	RI >90th centile and bilateral notching CW
Coleman, 1993	IN: essential and secondary hypertension, renal disease, SLE, APLS, previous PE or placental abruption EX: multiple pregnancies, foetal abnormalities 31 (19–43) years[b] New Zealand	116	22–24	27.6	RR ⩾140/90 mmHg and rise DBP >15 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick. Superimposed PE: RR >140 mmHg and rise of RR ⩾30/15 mmHg with new proteinuria or doubling of existing proteinuria	Any RI >0.58 and any notching Any RI ⩾0.7 and any notching Both RI ⩾0.7 and any notching
Driul, 2002	Age NR Italy	840	24	1.2	Not specified	RI >0.6 and/or monolateral notching CD

continued

TABLE 63 *Methodological and reporting characteristics of studies on Doppler combinations of flow velocity waveforms (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Driul, 2005	IN: negative for lupus anticoagulant and anticardiolipin antibodies, all used folic acid, no family or personal history of thrombo embolic disease 31.5 ± 4.6 years Italy	103	20	37.9	ACOG guidelines	RI >0.58 and bilateral notching CD + PW
Frusca, 1996	IN: history of PE Age NR Italy	56	24	5.4	DBP ⩾90 mmHg twice 4 h apart in 3rd trimester; proteinuria >0.3 g/24 h; no UTI	Mean RI >0.58 and bilateral notching CD + PW
Frusca, 1997	IN: nulliparae without risk factors EX: CH, DM, auto immune disorders Age NR Italy	36	24	11.1	RR >140/90 mmHg twice >4 h apart; proteinuria >0.3 g/24 h	RI >0.58 and notching CW + CD
Geipel, 2001	IN: intracytoplasmic sperm injection (ICSI) patients and controls (low risk), singleton pregnancies 32.5 years Germany	170	18–24	3.5	RR ⩾140/90 mmHg repeated; proteinuria ⩾0.5 g/24 h	Bilateral notching and mean RI >0.55; unilateral notching and mean RI >0.65; no notch and RI >0.7 CD
	IN: ICSI patients and controls (high risk), singleton pregnancies: CH, DM, adiposity (BMI >27), nulliparae ⩾35 years; multiparae with history of IUGR, PE, placental abruption, IUD	58	18–24	19.0		
Geipel, 2002	IN: dichorionic twins EX: foetal malformation, PPROM, unclear chorionicity 31.5 ± 4.2 years Germany	256	18–24	8.6	RR ⩾140/90 mmHg repeated; proteinuria ⩾0.3 g/24 h	RI >95th centile (twin reference) and notching ATL HDI 5000, Acuson 128 XP10
Harrington, 1991	Unselected Age NR UK	2437	20	2.0	Initial DBP <90 mmHg + rise ⩾25 mmHg twice 4 h apart; proteinuria >0.5 g/24 h	RI >95th centile and/or notching CW + CD
Harrington, 1996	EX: multiple pregnancies, foetal anomalies, PE or IUGR <24 weeks Age NR UK	1204	18–21	3.7	Rise RR ⩾30/25 mmHg twice 4 h apart or DBP ⩾110 mmHg; proteinuria 0.5 g/24 h	RI >95th centile or notching CD + PW

continued

TABLE 63 *Methodological and reporting characteristics of studies on Doppler combinations of flow velocity waveforms (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Harrington, 2004	IN: CH, previous PE, GH, IUGR, preterm labour, placental abruption, IUD, DM, renal or other medical disease EX: foetal anomalies Age NR UK	170	19–21	11.8	DBP ⩾90 mmHg twice 4 h apart, or DBP ⩾110 mmHg once; proteinuria >0.3 g/24 h or ++ dipstick twice 4 h apart; no UTI	RI ⩾0.55 (50th centile) and bilateral notching; or mean RI ⩾0.65 (80th centile) and unilateral notching CD
	IN: unselected multiparae with singleton pregnancies	458	19–21	0.44		
Kurdi, 1998	IN: unselected women EX: multiple pregnancies, foetal anomalies, women already on low-dose aspirin Age NR UK	946	19–21	2.2	Baseline DBP <90 mmHg and rise of 25 mmHg, baseline DBP ⩾90 mmHg and rise of 15 mmHg; proteinuria + dipstick, no UTI	Mean RI >0.55 (50th centile) and bilateral notching; or mean RI >0.65 (90th centile) and unilateral notching; or mean RI >0.7 (95th centile) CD
North, 1994	IN: healthy nulliparae EX: renal disease, DM Age NR Australia	446	19–24	3.4	RR ⩾140/90 mmHg and rise DBP ⩾15 mmHg >4 h apart; proteinuria >0.3 g/24 h or ++ dipstick	RI or A/C >90th centile CD + PW
Subtil, 2003	No contraindication to aspirin 24.2 ± 4.4 years	1170	22–24	2.1	PIH, proteinuria ++ dipstick or ⩾0.5 g/l	RI >0.61 or any notching CD
Valensise, 1994	IN: chronic hypertension Age NR Italy	16	22, 24	43.8	Davey and MacGillivray[201]	RI >0.58 and/or notching CD
Pulsatility index and/or notching						
Albaiges, 2000	IN: singleton pregnancies, routine antenatal care 30 (18–44) years[b] UK	1757	22–25	3.7	RR ⩾140/90 mmHg twice >2 h apart; proteinuria ⩾0.3 g/24 h or dipstick 0.3 g/l	Mean PI >1.45 **and** bilateral notching CD + PW Mean PI >1.45 **or** bilateral notching

continued

TABLE 63 *Methodological and reporting characteristics of studies on Doppler combinations of flow velocity waveforms (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Papageorghiou, 2001	IN: singleton pregnancies attending for routine antenatal care EX: no foetal abnormality 29.7 (16–47) years[b] UK	7851	22–24	1.4	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick twice if no 24-h collection available	PI >1.63 or bilateral notching CD + PW
Yu, 2002	IN: twin pregnancies, 2 live foetuses, no foetal abnormality, no TTTS 31.7 (18–46) years[b] UK	351	22–24	6.0	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick twice if no 24-h collection available	PI >95th centile and notching CD + PW
S/D or D/S ratio and/or notching						
Benifla, 1992	IN; SLE, APLS 30.4 ± 4.2 years France	28	20, 30	14.3	NR	D/S <2 SD both arteries or notching persistent after 24 weeks PW
Haddad, 1995	IN: aspirin treatment because of poor previous outcome, PE, eclampsia, HELLP, placental abruption, IUGR, IUD 31.3 ± 4.5 years France	48	23.8 ± 2.6	10.4	SBP ⩾140 and/or DBP ⩾90 mmHg; proteinuria ⩾0.5 g/24 h	D/S <10th centile and/or unilateral notching CW
Morris, 1996	IN: all nulliparae 23.9 ± 7.3 years Australia	768	18	4.7	RR >140/90 mmHg and rise of DBP ⩾15 mmHg >twice 6 h apart; proteinuria + dipstick twice 6h apart or hyperuricaemia	S/D >3.3 (2 SD); or S/D >3.0 (90th centile) and unilateral notching CD + PW
Soutif, 1996	EX: nephropathy, CH, DM, systemic disorders, multiple pregnancies Age NR France	315	21, 24	1.3	SBP ⩾150 and/or DBP ⩾90 mmHg twice, proteinuria ⩾1.0 g/24 h	S/D >2.6 on either side and/or unilateral notching PW

A/B or S/D, peak systolic flow divided by late diastolic flow; A/C, peak systolic flow divided by early diastolic flow; APLS, antiphospholipid syndrome; D/S, late diastolic flow divided by peak systolic flow; PI, pulsatility index (peak systolic flow minus end diastolic flow) divided by mean flow [(A − B)/M]; RI, resistance index (peak systolic flow minus end diastolic flow) divided by peak systolic flow [(A − B)/A].

[a] Studies were cohort designs unless stated otherwise.

[b] Median age.

TABLE 64 *Methodological and reporting characteristics of studies on Doppler pulsatility index*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off (PI)	Index test
Yu, 2002	IN: twin pregnancies, 2 live foetuses, no foetal abnormality, no TTS 31.7 (18–46) years[b] UK	351	22–24	6.0	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick twice	>95th centile	CD + PW
Martin, 2001	IN: routine antenatal care 31.3 (16–47) years[b] UK	3045	11–14	2.1	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick twice	>2.35 95th centile	CD + PW
Papageorghiou, 2001	IN: singleton pregnancies, routine antenatal care EX: foetal abnormality 29.7 (16–47) years[b] UK	7851	22–24	1.4	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick	>1.63	CD + PW Several ultrasound machines
Aardema, 2000	IN: healthy nulliparae, singleton pregnancies Age NR The Netherlands	531	21–22	0.9	DBP ⩾90 mmHg twice; proteinuria ++ dipstick	>1.3	CD + PW Acuson 128 XP 10
Aardema, 2000	IN: multiparae with history of hypertensive disorders in previous pregnancy, no current pathology, singleton pregnancies	94	21–22	7.5	DBP ⩾90 mmHg twice; proteinuria ++ dipstick	>1.3	CD + PW Acuson 128 XP 10
Albaiges, 2000	IN: singleton pregnancies, routine antenatal care 30 (18–44) years[b] UK	1757	22–25	3.7	RR ⩾140/90 mmHg twice >2 h apart; proteinuria ⩾0.3 g/24 h or dipstick testing 0.3 g/l	>1.45 (mean)	CD + PW Acuson Aspen, Aloka SSD 1700
Zeeman, 2003	IN: chronic hypertension requiring medication 32.0 ± 6.2 years USA	52	16–20	21.2	RR exceeding early pregnancy values; proteinuria ⩾0.3 g/24 h or + dipstick (30 mg/dl)	>95th centile	CD + PW Acuson XP10
Yu, 2004	IN: healthy singleton pregnancies EX: CH, cardiovascular and renal disease, DM, bleeding disorders, SLE, foetal anomalies 30 (15–47) years[b] UK	683	22–24	8.8	DBP ⩾90 mm/Hg twice 4 h apart or DBP ⩾120 mmHg once; proteinuria ⩾0.3 g 24 h or ++ dipstick	>1.6 >95th centile	NR
Sato,1995	31.7 (18–46) years[b] Japan	333	16–23	4.8	Gestose index 2	⩾1.2	CD + PW Aloka SSD 870

[a] All studies were cohort designs.
[b] Median age.

TABLE 65 *Methodological and reporting characteristics of studies on Doppler resistance index*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off (RI)	Index test
Geipel, 2002	IN: dichorionic twins EX: foetal malformation, PPROM, unclear chorionicity 31.5 ± 4.2 years Germany	256	18–24	8.6	RR ⩾140/90 mmHg repeated; proteinuria ⩾0.3 g/24 h	>95th centile (singleton reference) >95th centile (twin reference)	Colour NR ATL HDI 5000, Acuson 128 XP 10
Tranquilli, 2000	EX: CH, foetal anomalies, IUGR, primigravidae 23–38 years Italy	75	24	18.7	Hypertension and proteinuria, not quantified	>0.58	CD Ansaldo Hitachi AU 590
Soregaroli, 2001	IN: history of GH, PE, SGA, IUD; CH, autoimmune disorders, renal diseases EX: multiple pregnancies, foetal or chromosomal anomalies, pregnancy complications <24 weeks Age NR Italy	271	24	3.3	RR >140/90 mmHg twice >4 h apart; proteinuria >0.3 g/24 h	>0.6	CD Toshiba SSH 140 A
Ohkuchi, 2000	IN: healthy singleton pregnancies 28.7 ± 4.0 years Japan	288	16–23.9	3.1	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick	>91st centile	CD + PW EUB 165A
Aquilina, 2000	IN: unselected primiparae, routine antenatal care Age NR UK	550	18–22	7.3	DBP ⩾90 mmHg twice >4 h apart or DBP ⩾110 mmHg once; proteinuria ⩾0.3 g/24 h or ++ dipstick twice; no UTI	NR	CD + PW Philips SD-800/ HP Sonos 550
Caforio, 1999	EX: congenital defects, chromosomal abnormalities, multiple pregnancies, infections, Rh isoimmunisation, non-immune hydrops, PPROM, IUD, delivery <26 weeks 31 ± 4.8 years Italy	530	18–20	0.6	Davey and MacGillivray[201]	>90th centile	CD + PW Esaoute AU570A
			22–24			>90th centile	
Caforio, 1999	IN: CH, DM, autoimmune disease, SLE, renal disease; history of stillbirths, IUGR, PE, habitual abortion Italy	335	18–20	12.5	Davey and MacGillivray[201]	>90th centile	
			22–24			>90th centile	

continued

TABLE 65 *Methodological and reporting characteristics of studies on Doppler resistance index (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off (RI)	Index test
Frusca, 1998	IN: CH EX: multiple pregnancies, foetal anomalies Age NR Italy	78	24–25	3.9	Superimposed PE: aggravated hypertension (rise DBP >15 mmHg); proteinuria >0.3 g/24 h	>2 SD	CD + PW Toshiba SSH 140A
Frusca, 1997	IN: nulliparae without risk factors EX: CH, DM, autoimmune disorders Age NR Italy	419	24	1.9	RR >140/90 mmHg twice >4 h apart; proteinuria >0.3 g/24 h	>0.58	CW + CD Doptek
Caruso, 1996	IN: CH, singleton pregnancies EXC: autoimmune diseases, foetal anomalies, Rh isoimmunisation 32 (23–44) years[b] Italy	42	23–24	21.4	SBP ⩾140 or DBP ⩾90 mmHg and exacerbation of hypertension; >0.3 g/l or + dipstick in 2 random samples or ⩾0.3 g/l in 24 h urine collection; no UTI	>90th centile	CD Ansaldo Esacord 81
Konchak, 1995	IN: increased MSAFP >2MoM twice or >2.5MoM once, singleton pregnancies, normal amniotic fluid volume EX: foetal anomalies 27.1 ± 5.1 years USA	103	17–22	5.8	Not specified	>95th centile	CD + PW Acuson XP10
Chan, 1995	IN: high risk due to age >35 years, poor obstetric history, medical complications of pregnancy, low prepregnancy weight, single mother, smoker >10 per day Age NR Hong Kong	334	20	6.9	RR ⩾140/90 mmHg twice 6 h apart; proteinuria >0.3 g/24 h or ++ dipstick	>95th centile	CW Doptek
Ferrier, 1994	IN: renal disease other than diabetic nephropathy 28 ± 6 years Australia	51	19–24	7.8	RR ⩾140/90 mmHg and rise DBP ⩾15 mmHg >4 h apart; proteinuria >0.3 g/24 h or doubling of 24-h urinary protein excretion if already present <20 weeks	>90th centile	CD Acuson

continued

TABLE 65 *Methodological and reporting characteristics of studies on Doppler resistance index (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off (RI)	Index test
North, 1994	IN: healthy nulliparae EX: renal disease, DM Age NR Australia	446	19–24	3.4	RR ⩾140/90 mmHg and rise DBP ⩾15 mmHg >4 h apart; proteinuria >0.3 g/24 h or ++ dipstick	>90th centile >0.57	CD + PW Acuson 128 XP10
Rizzo, 1993	IN: dichorionic twin pregnancies Age NR Italy	64	20–24	34.3	DBP ⩾90 mmHg twice >4 h apart or DBP ⩾110 mmHg once; proteinuria ⩾0.3 g/24 h	Mean RI (twins)	CD + PW Ansaldo AU 560
Caruso, 1993	IN: APLS 19–42 years Italy	28	18–24	17.9	Davey and MacGillivray, 1988	>90th centile	CD + PW NR
Pattinson, 1991	IN: women at high risk for complications 28.5 ± 4.7 years South Africa	53	16–28	13.2	Davey and MacGillivray, 1988	>0.58	CW Doptek 9000
Parretti, 2003	IN: normotensive, white women with risk factors (previous PE, stillbirth, placental abruption, IUGR) EX: smokers, cardiovascular and renal disease, DM, multiple pregnancies, foetal chromosomal abnormalities, women on low-dose aspirin 34.5 (27–41) years[b] Italy	144	24	25.0	RR >140/90 mmHg twice within 24 h period; proteinuria >0.3 g/24 h; no UTI	⩾0.58 (mean)	AU5 Epi
Valensise, 1993	IN: primiparae, no current or previous relevant medical history (n = 104). History of PIH, IUGR, IUD (n = 88) EX: IUGR, oligohydramnion 30.0 ± 4.7 years Italy	192	24	4.7	Gestational hypertension (Davey and MacGillivray;[201] proteinuria >0.3 g/24 h	>0.58	CD Ansaldo Hitachi AU 590
Valensise, 1993	EX: history of hypertension, DM, SLE, pharmacological induction of ovulation, foetal or chromosomal abnormalities 26.4 ± 2.7 years Italy	272	24	3.3	Davey and MacGillivray;[201] proteinuria >0.3 g/l/24 h	>0.58	CD Ansaldo Hitachi AU 590

continued

TABLE 65 *Methodological and reporting characteristics of studies on Doppler resistance index (cont'd)*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off (RI)	Index test
Arenas, 2003	Unselected women EX: multiple pregnancies, congenital defects 30.5 (16–43) years[b] Spain	319	20	3.5	RR ⩾140/90 mmHg; proteinuria >0.3 g/24 h	⩾0.59	CD + PW Aloka SSD 2000
Frusca, 1996	IN: history of PE Age NR Italy	56	24	5.4	DBP ⩾90 mmHg twice 4 h apart in 3rd trimester; proteinuria >0.3 g/24 h; no UTI	>0.58	CD + PW Toshiba SSH 140a
Coleman, 1993	IN: essential and secondary hypertension, renal disease, SLE, APLS, previous PE or placental abruption EX: multiple pregnancies, foetal abnormalities 31 (19–43) years[b] New Zealand	116	22–24	27.6	RR ⩾140/90 mmHg and rise DBP >15 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick. Superimposed PE: RR >140 mmHg and rise of RR ⩾30/15 mmHg with new proteinuria or doubling of existing proteinuria	Any >0.58 Both >0.58 Any ⩾0.7 Both ⩾0.7	CD Toshiba 270 or Diasonics
Axt-Fliedner, 2005	IN: singleton pregnancies with history of PE, IUGR, IUD, placental abruption 32.8 (23–46) years Germany	52	19–26	7.7	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h, no UTI	Any >0.58 Both >0.58 Any >0.7 Both >0.7	CD Elegra or Acuson 128 XP1
Schwarze, 2005	EX: essential hypertension, DM, autoimmune disorders, history of PE, IUGR, IUD, placental abruption, multiple pregnancies, foetal abnormalities 31.4 (17–46) years Germany	346	19–26	4.9	RR >140/90 mmHg; proteinuria ⩾0.3 g/24 h; no UTI	Any >0.58 Both >0.58 Any >0.7 Both >0.7	CD Elegra (Siemens) or Acuson 128 XP 10
Sato, 1995	31.7 (18–46) years[b] Japan	341	16–23	4.7	Gestose Index (GI) 2	>0.60	CD + PW Aloka SSD 870

[a] All studies were cohort designs.
[b] Median age.

TABLE 66 *Methodological and reporting characteristics of studies on Doppler SD ratio*

Study	Population Age Country (study design[a])	No. of women analysed	Gestational age at test (weeks)	Incidence of PE (%)	Reference standard	Cut-off Index test
Schulman, 1987	IN: normal pregnancies Age NR USA	71	>20	26.8	Not specified	S/D >2.6 CW
Saccini, 1995)	EX: CH, other maternal medical diseases (e.g. DM, cardiac or renal disease, SLE) 31.6 ± 5.0 years Italy	38	18	65.8	DBP ⩾90 mmHg twice 4 h apart or DBP ⩾110 mmHg, proteinuria >0.3 g/24 h or 1 g/l in random urine collection	S/D >2.6 Duplex Doppler
Aquilina, 2000	IN: unselected primiparae, routine antenatal care Age NR UK	550	18–22	7.3	DBP ⩾90 mmHg twice >4 h apart or DBP ⩾110 mmHg once; proteinuria ⩾0.3 g/24 h or ++ dipstick twice; no UTI	A/B; A/C CD + PW
North, 1994	IN: healthy nulliparae EX: renal disease, DM Age NR Australia	446	19–24	3.4	RR ⩾140/90 and rise DBP ⩾15 mmHg >4 h apart; proteinuria >0.3 g/24 h or ++ dipstick	A/C >90th centile CD + PW
Ohkuchi, 2000	IN: healthy women, singleton pregnancies 28.7 ± 4.0 years Japan	288	16–23.9	3.1	DBP ⩾90 mmHg twice >4 h apart; proteinuria ⩾0.3 g/24 h or ++ dipstick	A/C >91st centile CD + PW
Ferrier, 1994	IN: renal disease other than diabetic nephropathy 28 ± 6 years Australia	51	19–24	7.8	RR ⩾140/90 and rise DBP ⩾15 mmHg >4 h apart; proteinuria >0.3 g/24 h or doubling of 24-h urinary protein excretion if already present <20 weeks	A/C >90th centile CD
Aardema, 2000	IN: multiparae with history of hypertensive disorders in previous pregnancy, but no current pathology, singleton pregnancies The Netherlands	94	21–22	7.5	DBP ⩾90 mmHg twice; proteinuria ++ dipstick	NI >0.03 CD + PW
Aardema, 2000	IN: healthy nulliparae, singleton pregnancies Age NR The Netherlands	531	21–22	0.94	DBP ⩾90 mmHg twice; proteinuria ++ dipstick	NI >0.03 CD + PW

A/B or S/D, peak systolic flow divided by end diastolic flow; A/C, peak systolic flow divided by early diastolic flow; NI, notch index (peak of notch minus nadir of notch) divided by mean flow [(D − C)/M].
[a] Studies were cohort designs unless stated otherwise.

Appendix 8

Diagnostic test quality charts

TABLE 67 *Body mass index quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Sibai, 1997	RCT	?	–	+	–	+	+	–
Baeten, 2001	+	?	–	–	–	–	+	?
Bianco, 1998	+	?	–	+	+	–	+	?
Bowers, 1999	+	?	–	?	–	–	+	?
Knuist, 1998	+	+	–	+	+	+	+	–
Lee, 2000	+	+	–	–	+	–	+	–
Ogunyemi, 1998	+	+	–	+	–	+	+	?
Ros, 1998	+	+	–	+	–	–	+	–
Sebire, 2001	+	?	–	?	+	–	+	?
Steinfeld, 2000	+	+	–	+	–	–	+	?
Thadhani, 1999	+	?	–	+	+	+	+	–

TABLE 68 *AFP quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Morssink, 1997	+	+	–	+	+	–	–	–
Yaron, 1999	+	+	–	+	+	?	+	?
Wenstrom, 1996	+	–	–	+	+	–	+	?
Jauniaux, 1996	+	?	?	–	–	+	+	–
Leung, 1999	+	?	?	?	+	?	+	–
Pouta, 1998	+	+	?	?	–	?	+	–
Milunsky, 1994	+	+	–	+	+	–	+	?
Waller, 1996	+	–	–	+	+	–	+	?
Capeless, 1992	+	?	?	?	+	+	–	?
Simpson, 1995	+	–	?	–	–	–	+	+
Severe PE								
Raty, 1999	+	–	–	?	–	–	+	–
Stamilio, 2000	+	+	–	+	–	–	–	–

TABLE 69 *Cellular and total fibronectin quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Chavarria, 2002	NMCC	+	?	+	–	+	+	–
Lockwood, 1990	NMCC	+	?	+	–	+	+	–
Soltan, 1996	+	?	?	+	–	+	?	–
Paarlberg, 1998	+	+	?	+	–	+	+	–

NMCC, nested and matched case–control.

TABLE 70 *Foetal DNA quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Cotter, 2004	NMCC	?	+	+	?	–	+	+
Farina, 2004	NCC	–	?	+	–	?	+	+
Leung, 2001	NMCC	–	+	+	?	+	+	–

NCC, nested case–control; NMCC, nested and matched case–control.

TABLE 71 *Haemoglobin/haematocrit quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of index test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Goh, 1991	+	+	?	+	–	–	–	–
Heilmann, 1993	+	?	?	+	–	+	–	?

TABLE 72 *HCG quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Yaron, 1999	+	+	?	+	+	?	?	?
Morssink, 1997	+	+	?	+	+	–	–	–
Lambert–Messerlian, 2000	CC	–	?	+	?	–	?	–
Heinonen, 1996	+	+	?	+	–	?	?	?
Lee, 2000	NCC	?	?	?	+	–	+	+
Aquilina, 2000	+	+	?	+	–	–	?	–
Muller, 1996	+	+	?	+	+	–	+	–
Ashour, 1997	+	+	?	–	+	–	?	+
Luckas, 1998	+	+	+	+	–	+	+	?
Onderoglu, 1997	+	–	?	+	+	–	?	–
Vaillant, 1996	+	+	?	+	+	–	?	–
Pouta, 1998	+	+	?	?	–	?	+	–
Jauniaux, 1996	+	?	?	–	–	+	+	–
Early test								
Haddad, 1999	+	+	?	+	+	–	?	–
Yaron, 2002	+	+	?	+	+	?	+	–
Severe PE								
Lee, 2000	NCC	?	?	?	+	–	+	+
Stamilio, 2000	+	+	–	+	–	–	–	–

CC, case–control; NCC, nested case–control.

TABLE 73 *Oestriol quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Yaron, 1999	+	+	?	+	+	?	+	?
Kowalczyk, 1998	+	?	?	–	–	–	+	+
Severe PE								
Stamilio, 2000	+	+	–	+	–	–	–	–

TABLE 74 *Serum uric acid quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Jauniaux, 1996	+	?	?	–	–	+	?	–
Salako, 2003	+	+	?	–	–	+	?	–
Conde–Agudelo, 1994	+	?	+	–	+	+	?	–
Winocour, 1989	+	?	?	+	–	+	?	–
Jacobson, 1990	+	?	?	+	–	–	?	–

TABLE 75 *Urinary calcium excretion/urinary calcium/creatinine ratio quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Sanchez-Ramos, 1991[a]	+	+	+	–	–	+	?	–
Nisell, 1996[a]	+	?	?	?	–	+	–	+
Baker, 1994[a,b]	+	?	+	?	+	+	–	–
Suarez, 1996[a,b]	+	–	+	–	–	+	?	–
Soltan, 1996[b]	+	?	?	–	–	+	–	–
Rogers, 1994[b]	+	?	?	+	–	+	+	–
Conde, 1994[b]	+	?	+	–	+	+	?	–
Kazerooni, 2003[b]	+	+	?	–	–	+	–	–

[a] Studies included for UCE.
[b] Studies included for UCCR.

TABLE 76 *Proteinuria quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Sibai, 2000	RCT	–	?	+	?	+	+	–
Combs, 1993	CC	?	?	+	?	?	+	–
Sibai, 1998	RCT	–	?	+	?	+	+	–
Delmis, 1993	+	+	?	?	–	–	–	+
Ekbom 2, 1999	+	?	?	+	–	+	+	–
Winocour, 1989	+	?	?	+	–	?	+	–
Gonzalez, 2003	+	?	?	+	–	+	+	–
Soltan, 1996	+	?	?	–	–	+	–	–
Masse, 1993	+	+	?	–	–	+	+	–
Millar, 1996	XSEC	+	?	+	+	+	+	–
Winkler, 1988	+	?	?	+	–	+	–	+

XSEC, cross-sectional study.

TABLE 77 *Doppler any/unilateral notching of the main uterine arteries quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Geipel, 2002	+	+	?	+	–	–	–	+
Venkat–raman, 2001	+	+	–	+	–	+	–	+
Antsaklis, 2000	+	+	+	+	+	+	–	+
Aardema, 2000	+	+	+	+	–	+	–	–
Ohkuchi, 2000	+	+	?	+	+	+	–	–
Frusca, 1998	+	+	–	+	+	+	–	–
Harrington, 1997	+	?	?	+	–	+	–	+
Harrington, 1996	+	?	?	+	+	?	–	–
Konchak, 1995	+	?	?	+	–	?	–	?
Bower, 1993	+	+	?	+	+	+	+	–
Phupong, 2003	+	+	+	+	–	+	–	+
Marchesoni, 2003	+	?	?	+	+	–	–	+
Frusca, 1996	+	?	?	+	–	?	–	–
Coleman, 1993	+	?	–	+	–	+	–	–
Prefumo, 2004	+	+	?	+	+	–	–	+
Carbillon, 2004	+	+	?	+	–	+	–	+
Axt–Fliedner, 2005	+	?	+	+	–	+	–	+
Audibert, 2005	+	–	?	+	+	–	–	–
Schwarze, 2005	+	+	+	+	–	+	–	+

TABLE 78 *Doppler bilateral notching of the main uterine arteries quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Zimmerman, 1997	RCT	?	?	+	–	+	–	–
Geipel, 2002	+	+	?	+	–	–	–	+
Yu, 2002	+	+	?	+	–	+	–	–
Papageorghiou, 2001	+	+	?	+	+	+	–	+
Venkat–raman, 2001	+	+	–	+	–	+	–	+
Geipel (low risk), 2001	+	+	?	+	–	–	–	–
Geipel (high risk), 2001	+	+	?	+	–	–	–	–
Antsaklis, 2000	+	+	+	+	+	+	–	–
Ohkuchi, 2000	+	+	?	+	+	+	–	+
Albaiges, 2000	+	+	?	+	+	+	–	+
Mires, 1998	+	+	?	+	–	+	–	–
Kurdi, 1998	+	+	+	+	+	+	–	?
Frusca, 1998	+	+	–	+	+	+	–	+
Harrington, 1997	+	?	?	+	–	+	–	–
Harrington, 1996	+	?	–	+	+	–	–	–
Marchesoni, 2003	+	?	?	+	+	–	–	–
Uludag, 2002	+	–	?	+	–	+	–	–
Coleman, 1993	+	?	–	+	–	+	–	–
Prefumo, 2004	+	+	?	+	+	–	–	–
Carbillon, 2004	+	+	?	+	–	+	–	–
Axt–Fliedner, 2005	+	?	+	+	–	+	–	–
Audibert, 2005	+	–	?	+	+	–	–	–
Schwarze, 2005	+	+	+	+	–	+	–	–

TABLE 79 *Doppler single ratios of the uterine artery quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Schulman, 1987	+	–	?	+	–	?	–	?
Saccini, 1995	+	?	?	+	–	?	–	–
Aquilina, 2000	+	+	?	–	–	+	–	–
North, 1994	+	?	+	+	+	+	+	–
Ohkuchi, 2000	+	+	?	+	+	+	–	–
Ferrier, 1994	+	?	?	+	–	+	+	–
Aardema (high risk), 2000	+	+	?	+	–	+	–	–
Aardema (low risk), 2000	+	+	?	+	+	+	–	–

TABLE 80 *Doppler pulsatility index of the main uterine artery quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Yu, 2002	+	+	?	+	–	+	–	–
Martin, 2001	+	+	?	+	+	+	–	–
Papageorghiou, 2001	+	+	?	+	+	+	–	–
Aardema, 2000	+	+	?	+	+	+	–	–
Aardema, 2000	+	+	?	+	–	+	–	–
Albaiges, 2000	+	+	?	+	+	+	–	+
Zeeman, 2003	+	?	+	+	–	+	–	?
Yu, 2004	+	–	?	+	–	–	–	–
Sato, 1995	+	?	?	?	–	+	–	–

TABLE 81 *Doppler resistance index of the main uterine artery quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Geipel, 2002	+	+	?	+	–	–	–	+
Tranquilli, 2000	+	?	?	?	–	+	?	?
Soregaroli, 2001	+	+	?	+	+	+	–	+
Ohkuchi, 2000	+	+	?	+	+	+	–	–
Aquilina, 2000	+	+	?	–	–	+	–	–
Caforio (low risk), 1999	+	?	+	?	+	?	–	–
Caforio (high risk), 1999	+	?	+	?	–	?	–	–
Frusca, 1998	+	+	–	+	+	+	–	–
Frusca, 1997	+	?	+	+	+	?	–	+
Caruso, 1996	+	?	+	+	–	?	–	+
Konchak, 1995	+	?	?	+	–	?	–	?
Chan, 1995	+	?	?	+	–	?	–	–
Ferrier, 1994	+	?	?	+	–	+	+	–
North, 1994	+	?	+	+	+	+	+	–
Rizzo, 1993	+	?	?	+	–	–	–	–
Caruso, 1993	+	?	?	+	–	+	–	–
Pattinson, 1991	+	+	?	?	–	+	–	–
Parretti, 2003	+	+	+	+	–	+	–	+
Valensise, 1993	+	?	?	+	–	+	+	?
Valensise, 1993	+	?	?	+	+	?	–	?
Arenas, 2003	+	–	?	+	+	+	+	+
Frusca, 1996	+	?	?	+	–	?	–	–
Coleman, 1993	+	?	–	+	–	+	–	–
Axt–Fliedner, 2005	+	?	+	+	–	+	–	+
Schwarze, 2005	+	+	+	+	–	+	–	+
Sato, 1995	+	?	?	?	–	+	–	–

TABLE 82 *Doppler combinations of flow velocity waveforms of the main uterine artery quality characteristics*

Study	Study design (cohort)	Consecutive recruitment	Blinding of test results	>90% verification of diagnosis	Incidence of pre-eclampsia <4%	Prospective data collection	Adequate test description	Adequate reference standard
Resistance index and/or notching								
Aquilina, 2001	+	+	?	–	–	+	+	–
Bower, 1993	+	+	?	+	+	+	–	–
Campbell, 2000	+	+	?	–	–	+	–	+
Chan, 1995	+	?	?	+	–	?	–	–
Coleman, 1993	+	?	–	+	–	+	–	–
Driul, 2002	+	?	?	–	+	+	–	?
Driul, 2005	CC	?	?	+	–	–	–	?
Frusca, 1996	+	?	?	+	–	?	–	–
Frusca, 1997	+	?	+	+	–	?	–	+
Geipel (low risk), 2001	+	+	?	+	+	–	–	–
Geipel (high risk), 2001	+	+	?	+	–	–	–	–
Geipel, 2002	+	+	?	+	–	–	–	+
Harrington, 1991	+	?	?	+	+	+	–	–
Harrington, 1996	+	?	–	+	+	?	–	–
Harrington (high risk), 2004	+	+	?	+	–	+	–	–
Harrington (low risk), 2004	+	+	?	+	+	+	–	–
Kurdi, 1998	+	+	+	+	+	+	–	–
North, 1994	+	?	+	+	+	+	+	–
Subtil, 2003	RCT	?	?	+	+	+	–	?
Valensise, 1994	+	?	?	+	–	?	–	?
Pulsatility index and/or notching								
Albaiges, 2000	+	+	?	+	+	+	–	+
Papageorghiou, 2001	+	+	?	+	+	+	–	–
Yu, 2002	+	+	?	+	–	+	–	–
S/D ratio and/or notching								
Benifla, 1992	+	?	?	+	–	+	–	?
Haddad, 1995	+	+	?	+	–	?	–	–
Morris, 1996	RCT	+	–	–	–	+	–	–
Soutif, 1996	+	+	?	+	+	+	–	–

CC, case control.

Appendix 9

Effectiveness reviews tables of methodological and reporting characteristics of included studies

TABLE 83 *Trial details of bed rest with or without hospitalisation for hypertension during pregnancy*

Study	Methods	Participants	Interventions	Outcomes	Notes
Crowther, 1986	R: random number tables, variable block size AC: consecutively numbered opaque, sealed envelopes (A) FU: no losses (A) B: none	105 women with singleton pregnancy at 28–38 weeks, proteinuric HT (DBP 90–109 mmHg and proteinuria ⩾1+). No other complications of pregnancy	Rest: strict bed rest in hospital until delivery. Ambulation only to toilet. Control: allowed to move around the hospital ward as desired	Woman: severe HT (DBP >109 mmHg); increased proteinuria; fulminating PE; eclampsia; placental abruption; IOL Baby: NND; stillbirth; preterm birth; low BW; very low BW; meconium; Apgar; intubation; SCBU admission	Setting: Zimbabwe. One hospital
Crowther, 1992	R: blocked, stratified by parity and type of HT AC: consecutively numbered, opaque, sealed envelopes (A) FU: no losses (A) B: for baby outcomes only	218 primigravid and multigravid women with singleton pregnancy at 28–38 weeks, non-proteinuric HT (BP ⩾140/90 mmHg). Excluded: DBP ⩾110 mmHg, symptomatic, Caesarean section scar or APH during pregnancy	Rest: rest in hospital, voluntary movement in the ward. 4-hourly BP + daily urinalysis Control: normal activity at home, no restrictions. Daily self analysis of urine for protein. Weekly BP, weight, bloods	Woman: severe HT (⩾160/110 mmHg); proteinuria; Caesarean section; IOL Baby: perinatal death BW (mean); BW (<2500 g); SGA (<10%ile); admission to NICU; length of stay in hospital; Apgar	Setting: Zimbabwe. One hospital and 13 peripheral clinics
Leung, 1998	R: "allocated randomly". No other information AC: consecutively numbered, opaque, sealed envelopes (A) FU: 26% excluded. Only 4% excluded from women's views B: none	90 primigravid and multigravid women with singleton pregnancy at 28–38 weeks, non-proteinuric HT (DBP 90–100 mmHg) after 5 minutes' rest Excluded: proteinuria ⩾1+ or symptoms of severe PE	Rest: admission to hospital, advice to rest in bed as much as possible Control: normal activity at home. Daily self analysis of urine for protein. Reviewed weekly in day-care unit or clinic for BP, foetal monitoring, urinalysis, bloods	Woman: HT (DBP >90 mmHg × 2), severe HT; proteinuria; mode of delivery; IOL; antihypertensive drug; women's views and preferences (questionnaire) Baby: stillbirth, neonatal death; BW (mean); SGA; admission NICU; length of stay in hospital; Apgar	Setting: Hong Kong. One centre. All data excluded except for women's views, as data for >20% women not available

continued

TABLE 83 *Trial details of bed rest with or without hospitalisation for hypertension during pregnancy (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Mathews, 1982	R: "at random". No other information. AC: sealed envelopes (B) FU: 13% excluded (C) B: none	40 women with singleton pregnancy at 26 to over 36 weeks, with proteinuric HT (DBP 90–109 mmHg + >trace proteinuria) and asymptomatic	Rest: admission for strict bed rest Control: allowed to move around the ward Both groups: pedometer	Women: plasma urea and urate; serum human placental lactogen and oestriol; imminent eclampsia; HT; proteinuria; mode of delivery Baby: perinatal death, gestation at birth, BW, SGA	Setting: two UK hospitals. Data for perinatal death included in review, other outcomes only for 10 high-risk women

AC, allocation concealment; APH, antepartum haemorrhage; B, blinding; BP, blood pressure; BW, birthweight; DBP, diastolic blood pressure; Exp, experimental; FU, follow-up; HT, hypertension; IOL, induction of labour; NICU, neonatal intensive care; NND, neonatal death; PE, pre-eclampsia; R, randomisation; SCBU, special care baby unit; SGA, small for gestational age.

TABLE 84 *Trial details of exercise or other physical activity for preventing pre-eclampsia and its complications*

Study	Methods	Participants	Interventions	Outcomes	Notes
USA, 1997	R: random number table, blocked AC: opaque sealed envelopes (A) FU: 4 (12%) excluded (C) B: for participants not possible, for caregiver and outcome assessor no	33 women <34 weeks' gestation with gestational diabetes. Excluded: any other medical or obstetric complications (not specified), unable to read/write English, current exercise regimen for 30 minutes >2×/week	Exercise: moderate/hard intensity (70% max. heart rate) for 30 minutes ×3–4/week until delivery (5 minutes' warm up, 20 minutes' steady state, 5 minutes' cool down). Cycle ergometer 2 supervised sessions + walking or cycling unsupervised ×1–2/week Control: usual physical activity Both groups: dietary counselling	Woman: PIH, Caesarean section, blood glucose (mean), Hb A1C level, need for insulin, cardiorespiratory fitness, weight change Baby: preterm birth, gestation at birth (mean), FHR patterns during exercise, birthweight (mean and >4 kg), Apgar (median)	144 women screened: 40 not eligible, 68 declined, 3 exercise recommended by carer. Good compliance with exercise
USA, 2000	R: random number table AC: sealed numbered opaque envelopes (A) Follow-up: no losses (A) Blinding: for participants not possible, for caregiver not reported, for outcome assessor yes	16 women ⩾18 years, at 18 weeks' gestation with either mild HT, or history or family history of hypertensive disorders of pregnancy. Excluded: renal disease, diabetes, multiple pregnancy, and vigorous exercisers with RPE >14	Exercise: 45 minutes' moderate (RPE = 13) intensity exercise ×3/week for 10 weeks (warm up 5 minutes, steady state 30 minutes, and cool down 10 minutes). At exercise laboratory under supervision, on bicycle and treadmill Control: normal daily physical activity	Woman: PIH, pre-eclampsia, severe hypertension, change in SBP and DBP over 10 weeks, change in percentage body fat (mean) Child: preterm birth, small for gestational age, death	Good compliance with exercise programme

DBP, diastolic blood pressure; FHR, foetal heart rate; Hb, haemoglobin; PIH, pregnancy-induced hypertension; RPE, rating of perceived exertion; SBP, systolic blood pressure.

TABLE 85 *Trial details of rest during pregnancy for women with normal blood pressure*

Study	Methods	Participants	Interventions	Outcomes	Notes
Herrera, 1993	R: computer-generated AC: closed envelopes, no other information (B) FU: not reported B: for participants and caregivers yes, for outcome assessor not reported	74 primigravid women at 28–29 weeks' gestation, with normal BP, positive roll-over test and MAP ⩾80 mmHg	Rest: advised rest at home in left lateral position for 15 minutes ×2/day, plus oral supplement ×3/week (soy protein 25 g, calcium 300 mg, linoleic acid 300 mg) Control: no advice to rest, placebo ×3/week (ferrous sulfate 105 mg) Both groups: until delivery	Woman: gestational HT (BP ⩾140/90 × 2, 6 h apart), PE (gestational HT + >0.5 g/l proteinuria), Caesarean section Baby: gestation at birth (mean), birthweight (mean)	Compliance: no information. Conducted in Colombia
Spinapolice, 1983	R: computer-generated AC: closed envelopes, no other information (B) FU: not reported B: of participants not possible, of caregivers no, of outcome assessor not reported	32 nulliparous women at 28–32 weeks' gestation with normal BP and positive roll-over test	Rest: advised rest at home in left lateral recumbent position for 4 h/day until delivery. If MAP increased ⩾9 mmHg, rest increased to 6 h/day Control: no advice to rest Both groups: seen every 2 weeks	Woman: gestational HT (BP ⩾140/90 or increase by 30/15 mmHg ×2 at least 6 h apart), PE (not defined), induction of labour, mode of delivery Baby: gestation at birth (mean), birthweight (mean), Apgar (mean)	Data for both groups only reported for gestational hypertension and PE Compliance: rest group home visits by nurse ×3/week Conducted in USA

AC, allocation concealment; B, blinding; BP, blood pressure; Exp, experimental; FU, follow-up; HT, hypertension; MAP, mean arterial pressure; PE, pre-eclampsia; R, randomisation.

TABLE 86 *Trial details of altered dietary salt for preventing pre-eclampsia, and its complications*

Study	Methods	Participants	Interventions	Outcomes	Notes
The Netherlands, 1997	R: method not stated AC: "closed envelope system", no other information (B) FU: 28 (10%) excluded (B) B: for participants no, for caregivers and outcome assessor not reported	270 nulliparous women with singleton pregnancy after 12 weeks, by dates and ultrasound. Excluded: pre-existing HT, diabetes, renal disease, cardiovascular disease	Low: diet with about 20 mmol sodium per day. Oral and written instruction by dietician, no added salt and ready-made foods only if no salt in preparation Normal: no dietary restriction	Woman: PIH, PE, severe HT Baby: death, SGA, preterm delivery	2 hospital clinics. Mean urinary sodium after randomisation 70 mmol/day low-sodium group, 135 mmol/day normal diet
The Netherlands, 1998	R: random numbers in blocks of 10. Stratified by centre AC: sealed numbered opaque envelopes (A) FU: no losses (A) B: for participants no, for caregiver only to urinary sodium concentration, for outcome assessor not reported	361 women booked for midwifery care, nulliparous, DBP <90 mmHg at booking visit <20 weeks. Randomised if dBP >85 ×2 in subsequent visit, or weight gain >1 kg/week 3 consecutive weeks, or excess oedema Excluded: planning to leave city, or risk factors for PIH	Low: sodium-restricted diet, aimed at <50 mmol/day Written dietary instructions given by midwife Normal: asked not to change eating habits	Woman: highest DBP, PE, eclampsia, hospital referrals and admissions for HT, time to delivery, abruption, mode of delivery Baby: death, gestation at birth (mean), birthweight, Apgar, NICU admission	9 centres, midwifery practices and hospital clinic. Mean urinary sodium after randomisation 84 mmol/day low-sodium group, 124 mmol/day normal diet

AC, allocation concealment; B, blinding; DBP, diastolic blood pressure; HT, hypertension; NICU, neonatal intensive care unit; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; SGA, small for gestational age.

TABLE 87 *Trial details of antioxidants for preventing pre-eclampsia and its complications*

Study	Methods	Participants	Interventions	Outcomes	Notes
Beazley, 2002	R: "randomised", no other information AC: no information (B) FU: 9 (8%) women lost to follow-up B: "double blind" stated	109 women between 14 and 20 weeks' gestation at "high risk of PE", based on previous PE, chronic HT, diabetes mellitus and multifoetal gestation	Antioxidant: 1000 mg vitamin C + 400 IU vitamin E daily Control: placebo, no other details	Woman: PE (not defined) Baby: gestation at birth (mean), preterm birth (<37 weeks), birthweight (<10 centile)	Compliance: no information Location: USA
Chappell, 1999	R: computer-generated list, blocks of 10 AC: in hospital pharmacy (A) FU: complete B: for caregivers and researchers yes	283 women between 16 and 22 weeks' gestation with abnormal Doppler waveform at 18–22 weeks' gestation or past history of PE necessitating delivery <37 weeks', eclampsia or HELLP syndrome Excluded: heparin or warfarin treatment, abnormal foetal-anomaly scan, multiple pregnancy	Antioxidant: 1000 mg vitamin C + 400 IU vitamin E daily Control: identical placebo	Woman: PAI-1:PAI-2 ratio, PE (defined according to ISSHP), abruption, spontaneous preterm delivery (<37 weeks), SBP and DBP before delivery, biochemical indices of oxidative stress and placental function Baby: stillbirth, SGA (≤10th centile), gestation at birth, birthweight	Location: UK 1512 women screened, 273 had abnormal Doppler, 242 consented. 41 with history of PE also consented. Of 283 randomised, 160 completed protocol
Han, 1994	R: "divided into two groups randomly", no other information AC: unclear (B) FU: no reported losses B: for participants yes, for carers or outcome assessors not stated	100 women with "high risk factors of PIH". No other information	Antioxidant: 100 μg/day selenium, as a "natural dietetic liquid" for 6–8 weeks "during late pregnancy" Control: placebo, given in "the same manner"	Women: change in maternal and umbilical blood selenium, change in SBP and DBP, PIH (not defined), oedema, proteinuria, side-effects Baby: birthweight	Compliance: unclear, no information Location: China
People's League, 1942	R: "divided into two groups by placing them alternatively on separate lists" AC: (C) FU: 622 (11%) women excluded: 494 evacuated, 39 twins and 89 miscarried B: no information	5021 women ≤24 weeks' gestation, attending antenatal clinics and in "good health" Excluded: any disease or physical abnormality	Antioxidant: 100 mg vitamin C in multivitamin with ferrous iron 0.26 g, calcium 0.26 g, minute quantities of iodine, manganese and copper, adsorbate of vitamin B_1, halibut liver oil 0.36 g containing vitamin A (52,000 IU/g) and vitamin D (2500 IU/g) daily Control: no placebo	Woman: "toxaemia" classified as HT only, proteinuria ± HT, or HT with proteinuria, sepsis. length of gestation, breastfeeding Baby: stillbirth, early neonatal death, birthweight	Compliance: unclear, no information Location: UK

continued

TABLE 87 *Trial details of antioxidants for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Rivas, 2000	R: "randomly divided into two subgroups" AC: unclear (B) FU: no losses reported B: stated "triple blind", but no other details	127 women <29 weeks' gestation with "high risk for PE", including nulliparity, previous PE, obesity, HT, <20 years old, diabetes, nephropathy, mean arterial pressure >85 mmHg, positive roll-over test, black race, family history HT or PE, twin pregnancy and poor socio-economic conditions	Antioxidant: 500 mg vitamin C and 400 IU vitamin E/day, plus 1 g fish oil ×3/ day and 100 mg aspirin ×3/week Control: placebo, given "at the same posology and presentation"	Women: PE (not defined)	Compliance: no information Location: Venezuela Published in abstract format only
Sharma, 2003	R: computer generated AC: numbered opaque envelopes (A) FU: no losses reported B: for women, caregivers, research staff and outcome assessors yes	251 primigravidas between 16 and 20 weeks with no medical complication such as renal disease, primary HT, cardiovascular disease, diabetes or connective tissue disease	Antioxidant: 2 mg lycopene ×2/day until delivery Control: placebo, similar tablets	Woman: PE (defined according to ISSHP), eclampsia, DBP (mean) Baby: IUGR (<10th centile), birthweight	Compliance: assessed by pill counts, but no other information Location: India
Steyn, 2002	R: by drug company AC: numbered containers, code held by drug company (A) FU: no losses reported B: stated "double blind"	200 women <26 weeks' gestation with history of previous preterm birth Excluded: previous iatrogenic preterm labour, multiple pregnancy, proven cervical incompetence, other reasons for preterm labour	Antioxidant: 250 mg vitamin C ×2/day until 34 weeks' gestation Control: "exact matching" placebo	Women: PE, HT, APH (including abruption), preterm labour, gestation at delivery Baby: birthweight (median), miscarriage, stillbirth, neonatal death, length of stay in hospital	Trial stopped early by independent panel as "further recruitment will not have resulted in a significant difference" Compliance: not reported Location: South Africa

AC, allocation concealment; B, blinding; FU, follow-up; HELLP, haemolysis, elevated liver enzymes and low platelets; HT, hypertension; IP, isoprostane; IQR, interquartile range; ISSHP, International Society for the Study of Hypertension in Pregnancy; PAI-1, plasminogen activator inhibitor-1; PAI-2, plasminogen activator inhibitor-2; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; RDI, recommended daily intake; SGA, small for gestational age; TAS, total antioxidant status.

TABLE 88 *Trial details of calcium supplementation during pregnancy for preventing hypertensive disorders and related problems*

Study	Methods	Participants	Interventions	Outcomes	Notes
Belizan, 1991	R: not stated AC: numbered, sealed opaque envelopes (A) FU: 29 (2%) lost, incomplete data for 98 (8%)	1194 nulliparous women, <20 weeks; BP <140/90 mmHg (mean of 5 measurements); no present or past disease; not taking medication; normal oral glucose tolerance tests	Calcium: 2 g, as 500-mg calcium carbonate tablets Control: identical placebo	Women: gestational HT (DBP ⩾90, SBP ⩾140 mmHg, ×2 6 h apart); PE (gestational HT + proteinuria >0.3 g/l) Baby: perinatal death, BP >95th percentile for sex, age and height at age 5–9 years	Three hospitals in Rosario, Argentina Compliance: 85% Long-term follow-up of
CPEP, 1997	R: computer-generated AC: numbered treatment packs (A) FU: 253 (6%) lost	4589 nulliparous women at 13–21 weeks who passed compliance test; BP ⩾134/84 mmHg; protein dipstick negative or trace Excluded: taking medication; absorption or metabolism of calcium; elevated serum creatinine or calcium; renal disease; haematuria; history or family history of urolithiasis	Calcium: 2 g/day as calcium carbonate until delivery or PE Control: placebo. Both groups: 50 mg calcium/day and asked to drink 6 glasses of water/day	Woman: gestational HT (DBP ⩾90 mmHg ×2 occasions 4 h–1 week apart); proteinuria (⩾300 mg/24 h, ⩾2+ or more, protein/creatinine ratio ⩾0.35); PE (gestational HT + proteinuria); renal insufficiency; urolithiasis Baby: prematurity (<37 weeks); small for gestational age; perinatal death	5 US university centres Compliance: 64% calcium group, 67% placebo group
Crowther, 1999	R: computer generated, stratified by centre, variable blocks AC: telephone (A) B: double-blind	456 nulliparous women; singleton pregnancy; <24 weeks' gestation; BP <140/90 mmHg Excluded: antihypertensive therapy; contraindication to calcium supplementation	Calcium: calcium carbonate 1.8 g/day until delivery Control: placebo	Woman: PIH (DBP ⩾90 mmHg ×2 4 h apart, or 110 mmHg once); PE (as above plus proteinuria ⩾0.3 g/24 h or ⩾2+ protein ×2); Baby: preterm birth (<37 weeks, <32 weeks; <28 weeks)	5 hospitals in Australia. Trial stopped prematurely for financial reasons Compliance: 31% calcium group and 24% placebo stopped taking the tablets
Lopez-Jaramillo, 1989	R: random numbers AC: not stated (B) FU: no losses	106 nulliparous women age ⩽25 years; certain menstrual dates; <24 weeks gestation; normotensive; no medical disorders; not taking medication or vitamin/mineral preparations	Calcium: 2 g as calcium gluconate 500 mg ×4/day until delivery Control: identical placebo	Women: gestational HT (BP ⩾140/90 mmHg, or rise 30 mmHg systolic or 15 mmHg diastolic, ×2 6 h apart); weekly weight gain Baby: birthweight; length of gestation	Conducted in Ecuador

continued

TABLE 88 *Trial details of calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Lopez-Jaramillo, 1990	R: randomised, "each patient was assigned independently in sequence" AC: not stated (B) FU: no losses B: double-blind	56 nulliparous high-risk women with positive roll-over test at 28–30 weeks' gestation	Calcium: 2 g elemental calcium/day until delivery Control: placebo	Women: gestational HT (BP >140/90 mmHg ×2 6 h apart); proteinuria (300 mg/l) Baby: birthweight, gestation at birth	Conducted in Ecuador. Discrepancy in size of groups not accounted for
Lopez-Jaramillo, 1997	R: randomised AC: (A) FU: 14 (5%) lost after randomisation B: double-blind	274 nulliparous women with low calcium intake; <20 weeks' gestation; certain menstrual dates; BP ⩾120/80 mmHg; no underlying medical disorders; no drug, mineral or vitamin therapy	Calcium: 2 g/day as calcium carbonate Placebo: placebo	Women: PE (BP >140/90 mmHg × 2 > 6 h apart + proteinuria >300 mg/L or >1+ ×2 4–24 h apart) Baby: gestation at birth	Conducted in Ecuador
Niromanesh, 2001	R: "randomly assigned", no other information AC: coded by pharmacy (A) FU: no losses B: double-blind	30 high-risk women with positive roll-over test and at least one risk factor for PE; 28–32 weeks' pregnant; BP <140/90 mmHg Excluded: chronic medical conditions	Calcium: 2 g daily (500 mg 6-hourly) Control: placebo	Woman: PE: duration of pregnancy; weekly maternal weight increase Baby: birthweight	
Purwar, 1996	R: computer-generated list AC:, (A) FU: 11 (5.5%) lost to follow-up B: double-blind	201 nulliparous women; singleton pregnancy; <20 weeks; normal glucose tolerance test; no HT; no underlying medical disorder Excluded: renal disease; collagen vascular disease; chronic HT; endocrinological disease; taking medication	Calcium: 2 g daily Control: placebo	Woman: gestational HT (SBP >140 mmHg and DBP >90 mmHg, ×2 6 h apart), PE (HT + proteinuria ⩾0.3 g/24 h)	Conducted in India
Sanchez-Ramos, 1994	R: computer-generated list AC: (A) FU: 4 (6%) lost B: double-blind	67 normotensive nulliparas; positive roll-over test and positive angiotensin II infusion test at 20–24 weeks' gestation Excluded: renal disease, collagen vascular disease, diabetes mellitus, chronic HT, multifoetal pregnancy	Calcium: 2 g/day as 500 mg calcium carbonate ×4 Control: placebo	Women: gestational HT (BP ⩾140/90 mmHg ×2 4–6 h apart); PE (gestational HT + proteinuria: 1+ or 300 mg/24 h); severe PE Baby: birthweight; gestation at birth (mean) Apgar; cord arterial pH, foetal growth	Conducted in US, university hospital serving low-income population. Compliance was 80%

continued

TABLE 88 *Trial details of calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Villar, 1987	R: Random numbers AC: closed envelopes (A) FU: no losses B: double-blind	52 nulliparous or primiparous; 26 weeks' gestation; age 18–30 years; singleton pregnancy; negative roll-over test Excluded: underlying medical disorders	Calcium: calcium carbonate 1.5 g (500-mg tablets) Control: placebo	Woman: weight gain in last trimester; BP increase; gestational HT	Conducted in USA and Argentina Women in US also received daily vitamin tablets containing 200 mg calcium
Villar, 1990	R: computer-generated list AC: opaque numbered envelopes (A) B: double-blind	178 women ⩽17 years; no underlying medical disorder; singleton pregnancy	Calcium: 2 g as 500 mg calcium carbonate ×4 Control: placebo	Woman: preterm delivery (<37 weeks) Baby: birthweight <2500 g; postdates >42 weeks; impaired foetal growth; premature rupture of membranes; Apgar	Conducted in USA All women prescribed vitamin tablets containing 200 mg calcium
WHO, 2006	R: stratified by centre, computer-generated blocks of 6–8 AC: consecutively numbered treatment packs (A) FU: 13 (0.2%) lost. 298 (4%) with some data B: double blind	8325 primiparous women <20 weeks' gestation. Low calcium intake Excluded: renal disease, urolithiasis; parathyroid disease; SBP >140 mmHg or DBP >90 mmHg; history of HT; antihypertensive therapy; diuretic, digoxin, phenytoin or tetracycline treatment	Calcium: 1.5 g as chewable calcium carbonate 500 mg ×3/day until delivery Control: identical placebo	Woman: PE (DBP ⩾90 mmHg or SBP ⩾140 mmHg, plus proteinuria 2+ or 300 mg/day); severe PE, PIH, eclampsia; abruption Baby: preterm birth (<37 weeks). birthweight <2500 g; admission NICU for >2 days; stillbirth, death before discharge from hospital	Centres in Argentina, Egypt, India, Peru, South Africa and Vietnam. 14,362 women screened, 8325 randomised. Treatment compliance 84.5% and 86.2%, respectively. Baseline characteristics well matched

BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean.

TABLE 89 *Trial details of garlic for the prevention of pre-eclampsia and its complications*

Study	Methods	Participants	Interventions	Outcomes	Notes
Iran, 2001	R: "randomly divided", no other information AC: no information (B) FU: none B: participants only	100 primigravid women between 28 and 32 weeks' gestation with a positive roll-over test	Garlic: 2 garlic tablets/day, total 800 mg/day (dry powder with 1000 μg allicin in each tablet) for 8 weeks Control: 2 placebo tablets for 8 weeks	Woman: hypertension, pre-eclampsia, weight gain (mean), Caesarean section, garlic odour, side-effects, plasma lipid levels, platelet aggregation Baby: perinatal death, gestation at birth (mean), birthweight (mean), Apgar	300 women screened, 100 recruited Tablets stated to be odour controlled Conducted in Iran

AC, allocation concealment; B, blinding; FU, follow-up; R, randomisation sequence.

TABLE 90 *Trial details of energy and protein intake in pregnancy*

Study	Methods	Participants	Interventions	Outcomes	Notes
Atton, 1990	Alternate allocation	148 non-obese Asian women with triceps skinfold thickness <2 mm from 18 to 28 weeks	Flavoured milk supplement with energy and protein Control: normal diet	Mean gestational age, birth weight, length, head circumference	25 non-compliers excluded
Badrawi, 1993	Allocation method not reported	100 obese multiparous Egyptian women aged 25–35 years	Balanced low-energy diet Control: normal diet	Gestational weight gain, birth weight, PIH	Criteria for obesity not reported
Blackwell, 1973	Interventions assigned "randomly and blindly", methods not specified	Well nourished Taiwanese with "marginal diets"	Chocolate-flavoured supplement with protein, energy and vitamins/minerals Control: vitamins/minerals only, same time and duration	Gestational weight gain, preterm birth, SGA, length, head circumference, IQ at age 5 years	High alleged energy supplement not associated with higher gestational weight gain
Briley, 2002	R: not reported, no blinding	27 low-income African-American women	Minimum 6 home nutrition assessment and counselling Control: two home visits without counselling	Energy intake, gestational weight gain, birthweight, preterm birth	7/27 dropped out and not included in analyses
Campbell, 1975	Allocation method not reported	153 Scottish women with high gestational weight gain between 20 and 30 weeks	Low-energy diet starting at 30 weeks Control: no intervention	Gestational weight gain, PIH, PE	No report on compliance

continued

TABLE 90 *Trial details of energy and protein intake in pregnancy (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Campbell, 1983	Allocation method not reported	182 obese primiparous Scottish women with normal IVGTT at 28 weeks	Low-energy diet Control: no intervention	Gestational weight gain, birth weight, birth length, preterm birth, PE	
Campbell-Brown, 1983	Strict alternate allocation	180 (90 matched pairs) Aberdeen primipara at high risk for low birth weight delivery because short, thin or low weight gain	Milk or cheese supplement started at 29 weeks Control: normal diet	Gestational weight gain, preterm birth, birth weight, length, head circumference	Gestational age biased by replacement of women delivering <37 weeks
Ceesay, 1997	Cluster randomised by village using stratified design according to village size. R not given	Rural Gambian women from 28 villages with chronic marginal nutrition	Energy, protein, calcium, iron supplement biscuits eaten daily in presence of birth attendants, from 20 weeks Control: no supplement	Gestational weight gain, gestational age, birth weight, head circumference, stillbirth, neonatal death	Effects reported by individual birth not cluster, results in review adjusted by $1 + (n - 1)r$, where $r = 0.01$
Elwood, 1981	R: random numbers in sealed envelopes	1251 Welsh women in two towns at first reporting of pregnancy	Free tokens of $^1/_2$ pint milk Control: no tokens	Gestational age, preterm birth, low birth weight, length, head circumference	24% loss to follow-up, high in controls
Girija, 1984	Alternate allocation	20 poor Indian women in last trimester	Energy and protein cake Control: normal diet	Gestational weight gain, birth weight, length, head circumference, breast milk output	No information on compliance
Hankin, 1962	Allocation by week day	149 primi- and secundigravid Australian women, at first clinic visit <20 weeks	Advice to improve protein in diet Control: no advice	Protein and energy intake, PE	13 lost to follow-up
Hunt, 1976	R: not reported	344 Spanish women at <21 weeks	Nutrition classes, control no class	Protein and energy intake	65 lost to follow-up
Iyengar, 1967	Allocation method not reported	25 low SES Indian women 25–40 years, low energy and protein diet	Hospitalisation + energy, protein, iron, vitamin supplement Control: same without protein	Gestational weight gain, birthweight	No information on total number allocated to treatments and losses to follow-up

continued

TABLE 90 *Trial details of energy and protein intake in pregnancy (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Kafatos, 1989	R: 20 clinics using computer-generated random numbers	568 rural Greek women, <27 weeks	Nutrition counselling Control: no counselling	Energy and protein intake, gestational weight gain, birthweight, birth length, head circumference, gestational age, LBW, SGA, preterm birth, stillbirth, neonatal death	Analysis based on individual women, results in review adjusted by $1 + (n - 1)r$, where $r = 0.01$
Kardjati, 1988	"Blind" randomisation based on household numbers using random number tables	747 women in 3 villages, Java, at 26–28 weeks, nutritionally vulnerable	Energy and protein supplement Control: low-energy supplement	Gestational weight gain, birth weight, breast milk output	
Mardones, 1988	Alternate allocation	Low-income Chilean women, <20 weeks with low weight for height at first visit	High protein supplement Control: normal protein supplement with iron	Gestational weight gain, birth weight, head circumference, IUGR, LBW, gestational age, preterm birth, stillbirth, neonatal death	Large losses to follow-up
Mora, 1978	Allocation method not reported	456 poor first- or second-trimester Bogota slum residents	Energy and protein supplement from 3rd trimester Control: normal diet	PE, gestational age, preterm birth, birth weight, LBW, stillbirth, perinatal mortality, neonatal mortality	Compliance assessed but results not presented, results odd
Ross, 1938	Alternate allocation, no blinding	56 young, poor primipara, US women with 'marginal' diets	Protein, energy and iron supplement Control: regular diet	PE, gestational weight gain	Very high PE rate, no information on compliance
Ross, 1985	Allocation method not reported	127 black women from South Africa, <20 weeks	Energy and protein supplement Control: placebo pills	Gestational weight gain, gestational age, birth weight	No information on compliance, 10% loss to follow-up
Rush, 1980	Stratified randomisation based on random number table, sealed envelope and blinding of all research staff	1051 low-income black women, New York, USA, <30 weeks at risk for low birth weight	1. Balanced energy, protein, vitamin and mineral supplement 2. High-protein, vitamin and mineral supplement Control: vitamin and mineral only	Gestational weight gain, gestational age, preterm birth, SGA, birth weight, LBW, stillbirth, neonatal mortality	25% loss to follow-up
Sweeney, 1985	Stratified randomisation using "biased coin methodology", probably not blinded	47 healthy women, <20 weeks	Advice on protein and energy intake Control: no advice	Protein and energy intake, gestational weight gain, birth weight, gestational age	

continued

TABLE 90 *Trial details of energy and protein intake in pregnancy (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Viegas, 1982b	Allocation method not reported	130 Asian UK women, <20 weeks?, nutritionally adequate	Protein, energy and vitamin supplement Control: iron and vitamin C	Gestational age, gestational weight gain, birth weight, length, head circumference	No information on compliance

AC, allocation concealment; B, blinding; FU, follow-up; IVGTT, intravenous glucose tolerance test; LBW, low birth weight; R, randomisation sequence.

TABLE 91 *Trial details of magnesium supplementation during pregnancy*

Study	Methods	Participants	Interventions	Outcomes	Notes
Angola, 1992	R: according to random number table, placebo (olive oil) Non-blinded outcome assessment Post-randomisation exclusions not stated	100 primi- and multi-parous women aged 14–40 years	500 mg magnesium oxide daily from 4 months gestation	PE, LBW	Placebo group had better diet than two treatment groups
Austria, 1997	R: computer-generated list, no placebo, non-blinded outcome assessment, 7.5% post-randomisation exclusions	530 women with non-risk pregnancies	15 mmol magnesium citrate	Preterm labour, LBW	
China, 1997	R: not stated, separate for high- and low-risk pregnancies, blinded outcome assessment, no post-randomisation exclusions	52 women high-risk, 50 low-risk pregnancies aged 24–35 years	2 g/day magnesium gluconate from 28–30 weeks then 3 g/day to delivery	Pregnancy-induced hypertension	
Hungary, 1988	R: cluster 8 magnesium, 7 placebo centres, blinded outcome assessment, 13% post-randomisation exclusions	985 women with single pregnancies	15 mmol/day magnesium aspartate at 6–21 weeks until delivery	Preterm birth, IUGR, low birthweight	High non-compliance rate
Memphis, 1989	R: computer-generated, placebo, allocation by pharmacy, blinded outcome assessment, 7% post-randomisation exclusions	400 normotensive, primigravid women aged 13–25 years	365 mg elemental magnesium as Mg Asp HCl daily from 13–24 weeks to delivery	BP, PE	All women also received vitamin supplements which included 100 mg magnesium and 200 mg calcium/day
Mississippi, 1992	R: method not given, placebo, blinded outcome assessment, 13% post-randomisation exclusions	54 women with risk factors for preterm delivery	4 g magnesium gluconate/day from approx. 23 weeks' gestation	Preterm labour	
Zurich, 1988	R: based on subjects' date of birth, placebo, blinded outcome assessment, 1% post-randomisation exclusions	568 women at 16 weeks' gestation with normal and high-risk pregnancies	15 mmol magnesium aspartate HCl/day from 16 weeks to delivery	PE, preterm labour, gestational age at delivery, LBW	

AC, allocation concealment; B, blinding; FU, follow-up; Mg Asp HCl, magnesium aspartate hydrochloride; R, randomisation sequence.

TABLE 92 *Trial details of marine oil and other prostaglandin supplementation during pregnancy*

Study	Methods	Participants	Interventions	Outcomes	Notes
Angola, 1992	R: random number table AC: no information (B) FU: not reported B: Outcome assessments partially blinded – olive oil and evening primrose oil + fish oil capsules identical, but both different to magnesium oxide	100 primiparous and multiparous women, 14–40 years and ≤16 weeks' gestation	Marine oil: 8 capsules/day evening primrose oil + fish oil (providing 296 mg GLA, 144 mg EPA, 80 mg DHA/day) Control: 8 capsules olive oil/day	Women: PIH, oedema, PE, eclampsia. Babies: birthweight (<2000 g and >2000 g)	No estimate of sample size is given. Reported dietary intake of women at study entry was poor. 3-arm study – 50 women allocated magnesium oxide excluded from this review
Denmark, 1992	R: 3-arm trial in a ratio of 2:1:1 AC: sealed, opaque envelope containing a randomisation number (A) FU: complete (A) B: patients and outcome assessment was blinded, but 85% of women in the fish oil group and 50% in the olive oil group correctly identified their group allocation	533 women, approximately 30 weeks' gestation, aged 18–44 years. Excluded: history of placental abruption, serious bleed in current pregnancy, use of prostaglandin inhibitors, multiple pregnancy, fish allergy or regular intake of fish oil	Marine oil: fish oil (2.7 g *n*-3 fatty acids/day) given as 4 × 1-g capsules/day. Control: either 4 × 1-g capsules olive oil/day or no supplement	Women: SBP, DBP, PIH, PE. Babies: duration of gestation, birthweight, birth length	Sample size estimates were done but not reported in the papers because they were regarded as post-festum by authors (personal communication). Women completed baseline information regarding fish intake
England, 1995	R: computer-generated random numbers AC: sealed, opaque, numbered envelopes in hospital pharmacy. Pharmacy staff allocated the trial treatments (A) FU: 0.4% excluded (A) B: for participants and outcome assessors yes, for carers not stated	232 women at 19–26 weeks with high-risk singleton pregnancy: history of 1 or more small babies (birthweight <3rd centile), pregnancy hypertension, unexplained stillbirth, or a primigravida with abnormal uterine Doppler at 24 weeks' gestation	Marine oil: fish oil (2.7 g of MaxEPA/day) given as 9 capsules/day (provided 1.62 g EPA and 1.08 g DHA/day) Control: matching air-filled capsules. Treatment stopped at 38 weeks' gestation	Women: PIH, PE Babies: birthweight <3rd centile	Sample size estimate is given for proteinuric hypertension. All women were asked to avoid NSAIDs Compliance: 50% of women in the fish oil group and 57% of women in the placebo group took <70% of capsules
Europe, 2000	R: "packages ordered in a random way as to oil type" AC: "randomisation identified a package number at the relevant centre" (A) FU: 3% excluded (A) B: participants and outcome assessments blinded, but a questionnaire	Subset A–D recruited 1477 women at ≤16 weeks' gestation. Subset A included 232 women with a previous preterm birth. Subset B included 280 women with previous IUGR. Subset C included	Marine oil: fish oil (1.3 g EPA and 0.9 g DHA/day), given as 4 capsules/day. Control: matching olive oil capsules	Subset A: preterm birth, low birthweight. Subset B: small-for-gestational age, low birthweight. Subset C: PIH and PE Subset D: preterm birth, small for	Multicentre study with 6 subsets (A–F). Each had a standard protocol, and were mutually exclusive. Subsets A–D included in this review Sample size estimates were modified during the course of the study

continued

TABLE 92 *Trial details of marine oil and other prostaglandin supplementation during pregnancy (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
	indicated 80% of women in fish oil group could guess their allocation	386 women with previous PIH. Subset D included 579 women with twins. All subsets excluded women with diabetes mellitus, severe foetal malformation, previous placental abruption, drug or alcohol abuse, use of NSAIDs, use of fish oil or fish allergy		gestational age, low birthweight. For the combined subsets: prolonged gestation, maternal morbidity and mortality, infant morbidity	Subsets E–F excluded as "therapeutic" – women with PE (E) or suspected IUGR (F)
The Netherlands, 1994	R: randomisation performed by hospital pharmacy. No other information AC: unclear (B) FU: 7.3% excluded (B) B: participants and outcome assessors were blinded	63 women at 12–14 weeks' gestation with a history of IUGR, ±PIH in the previous (index) pregnancy	Marine oil: 3 g EPA/day, given as 12 capsules/day. Each capsule contained 250 mg EPA. No information about the DHA content of the capsules. Control: 12 capsules coconut oil/day	Women: pregnancy induced hypertension Babies: birthweight <10th percentile	Sample size estimate was based on the first randomised study of aspirin in high-risk pregnancies
USA, 2003	R: computer-generated randomisation schedule AC: unclear (B) FU: 17% excluded (C) B: for women, and outcome assessors yes, for carers, not reported	350 women with singleton pregnancies, 16–36 years, between 24 and 28 weeks' gestation at enrolment. Excluded if diabetic. Majority of women were socially disadvantaged and black (73%)	Marine oil: DHA-enriched eggs. Each egg had 133 mg DHA. Women were asked to eat 12 eggs per week but reported eating 5.5 per week. Control: ordinary eggs. Each egg had 33 mg DHA. Women were asked to eat 12 eggs per week but reported eating 5.4 per week	Women: duration of gestation Babies: birthweight	Initial sample size was 285, but increased to 350 after a blinded review of the data was undertaken, after that first 100 births to refine power analysis

AC, allocation concealment; B, blinding; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FU, follow-up; GLA, γ-linolenic acid; IUGR, intrauterine growth restriction; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; R, randomisation sequence.

TABLE 93 *Trial details of antihypertensive drug therapy for mild to moderate hypertension during pregnancy (versus placebo only)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Caribbean Islands,1990	R: not stated AC: women given number corresponding to sealed envelope and treatment batch. Envelope with allocation kept by investigator, only opened if necessary. Envelopes collected at end of study (A) FU: 1 woman lost	155 women with singleton pregnancy at 20–36 weeks gestation, DBP <85 mmHg ×2 before 20 weeks and >84 mmHg after 20 weeks. Excluded: type 1 diabetes, congestive heart failure, cardiac block, asthma, prepregnancy HT, antihypertensive drug during current pregnancy	Exp: oxprenolol 160–320 mg ×2/day. Hydralazine 50–100 mg added if necessary to keep DBP <86 mmHg Control: Placebo, identical appearance	Women: death, mean BP, severe HT, proteinuria (>1+ or 0.25 g/l), additional antihypertensive, eclampsia, side-effects, elective delivery, Caesarean section, hospital admission, abruption Babies: perinatal death, preterm birth (<37 weeks), birthweight (mean), SGA (undefined), Apgar, admission to SCBU, RDS	Two centres. For 23 women (15%), treatment unblinded and other treatment started. Additional data provided by authors
Hong Kong, 1990	R: "randomised double-blind" AC: not stated (B)	41 nulliparous women admitted for PE (BP ⩾140/90 mmHg ×2 within 24 h)	Exp: labetalol 200 mg ×3/day. Control: placebo (character not stated)	Women: BP, severe HT, additional drug. Babies: birthweight (mean), SGA (<10th centile), gestation at birth (mean)	Trial reported as in progress in 1990. Missing data for some babies. Available only as an abstract
Ireland, 1991	R: cards with "test" or "control" sealed in envelopes, shuffled and then numbered in sequence AC: consecutive envelopes opened (B)	36 women <38 weeks' gestation, BP ⩾140/90 mmHg on two separate days, no proteinuria Excluded: If lived too far from the hospital to attend frequently	Exp: choice between atenolol 50–100 mg/day or methyldopa 750–2250 mg/day. If necessary, two drugs combined. Bendrofluazide 2.5–5.0 mg added as a third agent when necessary Control: no antihypertensive	Women: MAP, proteinuria Babies: perinatal death, Apgar, gestation at delivery, birthweight	Additional data provided by authors
Israel, 1992	R: blocks of 6 AC: trial drug supplied by pharmacy in packs with serial numbers (A)	60 women <35 weeks' gestation with DBP 85–99 mmHg ×2 12 h apart, and no treatment for HT during this pregnancy Excluded: multiple pregnancy, insulin-dependent diabetes	Exp: pindolol 5 mg ×2/day. Increased if necessary to 10 mg ×2/day Control: identical placebo If necessary, hydralazine added for pindolol group. In placebo group, pindolol given first, then hydralazine	Women: additional drug, days in hospital, proteinuria >2+ or >0.5 g/l, side-effects, Caesarean section Babies: perinatal death, gestation at delivery (mean), birthweight, Apgar, SGA (<10th centile), hypoglycaemia, jaundice	

continued

TABLE 93 *Trial details of antihypertensive drug therapy for mild to moderate hypertension during pregnancy (versus placebo only) (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Italy, 1997	R: "randomly allocated" AC: not stated (B)	100 primigravid women at 26–36 weeks' gestation with SBP 140–160 mmHg and DBP 90–110 mmHg and proteinuria <300 mg/24 h Excluded: if other medical maternal or foetal pathology	Exp: nifedipine 40–120 mg/day orally and bed rest Control: bed rest alone	Women: severe HT, proteinuria, days in hospital before delivery Babies: Stillbirth, neonatal death, gestation at delivery (mean), birthweight, placental weight, SGA (undefined)	
Italy, 1998	R: stratified by centre and type of hypertension AC: central telephone (A) FU: 22 (8%) lost. Follow-up of children at 18 months: 190/252 (77%) responded to postal survey	283 women at 12–34 weeks' gestation, with mild–moderate HT (DBP 90–110 mmHg ×2 4 h apart) Excluded: chronic diseases (diabetes, renal disease), foetal malformation, previous antihypertensive drug	Exp: slow release nifedipine 20–80 mg ×2/day orally. Control: no antihypertensive	Women: Severe HT, proteinuria, Caesarean section, admission to intensive care Babies: perinatal death, birthweight, SGA (<10th centile), preterm birth, admission to SCBU, hyperglycaemia, jaundice, RDS, other serious neonatal problems	Multicentre, 33 hospitals Data from follow-up excluded as >20% lost
South Africa, 1991	R: cards in a box AC: cards labelled R and Q picked blindly from a box, these identified drug container (B)	32 women at 12–30 weeks' gestation with singleton pregnancy, BP ⩾140/90 mmHg ×2 at least 6 h apart, no proteinuria, no antihypertensive drug, no other drug treatment	Exp: prazosin 1–5 mg ×3/day Control: identical placebo	Women: severe HT, proteinuria, abruption, Caesarean section Babies: perinatal death, gestation at delivery (mean), birthweight, SGA (<10th centile) preterm birth	The trial stopped early
Sweden, 1984	R: not stated AC: telephone randomisation, no further details (B)	52 women in clinic, <37 weeks gestation, singleton pregnancy, BP ⩾140/90 mmHg or increase of ⩾30 mmHg SBP or 15 mmHg DBP ×2 within 24 h Excluded: imminent eclampsia, serious foetal distress, severe HT, Rhesus disease, diabetes, "social or psychological handicaps"	Exp: metoprolol 100–200 mg ×2/day Control: identical placebo ×2/day	Women: proteinuria ⩾2+, severe HT, side-effects, hospital admission, abruption, Caesarean section Babies: perinatal death, gestation at delivery (mean), Apgar (mean)	Additional data provided by authors

continued

TABLE 93 *Trial details of antihypertensive drug therapy for mild to moderate hypertension during pregnancy (versus placebo only) (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Sweden, 1985	R: not stated AC: "envelope randomisation". No further details (B) FU: 7 (4%) lost	168 women in ward, singleton pregnancy, <37 weeks, DBP ⩾90 mmHg ×2, no proteinuria Excluded: diabetes, asthma, heart disease, psychiatric or psychological disorders	Exp: metoprolol 50–200 mg/day + hydralazine 50–300 mg/day Control: no antihypertensive	Women: severe HT, proteinuria (>1+ or 0.25 g/l), side-effects, abruption, Caesarean section Babies: stillbirth, neonatal death, preterm birth, SGA (undefined), bradycardia, hypoglycaemia, Apgar, RDS	Multicentre, not stated how many hospitals. Additional data provided by authors
Sweden, 1995	R: "randomised by numbers to treatment with capsules" in blocks of 6 AC: details of allocation in sealed envelopes, opened if severe complications or side-effects (B) FU: 7 (6%) lost	118 women at 26–37 weeks, singleton pregnancy, DBP 95–110 mmHg Excluded: if delivery expected within 1 week, alcohol or drug abuse	Exp: isradipine (slow release) 5 mg ×2/day Control: placebo ×2/day	Women: eclampsia, severe HT (DBP ⩾110 mmHg), proteinuria ⩾2+, additional drug, MAP, Caesarean section, induction of labour, side-effects Babies: perinatal death, gestation at delivery (mean), admission to SCBU, birthweight (mean)	6 centres
UK, 1968	R: "allocated at random" AC: not stated (B)	100 women with DBP ⩾90 mmHg or more ×2, 48 h apart	Exp: methyldopa 250–1000 mg ×2/day + bendrofluazide 5–10 mg/day Control: no treatment	Women: mean BP, proteinuria, HT, length of gestation Babies: birthweight (mean), perinatal death	Women divided into two groups: "moderate", DBP ⩾90 mmHg (n = 42) and "severe", DBP ⩾100 mmHg (n = 58). For main outcomes results presented together
UK, 1976	R: "randomly allocated" AC: not stated (B) FU: 5 (2%) lost. Follow-up of 202 live-born children: at 4 years 34 (17%) lost to follow-up; at 7 years 7 (3%) lost to follow-up	247 women with BP ⩾140/90 mmHg if <28 weeks' gestation, or ⩾150/95 mmHg if >28 weeks' gestation ×2 24 h apart Excluded: diabetes, multiple pregnancy, Rh immunisation. Women >36 weeks excluded during 1st year of trial, thereafter excluded if >32 weeks	Exp: methyldopa 750–4000 mg/day Control: no antihypertensive. Hydralazine if severe hypertension	Women: severe HT, proteinuria, Caesarean section, elective delivery, side-effects Babies: perinatal death, birthweight (mean), gestation at delivery (mean), SGA (<2 SD below mean), nursed in an incubator, neurodevelopment at 4 and 7 years	

continued

TABLE 93 *Trial details of antihypertensive drug therapy for mild to moderate hypertension during pregnancy (versus placebo only) (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
UK, 1982	AC: envelope randomisation, no further information (B)	126 women with either chronic HT or PIH, and DBP >95 mmHg if <20 weeks or 95–109 mmHg if >20 weeks	Exp: labetalol 100 mg ×2/day, increased to maximum of 1200 mg/day Control: no antihypertensive. If necessary, hydralazine	Women: severe HT, proteinuria (undefined), Caesarean section, abruption Babies: perinatal death, SGA (<10th centile)	Additional data provided by authors
UK, 1983	AC: "allocated in double-blind and randomised manner" (B) FU: some data missing for 35 (29%). Data for each outcome only available for >80%. 110 children (92%) seen at 1 year	120 women with PIH in third trimester admitted for bedrest, SBP 140–170 mmHg and DBP 90–110 mmHg ×2, 24 h apart	Exp: atenolol 100–200 mg/day Control: placebo	Women: proteinuria (>0.5 g/24 h), severe HT, additional drug, side-effects, admission to hospital, Caesarean section Babies: perinatal death, SGA (<10th centile), bradycardia, hypoglycaemia, jaundice, RDS. At 1 year: cerebral palsy, IQ, weight	
UK, 1989	R: random numbers AC: trial drugs dispensed in pharmacy (A) FU: 8 (5%) lost	152 women in hospital at 20–38 weeks gestation, SBP 140–160 mmHg and DBP 90–105 mmHg ×2, 24 h apart, no proteinuria Excluded: history of HT, renal, metabolic, cardiovascular, respiratory or collagen disease	Exp: labetalol 100–200 mg ×3/day Control: identical placebo	Women: mean BP, severe HT, proteinuria (undefined), induction of labour, Caesarean section, days in hospital (mean), side-effects Babies: perinatal death, preterm birth, SGA (<5th centile), admission to SCBU, RDS	5 centres
UK, 1990	R: "randomised", no other information AC: not stated (B) FU: 4 (12%) lost	33 women 12–24 weeks' gestation with SBP 140–170 mmHg and DBP 90–110 mmHg ×2, 24 h apart	Exp: atenolol 50–200 mg/day Control: placebo (character not stated)	Women: mean BP, severe HT, side-effects Babies: stillbirth, birthweight, SGA (<5th centile), gestation at delivery (mean)	The trial was stopped early when the principal investigator left Glasgow. Additional data provided by authors

continued

TABLE 93 *Trial details of antihypertensive drug therapy for mild to moderate hypertension during pregnancy (versus placebo only) (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
UK, 1992	R: Stratified by parity AC: numbered sealed opaque envelopes (A)	114 women with singleton pregnancy at 24–39 weeks gestation, DBP >90 mmHg for >24 h and no proteinuria Excluded: psychoneurosis, cardiac abnormality, diabetes, asthma, antenatal drug treatment	Exp: labetalol 100 mg ×2/day, increased up to 400 mg ×3/day Control: no antihypertensive	Women: proteinuria (>1+ or 0.25 g/l), stay in hospital, side-effects, elective delivery, Caesarean section Babies: perinatal death, gestation at delivery (mean), preterm birth (<37 weeks), SGA (<5th centile), admission to SCBU, stay in hospital (mean)	Additional data provided by authors
USA, 1979	R: "allocated randomly" AC: not stated (B)	58 women with HT before pregnancy or BP ⩾140/90 mmHg ×2 more than 24 h apart before 20 weeks Excluded: DBP >100 mmHg, nulliparous, other major medical or obstetric problem	Exp: methyldopa 750–2000 mg/day, hydrochlorothiazide 50 mg/day, hydralazine 75–250 mg/day Control: no antihypertensive	Women: severe HT, proteinuria (>1+ or >300 mg/l in 24 h), Caesarean section Babies: perinatal death, gestation at delivery, birthweight <2500 g, foetal distress, SGA (undefined)	In exp group 11 women had methyldopa + hydrochlorothiazide, 10 hydralazine + hydrochlorothiazide, 8 all three
USA, 1987	AC: physician drew sealed envelope with assignment (B) FU: 14 (7%) lost, but data reported for perinatal death	200 primigravid women in hospital at 26–35 weeks gestation, SBP 140–160 mmHg, DBP 90–110 mmHg, proteinuria >0.3 g/l, uric acid >4.6 mg/dl Excluded: associated medical and obstetric complications, other antihypertensive drug	Exp: labetalol 300 mg/day, increased to max. 2400 mg/day + hospitalisation Control: hospitalisation alone	Women: severe HT, increased proteinuria, eclampsia, abruption, Caesarean section, renal function Babies: perinatal death, gestation at delivery (mean), birthweight (mean), admission to SCBU, SGA (<10th centile)	
USA, 1987a	R: "randomly allocated" AC: not stated (B)	25 women at <34 weeks' gestation, singleton pregnancy, BP 140/90 mmHg ×2 at least 6 h apart, no proteinuria. Presumed chronic HT	Exp: methyldopa 750 mg ×3/day to 2000 mg ×4/day Control: placebo If severe PE, hydralazine or $MgSO_4$ added	Women: MAP, new proteinuria (⩾2+), PE (defined as sudden rise of 30 mmHg SBP or 15 mmHg DBP and weight gain >2 lb/week, or proteinuria >2+), elective delivery, side-effects Babies: perinatal death, gestation at delivery (mean), birthweight (mean)	

continued

TABLE 93 *Trial details of antihypertensive drug therapy for mild to moderate hypertension during pregnancy (versus placebo only) (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
USA, 1990	R: computer-generated random numbers AC: "envelope randomisation" (B) FU: 37 (12%) lost	300 women in ward with chronic mild-moderate HT at 6–13 weeks' gestation. All had chronic HT before pregnancy and no associated medical complications	Exp: (1) methyldopa 750–4000 mg/day (no other details). (2) Labetalol 300–2400 mg/day (no other details) Control: no antihypertensive	Women: PE (defined as HT, proteinuria, and hyperuricaemia), additional drug, hospital stay, abruption, congestive heart failure Babies: perinatal death, birthweight <2.5 kg, preterm birth, SGA (undefined), admission to SCBU, hypoglycaemia, Apgar	36% of women were taking an antihypertensive at the time of trial entry
USA, 1992	R: computer-generated random numbers AC: physician drew sealed envelope containing assignment (B) FU: 3 (2%) lost	200 primigravid women at 26–36 weeks' gestation, SBP 140–160 mmHg and/or DBP 90–110 mmHg 24 h after hospitalisation, proteinuria >300 mg/24 h, and/or uric acid >6 mg/dl Excluded: medical or obstetric complications, foetal compromise	Exp: nifedipine 40–120 mg/day Control: bed rest alone	Women: MAP, severe proteinuria (>5 g/24 h), antenatal hospital stay (mean), Caesarean section, abruption, HELLP syndrome Babies: stillbirth, neonatal death, birthweight, preterm birth, SGA (<10th centile), admission to SCBU	Method of measuring blood pressure not mentioned

AC, allocation concealment; BP, blood pressure; DBP, diastolic blood pressure; Exp, experimental; FU, follow-up; HELLP, syndrome of haemolysis, elevated liver enzymes and low platelets; HT, hypertension; IUGR, intra uterine growth restriction; MAP, mean arterial pressure; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; R, randomisation sequence; RDS, respiratory distress syndrome; SBP, systolic blood pressure; SCBU, special care baby unit; SGA, small for gestational age.

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications*

Study	Methods	Participants	Interventions	Outcomes	Notes
Australia, 1988	R: random number sequence linked to an identification number given to each woman at trial entry AC: in hospital pharmacy (B)	46 women with singleton pregnancy at 28–36 weeks and concern about foetal welfare, in whom umbilical artery velocity waveform systolic/diastolic ratio >95th centile Excluded: if DBP >110 mmHg or >90 mmHg with proteinuria, and if maternal condition likely to lead to delivery	Antiplatelet: aspirin 150 mg daily Control: placebo	Women: Caesarean section; induction; placental weight Babies: stillbirth; neonatal death; ventilation; admission to SCBU; cerebroventricular haemorrhage; birthweight; gestation at delivery; head circumference; Apgar scores	2 groups: high umbilical artery systolic/diastolic ratio (>95th but <99.5th centile) and extreme umbilical artery systolic/diastolic ratio (>99.5th centile). Data incomplete for second group, so only included if available for all women
Australia, 1993	R: "randomised" AC: capsules dispensed by pharmacy (B)	110 women at 12–24 weeks with either DBP ⩾90 or SBP ⩾140, or a history of PE	Antiplatelet: 100 mg aspirin. Control: placebo	Women: PE	
Australia, 1995	R: not reported AC: Instructions about tablets in numbered sealed opaque envelopes. Women shown 5 envelopes and asked to choose 1. (B)	51 women at 28–36 weeks with ultrasound diagnosis of restricted foetal growth, umbilical artery. Doppler systolic/diastolic ratio >95th centile. No previous aspirin during pregnancy	Antiplatelet: 100 mg aspirin Control: starch tablets	Women: none Babies: mean gestation at birth; birthweight (<3 and 10th centile); Apgar 5 minutes; admission SCBU; IVH	
Australia, 1995a	R: randomised by "envelope method", no other information AC: unclear (B) FU: 1 woman (5%) excluded as miscarriage at 20 weeks (B)	21 women with renal disease. 20 had previous early onset PE	Antiplatelet: dipyridamole 75–100 mg × 4/day + subcutaneous heparin 7500 u ×2/day Control: no treatment	Women: HT; proteinuria; 'complications'; Caesarean section Babies: neonatal death; premature birth (<37 weeks); IUGR (<10th centile)	Trial stopped early on advice of *ad hoc* committee, due to complications in control group
Australia, 1996	R: "randomised trial" AC: unclear (B) B: "double blind"	52 primigravid women with abnormal uterine artery waveforms on Doppler examination at 22–24 weeks	Antiplatelet: aspirin 60 mg/day. Control: placebo	Women: PIH, PE, Caesarean section, abruption Babies: death, preterm birth (<37 weeks), IUGR (<10th centile), admission to SCBU	

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Australia, 1996a	R: not reported AC: by taking the next in a series of number identical blister packs (A) FU: 2 women withdrew (2%), one from each group (A)	104 primiparous women with abnormal uterine Doppler flow at 18 weeks (systolic/diastolic ratio >3.3 or SBP/DBP >3 and early diastolic notch)	Antiplatelet: aspirin 100 mg/day Control: placebo	Women: PIH; PE; eclampsia; APH Babies: preterm birth; SGA	Selected from 955 women screened, of whom 186 had abnormal waveforms
Australia, 1997	R: series of random numbers AC: unclear (B) FU: 10% (12) of women excluded as they withdrew before starting treatment (C)	120 women at high risk of PE because of one of: pre-existing HT (BP ⩾140/90 mmHg prior to pregnancy ×2, or antihypertensive therapy), renal disease, previous early severe PE Excluded: aspirin allergy, aspirin-sensitive asthma, pre-existing bleeding diathesis or multiple pregnancy	Antiplatelet: aspirin 100 mg modified release daily from 17–19 weeks until delivery Control: placebo	Women: proteinuria; duration of pregnancy; indications for and mode of delivery; maximum antenatal BP; "complications" Babies: perinatal death; birthweight; Apgar scores	
Austria, 1992	R: unclear AC: coded packages of medication (A) B: participants and assessment of primary outcome blinded	41 primigravid women with positive roll-over test (increase of 20 mmHg in DBP) at 28–32 weeks Exclusions: existing HT, renal gut, lung or heart disease, IUGR, impending preterm birth	Antiplatelet: aspirin 80 mg/day until 37 weeks Control: placebo	Women: PIH; PE; Caesarean section; preterm birth (37 weeks) Babies: stillbirths; neonatal death; SGA (<10th centile); neonatal bleeding; admission to SCBU	
Barbados, 1998	R: computer-generated AC: randomly numbered treatment packs dispensed by pharmacist (A) FU: 55/3697 women (1.5%) excluded: 42 because of pack labelling errors, 8 not pregnant and 6 lost to follow-up (A)	3697 women at 12–32 weeks' gestation Excluded: if increased risk of bleeding, aspirin allergy, high likelihood of immediate delivery or previous placental abruption	Antiplatelet: aspirin 75 mg controlled release daily until delivery Control: placebo	Women: PE; APH; PPH; Caesarean section; duration of pregnancy; use of antihypertensives and anticonvulsants Babies: stillbirth; death before hospital discharge; days in SCBU; bleeding problems; birthweight	

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Brazil, 1996	R: central telephone randomisation AC: (A) FU: 39/1009 women (4%) lost to follow up (A)	1009 women at 12–32 weeks' gestation (41% ≤20 weeks) "who the obstetrician thought were at risk" of PE – generally low/moderate risk (primip 47%, chronic hypertension 47%, diabetes 6%) Excluded: bleeding risk, asthma, allergy to aspirin, gastric ulcer, placenta praevia	Antiplatelet: aspirin 60 mg/day Control: placebo	Women: PE; Caesarean section; APH Babies: SGA; perinatal death; preterm birth; neonatal bleeding	Conducted in 12 university teaching hospitals and 182 obstetric offices
Brazil, 1992a	R: randomly divided into 2 groups. No further information AC: unclear (B) FU: 4 women excluded (7%) (B) B: not reported	56 women in 2nd or 3rd quarter of pregnancy who were young primigravidas, or had chronic HT, diabetes, previous PIH, twin pregnancy, or a family history of HT	Antiplatelet: acetylsalicylic acid 60 mg/day in a solution of 50% D-lysine Control: no intervention	Women: PIH Babies: death, birthweight (mean)	
China, 1996	R: "randomised study" AC: unclear (B) B: "double-blind"	84 women with a singleton pregnancy at high risk of IUGR, and 28–34 weeks' gestation	Antiplatelet: 75 mg aspirin, from 28 to 34 weeks for 6–8 weeks Control: placebo	Women: PIH; Caesarean section; preterm delivery Babies: neonatal death; IUGR; IVH	
China, 1999	R: randomisation by offering patient 5 sealed envelopes (2 aspirin, 2 calcium, 1 placebo) AC: sealed envelopes (B) FU: 22 women (6%) lost to follow-up (B)	215 primigravid women with MAP >80 and <106 early in 2nd trimester and MAP >60 at 22–24 weeks	Antiplatelet: aspirin 80 mg/day until delivery Control: unclear, no placebo mentioned	Women: PIH; PE; eclampsia; Caesarean section Babies: gestation at delivery (mean); birthweight; Apgar scores	Authors provided additional information. 132 women allocated aspirin, 154 calcium and 83 control. Women allocated calcium excluded from this review
CLASP, 1994	R: centralised computer randomisation AC: by telephoning a central randomisation service. (A) FU: 0.6% (55) lost (A) Follow-up of surviving children with GP letter at 12 months in UK (4688 with 4675	9364 women at 12–32 weeks' gestation at risk of PE or IUGR, or women with established PE or IUGR	Antiplatelet: aspirin 60 mg daily until delivery Control: placebo	Women: death; eclampsia; PE; bleeding complications; Caesarean section; induction; problems with epidural analgesia; PPH; transfusion; use of antihypertensives or anticonvulsants; compliance	International study Compliance: 96% started treatment, 88% took it for at least 80% of the time from entry-delivery. For some outcomes data not presented

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
	alive at 12 months) and parental questionnaire at 18 months in UK and Canada (410 with 407 alive at 18 months). For GP letter, 89% response rate, for parental questionnaire 86% responded			Babies: stillbirth; neonatal death; mortality at 1 year; birthweight (mean) and centile (< 3rd); gestation at delivery; admission to SCBU; IVH; other neonatal bleeding. Follow-up at 12–18 months: developmental delay; congenital malformations; respiratory problems; hospital admissions	separately for prophylaxis and treatment. Follow-up data only for centres in the UK and Ottawa, Canada
Colorado, 1993	R: "randomised", no further information AC: unclear (B) FU: unclear	100 nulliparous women with multiple pregnancy in "early pregnancy"	Antiplatelet: aspirin 81 mg/day Control: placebo	Women: PIH; PE. Babies: none reported	Multicentre trial, stopped early due to slow recruitment
EPREDA, 1991	R: randomised by centre with stratification for one or two previous poor outcomes AC: unclear (B) FU: 1 woman excluded after randomisation (A)	323 women at 15–18 weeks' gestation with poor outcome during previous 2 pregnancies, at least one being IUGR, or IUGR in one previous pregnancy Excluded: twins, uterine malformation, renal disease, secondary hypertension, diabetes, cardiac disease	Study 1: antiplatelet: aspirin 150 mg daily, or aspirin 150 mg plus dipyridamole 225 mg daily Control: placebo Study 2: Antiplatelet: aspirin 150 mg and dypridamole 225 mg daily Control: aspirin 150 mg daily	Women: death; DBP >90 mmHg; proteinuria; abruption; Caesarean section <34 weeks; "poor outcome" Babies: stillbirth; neonatal death; ventilation; transfer to intensive care; birthweight <10th centile; duration of hospital stay (mean)	Two separate comparisons within the one study. Only data for study 1 included in the review
ERASME, 2003	R: computer-generated randomisation codes, stratified by centre in blocks of 8 AC: via online 24-hour computer (A)	3294 primiparous women at 14–20 weeks' gestation with singleton or multiple pregnancy Excluded: known HT, indication or contraindication to aspirin	Antiplatelet: aspirin 100 mg to 34 weeks Control: placebo	Women: PIH; PE; placental abruption; Caesarean section; induction; HELLP; PPH; hospital admission; side-effects Babies: stillbirth; neonatal death; SGA (<10th and <3rd centile); neonatal IVH; other bleeding; admission to SCBU	Multicentre, 28 centres in France and one in Belgium

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Finland, 1993	R: unclear AC: sealed envelopes, no further details (B) FU: 5% (11) women excluded (B) B: double-blind	208 women with pre-existing HT (BP >140/90 mmHg before pregnancy) or previous severe PE (in immediately preceding pregnancy), and 12–18 weeks gestation Excluded: women proteinuric before pregnancy	Antiplatelet: aspirin 50 mg daily Control: placebo	Women: exacerbation of HT ± proteinuria; Caesarean section; blood loss at delivery (mean); hospitalisation during pregnancy; bleeding time, DBP at 36 weeks (mean) Babies: perinatal death; admission SCBU; birthweight; SGA; gestation at delivery	3 centres
Finland, 1997	R: "randomised", no other information AC: unclear (B)	26 high-risk women with uterine artery bilateral notches on Doppler, at 22–24 weeks	Antiplatelet: aspirin 50 mg Control: no treatment	Women: PIH; PE; placental abruption; delivery <37 weeks Babies: stillbirth; IUGR (<10th centile); IVH on ultrasound; gestation at delivery (mean); birthweight	
Finland, 2002	R: randomisation in pharmacy AC: code broken when last woman delivered (A) FU: 4 women lost (A)	90 women at risk of PE or IUGR with abnormal uterine Doppler. 12–14 weeks' gestation	Antiplatelet: aspirin 0.5 mg/kg/day Control: placebo	Women: PIH; PE; Caesarean section Babies: death; gestation at delivery (mean); birthweight <2500 g; admission to SCBU; IVH	
France, 1985	R: "randomly allocated to group A or B", no other information AC: unclear (B) FU: 9% (9 women) excluded from analysis (2 lost to FU, 7 had miscarriage <16 weeks) (B)	102 women at high risk of PE or IUGR, i.e. several previous complicated pregnancies or vascular risk factors such as essential HT (BP >160/95 mmHg) or a family history of HT Excluded: women with secondary HT or known or suspected renal disease	Antiplatelet: aspirin 150 mg and dipyridamole 300 mg daily, from 3 months until delivery Control: no antiplatelet agent	Women: PIH (BP ⩾140/85 mmHg; PE; Caesarean section; abnormal bleeding during delivery or Caesarean section; abruption; headache Babies: stillbirth; neonatal death; foetal malformation; birthweight <10th and <3rd centile (livebirths only); haemorrhagic complication (undefined)	
France, 1990	R: "randomised study", no other information AC: unclear (B)	91 women at high risk of PIH because of previous early onset PE, severe IUGR or foetal death due to placental insufficiency	Antiplatelet: aspirin 100 mg and dipyridamole 300 mg daily until delivery Control: no treatment	Women: PIH ± PE; duration of pregnancy (mean) Babies: foetal death; birthweight (mean)	Published in abstract form only

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Germany, 2000	R: computer-generated AC: blister packs, and the code held separately from person doing randomisation (A)	43 women with singleton pregnancy, <20 weeks' gestation with early IUGR, impaired uteroplacental flow, chronic HT, or history of IUGR, stillbirth, or PE Excluded: diabetes, pre-existing HT or proteinuria, foetal malformation	Antiplatelet: aspirin 100 mg/day Control: placebo	Women: PE Babies: gestation at birth (mean); birthweight (mean)	
India, 1993	R: unclear AC: not reported (B) B: assessment of outcome not blinded	100 women with PIH at 24–36 weeks' gestation	Antiplatelet: aspirin 60 mg/day Control: "standard treatments only"	Women: severe PIH (proteinuria not specified); eclampsia; preterm (gestation not specified) Babies: stillbirths; neonatal deaths; SGA	Unclear whether aspirin group also had "standard treatment"
India, 1994	R: "randomly allocated", no other information AC: unclear (B)	94 nulliparous women with PIH in the 3rd trimester (SBP ⩾140 mmHg, and/or DBP ⩾90 mmHg, on two occasions more than 6 h but less than 24 h apart)	Antiplatelet: aspirin 75 mg daily, until 10 days before EDD Control: no antiplatelet agent	Women: development of PE; eclampsia or abruption; mean fall in BP; rise in BP Babies: neonatal death; admission to SCBU; gestational age at delivery (mean); birthweight (mean); Apgar at 1 minute; macroscopic haematuria	Exclusion criteria not described
India, 1999	R: "randomised trial", no further details AC: unclear (B) FU: 3 women (2%) lost to follow-up (A)	163 women with PIH at 20–32 weeks	Antiplatelet: aspirin 60 mg daily Control: placebo	Women: PE; eclampsia Babies: perinatal death; IUGR <10th centile	Available as an abstract only
Israel, 1989	R: computer-generated randomisation list AC: coded packages of 100 pills allocated according to random number list (A)	65 women with either twin pregnancy, a history of PE or in first pregnancy, and a positive roll-over, test at 28–29 weeks' gestation	Antiplatelet: aspirin 100 mg daily Control: placebo	Women: PIH ± proteinuria (BP >140/90 mmHg on at least two occasions within 24 h; proteinuria >1 g/24 h); Caesarean section; length of hospitalisation (mean) Babies: stillbirth; neonatal death; gestation at birth (mean); born <37 weeks; birthweight <10th centile; Apgar scores; ventilation; admission to SCBU; IVH; haematuria; cephalhaematoma; sepsis workup	

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Israel, 1990	R: "divided randomly into two groups", no other information AC: unclear (B)	47 nulliparous at 30–36 weeks with mild PIH (BP >140/90 but <165/110 mmHg), no signs of PE, normal platelets and proteinuria >500 mg/24 h Excluded: if aspirin sensitivity, chronic hypertension, renal disease or antihypertensive drugs	Antiplatelet: aspirin 100 mg until 5 days before EDD Control: placebo	Women: PE (BP >165/110 mmHg with low platelet count and/or proteinuria >500 mg/24 h); Caesarean section Babies: gestation at delivery; birthweight (mean); Apgar score at 5 minutes (mean)	
Israel, 1994	R: randomisation list AC: allocated to a coded package according to randomisation list (B) FU: 1 woman withdrawn as thrombocytopaenia – data included where possible (A)	48 women with twin pregnancies at about 18 weeks	Antiplatelet: aspirin 100 mg/day Control: placebo	Women: PIH; PE; Caesarean section; IUGR Babies: preterm birth; perinatal mortality; birthweight discordancy (15%)	
Italy, 1989	R: "randomly assigned", no other information AC: unclear (B)	33 women at risk of HT because of essential HT or a significant previous obstetric history (placental insufficiency causing foetal death, severe IUGR or PE <32 weeks) Excluded: if antiphospholipid antibodies	Antiplatelet: aspirin 60 mg daily from 12 weeks until delivery Control: placebo	Women: PIH (BP >140/90 mmHg and BP previously normal); gestation at delivery (mean) Babies: perinatal death; assisted ventilation; haemorrhagic complications; birthweight <10th centile; born <37 weeks' gestation; Apgar scores, RDS	
Italy, 1993	R: telephone randomisation AC: by telephone call to one of two randomisation centres. (A) FU: 6% (64) of women lost to follow-up (B) Follow-up of children: postal questionnaire to parents for 1083 children at 18 months (excludes 41 born before follow-up started). One reminder and up to	1106 women at 16–32 weeks' gestation. Prophylactic: age <18 or >40 year, mild-moderate chronic HT, nephropathy with normal renal function and BP, PIH or IUGR in previous pregnancy, twin pregnancy) Therapeutic: PIH (DBP 90–110 mmHg) or early IUGR (foetal	Antiplatelet: aspirin 50 mg daily Control: no treatment	Women: PIH ± proteinuria; abruption; induced or spontaneous abortion; Caesarean section Babies: perinatal mortality; gestation at delivery; birthweight <10th or <5th centile; admission to SCBU; IVH; gastric bleed. At 18 months: death; malformations height and weight <10th centile, and respiratory; motor; sight; hearing or language problems	Data not presented separately for prophylaxis and treatment, so all women included in prophylaxis for this review For follow-up, no difference between responders and non-responders in

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
	3 telephone calls for non-responders. Data for 427 aspirin (72%) and 361 no treatment (73%)	abdominal circumference ⩾2 SD below mean for gestational age) Excluded: chronic disease, allergy to aspirin, foetal malformation			baseline characteristics and outcome at discharge from hospital. Also, no differences in information collected by post or by telephone
Italy, 1999	R: "randomised" AC: unclear (B) FU: 9 women (4%) stopped treatment early, 4 aspirin and 5 control (A)	216 women aged 18–36 years with pre-existing HT or history of severe PE, at 12–26 weeks	Antiplatelet: 50 mg aspirin/day Control: placebo	Women: PE	
Jamaica, 1998	R: women given sequential numbers on admission which identified a bottle containing either aspirin or placebo AC: unclear (B) FU: 179 (3%) lost to follow-up. 50 women with multiple pregnancy excluded. Some women entered twice and given aspirin and placebo excluded, but numbers not given (A)	6275 primiparous women, 12–32 weeks' and no contraindication to aspirin	Antiplatelet: aspirin 60 mg daily until delivery Control: placebo	Women: HT (DBP ⩾90 mmHg or SBP ⩾140 mmHg or rise of 25 mmHg DBP or 40 mmHg SBP); PE; eclampsia; Caesarean section; antenatal admission; PPH Baby: perinatal death; preterm birth; birthweight <2500 g; admission to SCBU; Apgar; IVH; other neonatal bleeding	144 aspirin-treated women and 161 placebo randomised after 32 weeks, but included in analysis
Japan, 1999	R: "enrolled randomly", no further information AC: unclear (B)	40 women with severe PE in previous pregnancy. Enrolled at 6–18 weeks, treatment started at 20 weeks	Antiplatelet: ozagrel hydrochloride, 400 mg/day from 20 weeks to delivery Control: placebo	Women: PE Babies: preterm delivery; delivery <32 weeks; SGA	Ozagrel is a thromboxane synthetase inhibitor
The Netherlands, 1986	R: randomisation list AC: coded packages, allocated according to list (B) FU: 2 women in treatment group excluded because of non-compliance, but data for some clinical outcomes reported (A)	46 angiotensin II-sensitive primigravid women at 28 weeks' gestation with uncomplicated pregnancies, no history of HT, cardiovascular or renal disease, DBP <80 mmHg and taking no drugs except iron	Antiplatelet: aspirin 60 mg daily Control: placebo	Women: eclampsia; PIH (DBP at least 95 mmHg on two or more occasions 6 h apart); PE (HT as above plus proteinuria >0.5 g/l); preterm delivery (<37 weeks); Caesarean section Babies: stillbirth; neonatal death; RDS; birthweight for gestational age <10th or <3rd centile	

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
The Netherlands, 1989	R: randomisation list AC: coded packages, allocated according to list (B)	10 primigravid women with chronic HT and a positive angiotensin II sensitivity test at 26 weeks' gestation. No proteinuria, BP <90 mmHg diastolic, serum creatinine <70 μmol/l and an adequately grown foetus	Antiplatelet: aspirin 60 mg Control: placebo	Women: PIH (rise in DBP of 20 mmHg or more); PE (HT as before + proteinuria ⩾500 mg/l); Caesarean section Babies: birthweight <10th centile	All women had methyl dopa
The Netherlands, 1991a	R: randomisation sheet AC: coded packages allocated according to a randomisation sheet. Code broken at 34 weeks, some women then started aspirin (B)	36 women with a positive angiotensin II sensitivity test at 28 weeks	Antiplatelet: aspirin 60 mg daily from 28 to 32 weeks Control: placebo	Women: HT at 34 weeks Babies: stillbirths	
South Africa, 1988	R: computer-generated random numbers, no other information AC: unclear (B) FU: 1 woman (2%) lost (A)	44 women with elevated mid-trimester BP, 12–28 weeks' gestation, DBP 80–105 mmHg, and otherwise normal	Antiplatelet 1: aspirin 81 mg daily Antiplatelet 2: aspirin 81 mg + dipyridamole 200 mg daily Control: no antiplatelet agent	Women: PE Babies: stillbirth	Published only as an abstract
Spain, 1997	R: computer-generated random numbers AC: tablets in identical blister packs. Allocated to 6 groups, according to treatment and timing of administration (A) FU: 7 women (6%) excluded, because poor compliance or incomplete BP assessments (B)	107 women aged 18–40 years at <16 weeks' gestation and at moderate risk of PE. For example, family or own history of PIH, PE, chronic HT, cardiovascular or endocrine problem, bleeding or endocrine disease Excluded: multiple pregnancy	Antiplatelet: 100 mg aspirin Control: placebo	Women: PIH; PE; Caesarean section; abruption Baby: death; preterm birth (<37 weeks); IUGR	Testing the hypothesis that aspirin effects are time dependent, being greater in the evening

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
Spain, 1999	R: randomised. AC: tablets in identical blister packs. Allocated to 6 groups, according to treatment and timing of administration (A) FU: 15 women excluded (6%) because poor compliance or incomplete BP assessment (B)	255 women aged 18–40 years at <16 weeks' gestation at moderate risk of PE. For example, family or own history of PIH, PE, chronic HT, cardiovascular or endocrine problem, bleeding or endocrine disease Excluded: multiple pregnancy	Antiplatelet: 100 mg aspirin Control: placebo Each treatment group could also be allocated to 3 different times of the day	Women: mean 24 h BP Baby: IUGR	Testing the hypothesis that aspirin effects are time dependent, being greater in the evening. Data entered into the review from the main publication. Data for 341 women have been presented, but in abstract only and incomplete
Tanzania, 1995	R: unclear AC: packages coded A and B. No other information (B)	127 women with positive roll-over test Excluded: HT or increased BP before screening, proteinurea >300 mg	Antiplatelet: 80 mg aspirin daily Control: placebo	Women: PIH; PE Baby: none	
Thailand, 1996	R: unclear AC: identical treatment and placebo tablets in identical containers (100 per box) – patient chose a container "at random" FU: 10% lost to FU (C)	1500 low-risk nulliparous women at 18–22 weeks, ultrasound to confirm dates (mean age at randomisation 20.7 weeks). Exclusions: renal or cardiovascular disease, diabetes, twins, hypertension	Antiplatelet: aspirin 60 mg/day, until birth Control: placebo	Women: death; PIH; PE; eclampsia; Caesarean section; APH Babies: stillbirth; preterm birth; SGA	Author clarification of randomisation provided Compliance testing – 86% aspirin, 81% placebo
UK, 1990	R: computer-generated randomisation list AC: serially numbered bottles dispensed by pharmacist (A) FU: 6% (6) excluded (B)	106 primigravid women with persistently abnormal Doppler waveform studies at 24 weeks' gestation Excluded: aspirin allergy, diabetes, bleeding disorders, peptic ulceration, systemic lupus erythematosus	Antiplatelet: aspirin 75 mg daily Control: placebo	Women: PIH; proteinuria; HT <37 weeks' gestation; Caesarean section for complications of HT Babies: perinatal death; birthweight <5th centile	*Lancet* contacted to confirm this study has not been retracted

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
UK, 1992	R: "Simply randomised with block size four" AC: unclear (B)	(a) 18 normal primigravidae, 16 weeks' gestation, and (b) 16 primigravidae with gestational HT but no proteinuria at >20 weeks	Antiplatelet: aspirin 60 mg daily until delivery Control: placebo	Women: duration of labour; blood loss at delivery Babies: <36 weeks at delivery; birthweight <10th centile; minor bruising of newborn	Continuous data only presented for some outcomes
UK, 1992b	R: "randomly allocated", no other information given AC: unclear (B)	26 women with history of recurrent miscarriage or connective tissue disorder, and positive anticardiolipin antibodies	Antiplatelet: aspirin 75 mg daily Control: no treatment	Women: miscarriage Babies: neonatal death	
UK, 1995	R: computer-generated randomisation list AC: sealed envelopes (B) FU: 4 women (3%) excluded (A)	122 women with no previous pregnancy proceeding beyond 12 weeks, Hb >13.2 g/dl at 12–19 weeks gestation, DBP <90 mmHg and no proteinuria Excluded: multiple pregnancy, diabetes, recurrent miscarriage or contraindication to aspirin	Antiplatelet: aspirin 75 mg from 18 weeks until delivery Control: placebo	Women: PIH; PE; eclampsia; abruption; Caesarean section; induction of labour; side-effects Babies: perinatal mortality; delivery <34 weeks' gestation; admission to SCBU; birthweight <5th centile	Trial conducted 1989–92
USA, 1993	R: unclear AC: "efforts were made to conceal randomisation" (B) FU: <1% loss (A) B: participants and outcome assessment blinded	604 primiparous women at 24 weeks, in single antenatal clinic Excluded: renal or collagen disease, diabetes, essential HT, multiple pregnancy	Antiplatelet: aspirin 60 mg/day, from 22 weeks Control: placebo	Women: PIH; PE; eclampsia; APH; Caesarean section; preterm delivery (<37, <34, <32 weeks) Babies: perinatal death; SGA	
USA, 1993a	R: "assigned randomly", no further details AC: unclear (B) FU:150 (5%) lost to follow-up (A)	3135 nulliparous women at 13–25 weeks with BP <135/85 mmHg and no proteinuria; out of the 4241 entered into a run-in compliance phase Excluded: chronic HT, diabetes, renal disease, other medical illness	Antiplatelet: aspirin 60 mg/day Control: placebo	Women: PIH; PE; eclampsia; Caesarean section; abruption; preterm delivery; PPH Babies: stillbirths; neonatal deaths; SGA <10th centile; bleeding	Mean gestation at trial entry 19.8 weeks

continued

TABLE 94 *Trial details of antiplatelet agents for preventing pre-eclampsia and its complications (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
USA, 1994	R: "randomised", no further details AC: unclear (B) FU: 5 (9%) women lost to follow-up (B)	54 women with chronic HT or previous severe PE, enrolled at 13–15 weeks	Antiplatelet: aspirin 100 mg sustained release/day until 37 weeks Control: placebo	Women: PE Babies: stillbirth; SGA	Published as abstract only
USA, 1998	R: computer-generated random numbers AC: packets with assigned numbers opened consecutively in each centre (A) FU: 36 women (1%) lost to follow-up (A)	2539 women at 13–26 weeks' gestation with insulin-treated diabetes, chronic HT, multiple pregnancy or PE in a previous pregnancy. Women with multiple pregnancy excluded if also diabetes, chronic HT or proteinuria	Antiplatelet: aspirin 60 mg daily Control: placebo	Women: PIH; PE; abruption; preterm delivery; PPH Baby: death; IUGR (<10th centile); IVH; other neonatal bleeding	Additional data provided by the authors
Venezuela, 2000	R: "randomised", no further information AC: unclear (B)	127 nulliparous women <29 weeks' gestation. At risk of PE because previous PE, obesity, HT, diabetes, nephropathy, MAP >85, positive roll-over test, family history of PE, multiple pregnancy or <20 years old	Antiplatelet: aspirin 100 mg ×3/week + vitamin C 500 mg/day + vitamin E 400 IU/day, fish oil ×3/day	Women: PE	Abstract only
Zimbabwe, 1998	R: randomisation list AC: list used to determine sequence of numbered containers. (B) FU: 20 (8%) women lost to follow-up (B)	250 women at 20–28 weeks with a history of PE in a previous pregnancy, especially if at <32 weeks, or chronic HT Excluded: hypersensitivity to aspirin, PE this pregnancy, bleeding or peptic disorder	Antiplatelet: aspirin 75 mg/day Control: placebo	Woman: PE; antihypertensive drug; preterm delivery; PPH; Caesarean section. Baby: death; IUGR; admission SCBU	

AC, allocation concealment; APH, antepartum haemorrhage; AST, aspartate aminotransferase; B, blinding; DBP, diastolic blood pressure; DM, diabetes mellitus; EDD, estimated date of delivery; FU, follow-up; HT, hypertension; IUGR, intrauterine growth restriction; Hb, haemoglobin; IVH, intraventricular haemorrhage; MAP, mean arterial pressure; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; PPH, postpartum haemorrhage; R, randomisation sequence; RDS, respiratory distress syndrome; SBP, systolic blood pressure; SCBU, special care baby unit; SGA, small for gestational age.

TABLE 95 *Trial details of diuretics for preventing pre-eclampsia*

Study	Methods	Participants	Interventions	Outcomes	Notes
Fallis, 1964	R: "randomly assigned" to one of two groups, no further information AC: not reported (B) FU: 6 women (8%) excluded, all from the active group (B) B: "double blind"	80 primigravid women at <27 weeks' gestation with DBP <90 mmHg and no proteinuria or oedema	Diuretic: hydrochlorothiazide 50 mg daily until delivery Control: placebo taken until delivery	Women: PE (SBP >140 or rise by >30 mmHg or DBP >90 or rise by >15 mmHg, with or without proteinuria, or oedema after 24 weeks); medication stopped due to side-effects; biochemical outcome Baby: stillbirth; neonatal death	Compliance: >80% for all patients except 2 who took >50% of pills Diet: all new patients given instruction on salt restricted diet Race: 97.5% women randomised were black. For analysis, 100% were black Single centre, USA
Flowers, 1962	R: treatment given "at random" to four groups, no further information AC: sealed envelopes with a code known only to the hospital pharmacist (B) FU: 74 women (14%) excluded due to excess weight gain/oedema, poor compliance, insufficient data, or intolerance to side-effects. (C) B: "double blind"	519 primiparous and multiparous women, up to 30 weeks' gestation	Diuretic 1: 134 patients received chlorothiazide 250 mg daily Diuretic 2: 141 patients received chlorothiazide 500 mg daily Diuretic 3: 110 patients received chlorothiazide 750 mg daily Control: 134 patients received placebo All medication taken until delivery	Women: toxaemia (defined as SBP ⩾140 or DBP ⩾90 mmHg ×2 in previously normotensive women or appreciable change in BP in women with chronic HT); changes in maternal weight (mean) and BP (mean); side-effects; biochemical outcomes Baby: perinatal death (foetal deaths and neonatal deaths up to 28 days of life in infants weighing >1 kg); premature birth (not defined); neonatal jaundice (60% participants excluded for this outcome, so not reported in review)	Compliance: >80% for 60–69% women in all 4 groups. Wide variation in compliance in the remaining 30–40% of patients in each group Diet: all patients advised a low-sodium diet (1800 mg sodium) For review, 3 diuretic arms combined and compared with placebo Single centre, USA
Kraus, 1966	R: "randomised investigation", no further information AC: not reported (B) FU: 109 women (10%) excluded due to poor compliance with treatment. Women delivering before 28 weeks or	1139 nulliparous and multiparous women between 20 and 24 weeks' gestation Excluded: women with ITP, diabetes, or sickle cell disease	Diuretic: chlorothiazide 50 mg daily Control: placebo. Treatment continued until delivery (average 17 weeks)	Women: PE (SBP >140 or rise by >30 mm Hg or DBP >90 or rise by >15 mmHg, with or without proteinuria, or oedema after 24 weeks); HT; weight gain, eclampsia; severe PE; use of additional	Compliance: patients with poor compliance excluded from study. No further information Diet: advice given regarding salt intake (3–5 g) and calories (1800 kcal)

continued

TABLE 95 *Trial details of diuretics for preventing pre-eclampsia (cont'd)*

Study	Methods	Participants	Interventions	Outcomes	Notes
	at another hospital also excluded (B) B: "double blind"			thiazide diuretic; side-effects; biochemical outcomes Baby: perinatal death (stillbirth and neonatal death); birthweight	Race: 93% women non-white Single centre, USA
Sibai, 1984	R: "randomly assigned" to one of two groups, no further information AC: not reported (B) FU: complete (A) B: not blinded	20 women in first trimester of pregnancy, with long-term mild to moderate chronic HT (DBP 90–110 mmHg), who were receiving thiazide diuretics prior to pregnancy. All women were on diuretic therapy at trial entry	Diuretic: advised to continue thiazide diuretic throughout pregnancy Control: advised to stop diuretic therapy immediately	Women: superimposed PE (not defined); Caesarean section; additional antihypertensive; weight gain (mean); mean arterial BP; plasma volume; placental weight; biochemical outcomes Baby: gestational age (mean); birthweight; IUGR; SGA; prematurity (<37 weeks); perinatal death; Apgar; postmaturity	Compliance: not reported Diet: advised restricted salt intake (2 g) and to avoid addition of salt to diet Single centre, USA
Weseley, 1962	R: "assigned randomly" to two groups, no further information AC: not reported (B) FU: complete (A) B: "double blind"	267 women in second or third trimester, with weight gain 5 lb or more in 2 weeks or increasing oedema of extremities Excluded: HT or proteinuria or prenatal care in a different hospital	Diuretic: 2 groups, both received chlorothiazide 500 mg ×2 tablets daily Control: 2 groups, both received placebo	Women: PE (SBP >140 or rise by >30 mm Hg or DBP >90 or rise by >15 mmHg, with or without proteinuria, or oedema after 24 weeks); severe PE (not defined) Baby: perinatal mortality	Compliance: not reported Diet: salt restricted. No other information Single centre, USA

AC, allocation concealment; B, blinding; BP, blood pressure; DBP, diastolic blood pressure; FU, follow-up; HT, hypertension; ITP, idiopathic thrombocytopenic purpura; IUGR, intrauterine growth restriction; PE, pre-eclampsia; R, randomisation sequence; SBP, systolic blood pressure; SGA, small for gestational age.

TABLE 96 *Trial details of nitric oxide donors and precursors for preventing pre-eclampsia and its complications*

Study	Methods	Participants	Interventions	Outcomes	Notes
Davis, 2001	R: computer-generated random numbers AC: by telephone (A) FU: complete (A) B: caregiver only	16 women with gestational hypertension	NO: glyceryl trinitrate skin patch (10 mg) 12 h/day until delivery Control: no patch	Woman: PE; side-effects	Study stopped early due to severe headaches in active group
Facchinetti, 2002	R: by pharmaceutical company AC: investigators given list of consecutive numbers allocated A or B. Code not known to trialists (A) FU: 6/80 (7.5%) excluded from analysis (B) B: for participants and caregivers yes, for outcome assessment no	74 women between 24 and 36 weeks' gestation with gestational HT (BP >140/90 ×2 after 20 weeks) or PE (as above + proteinuria >300 g/24 h) Excluded: BP raised <20 weeks' gestation, severe HT, severe PE, antiphospholipid syndrome, heart kidney or liver disease, <2 antenatal visits before enrolment	NO: L-arginine 20 g/500 ml i.v. daily for 5 days, then 4 g/day oral for 2 weeks Control: placebo	Woman: BP; platelet aggregation; time to delivery; PE; severe PE (one of : BP >170/110 mmHg, proteinuria >5 g/24 h, HELLP, coagulation disorders, arrested foetal growth) Baby: perinatal death; preterm birth; birthweight (mean); gestation at birth (mean)	Unpublished data for women without proteinuria at trial entry used for the review
Lees, 1998	R: by study pharmacist in one centre AC: by pharmacist, code not available to clinicians until after last woman delivered (A) FU: complete (A) B: for participants and caregivers yes, for outcome assessment no	40 women with singleton pregnancy, normal BP and abnormal uterine Doppler at 24–26 weeks (bilateral diastolic notches and resistivity index >0.58) Excluded: pre-existing HT, diabetes, renal disease, antihypertensive or cardiovascular drug, IUGR, foetal abnormality	NO: glyceryl trinitrate skin patch 5 mg 15 h/day until delivery. Stopped if: BP >140/90 mmHg, antihypertensive, foetal growth restriction or clinical indication to stop (including side-effects) Control: placebo patches with same instructions	Woman: PE, gestation of onset of PE, maternal BP changes; HELLP, side-effects (skin rash and headaches); abruption; Doppler indices Baby: preterm birth; small for gestational age; birthweight (mean)	Two centres, UK and Italy
Picciolo, 2000	R: random number list AC: no information (B) FU: not reported B: not reported	68 women at <16 weeks gestation, with either chronic HT or previous history of PE before 34 weeks and/or IUGR	NO: glyceryl trinitrate skin patch 5mg 14–16 h/day, to 38 weeks' gestation Control: observation only	Woman: PE; abruption; Doppler notch at 24 weeks Baby: neonatal death; preterm birth; IUGR; Apgar; admission to NICU; RDS; IVH	Two centres in Italy

AC, allocation concealment; B, blinding; BP, blood pressure; DBP, diastolic blood pressure; FU, follow-up; HELLP, haemolysis, elevated liver enzymes, low platelets syndrome; HT, hypertension; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; NO, nitric oxide; PE, pre-eclampsia; RDS, respiratory distress syndrome; SBP, systolic blood pressure.

TABLE 97 *Trial details of progesterone for preventing pre-eclampsia and its complications*

Study	Methods	Participants	Interventions	Outcomes	Notes
Dalton, 1962	R: "at random", no other information AC: "numbered envelope system", no other information (B) FU: 22 (15%) excluded (C) B: for participant and caregiver no, for outcome assessment not reported	150 women at 16–28 weeks' gestation with two or more "toxaemic symptoms" (nausea, vomiting, lethargy, backache, headache, vertigo, fainting, cramp or paraesthesia), blood pressure <140/90 mmHg and no proteinuria	Progesterone: 100 mg i.m. daily or on alternate days for 1 week. Then, dose and frequency of injection adjusted depending on symptoms (range 300 mg daily to 50 mg on alternate days). Stopped if symptoms disappeared, or when labour started Control: simple symptomatic relief as required, such as alkalis, analgesics, sedatives, antihistamines	Woman: PE (BP >140/90 mmHg + either oedema or proteinuria after 28 weeks); side-effects in progesterone group only Baby: stillbirth, neonatal death	385 interviewed, 150 eligible and recruited. Definition of PE included oedema, so data for proteinuria used for review. Follow-up of children excluded due to large losses (54% at 1 year and 80% at 16 years)

AC, allocation concealment; B, blinding; BP, blood pressure; FU, follow-up; PE, pre-eclampsia; R, randomisation sequence.

Appendix 10

Data extraction sheet for economics section

Data required from Accuracy Reviews

FOR ALL REVIEWS NEED TO HAVE A CONSENSUS VALUE FOR

1. Pre-test Prevalence or risk factor for developing Pre-eclampsia

Essential Items from each individual accuracy review are:

2. Sensitivity and Specificity of test in detecting target risk factor

OR

The +ve and –ve likelihood ratios

Desirable information (but not essential) from individual Accuracy Reviews

3. Information on whether detection can avert early or late pre-eclampsia

Summary of info required from Accuracy Reviews

Accuracy Review	**Result required for:**	**Value**	**Comment**
E.g. Doppler	1. Pre-test probability of developing Pre-eclampsia	**?**	***Need agreed value on this for all Accuracy Reviews*** ***SEE Ducket Review***
Essential	2. Sensitivity and specificity of test in detecting target risk factor ***OR***		*This is all could get but enough to be useful*
	2. the +ve and –ve likelihood ratios		
Desirable	3. Available data on whether detection can avert early or late pre-eclampsia	**N/a**	
Please describe procedure for carrying out the test			E.g. Ultrasound scan lasting approx. 10 minutes
Does the paper present any information regarding resource use: if so please describe and include the relevant references			*E.g. Trained ultrasonographer, Doppler machine, etc.*

Data Required from Effectiveness of Treatment Reviews

Essential Items from each Treatment/effectiveness Review are:
1. Probability ratio of developing pre-eclampsia if treated compared to not

Desirable information (but not essential) from individual Accuracy Reviews
2. Any variation according to risk factors or distinction between early and late pre-eclampsia

Summary of info required from Accuracy Reviews

Treatment/Effectiveness Review	**Result required for:**	**Value**	**Comment**
E.g. Aspirin			
Essential	1. Probability ratio of developing pre-eclampsia if treated compared to not		*Enough info to be useful*
Desirable	2. Any variation according to risk factors or distinction between early and late pre-eclampsia		
Evidence of other outcomes avoided as a result of this review. If yes please specify and provide reference			Explain
Resource use involved			E.g. An aspirin!

Appendix 11

Economic evaluation case 6 results

TABLE 98 *Case 6: costs, effects and ICERs for most cost-effective combinations of test and treatment pairs from any test combined with any intervention, i.e. as case 1, base case, group 1 and group 2 interventions considered (No test/rest_all dominates all options below[a])*

Test/treatment combination	Mean cost per woman (UK£ 2005)	Difference in costs (UK£ 2005)	Effectiveness[b]	Absolute risk reduction	ICER[c]	NNT
Partial analysis: excludes the costs of pre-eclampsia in the comparator arm of the model						
No test/salt reduction_all[d]	0		0.972			
No test /no treatment	0	0	0.975	0.003	0	357
No test/antiplatelets_all[d]	2.7	2.7	0.980	0.005	566.32	208
Total fibronectin/progesterone_positive	9	6.4	0.988	0.008	785.65	123
Total albuminuria/progesterone_positive	14.6	5.6	0.989	0.001	5625.32	1000
No test/progesterone_all	54.1	39.5	0.995	0.006	6666.84	169
Microalbumin_Creatinine/ progesterone_all[e]	62	7.9	0.995	0		
Microalbuminuria/progesterone_all[e]	62	0	0.995		Dominated	
Complete analysis: includes the cost of pre-eclampsia in the comparator arm of model						
Nothing/progesterone_all	101.2		0.995		Dominant	
Microalbumin_Creatinine/ progesterone_all[e]	109.1	7.9	0.995	0	These are all dominated	
Total albuminuria/progesterone_all[e]	109.1	0	0.995	0		

[a] The no test_rest option is the most effective option, achieved at zero additional cost, and is thus self-evidently the most cost-effective approach. It was therefore not incorporated into the model whose results are reported in this table, which primarily explores the second most cost-effective option after the no test/rest_all option.

[b] Effectiveness is defined as the proportion of women remaining free of pre-eclampsia. Therefore, the difference in effectiveness between two strategies is the absolute risk reduction.

[c] ICER: incremental cost-effectiveness ratio expressed as the additional cost per additional case of pre-eclampsia prevented.

[d] Universal advice to reduce salt intake appears to be worse than no test_no treatment because it appears to increase the number of cases of pre-eclampsia: RR 1.11, 95% CI 0.46 to 2.66.

[e] These 'test all/treat all' strategies were included in the model for completeness (elaborated in more detail in the economic evaluation section, p. 100). Each is more costly and no more effective than a strategy of treating all women without testing.

Appendix 12

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Body mass index

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We look forward to hearing from you.

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