TITLE PAGE

PREDICTORS FOR ADVERSE MATERNAL AND FETAL OUTCOMES IN HIGH RISK PREGNANCY

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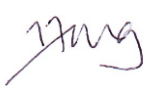
Signature: 

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Details of collaboration and publications

DETAILS OF COLLABORATION

Chapter 4.1

Collaboration with Shakila Thangaratinam (supervisor), Robert Walton (supervisor, genetics input), Manpreet Sahemey (co-reviewer, study selection, data extraction, quality assessment), Valerie Kuan (co-reviewer, genetics input), Golnessa Hamedi (data extraction and quality assessment), Rachael Eyitayo (data extraction and quality assessment), Derick Yates (search strategy input).

Chapter 4.2

Collaboration with Joost Akkermans (co-reviewer, data extraction, quality assessment, data analysis), Shakila Thangaratinam (supervisor), Javier Zamora (data analysis and statistical input).

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My contribution to each chapter is detailed at the end of each chapter.

PUBLICATIONS IN PEER REVIEWED JOURNALS FROM THE THESIS

1. Cheong-See F, Schuit E, Arroyo-Manzano D, Khalil A, Barrett J, Joseph KS, Asztalos E, Lewi L, Lim A, Liem S, Norman JE, Morrison J, Combs CA, Garite TJ, Maurel K, Serra V, Perales A, Rode L, Worda K, Nassar A, Aboulghar M, Rouse D, Thom E, Breathnach F, Nakayama S, Russo FM, Robinson JN, Dodd JM, Newman RB, Bhattacharya S, Tang S, Mol BWJ, Zamora J, Thilaganathan B, Thangaratinam S. (2016) Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. *BMJ* 2016; 354:i4353
2. Cheong-See F, Allotey J, Marlin N, Mol BW, Schuit E, Ter Riet G, Riley RD, Moons K, Khan KS, Thangaratinam S. (2016) Prediction models in obstetrics: understanding the treatment paradox and potential solutions to the threat it poses. BJOG 2016,doi 10.1111/1471-0528.13859.
3. Kleinrouweler CE, Cheong-See FM, Collins GS, Kwee A, Thangaratinam S, Khan KS, Mol BW, Pajkrt E, Moons KG, Schuit E. (2016) Prognostic models in obstetrics: available, but far from applicable. AJOG 2016 214(1):79-90.e36. doi: 10.1016/j.ajog.2015.06.013.
4. Fong F, Rogozinska E, Allotey J, Kempley S, Shah DK, Thangaratinam S. (2014) Development of Maternal and Neonatal Composite Outcomes for Trials Evaluating Management of Late-onset Pre-eclampsia. Hypertens Pregnancy. 2014 May; 33(2): 115-31. Doi: 10.3109/10641955.2013.837176.
5. Fong FM, Sahemey MK, Hamedi G, Eyitayo R, Yates D, Kuan V, Thangaratinam S, Walton R. (2014) Maternal Genotype and Severe Preeclampsia: A HuGE Review. Am J Epidemiol. *Am J of Epidemiol 2014; 180 (4): 335:345.*

6. Cheong-See F, Akkermans J, Zamora J, Thangaratinam S. Accuracy of individual tests to predict complications in women with pre-eclampsia: a systematic review (submitted and under review by Hypertension in Pregnancy journal)

ABSTRACT

This thesis aims to undertake health technology assessments in high risk pregnancies through the following objectives:

1. In women with pre-eclampsia,
    a) To evaluate the association of maternal genotype and severe pre-eclampsia
    b) To assess the accuracy of tests in predicting adverse pregnancy outcomes
    c) To develop composite outcomes for reporting in trials on late onset pre-eclampsia
2. In women with multiple pregnancy,
    a) To study the association between chorionicity and stillbirth
    b) To identify the optimal timing of delivery in monochorionic and dichorionic twin pregnancies
3. In the field of prediction research in obstetrics
    a) To provide an overview of the existing prognostic models and their qualities
    b) To evaluate the methodological challenges and potential solutions in developing a prognostic model for complications in pre-eclampsia

Methods

The following research methodologies were used: Delphi survey, systematic reviews and meta-analyses.

Results

1. a) Maternal genotype and severe pre-eclampsia:

    57 studies evaluated 50 genotypes; increased risk of severe pre-eclampsia with thromobophilic genes.

    b) Accuracy of tests in predicting pre-eclampsia complications:

37 studies evaluated 13 tests. No single test showed high sensitivity and specificity.

c) Delphi survey of 18/20 obstetricians and 18/24 neonatologists identified clinically important maternal and neonatal outcomes and maternal and neonatal composite outcomes were developed.

2. Prospective risk of stillbirth and neonatal deaths in uncomplicated monochorionic and dichorionic twin pregnancies:
   32 studies were included. In dichorionic twin pregnancies, the risk of stillbirths was balanced against neonatal death at 37 weeks' gestation. In monochorionic pregnancies, there was a trend towards increase in stillbirths after 36 weeks but this was not significant.

3. a) From 177 studies included, 263 obstetric prediction models were developed for 40 different outcomes, most commonly pre-eclampsia, preterm delivery, mode of delivery and small for gestational age neonates.
   b) The obstetric prognostic model challenge of dealing with treatment paradox was explored and seven potential solutions proposed by expert consensus.

Conclusion

I have identified the strength of association for genes associated with complications in pre-eclampsia, components for composite outcomes for reporting in studies on pre-eclampsia, and the optimal timing of delivery for twin pregnancies. My work has highlighted the gaps in prediction research in obstetrics and the limitations of individual tests in pre-eclampsia.

DEDICATION

To Patrick, Jacob, Mum and my family

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACOG	American College of Obstetricians and Gynaecologists
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BAPM	British Association of Paediatric Medicine
BPD	Bronchopulmonary dysplasia
Cardio	Cardiology
CI	Confidence interval
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CPL	Cystic periventricular leukomalacia
CS	Caesarean section
CTLA	Cytotoxic T Lymphocyte Antigen
CX3CR1 CX3	Chemokine Receptor 1
DBP	Diastolic blood pressure
DC	Dichorionic
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
EFW	Estimated Fetal Weight
GCS	Glasgow Coma Scale
GWAS	Genome Wide Association Study
Haem	Haematology
HELLP	Haemolysis Elevated Liver enzymes and Low Platelets syndrome

HDU	High dependency unit
HIE	Hypoxic Ischaemic Encephalopathy
ICAM	Intracellular Adhesion Molecule
ICSI	Intracytoplasmic Sperm Injection
IFN	Inteferon
IL	Interleukin
IPD	Individual patient data
IQR	Interquartile range
ISSHP	International Society for the Study of Hypertension
IUFD	Intrauterine fetal demise
IUGR	Intrauterine growth restriction
IVF	In Vitro Fertilisation
IVH	Intraventricular haemorrhage
K^+	Potassium
LDH	Lactate dehydrogenase
LEPR	Leptin Receptor
LR	Likelihood ratio
MAP	Mean arterial pressure
MC	Monochorionic
$MgSO_4$	Magnesium sulphate
MOOSE	Meta-analysis of observational studies in epidemiology
MTHFR	Methylene tetrahydrofolate reductase
Na^{2+}	Sodium
NADPH/NADH	Nicotinamide adenine (diphosphate) oxidase
NEC	Necrotising enterocolitis

NGAL	Neutrophil gelatinase-associated lipocalin
NICE	National Institute of Clinical Excellence
NICU	Neonatal intensive care unit
NND	Neonatal death
PAPP-A	Pregnancy-associated plasma protein
PCR	Protein creatinine ratio
PE	Pre-eclampsia
PlGF	Placental growth factor
PP-13	Placental protein 13
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVL	Cystic periventricular leukomalacia
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomised Control Trial
RDS	Respiratory distress syndrome
RIND	Reversible Ischaemic Neurological Deficit
ROP	Retinopathy of prematurity
SBP	Systolic blood pressure
SCBU	Special Care Baby unit
SD	Standard Deviation
sEng	Soluble endoglin
sFlt-1	Soluble fms-like tyrosine kinase 1
SGA	Small for gestational age
SNP	Single nucleotide polymorphism
SOD	Superoxide Dismutase
TGF	Transforming growth factor

TNF	Tumour necrosis factor
TRAP	Twin Reversed Arterial Perfusion
TSHRc	Thyroid Stimulating Hormone Receptor
TTTS	Twin to twin transfusion syndrome
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation

CHAPTER 1: BACKGROUND

1.1. INTRODUCTION

1.1.1. High risk pregnancy

Antenatal care of mothers is focussed on identifying women and offspring at risk of complications. Early identification of high-risk women at risk will enable targeted care, including close monitoring and early delivery. Currently, women who enter pregnancy with underlying conditions such as chronic hypertension, diabetes mellitus, respiratory disease, cardiac disease, neurological conditions, renal disease, or develop conditions such as gestational diabetes, and pre-eclampsia in pregnancy are considered to be at high risk of adverse pregnancy outcomes. Additionally, the status of the pregnancy itself concurs risks to the mother and fetus such as in multiple pregnancy.

Of the above conditions, pre-eclampsia, which affects around 6-8% of all pregnant women continues to be one of the major contributors to adverse outcomes in the mother and fetus both in the UK and worldwide. With the advancing maternal age, and sophisticated assisted reproductive technologies, multiple births are on the rise, accounting for 3% of all livebirths in the UK.[1] Mothers often need close monitoring in both conditions, with high risks of admission to the high dependency unit (HDU) due to complications, and neonatal intensive care unit (NICU) admission for the fetus, leading to prolonged stays in the hospital.[2, 3] They contribute significantly to spontaneous and iatrogenic prematurity of the newborn.

In both pre-eclampsia and multiple pregnancy, clinicians face the challenge of deciding on the optimal timing the delivery of the fetus.[4, 5] In pre-eclampsia, the delivery of the baby is considered to be the treatment for the condition.[6] While expectant management may increase the risk of complications in the mother, early delivery could predispose to prematurity-related

complications in the fetus.[7] In multiple pregnancies, a delay in delivery could increase the risk of stillbirth compared to prematurity complications from early delivery.[8]

Overall, premature births, complicate 7.2% of all pregnancies and continues to be one of the major factors of neonatal mortality,[9] and adverse outcomes in the short and long term. Preterm birth is estimated to cost the UK public sector £2.9 billion over childhood (direct and indirect costs), equating to around £939 million per year.[10] As pre-eclampsia and multiple pregnancy contribute greatly to iatrogenic prematurity, accurate prediction of risks in these conditions can help to select the cases where intervention is needed, thereby minimising unnecessary intervention and helping to lessen the burden of some cases of prematurity.

My thesis focuses on optimising the maternal and offspring outcomes in women with pre-eclampsia and multiple (twin) pregnancy, two common high-risk pregnancy conditions, through prognostic research.

1.1.2. Pre-eclampsia

Pre-eclampsia is characterised by hypertension and proteinuria in pregnancy and affects 6-8% of pregnant women.[11, 12] This multi-systemic disorder is associated with significant maternal and fetal morbidity and mortality accounting for 10-15% of direct maternal deaths in the UK and 20% of stillbirths.[13] The underlying pathophysiology is complex and as yet not fully understood. The prevailing theory is that pre-eclampsia is a disease of the placenta arising from incomplete invasion of the spiral arteries due to defective endovascular cytotrophoblast, combined with inappropriate endothelial cell activation and an exaggerated inflammatory response.[14, 15] The two-stage model of pre-eclampsia proposes that the first stage consists of an increased inflammatory response associated with pregnancy and reduced fetal and/or

placental perfusion. These can both interact with maternal constitutional factors (such as genetic, behavioural or environmental factors) that trigger off the maternal pathophysiological changes which cannot be tolerated resulting in the clinical and heterogeneous syndrome of pre-eclampsia.[16, 17]

The timing of onset of pre-eclampsia has been recognised as being increasingly important in the underlying pathogenesis of the condition and the spectrum of severity and potential complications that may manifest. Early onset pre-eclampsia usually develops between 20 to 34 weeks' gestation of pregnancy. The abnormal placentation process is thought to render a state of placental hypoxia which results in the expression of factors that contribute towards maternal endothelial dysfunction.[18] These factors include soluble fms tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which can act upon the maternal endothelium to raise maternal blood pressure; and affect the fenestration of the glomerular capillaries resulting in proteinuria. Late onset pre-eclampsia, which develops after 34 weeks' gestation of pregnancy is thought to arise due to compromise of the mother's ability to adapt to the physiological haemodynamic and metabolic changes of the pregnancy resulting in difficulty maintaining a normal blood pressure and regulating insulin metabolism.

Underlying genetic predisposition

One of the underlying maternal constitutional factors, which has long been of interest is the genetic component to pre-eclampsia. Epidemiological studies point towards a genetic aetiology for pre-eclampsia with a positive family history of pre-eclampsia conferring a threefold risk to developing the condition.[19] The exact mode of inheritance still eludes us but appears to involve a complex interplay of maternal, fetal and paternal contributions. Women with first-degree relatives who developed pre-eclampsia during pregnancy are five times

more likely to develop pre-eclampsia than those without a positive family history.[20] Men who were born from a pregnancy complicated by pre-eclampsia also have a higher risk of fathering a pregnancy affected by pre-eclampsia.[21] Our understanding, albeit limited, of the different systems involved in the pathogenesis of pre-eclampsia has led to hypotheses of potential candidate genes that may have a single or combined role in developing the disease. Further work in the area of familial aggregation studies and genome-wide scans has generated other putative candidates.

Complications in pre-eclampsia

The adverse maternal outcomes that may progressively develop can affect one or more systems including the central nervous system (intraventricular haemorrhage, eclampsia, cortical blindness), respiratory (pulmonary oedema), renal (failure), hepatic (dysfunction, failure, hepatic capsule rupture or haemolysis, elevated liver enzymes and low platelets syndrome), systemic vasculature (severe hypertension) and coagulation system (coagulopathy).[17] Fetal complications include placental abruption, intrauterine fetal death, fetal growth restriction and increased neonatal morbidity and mortality primarily due to preterm birth.

The only known cure for pre-eclampsia is delivery of the fetus.[22] However there is increasing evidence that this may only be a transient remission and that women who develop pre-eclampsia are at increased risk of prematurely developing chronic conditions associated with subclinical endothelial dysfunction, insulin resistance and metabolic syndrome such as hypertension, cardiovascular disease, renal impairment and diabetes mellitus.[23] Early onset pre-eclampsia, severe pre-eclampsia and recurrent pre-eclampsia are recognised independent risk factors for cardiovascular disease.[24, 25]

Tests in pre-eclampsia

The assessment of risk is based on a combination of patient characteristics, symptoms, signs and investigations. Due to the multi-systemic nature of pre-eclampsia and heterogeneity of the manifestations of the syndrome in different individuals, there is no single test that has been proved to be sensitive and specific enough to predict complications of pre-eclampsia.

The table 1 summarises the battery of tests that women being diagnosed with and who are being monitored with pre-eclampsia commonly undergo regularly to assess for and predict the disease and the development of any maternal and fetal complications.

Table 1 Clinical Tests Used in Diagnosing and Monitoring Women with Pre-eclampsia

Tests
Prediction
Clinical history - pre-existing chronic conditions (hypertension, diabetes mellitus, renal disease, autoimmune disease) and previous pre-eclampsia
Ultrasound - maternal uterine artery Doppler
Diagnosis
Clinical examination - blood pressure
Urine tests - estimation of proteinuria (dipstick, protein creatinine ratio, 24 hour urinary collection)
Prognosis

Clinical history

- symptoms (headache, visual disturbances, epigastric pain, abdominal pain, nausea, vomiting, chest pain, dyspnoea)
-

Clinical examination

- hyperreflexia
- papilloedema
- pulse oximetry

Urine tests

- estimation of proteinuria (dipstick, protein creatinine ratio, 24 hour urinary collection)

Blood tests

- full blood count
- urea & electrolytes (Na^{2+}, K^{+}, Urea, Creatinine)
- liver function (ALT, AST, LDH)
- serum uric acid

Ultrasound

- maternal uterine artery Doppler
- fetal umbilical artery Doppler
- fetal middle cerebral artery Doppler
- fetal ductus venosus Doppler
- fetal growth and liquor volume

Biomarkers

Biomarkers have received much interest and varying degrees of success in predicting the development of pre-eclampsia. Normal placental vascular development is regulated by angiogenic factors such as vascular endothelial growth factor (VEGF-1), VEGF-2, placental growth factor (PlGF) in addition to soluble fms-like tyrosine kinase-1 (sFlt-1), a splice variant of the VEGF-1 receptor and soluble endoglin (sEng), a TGF-beta co-receptor. These biomarkers have therefore been investigated for their role in diagnosing pre-eclampsia and prognosticating severity of the condition.[18] Other popular biomarkers include placental protein 13 (PP-13), pregnancy-associated plasma protein A (PAPP-A) and neutrophil gelatinase-associated lipocalin (NGAL).[26-28]

Genetic tests

Over 70 different genes have been the focus of candidate genetic association studies to evaluate putative roles in causing pre-eclampsia.[29] The clinical question that begs to be answered is whether underlying maternal genotype may contribute to development of the clinically relevant outcome, which is severe pre-eclampsia or complications of pre-eclampsia. Genetic tests could be incorporated into prognostic models together with routinely used predictive factors to better assess these women according to level of risk of complications from pre-eclampsia.

The estimated cost for each women with pre-eclampsia in terms of commonly performed tests to diagnose and monitor her condition is in the region of £9000.[30] As there is no clear guidance, management is determined by the clinician's interpretation of the test results for that particular patient. The roles of routinely performed tests in predicting risk of pre-eclampsia complications; being cost-effective in allowing better targeted care and their results positively affecting clinical care of women with pre-eclampsia remain uncertain. There is a strong need to examine and evaluate the best testing strategies with which to predict the development of complications in pre-eclampsia and optimise delivery of care.

Management of women with pre-eclampsia

The mainstay of treatment for pre-eclampsia is to stabilise the mother and fetus and to prevent the development of adverse maternal and fetal outcomes or to intervene before these complications arise. The diagnosis of pre-eclampsia is based on hypertension either newly diagnosed or superimposed on a background of chronic hypertension and the presence of significant proteinuria.

Hypertension is primarily the focus of treatment, and various antihypertensives have been used to stabilise maternal blood pressure. In the UK, these include selective beta blockers such as labetalol, calcium channel antagonists such as nifedipine, alpha channel blockers such as doxazosin, direct-acting smooth muscle relaxants such as hydralazine, and the alpha-2 adrenergic receptor agonist methyldopa. The firstline agent is usually labetalol but is tailored based on any contraindications, side effects and control of blood pressure. Combinations of antihypertensives may be required to achieve adequate control . Current NICE guidance is to maintain the pregnant woman's blood pressure within a target range below 150/100mmHg with a lower target range of 140/90mmHg in those with increased cardiovascular risk such as existing cardiovascular disease or target organ damage to minimise the risk of maternal complications. This balance is off-set with the risk of excessively lowering the blood pressure to compromise perfusion of the fetoplacental unit and hence affects fetal growth.

Magnesium sulphate is also given for its neuroprotective effect to women who are suspected of having a high risk of developing eclampsia or to those who have had an eclamptic seizure to prevent further seizures. Other treatment options are intervention with the delivery of the fetus to effectively 'cure' the condition, taking away the stimulus (pregnancy and the placenta). Dependent on the gestational age of the pregnancy and the presence or absence of intrauterine fetal growth restriction, steroids may be given to promote lung maturity up to 34^{+6} weeks in normally grown fetuses and up to 35^{+6} weeks if growth restriction is suspected.[31, 32] Delivery is considered when the benefits of prolonging the pregnancy outweigh the risks. This can often be a difficult decision balancing the risks of prematurity risks against developing complications of pre-eclampsia. Current national guidelines

recommend considering delivery for women with pre-eclampsia at 37 weeks gestation. When pre-eclampsia is diagnosed at a preterm gestation, the answer is less clear, with ongoing trials trying to address this exact question for the moderately preterm gestation between 34 and 37 weeks of pregnancy.[33-35] For early and extreme preterm gestations, the approach tends to be conservative unless severe pre-eclampsia is diagnosed.[36, 37]

The national guidance by NICE in the UK recommend intervention with delivery mainly based on blood pressure thresholds, differentiating women with pre-eclampsia into two groups: severe hypertension and mild to moderate hypertension.[38] Timing of birth is recommended after 34 weeks gestation for the former and between 34 to 36 weeks gestation for the latter.[38] About 15% of these women will develop significant maternal morbidity[17] and it is identifying this subgroup of women that will help not only with prevention, optimising treatment but also the difficult clinical decision-making of whether or not to expedite delivery.

1.1.3. Multiple pregnancy

Background

There has been a steady increase in the rates of twin pregnancies over the past decade,[9] owing to advancing maternal age and increased use of assisted reproductive technologies. Multiple pregnancy is considered a high risk pregnancy due to increased maternal, fetal and neonatal morbidity and mortality. The mother is at increased risk of conditions such as anaemia, pre-eclampsia, preterm labour, operative delivery, antepartum and postpartum haemorrhage and mortality. The fetuses and neonates are at increased risk of fetal growth restriction, twin to twin transfusion syndrome (TTTS) in monochorionic twin pregnancies, neonatal death and adverse short and long term neonatal outcomes mainly secondary to preterm delivery. Over

50% of twins are born preterm.[39] The lower the gestational age and birthweight at delivery, the higher the risk for long-term sequelae such as cerebral palsy, neurodevelopmental disability, learning difficulties and chronic respiratory illnesses. The costs of neonatal and long-term healthcare for twin births as a consequence of preterm delivery are thus a huge burden to the NHS.

Dichorionic and monochorionic twin pregnancy

The risks of twin pregnancies differ according to the chorionicity and amnionicity of the twins. With regard to chorionicity, dichorionic twin pregnancies have separate placentas whereas monochorionic twins share the same placenta. Due to the interconnections in the monochorionic twin placenta, these twins are at risk of twin to twin transfusion which occurs in about 15% of monochorionic twin pregnancies.[40] One twin becomes a donor twin and the other a recipient twin resulting in a gross imbalance of amniotic fluid volumes for the former and potential cardiac failure for the latter, accounting for 20% of stillbirths in this group.[1] Amnionicity also increases the risks with twins in a single amniotic sac (monoamnionicity) at higher risk of morbidity and mortality due to the potential for umbilical cord entanglement.

Complications in multiple pregnancy

Fetal and neonatal

Stillbirth risks in twin pregnancies are in the region of 2.6-5.8%.[41, 42] In comparison to singleton pregnancies, monochorionic and dichorionic twin pregnancies have thirteen-fold and five-fold higher risks of stillbirth in respectively.[43] The increased risk in the monochorionic twin pregnancies as aforementioned is mainly attributed to complications of placental and vascular sharing in a monochorionic placenta resulting in either fetal growth restriction or fetal transfusion syndrome.[44] It is unclear whether monochorionic pregnancies unaffected by these complications remain at much higher risk. Fetal growth restriction

appears to affect both monochorionic and dichorionic twin pregnancies more than in singleton pregnancies.

Prematurity and its complications

Preterm delivery refers to birth before 37 completed weeks of pregnancy. According to the World Health Organisation, an estimated 15 million babies are born prematurely each year.[45] Globally it is the leading cause of death in infants under the age of 5 years of age and accounts for 1 million child deaths each year due to its associated complications. Mortality aside, those who do survive are still at a risk of a lifetime of disability including learning difficulties, visual and hearing problems and physical handicap. The gestational age at which premature delivery presents together with birth weight greatly influences prognosis.

There are many different causes, the primary being spontaneous premature delivery but medical indications resulting in early induction if labour or Caesarean delivery also have significant contributions. Conditions such as pre-eclampsia, multiple pregnancies are very common indications for iatrogenic prematurity in an attempt to deliver the fetus(es) before maternal and fetal complications develop.

The preterm infant faces the challenge of the sudden need to adapt to extrauterine life with often both structurally and functionally underdeveloped organ systems. There is, therefore, a large spectrum of prematurity complications, with certain complications more prevalent in the extremely preterm infant (less than 28 weeks) compared to the moderate preterm infant (28-34 weeks) and the late preterm infant (34-37 weeks). As expected the more preterm the infant, the more complications the infant is at risk of. The maturity of the lung organ system is the single most important factor in determining the prognosis of the premature infant.[14]

Other common problems include difficulty regulating body temperature, establishing oral feeding and a higher risk of infection or sepsis. In the cardiovascular system, persistent patent ductus arteriosus can result in congestive cardiac failure; in the hepatic system, liver immaturity can be associated with severe neonatal jaundice leading to vulnerability to neurotoxic effects of unconjugated bilirubin; intracranial haemorrhage and necrotising enterocolitis are further risk factors. In extreme prematurity, chronic lung disease, retinopathy, cerebral palsy and developmental delay are more likely in the longer term.[46]

Management

The relatively low population prevalence of monochorionic twins has resulted in a paucity of epidemiological evidence on which to base clinical decisions about the optimal timing of monochorionic twin pregnancy delivery to avoid intrauterine fetal demise.[1] Currently, clinicians deliver monochorionic pregnancies electively at various late preterm gestations (usually before or at 36 weeks) and dichorionic twins at 38 weeks in efforts to minimise stillbirth risk. There is increasing evidence that late preterm births are associated with increased neonatal mortality, longer stays in the neonatal intensive care unit and an increased need for mechanical ventilation compared to term infants.[47] The optimal timing of delivery to strike a balance between minimising the fetal risk of stillbirth versus neonatal morbidity and mortality due to prematurity is an important research objective.

1.1.4. Role of prognostic research

Prognostic models have been increasingly used in the field of medicine.[48] In obstetrics, there are few prognostic models that are in everyday use such as the Bishop score for cervical

ripeness for induction of labour[49] and the Apgar score for need of resuscitation for the newborn[50] but many have been and are continuing to be developed.[51] The ability to predict the probability of a specified outcome empowers maternity caregivers to offer individualised risk counselling, and to target appropriate management stratified by the mother's risk status. Furthermore, it has been suggested that statistical prediction models may provide a more accurate prognosis than clinicians can achieve working on their own.[52]

Although many obstetric prediction models have been developed, they are not in clinical use. Prognostic modelling takes several stages, following development of a prediction model, external validity should be sought and assessment of the model's impact on clinical outcomes. Without these next steps, the prediction model is only effective for that particular patient population it was developed in and hence is of little use clinically.

Prognostic research presents specific challenges in obstetrics. In many obstetric situations, prognostic factors undergo spontaneous or iatrogenic changes due to the advancing pregnancy or as a result of an intervention that cannot be ethically withheld. An effective treatment may prevent a certain proportion of adverse outcomes, making a good prognostic factor and factors associated with it look poorer in their predictive performance, a so-called 'treatment paradox'.[53] An important research objective is to identify and evaluate the existing prognostic models in obstetrics, their clinical applicability and potential solutions to overcome this 'treatment paradox'.

1.1.5. Composite outcomes

Composite outcomes are composed of multiple endpoints that are combined and the attainment of one or more of these individual endpoints results in a primary outcome. They

help to increase statistical efficiency by increasing event rates and are often used in randomised trials. The improvement of population health, advances in and availability of new treatments contribute to overall lower event rates of outcomes. Composite outcomes have an important role to play in these circumstances, otherwise prohibitively and often unfeasibly large numbers would be needed for trials.

They are used widely in many different fields of research including prognostication such as prediction of pre-eclampsia outcomes based on angiogenic profiles,[54] diagnosis such as use of pulmonary function testing for chronic obstructive pulmonary disease[55] and treatment such as tranexamic acid versus placebo for bleeding trauma patients[56].

In the context of pre-eclampsia, the multisystemic disease that can cause a variety of complications, the rates of which are low, composite outcomes can be very helpful in the design of the trial. An example includes fullPIERS (Pre-eclampsia Integrated Estimate of RiSk Score), an outcome prediction model for adverse maternal outcomes in women admitted to hospital with pre-eclampsia. The individual components of their composite outcome were selected by a Delphi survey of experts.[57] Another pre-eclampsia trial using composite outcomes HYPITAT, a randomised trial of induction of labour versus expectant management for women after 36 weeks and who have either pregnancy-induced hypertension or non-severe preeclampsia.[35]

Composite outcomes are often used in obstetrics as the important outcomes such as maternal or neonatal deaths are rare. Other examples of obstetric randomised trials using composite outcomes include hbvthe Term Breech Trial and the Australasian Collaborative Trial of Magnesium Sulphate.[58, 59]

Gaps in evidence

The individual components of the composite outcome can vary in their importance to clinical care with death invariably being the most severe. As such the development of primary composite outcome can be driven by less important components and actually not include any of the most important components such as deaths. .

In the current age where trials are increasingly limited by resources for both funding and recruitment of patients, composite outcomes present an attractive solution towards the prohibitively large numbers needed when event rates are low and enabling more timely completion of the trial. Caution is however needed in the interpretation of the research when composite outcomes are used.

Conclusion

I have focused on two high risk pregnancy conditions in this thesis that account for many of the antenatal clinic and day assessment unit attendances in hospitals in the UK. Both pre-eclampsia and multiple pregnancy contribute greatly to preterm delivery, maternal and neonatal morbidity and mortality. The ability to predict or stratify a pregnant woman's risk of complications for these two common conditions is an important research objective. In hand with identifying important predictors of adverse outcomes is their potential utility in developing prediction models. This thesis has also looked into an overview of the existing obstetric prediction models and dealing with some of the challenges that may arise during this process.

CHAPTER 2: AIMS AND OBJECTIVES

2.1. AIMS OF THESIS

My thesis aims to undertake health technology assessments in high-risk pregnancy through the following objectives:-

1. In women with pre-eclampsia,
    a. To evaluate the association of maternal genetic factors and adverse outcomes
    b. To assess the accuracy of tests in predicting adverse maternal and fetal outcomes
    c. To develop composite outcomes for reporting in clinical trials on late onset pre-eclampsia by undertaking a Delphi survey
2. In women with multiple pregnancy,
    a. To study the association between chorionicity and the prospective risk of stillbirth
    b. To identify the optimal timing of delivery in monochorionic and dichorionic twin pregnancies
3. In the field of obstetrics
    a. To provide an overview of the existing prognostic models, their qualities and clinical applicability
    b. To evaluate the methodological challenges and potential solutions in developing a prognostic model for complications in women with pre-eclampsia

2.2. QUESTIONS ADDRESSED

The specific research questions that I have attempted to answer in this thesis are:

- What maternal genetic factors predispose women with pre-eclampsia to complications in pregnancy?
- How accurate are the routinely performed tests in women with pre-eclampsia to predict maternal and fetal complications?
- What outcomes are clinically relevant for evaluation in clinical trials on late onset pre-eclampsia?
- What are the prospective risks of stillbirth, neonatal morbidity and mortality associated with delivery at different gestational ages in monochorionic and dichorionic twin pregnancies?
- What is the optimal timing of delivery with the lowest stillbirth risk and serious neonatal adverse outcomes in uncomplicated monochorionic and dichorionic twin pregnancies?
- What is the quality of published obstetric prognostic models and what is their clinical usefulness?
- What are the methodological challenges of developing and applying an obstetric prognostic model and how can they be overcome?
- Which adverse maternal and neonatal outcomes are reported in trials on pre-eclampsia and how do they vary in quality and reporting?

Table 2.1 Structured questions for each chapter of this thesis

Chapter number	Population	Intervention or Test	Outcome(s)	Research Design
4.1	Women with pre-eclampsia	Maternal genotype	Adverse maternal and neonatal outcomes	HuGENet systematic review of observational studies
4.2	Women with pre-eclampsia	Tests including clinical history, examination and investigations	Adverse maternal and neonatal outcomes	Systematic review
4.3	Women with late-onset pre-eclampsia	Pregnancy complications	Composite maternal and neonatal adverse outcomes	Delphi survey
5.1	Women with uncomplicated twin pregnancies	Monochorionicity or dichorionicity and gestational age	Risk of stillbirth, neonatal morbidity and mortality	Systematic review
6.1	Pregnant women	Prognostic models	Quality and clinical applicability of models	Systematic review
6.2	Women with early-onset pre-eclampsia	Risk factors for complications	Prognostic model	Consensus

SECTION A

METHODS

In this section, I discuss the methodology used in this thesis: systematic review of the literature and the Delphi technique.

CHAPTER 3: METHODS

3.1. Systematic review of literature

One of the main methodologies used in this thesis to answer the research questions posed is a systematic review of the literature. This involves a rigorous, systematic approach with explicit methods to find, appraise, summarise and interpret the available research to answer the research question.

I employed the five-step approach to the conduct of systematic reviews.[60] The first step involved framing a question for reviews, by formulating a clear and focused question specifying the population(s) at hand, intervention (or exposures), specific outcomes related to the problem posed, and which study designs were suitable for addressing it. The subject matter included substantive research question where empirical studies have been published, but there was uncertainty about the results.

The second step was to identify the available evidence. This involved a thorough and usually, complex search strategy to adequately interrogate as many evidence sources as possible including electronic databases such as Medline, EMBASE, and the Cochrane library in addition to attempts to search the grey and unpublished literature, hand searching of references and conference proceedings. There was a pre-specified list of inclusion and exclusion criteria for identifying relevant studies. This step of screening and identifying relevant studies was conducted by at least two independent reviewers to eliminate bias in study selection with a discussion between the reviewers or involving a third reviewer where disputes arose. Reasons for study rejection were documented, and these details were demonstrated in a flow chart for transparent reporting.

The third step involved assessing the quality of the literature. This was performed by at least two independent reviewers to assess the risk of bias, and the quality assessment was based on each study's design, conduct and analysis. Based on the type of study, I used different published quality assessment checklists for use in systematic reviews.[61, 62] The qualities of the individual studies included in the review were described, and any variations in the quality were explored to help explain any differences in effect from study to study. Sensitivity analyses were be performed based on the different levels of quality of the studies. The quality assessment also helped direct future research recommendations on the conduct of studies.

The fourth step was summarising the evidence, which involved describing the data from the included studies and the measures of effect. The differences in effects between studies were investigated, and quantitative or qualitative synthesis was carried out where possible. Meta-analysis is a statistical method of quantitative synthesis, combining or pooling the individual effects of a number of studies addressing the same question to produce a summary effect. Any heterogeneity was explored both from clinical and methodological standpoints, and subgroup analyses were performed for different clinical groups, study designs or risk of bias. Publication or reporting bias was assessed, with a graphical representation using funnel plot for degrees of symmetry based on the results.[63]

The final step involved interpretation of the findings, with a critical evaluation of the conduct and results of the steps above to generate plausible conclusions in response to the research question.

Strengths and limitations of systematic reviews:

Systematic reviews of literature enable an objective and reproducible assessment of a well-framed research question according to the current state of clinical knowledge. The process incorporates critical evaluation of the included evidence. Hence, this forms a reliable basis for clinical decision-making and allows policy and guideline makers to come to evidence-based conclusions. They are considered the gold standard of research and reduce the biases that can occur with other approaches to reviewing research evidence. Furthermore quantitative synthesis using meta-analysis increases statistical power and provides narrower confidence intervals for statistical inference. Where there is variability with heterogeneity and inconsistency, meta-regression can be used. The latter can also enable indirect comparisons or network meta-analyses.

Transparency and reproducibility of the conduct of systematic reviews of literature are encouraged with the prospective enrolment of systematic reviews in publicly available databases such as PROSPERO,[64] Cochrane (for interventional and diagnostic accuracy studies) and clear reporting guidance of these papers for example with PRISMA and MOOSE guidelines.[65, 66]

Despite being hailed high in the hierarchy of research evidence, there are potential limitations with systematic reviews. The small study effect is one of these drawbacks; often there are only a few studies that may focus on the research question at hand and be of such low quality that inclusion of these studies may be misleading. Also, small studies with negative findings are often less likely to get published and hence the publication bias that arises may skew the summary effect estimates away from the true value. Another limitation is knowing when it is

appropriate to conduct a quantitative synthesis of the evidence as meta-analysis may not always be suitable.

Systematic reviews of genetic association studies

The systematic reviews performed in this thesis appraised a range of studies including observational studies, genetic association studies and studies of diagnostic test accuracy. Different techniques are required for analysis, assessment of quality for each type of study and they each encompass different challenges in their conduct and interpretation.

Genetic association studies identify whether candidate genes or genetic variants are associated with a specific disease. They generally have small effect magnitudes[67] and are particularly vulnerable to biases. Compared to conventional systematic reviews of observational studies, systematic reviews of genetic association studies need to account for extra factors for bias such as population stratification (confounding can arise due to different subpopulations within the sample differing in genotype prevalence and risk of disease), methods used in the collecting, handling, processing of deoxyribonucleic acid (DNA), blinding of laboratory staff and genotyping error.[68] The STrengthening the REporting of Genetic Association studies (**STREGA**) initiative has helped to address the transparency of reporting in individual genetic association studies and the checklist is useful in appraising the validity of such studies in systematic reviews.[69] The potential biases identified in individual studies can be addressed with sensitivity analyses during meta-analysis.

Systematic reviews of genetic association studies can follow published guidance on reporting set by the Human Genome Epidemiology network (HuGENet™), registering the review as a HuGE review.[70] The criteria for HuGE reviews are to describe population-based data on the

frequency of the identified genetic variant(s), to use a systematic search strategy to identify data and statistical methods such as meta-analysis to summarise the association, to assess for epidemiologic credibility, to present the findings in a population context and finally to highlight knowledge gaps for further research.[70] The guidance provides a template and set standard for systematic reviews of genetic association studies to adhere to.

Systematic reviews of diagnostic test accuracy studies

Diagnostic test accuracy studies investigate the ability of a test (the index test) to distinguish between patients with a condition and those without.[71] It is often difficult to capture studies of diagnostic test accuracy in literature searches as they are inadequately indexed. As such this often results in the need to screen thousands of studies when performing a systematic review.[72] There is often poor reporting of research methodology, study population characteristics and test procedures. Study quality can be appraised by recommended tools such as the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist taking into account the internal and external validity of the studies.[62] Meta-analysis may not be suitable as diagnostic test accuracy studies are often heterogeneous.[73] When this is not advisable, a qualitative descriptive analysis of the diagnostic research available can be done. Finally the results should be interpreted based on the impact upon the patient and not just on the accuracy of the test.

Clinical and statistical heterogeneity

The different studies combined in a meta-analysis will differ and the measure of this is the heterogeneity. Clinical heterogeneity is when there is variability or differences in participant or intervention characteristics, for example patient populations and treatment protocols. Statistical heterogeneity is when there are larger differences in the outcome of the individual

studies (summary treatment effects) than we would expect from chance alone. Clinical and methodological heterogeneity (variability in study design and risk of bias) can contribute to statistical heterogeneity. Preplanned subgroup analyses can help to investigate and explain clinical heterogeneity, for example stratifying for certain characteristics.[74] It is currently difficult to quantify the amount of clinical heterogeneity. Statistical heterogeneity can be assessed by tests such as the I^2 statistic which gives a percentage for the level of heterogeneity. By taking into account clinical and statistical heterogeneity, we can be guided to when it may not be appropriate to provide a pooled estimate in a meta-analysis.

The aim of systematic reviews is to provide the best research evidence through rigorous, objective and transparent methods. There are many checklists and standards to guide researchers on how to perform and report the different types of systematic reviews. The systematic review is not without its flaws though. It is important to be aware of the pitfalls and acknowledge any heterogeneity, potential for bias within the included studies and publication bias. Although meta-analysis can increase the precision of a result, it is also important to know when it is inappropriate to conduct a meta-analysis to ensure reliable and accurate results.

Delphi technique

The Delphi technique is a structured method of collating anonymous responses from an expert panel over several rounds to reach a consensus.[75] It is commonly used in healthcare and is useful in situations where there is a lack of agreement or incomplete state of knowledge.

The Delphi technique is also known as the Delphi method or Delphi survey. It consists of asking one or more questions over a series of rounds to a panel of experts often by means of an online survey. After the first round, the facilitator feeds back to the panel of experts a summary of the answers anonymously so that the experts can reconsider their answers with the option to revise their initial response. Over the series of rounds, the range of answers decreases, gradually leading to a consensus. The endpoint is usually after a predetermined number of rounds or level of consensus. The answers can be assigned points so that the final results are based on mean or median scores of the answers from the last round, thereby using a statistical measure of average and dispersion for the level of agreement or consensus.

The original Delphi technique has the following essential features: a panel of experts; anonymity throughout the process; a minimum of three rounds with the first consisting of open-ended questions and the subsequent rounds of scoring responses based on their significance and feedback of the responses to the panel. The researcher selects the experts on the panel. They are often considered ‘experts' due to their knowledge and expertise regarding the question at hand. This is a potential area of bias as there is no clear guidance on selection criteria for Delphi panels and one panel of experts may well give very different responses to another panel of experts. Regarding the size of the panel, there are no specifications although Linstone suggests that the minimum number should be 7.[76] A recent systematic review of the use of the Delphi technique to determine which clinical outcomes to measure in clinical trials has recommended involving patients in addition to clinicians on the panel as often perspectives on the importance of outcomes differs among these two groups.[77] Anonymity is an important aspect as this prevents domination by certain individuals, which may well occur in a group of experts due to seniority or some being more outspoken than others. The lack of

interaction also enables this process to be more efficient, less costly and more feasible to organise compared to the traditional round table group discussion.

I used the Delphi technique to identify the components of composite outcomes. The first round was qualitative and was used to identify the issues around a certain topic by open-ended questions. The responses were collected and edited for the second round when the list of items was provided for the panellists to rate or rank quantitatively regarding their significance. After each round, the responses of the panel scoring and the participant's individual scoring was fed back so that each participant's decision can be reconsidered and their score revised. There are no criteria on how consensus is defined. Commonly used assessment tools include a Likert scale,[78] where median scores are calculated for each item and then fed back to the panellists. With this scale, the interquartile range can provide an indication of differing opinions and narrowing of the interquartile range between rounds, suggests increasing consensus.

Strengths and limitations of Delphi survey:

The strengths of this technique are that it structures and organises group communication effectively and democratically to develop consensus. In particular, with regard to determining outcomes to measure in clinical trials, this provides a form of standardisation to minimise bias from researchers randomly selecting the outcomes as the alternative. It also enables the combination of different groups such as patients and clinicians to seek agreement, an example being the international initiative OMERACT, with the integration of patients for outcome measures in Rheumatology.[79] The process allows impartial feedback and has the potential to educate the participants through the responses of successive rounds.

The weaknesses are that the process is dependent on that particular panel of members and their experiential knowledge of the topic. It also relies on their co-operation with every round and is likely to be subjective to attrition bias with those with minority opinions perhaps being more likely to drop out. There is little guidance on specific methodological criteria on the use of rating or ranking scales and more importantly how to define achievement of consensus. Furthermore, the consensus is reached by expert opinion without robust tools to assess and validate the underlying scientific merit. However, with the advent of recent recommendations for more transparent reporting, a clear and objective explanation of the approach will provide greater validity to the research.

SECTION B

PRE-ECLAMPSIA

In this section, I have undertaken a systematic review and meta-analysis of genetic association studies to identify candidate genes associated with severe pre-eclampsia; I have assessed the accuracy of tests in predicting severe pre-eclampsia and its complications by systematic review; I have identified the outcomes which are considered to be clinically relevant in the management of women with pre-eclampsia, and have developed composite outcomes for reporting in clinical trials on late onset pre-eclampsia by Delphi survey.

CHAPTER 4.1. MATERNAL GENOTYPE AND SEVERE PRE-ECLAMPSIA

Background: Severe pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity worldwide. Genetic factors are strongly implicated, and early identification of women at high risk of adverse events would allow targeted prevention and timely obstetric management. Individual genetic studies are underpowered to assess the risk of pre-eclampsia complications.

Objective: To perform a systematic review and meta-analysis of all maternal genotypes and severe pre-eclampsia.

Results: We compared genotype frequencies in women with severe pre-eclampsia (pre-eclampsia complicated by severe hypertension, eclampsia, HELLP syndrome or fetal growth restriction) to women without complications. Fifty-seven studies evaluated 50 genotypes in 5,049 cases and 16,989 controls. Meta-analysis by pre-defined gene function (thrombophilic, vasoactive, metabolic, immune, cell-signalling) showed increased risk of severe pre-eclampsia with thrombophilic genes (F5 rs6025 and MTHFR rs1801133). There were no associations with the other gene groups: vasoactive, metabolic, immune-related and cell-signalling. Individual genotype meta-analysis showed positive associations with severe pre-eclampsia for F5 (rs6025) (OR 1.90, 95% CI 1.42, 2.54, 23 studies, I^2=29%), F2 mutation G20210A (rs1799963) (OR 2.01, 95% CI 1.14, 3.55, 9 studies, I^2=0%) and leptin receptor (LEPR) polymorphism (rs1137100) (OR 1.75, 95% CI 1.15, 2.65, 2 studies I^2=0%) and the thrombophilic gene group (OR 1.87, 95% CI 1.43, 2.45, I^2= 27%). Heterogeneity between studies was moderate with bias from the inconsistent phenotypic definition and poor quality reporting of genotyping methods and success.

Conclusion: Pregnant women with genetic variants associated with thrombophilia appear to be at higher risk of severe pre-eclampsia. However, there is insufficient epidemiological

credibility to establish causality. More rigorously designed studies with larger sample sizes are needed to provide robust estimates of genetic risk for adverse outcomes of pregnancy related to pre-eclampsia and to evaluate the potential benefits of genetic screening in clinical practice.

Citation from work:

Fong F, Sahemey M, Hamedi G, Eyitayo R, Kuan V, Yates D, Thangaratinam S, Walton R. Maternal Genotype and Severe Pre-eclampsia: a HuGE Review. Am J of Epidemiol 2014; 180(4): 335-345.

Introduction

Pre-eclampsia is a multisystemic disorder of pregnancy associated with hypertension and proteinuria. The condition affects between 6- 8% of pregnancies worldwide and is one of the leading causes of maternal mortality and morbidity, accounting for more than 63,000 maternal deaths each year globally.[11, 12] In the UK alone, approximately 10-15% of direct maternal deaths and 20% of stillbirths are associated with pre-eclampsia.[13] The morbidity and mortality rates are even higher when severe pre-eclampsia develops, and complications of organ dysfunction ensue.[11]

Maternal complications include eclampsia (tonic-clonic seizures in a pregnant or recently delivered woman); HELLP syndrome, causing substantial widespread endothelial damage; stroke; renal failure; placental abruption; pulmonary oedema and venous thromboembolism.[80, 81] When pre-eclampsia is diagnosed around 20 weeks (early-onset pre-eclampsia), neonatal survival rates range between 18-50%.[17] Severe pre-eclampsia is associated with a stillbirth rate of 21 per 1000.[82] The prevalence of fetal growth restriction varies from 8.7% in pre-eclampsia to 18.2% in early-onset pre-eclampsia.[83] As delivery remains the only proven treatment option, iatrogenic prematurity resulting from early induction of labour contributes greatly to neonatal morbidity and mortality. Both fetal growth restriction and prematurity have serious and long-term implications for the health of the child. Care for preterm babies incurs extra costs to the NHS at around £939 million per year from neonatal intensive care admissions and hospital readmissions.[10]

Despite extensive research, it remains difficult to predict the risk of complications in women with pre-eclampsia in time for early intervention. With regard to preventative strategies, low-dose aspirin, if given early on in pregnancy, has been shown to prevent severe pre-eclampsia and perinatal death. Following a diagnosis of pre-eclampsia, delivery remains the most effective way of preventing complications and is often expedited to avoid increasing the risk to mother and child. Accurate estimates of risk could aid both in targeting preventative strategies and in decision-making on the timing of delivery to optimise maternal and neonatal outcomes. We are unable to reliably stratify for risk of complications with conventional methods of evaluation by clinical history, symptoms and investigations.[84-88]

Pre-eclampsia is known to cluster in families and evidence from twin and family genetic studies suggest a strong hereditary component.[19, 89, 90] The exact mode of inheritance is as yet unknown and appears complex, possibly polygenic with environmental influences.[91] The potential pathogenic roles of different pathways in developing pre-eclampsia such as the immune system, control of vascular resistance, blood coagulation, cell signalling and metabolic processes have resulted in various candidate genes implemented through these pathways in genetic association studies. Very few genetic studies to date have specifically addressed the inherited contribution to the severity of disease and development of complications. Furthermore, these studies are often underpowered to detect associations due to the small sample sizes. Systematic reviews in this area have focussed on the development of pre-eclampsia itself, with severe or complicated pre-eclampsia as a subanalysis or in combination with other adverse outcomes not necessarily associated with pre-eclampsia.[92-94]

Thus we systematically reviewed all available published evidence and conducted a meta-analysis to identify candidate genes associated with severe pre-eclampsia.

Methods

We conducted the systematic review in compliance with Human Genome Epidemiology (HuGE) recommendations for genetic meta-analysis.[70] A prospective protocol was registered in PROSPERO.[95] We defined severe pre-eclampsia as pre-eclampsia (hypertension (blood pressure ≥140/90mmHg) and proteinuria (≥300mg/24 hours or protein-creatinine ratio ≥30mg/dL) and at least one of the following complications: severe hypertension (systolic blood pressure ≥160mmHg and/or diastolic blood pressure ≥110mmHg); eclampsia (convulsions that could not be attributed to other causes); haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, (with platelet count <100,000/dl and raised serum transaminases above the upper limits of normal) or intrauterine fetal growth restriction (estimated fetal weight below than the 10th centile)).

There is currently no international consensus on criteria for the definition of severe pre-eclampsia. The definition for severe pre-eclampsia in our review was based on the recent classification and agreement from the International Society for the Study of Hypertension in Pregnancy[96] where difficulty controlling blood pressure, deterioration of the clinical condition such as development of HELLP syndrome, impending eclampsia, worsening thrombocytopenia and fetal growth restriction were considered to be indicators of severity and an indication to expedite delivery. If studies contained separate populations of cases of mild pre-eclampsia and severe pre-eclampsia, but their definition of severe pre-eclampsia

differed slightly from that of the International Society for the Study of Hypertension in Pregnancy, we took a pragmatic decision to include such studies.

Identification of studies and study selection

We searched Medline and Embase electronic databases from inception to August 2013 without language restrictions to include prospective and retrospective observational studies that examined an association between severe pre-eclampsia and maternal genotype variation (e.g., single nucleotide polymorphisms, microsatellite markers, insertion/deletions, repeat sequences). This search was subsequently updated to March 2017. The search strategy was developed with advice from an experienced librarian (DY) and details are found in Appendix 1.

We selected the studies in two stages: initially relevant citations were identified by titles and abstracts; this was followed by retrieval and review of full texts by four independent reviewers (FC, MS, GH, RE). The citations were divided into two groups, and two reviewers were assigned per group. Independent screening, study selection and data extraction were performed and any disagreements were resolved by consulting another reviewer (ST or RW). We included those studies that compared the genotype frequencies in women with severe pre-eclampsia to a control group comprising pregnant women with normal pregnancy, gestational hypertension or mild pre-eclampsia, without complications. Studies that provided genotype frequencies enabling 2x2 tables to be constructed for each genotype and severe pre-eclampsia were included. If the genotype frequency for the homozygous minor, homozygous and heterozygous groups combined was zero, the study was excluded.

Assessing the risk of bias in individual studies

We adapted the Newcastle-Ottawa Scale (NOS) and STrengthening the REporting of Genetic Association studies (STREGA) recommendations to form a modified quality assessment.[61, 69, 97] The Newcastle-Ottawa Scale assessed the selected studies for methodological quality. In cohort studies, we evaluated the representativeness, selection of the exposed and non-exposed cohorts, ascertainment of exposure, whether the outcome of interest was present from the start; comparability of the cohorts and outcome bias with length and adequacy of follow-up.[61] For case-control studies, representativeness, selection of cases and controls, comparability of the groups, ascertainment of exposure, ascertainment of outcome for cases and controls and the non-response rate were assessed. Stars for each category were awarded according to the criteria for the Newcastle-Ottawa Scale manual[61], if a study obtained four stars for selection (two for comparability, and three for the ascertainment of exposure, the risk of bias was low. Studies that received two or three stars for selection, one for comparability and two for exposure were considered to have a moderate risk of bias. Studies receiving none or one star for selection, comparability or exposure represented a high risk of bias.

We assessed reporting of genotyping methodology, success rates of genotyping, population stratification and whether genotypes were in Hardy-Weinberg equilibrium[98] were also taken into account following STREGA recommendations. We calculated statistics for Hardy-Weinberg equilibrium and compared results to those given by authors. We assessed epidemiologic credibility for maternal genotypes that showed a positive association with severe pre-eclampsia using the Venice criteria. This takes into account sample size, replication of results and level of protection from bias.[99, 100]

Data extraction and analysis

Four reviewers extracted data independently from the included studies. We compared heterozygous and homozygous genotypes of the minor allele combined to homozygous genotypes of the major allele. When percentages of groups were given in the studies, these were converted into actual numbers. We calculated odds ratios with 95% confidence intervals by comparing women with severe pre-eclampsia to a control group comprising normal pregnant women, women with gestational hypertension and uncomplicated pre-eclampsia. Random effects meta-analyses of the maternal genotypes were performed according to predefined gene function groups: thrombophilic; vasoactive; metabolic; immune-related and cell-signalling.

We performed subgroup analyses on individual genotypes taking into account study design, sample size >100 and ethnicity of the study populations for each genotype (comparing different ethnic groups with homogenous populations if there were sufficient numbers). We performed sensitivity analyses excluding studies where the definition of severe pre-eclampsia was unclear. Where there was more than one outcome reported for severe pre-eclampsia in the same study population, we included data for the 'worst' outcome (ranked in order of importance by prior consensus, namely eclampsia, severe pre-eclampsia, HELLP, intrauterine fetal growth restriction). When the same study population assessed more than one genotype, we included the genotype with the largest dataset. In cases of similarly important genotypes and complications, we undertook sensitivity analyses substituting for the other potential genotypes to assess for any difference in the overall results based on the study numbers that were included. We assessed heterogeneity in the meta-analysis using the I^2 statistic. We used

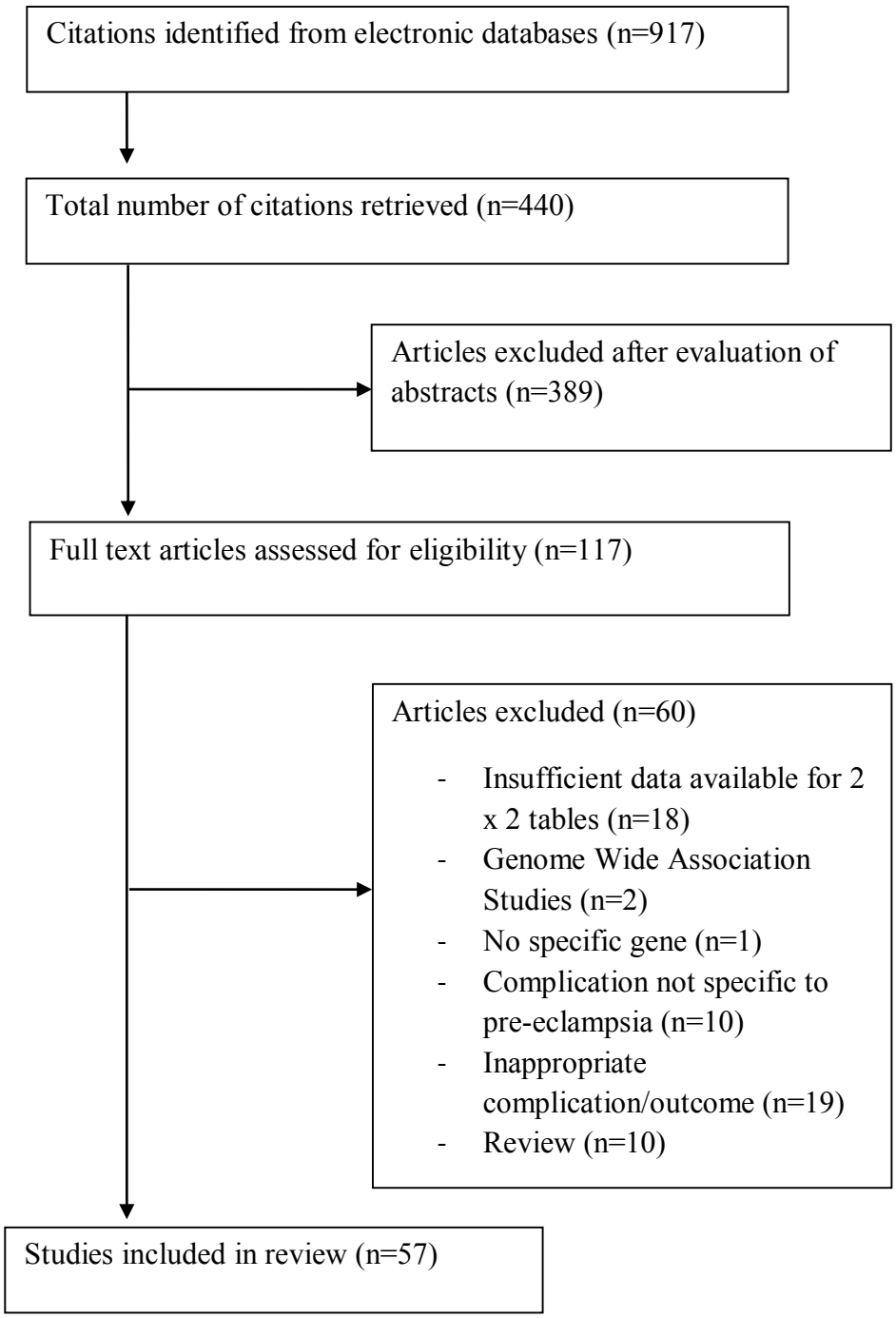
Harbord's modified test for small-study effects to assess for publication bias.[101] All analyses were carried out using RevMan, version 5.1.[102]

Results

Study identification and selection

We identified 917 citations from our search in Medline and Embase. After removing duplicated titles and assessment against inclusion criteria, 117 relevant studies were identified. The full texts of these studies were retrieved, and 57 studies were included in the review. (Figure 4.1.1)

Figure 4.1.1 Study identification and selection process for meta-analysis of relationships between maternal genotype and severe pre-eclampsia.



Characteristics of the included studies

The effects of 37 candidate genes and 50 maternal genetic variants on complications of pre-eclampsia were examined in 22,038 women (5,049 cases and 16,989 controls). The maternal genetic variants included single nucleotide polymorphisms, microsatellite markers and insertion/deletions. The definitions for severe pre-eclampsia for each study are summarised in Table 4.1.

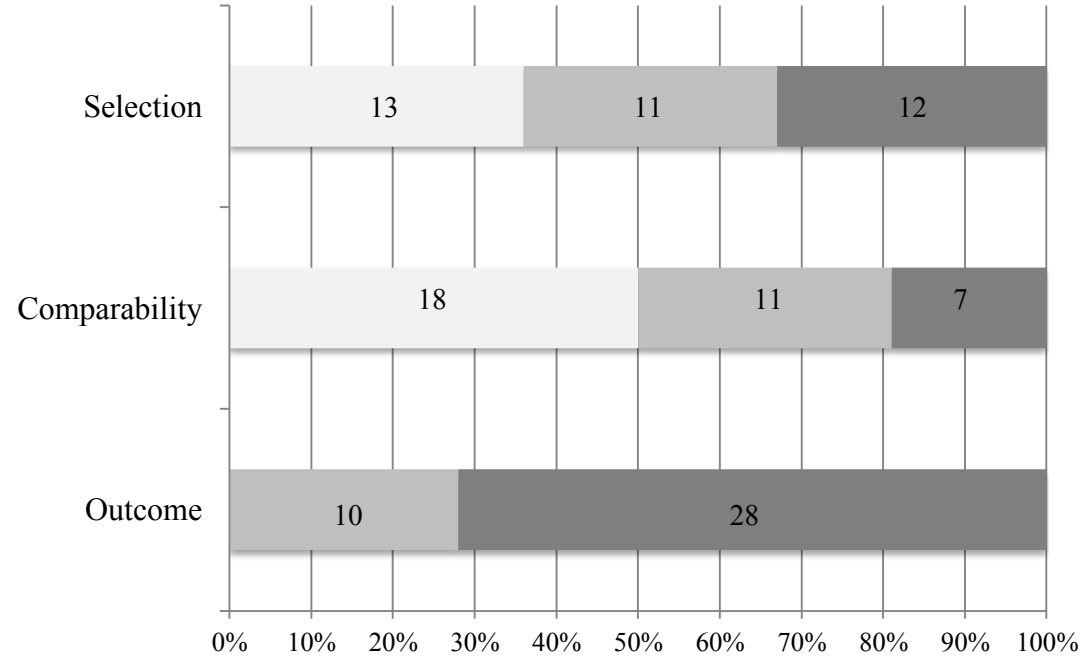
There were four studies that did not provide a clear definition of severe pre-eclampsia.[103-106] Thirteen studies did not describe exclusion criteria and one study excluded the use of aspirin in pregnancy.[107] Detailed study characteristics including population demographics, ethnicity, inclusion and exclusion criteria are provided in Appendix 2. Fifty-one of the included fifty-seven studies were cohort studies (41 prospective and 10 retrospective) and the remaining six were case-control studies.[103, 108-112] The publication years were from 1996 to 2012. The majority of the included studies did not assess severe pre-eclampsia as the primary outcome. Only 16 out of the 57 studies had study populations with more than 100 cases of severe pre-eclampsia.

Quality of the included studies

Of the included studies, 30% (17/57) had low levels of bias for selection of the exposed and non-exposed groups, 46% (26/57) had medium levels of bias and 24% (14/57), high levels of bias. Eleven of the included studies (19%, 11/57) had high levels of bias for comparability of the cohorts, 37% (21/57) had medium bias and 44% (25/57) had low levels of bias. Poor documentation of follow-up of the patients and insufficient length of time to identify relevant

complications resulted in high levels of bias in 42% (24/57) of the studies regarding identification of outcome (Figure 4.1.2).

Figure 4.1.2 Bar chart of the Newcastle Ottawa Scale methodological quality assessment of the included studies.



Key

Low level of bias
Medium level of bias
High level of bias

Numbers of studies with each different level of bias are marked on each bar.

Using the STREGA criteria,[69] we demonstrated that the majority of studies (49/57, 86%) had homogenous ethnic population groups. The ethnicities included Caucasian (Europe, USA, Australia and New Zealand), East Asian (India), Middle East Asian (Iran, Israel), South

Asian (Korea, Japan, China), Black African, South African, Latin American and mixed (Brazil/Mulatto, Israeli Ashkenazi/non-Ashkenazi, USA/African-American/Hispanic, France Caucasian/Maghrebian) (Appendix 3). There was documentation of genotyping success in 5% (3/57). Only five studies[113-116] documented methods of genotyping quality control with the use of repeated samples or additional controls. Thirty-two studies (56%) provided sufficient data for us to calculate the Hardy-Weinberg equilibrium and of these, ten deviated from equilibrium. In the reporting of Hardy-Weinberg equilibrium by the studies, twenty-three (40%) studies documented the genotypes to be in equilibrium but on recalculation, five were found to deviate from equilibrium.

Blinding of the staff performing the genotyping to the clinical outcome was reported in only four studies.[116-118] Power calculations were performed a priori in 17 studies (30%). Many of the included studies examined pre-eclampsia in addition to complications but for nine of the studies,[114, 118-122] power calculations were made a priori for severe pre-eclampsia. (Appendix 3)

Genetic association with severe pre-eclampsia

Individual genotypes

Meta-analysis was possible with the following genotypes ACE DD rs4646994 (4 studies)[115, 123-125]; Angiotensinogen M235T rs699 (3 studies)[115, 126, 127]; Estrogen receptor 1 PvuII rs2234693 (2 studies)[120, 127]; Factor V Leiden rs6025 (23 studies)[107-110, 112, 117, 122, 123, 127-141]; Leptin TTTNc (2 studies)[104, 142]; Leptin G1019A rs1137100 (2 studies)[118, 143] Leptin R223Q rs1137101 (4 studies)[104, 118, 143, 144]; MTHFR C677T rs1801133 (10 studies)[107, 109, 112, 122, 123,

[131-133, 135, 145]; Factor 2 Prothrombin G20210A rs1799963 (9 studies)[107, 109, 122, 127, 129, 132, 134, 135, 139]; TGF beta 1 codon 10 rs1982073 (2 studies)[111, 146]; TNF alpha G308A rs1800629 (4 studies)[146-149]. (Figure 4.1.3)

Figure 4.1.3 Summary estimates of maternal genotype and severe pre-eclampsia (Part 1/5) *Permission granted to reproduce this supplementary figure from American Journal of Epidemiology, Oxford University Press. Licence number 3998150855655*

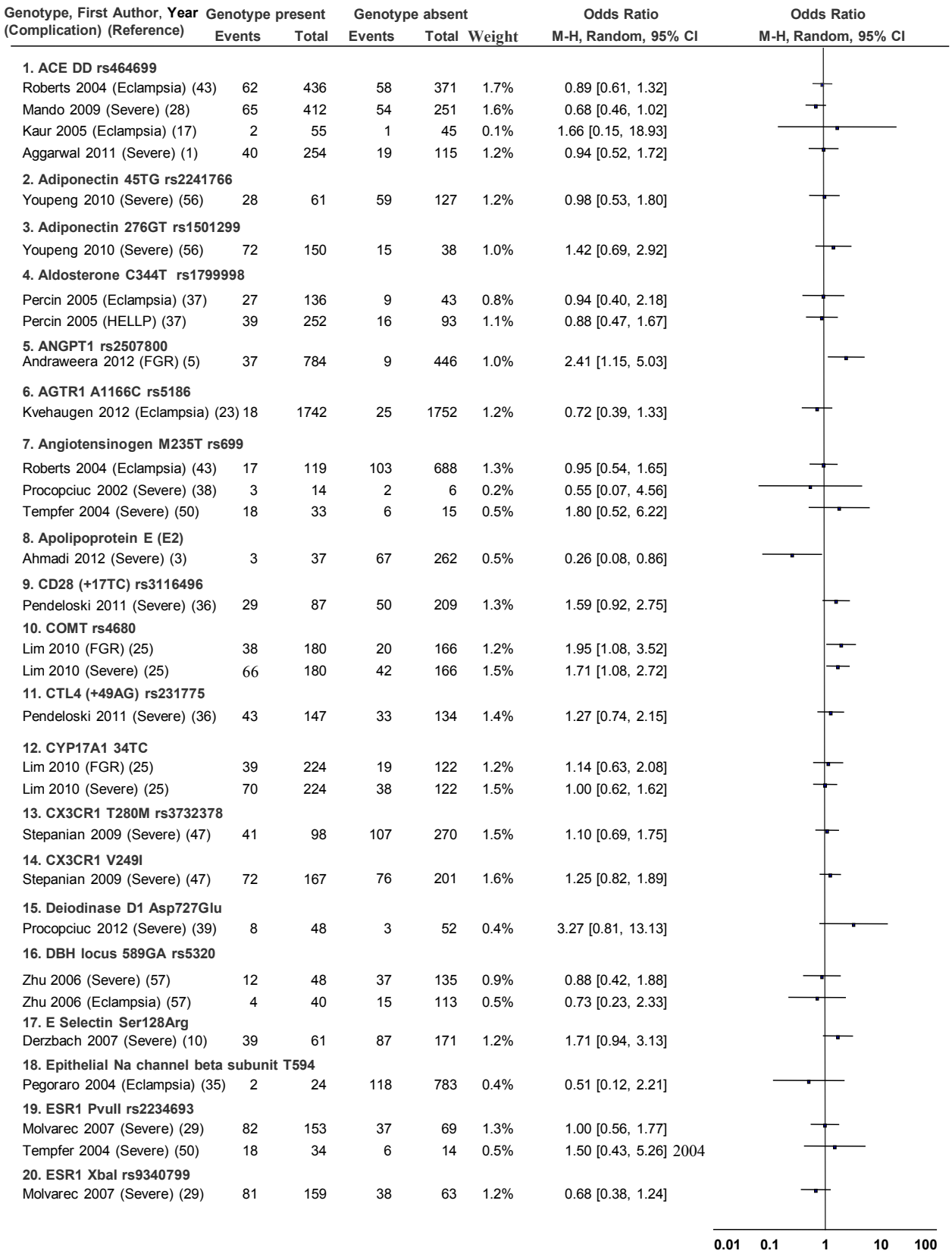


Figure 4.1.3 (Part 2/5)

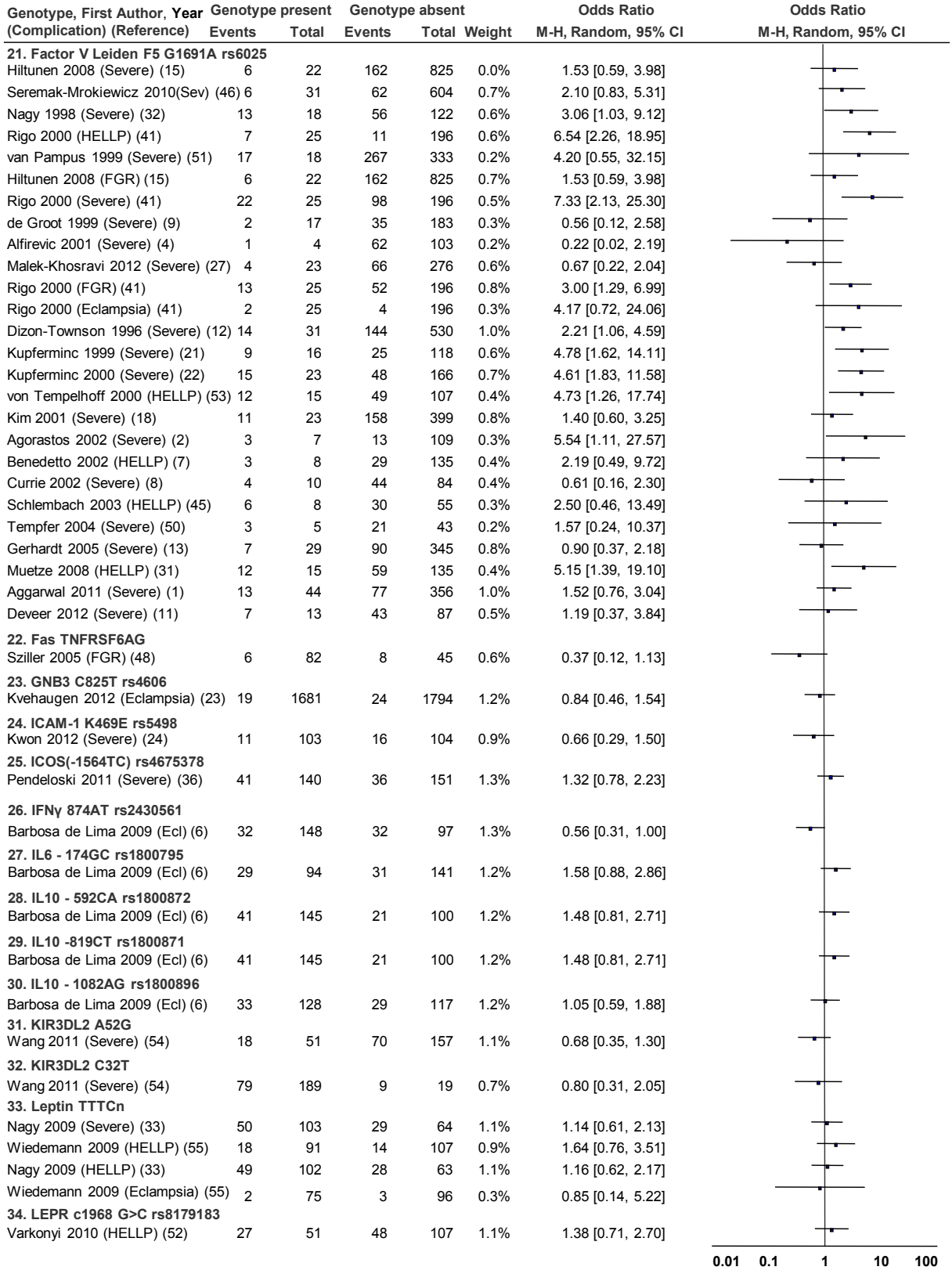


Figure 4.1.3 (Part 3/5)

Genotype, First Author, Year (Complication) (Reference)	Genotype present Events	Total	Genotype absent Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
35. LEPR c3024 A>G rs6403506						
Varkonyi 2010 (HELLP) (52)	49	92	26	66	1.1%	1.75 [0.92, 3.33]
36. LEPR c326AG rs1137100						
Varkonyi 2010 (HELLP) (52)	35	64	40	94	1.1%	1.63 [0.86, 3.09]
37. LEPR G1019A						
Rigo 2006 (Severe) (42)	89	151	35	80	1.3%	1.85 [1.07, 3.19]
Guan 2011 (Severe) (14)	77	140	130	319	1.6%	1.78 [1.19, 2.65]
38. Leptin PPAR γ2 rs1801282						
Wiedemann 2009 (Eclampsia) (55)	2	46	3	125	0.3%	1.85 [0.30, 11.43]
Wiedemann 2009 (HELLP) (55)	9	53	23	145	0.8%	1.08 [0.47, 2.52]
39. Leptin R223Q rs1137101						
Wiedemann 2009 (HELLP) (55)	19	128	13	70	0.9%	0.76 [0.35, 1.66]
Varkonyi 2010 (HELLP) (52)	50	101	25	57	1.1%	1.25 [0.65, 2.41]
Rigo 2006 (Severe) (42)	60	104	64	127	1.3%	1.34 [0.80, 2.26]
Wiedemann 2009 (Eclampsia) (55)	3	112	2	59	0.3%	0.78 [0.13, 4.83]
Guan 2011 (Severe) (14)	46	138	161	321	1.5%	0.50 [0.33, 0.75]
40. MBL2 Codon 54 rs1800450						
Sziller 2007 (FGR) (49)	8	73	57	243	0.9%	0.40 [0.18, 0.89]
Sziller 2007 (HELLP) (49)	13	73	68	243	1.1%	0.56 [0.29, 1.08]
41. MTHFR C677T rs1801133						
Rigo 2000 (Severe) (41)	74	133	46	88	1.3%	1.15 [0.67, 1.97]
Kobashi 2000 (Severe) (20)	46	180	19	108	1.2%	1.61 [0.88, 2.92]
Alfirevic 2001 (Severe) (4)	7	9	56	98	0.3%	2.63 [0.52, 13.29]
Kupferminc 2000 (Severe) (22)	15	27	48	162	0.8%	2.97 [1.29, 6.81]
Kim 2001 (Severe) (18)	101	294	92	259	1.7%	0.95 [0.67, 1.35]
Livingston 2001 (Severe) (26)	44	78	66	129	1.2%	1.24 [0.70, 2.17]
Gerhardt 2005 (Severe) (13)	8	36	89	338	0.8%	0.80 [0.35, 1.82]
Muetze 2008 (HELLP) (31)	41	85	30	65	1.1%	1.09 [0.57, 2.08]
Aggarwal 2011(Severe) (1)	18	106	72	294	1.2%	0.63 [0.36, 1.12]
Deveer 2012 (Severe) (11)	21	45	29	55	0.9%	0.78 [0.36, 1.73]
42. NADPH/NADH oxidase C242T						
Raijmakers 2002 (HELLP) (40)	27	85	28	88	1.1%	1.00 [0.53, 1.89]
43. P Selectin Thr715Pro						
Derzbach 2007 (Severe) (10)	16	37	110	195	1.0%	0.59 [0.29, 1.20]
44. Prothrombin F2 G2021A rs1799963						
Malek-Khosravi 2012 (Severe) (27)	2	7	68	292	0.3%	1.32 [0.25, 6.94]
Alfirevic 2001 (Severe) (4)	2	4	61	103	0.2%	0.69 [0.09, 5.08]
Seremak-M 2010 (Severe) (46)	5	13	63	622	0.5%	5.55 [1.76, 17.47]
Kupferminc 1999 (Severe) (21)	2	5	32	129	0.2%	2.02 [0.32, 12.64]
Benedetto 2002 (HELLP) (7)	2	3	30	140	0.1%	7.33 [0.64, 83.65]
Tempfer 2004 (Severe) (50)	1	2	23	46	0.1%	1.00 [0.06, 16.97]
Gerhardt 2005 (Severe) (13)	4	10	93	364	0.5%	1.94 [0.54, 7.04]
Muetze 2008 (HELLP) (31)	3	6	68	144	0.3%	1.12 [0.22, 5.72]
Deveer 2012 (Severe) (11)	1	3	49	97	0.1%	0.49 [0.04, 5.58]
45. RGS2 C114G rs5443						
Kvehaugen 2012 (Eclampsia) (23)	25	114	18	109	1.1%	1.42 [0.72, 2.78]
46. SOD3 G172A rs1799895						
Rosta 2009 (FGR) (44)	32	160	15	113	1.1%	1.63 [0.84, 3.18]
47. TGF β1 codon 10 +869TC rs1982073						
Kim 2010 (FGR) (19)	41	212	16	134	0.0%	1.77 [0.95, 3.30]
Barbosa de Lima 2009 (Ecl) (6)	39	167	13	60	1.0%	1.10 [0.54, 2.24]
Kim 2010 (Severe) (19)	76	207	41	139	1.4%	1.39 [0.87, 2.20]
48. TGF β1 codon 25 +915GC rs1800471						
Barbosa de Lima 2009 (Ecl) (6)	10	35	42	192	0.8%	1.43 [0.64, 3.21]

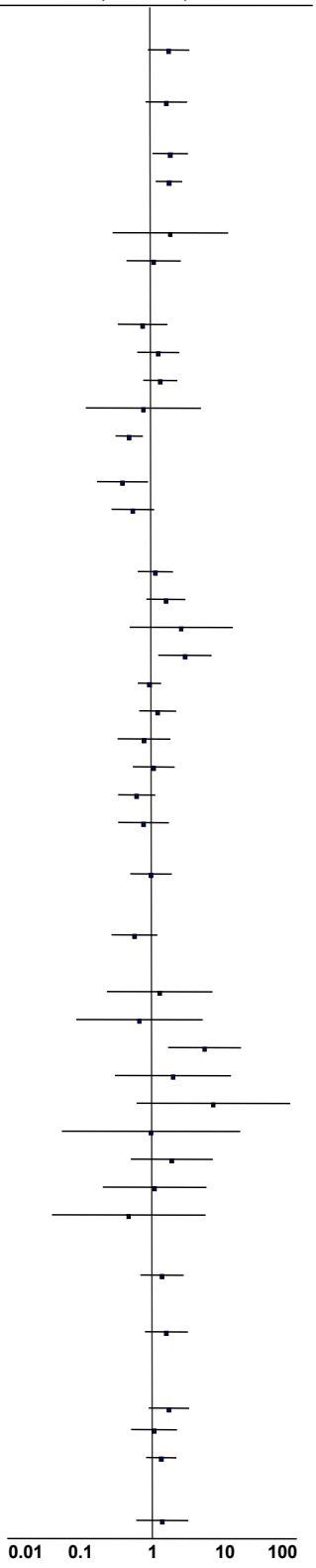


Figure 4.1.3 (Part 4/5)

Genotype, First Author, Year (Complication) (Reference)	Genotype present Events	Total	Genotype absent Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
49. TNFα G308A rs1800629						
Molvarec 2008 (HELLP) (30)	15	81	54	272	1.1%	0.92 [0.49, 1.73]
Pazarbasi 2007 (Eclampsia) (34)	5	24	34	208	0.6%	1.35 [0.47, 3.85]
Molvarec 2008 (FGR) (30)	19	66	43	218	1.1%	1.65 [0.88, 3.08]
Barbosa de Lima 2009 (Ecl) (6)	10	55	54	194	0.9%	0.58 [0.27, 1.22]
Kaiser 2004 (Eclampsia) (16)	29	110	22	163	1.1%	2.29 [1.24, 4.26]
50. TNFα C850T rs1799895						
Pazarbasi 2007 (Eclampsia) (34)	24	118	16	104	1.0%	1.40 [0.70, 2.82]

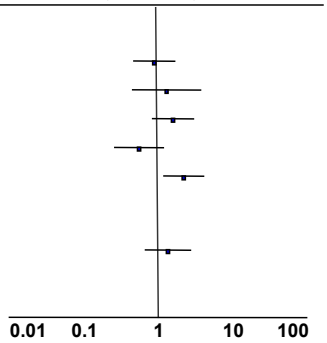
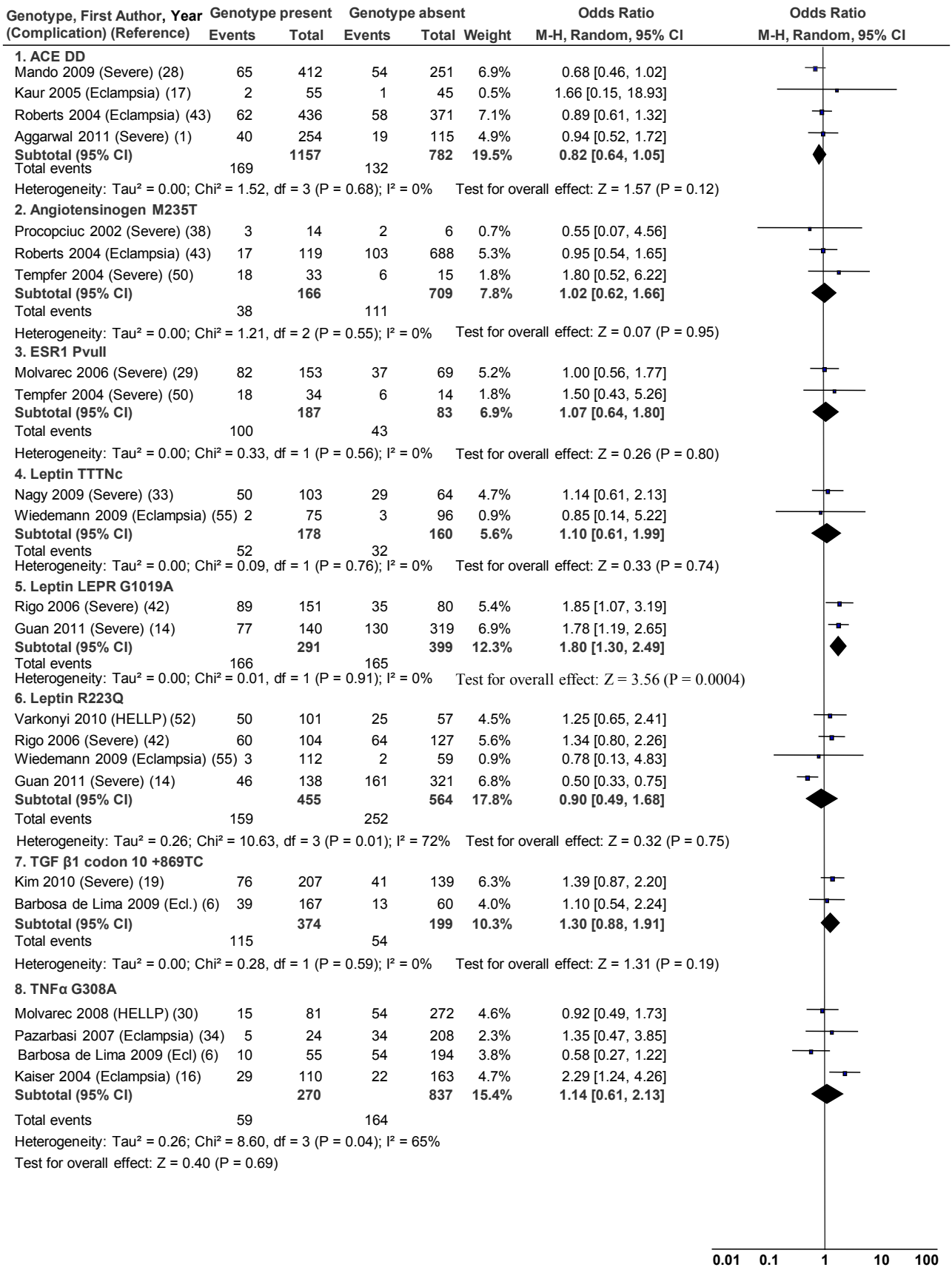
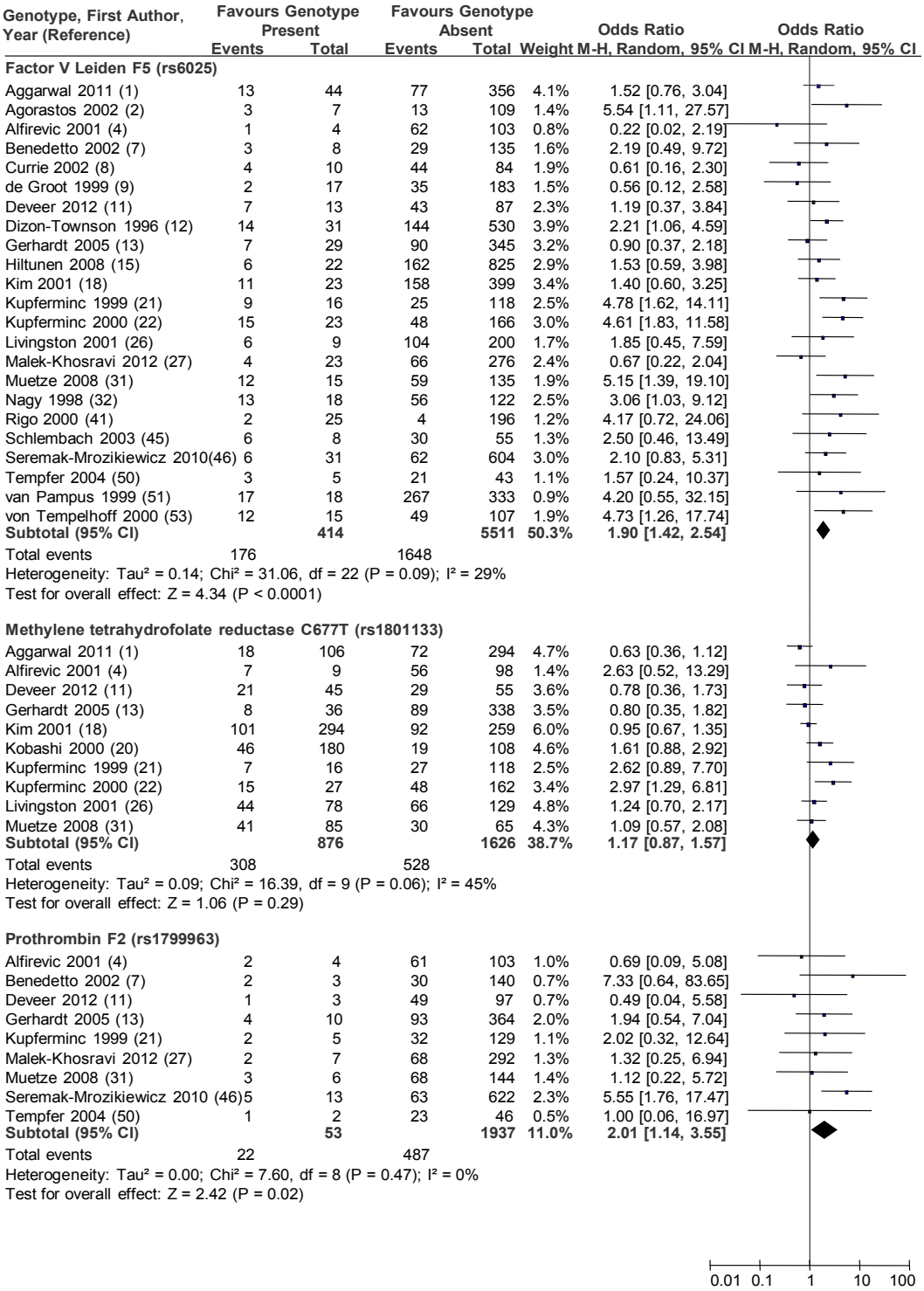


Figure 4.1.3 (Part 5/5)



Positive associations were seen with severe pre-eclampsia and Factor V Leiden rs6025, (OR 1.9, 95% CI 1.42, 2.54; LR 1.66, 95% CI 1.38, 2.00, 23 studies I_2=29%), Factor 2 Prothrombin G20210A rs1799963 (OR 2.01, 95% CI 1.14, 3.55; LR 1.80, 95% CI 1.30, 2.49, 9 studies I_2=0%) and LEPR G1019A rs1137100 (OR 1.75, 95% CI 1.15, 2.65, LR 1.38, 95% CI 1.18, 1.61, 2 studies I_2=0%). (Figure 4.1.4)

Figure 4.1.4 Summary Estimates for Thrombophilic Genotypes and Severe Pre-eclampsia compared with Controls *Permission granted to reproduce this figure from American Journal of Epidemiology, Oxford University Press. Licence number 3998150855655*



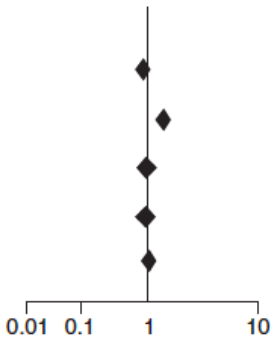
The prevalences in the respective control populations were 5.8% for Factor V Leiden rs6025 was 5.8%, 2.1% for Factor 2 Prothrombin G20210A rs1799963 and 34.8% for LEPR G1019A rs 1137100. For the other maternal genotypes, there were no significant associations. Subgroup analyses for Factor V Leiden rs6025 and Factor 2 Prothrombin G20210A rs1799963 stratifying for study design, ethnicity and sample size did not show any significant differences. (Table 4.1.2 and Table 4.1.3) A sensitivity analysis of the studies with an unclear definition of severe pre-eclampsia revealed no difference in results.

Predefined gene function groups

Thrombophilic genes were significantly associated with any adverse outcome compared to the control group (OR 1.87, 95% CI 1.43, 2.45; 24 studies, I^2=27%). There were no significant associations with vasoactive genes (OR 0.94, 95% CI 0.72, 1.24), metabolic genes (OR 1.08, 95% 0.76, 1.55), immunogenetic genes (OR 1.05, 95% 0.75, 1.46) and genes related to cell signalling pathways (1.31, 95% 0.99, 1.72). (Figure 4.1.5)

Figure 4.1.5 Summary odds ratio estimates for genotype by gene function with severe pre-eclampsia compared with controls (normal pregnancies and uncomplicated pre-eclampsia)

Gene Function	No. of Genotypes	Total No. of Studies	Total No. of Women	Odds Ratio (95% CI)
Vasoactive	6	9	6,910	0.94 (0.72, 1.24)
Thrombophilic	2	24	6,213	1.87 (1.43, 2.45)
Metabolic	6	11	2,316	1.08 (0.76, 1.55)
Immune	7	9	2,480	1.05 (0.75, 1.46)
Cell signalling	4	4	996	1.31 (0.99, 1.72)



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In some studies, the same population was tested for different genotypes with the same underlying gene function. All possible combinations of the genotypes without overlapping of populations were tested by sensitivity analyses for each gene function group with no significant differences were observed in the results.

Epidemiologic credibility of significant associations

Using the Venice criteria, the positive associations between severe pre-eclampsia and F5 rs6025, F2 G20210A rs 1799963, and LEPR rs11371000 were assessed for epidemiologic credibility. There was weak evidence of epidemiologic credibility for all three genetic variants. For F5 rs6025, there was moderate heterogeneity amongst the studies (I^2 = 29%), and risk of biases was present due to variations in phenotype definition, poor reporting of genotype methods, stratification for ethnicity and evidence based on published data only. For F2 G20210A rs1799963 and LEPR rs1137100, there was low heterogeneity, but the risk of biases was high for the same reasons as F5 rs6025 in addition to smaller sample sizes. (Table

4.1.4)

DISCUSSION

Genetic variants related to thrombophilia are significantly higher in women with severe pre-eclampsia. While most pregnancies with pre-eclampsia are uneventful, preventable complications pose a risk to mother and child and thus accurate estimation of baseline risk is an urgent priority because timely obstetric intervention can prevent maternal and fetal deaths and minimise illness in mother and child.

Genetic effects on pre-eclampsia

Incomplete understanding of the underlying pathophysiology and the complex mode of inheritance of pre-eclampsia have rendered genetic studies on pre-eclampsia difficult.[29] Candidate genes with diverse biological pathways have been tested including genes related to vasoactive proteins,[150] thrombophilia,[151] metabolic processes,[142, 144] cell signalling[152] and immunogenetic pathways.[153] However, individual studies are small, and their results are conflicting. Two recent large meta-analyses of genetic variants in pre-eclampsia found positive associations with polymorphisms of angiotensin-converting enzyme (ACE), cytotoxic T-lymphocyte antigen-4 (CTLA4), prothrombin factor 2 (F2), Factor V Leiden (F5), lipoprotein lipase (LPL) genes[154] and pre-eclampsia but that care should be taken into interpretation due to possible bias.[94]

Perhaps the most consistent associations with pre-eclampsia have been with thrombophilia which is a hypercoagulable state that may potentiate placental micro and macrovascular

thrombosis and in turn, cause placental insufficiency leading to the development of pre-eclampsia and complications.[155] The most common inherited thrombophilic disorders during pregnancy result from mutations in Factor V Leiden, prothrombin and MTHFR, all of which have been previously studied in the context of predisposition to pre-eclampsia. Here we show that several of the genes related to pre-eclampsia are also associated with the clinically more important endpoint of complications such as eclampsia, HELLP syndrome and fetal growth restriction.

The initial literature search was from inception to August 2013 and subsequently the search was updated to March 2017. From this update, there have been many more studies that meet the inclusion criteria for this review but investigating novel maternal genetic variants that have not been included in this review.[156-161] There has been one study published since August 2013 addressing the association of the genotypes already studied in this review (immune-related genes) with severe pre-eclampsia that we could update our analysis with.[162] Some have addressed early-onset pre-eclampsia as the outcome instead of 'severe' pre-eclampsia.[157, 159, 163] In line with our findings, Wang et al performed a systematic review looking at the association between thrombophilia gene polymorphisms and pre-eclampsia and found increased risk of pre-eclampsia and severe pre-eclampsia for Factor V Leiden rs6025 and prothrombin G20210A.[164]

Strengths and limitations

This is the first systematic review to assess the association between maternal genotype and complications of pre-eclampsia. We undertook a detailed search to identify all relevant publications without language restrictions. The quality of the individual studies was assessed,

and we took into account variations in assessing and reporting of effects amongst studies, following a standardised approach to data extraction.

However, the studies differed in population characteristics, ethnicity, polymorphisms evaluated, the definition of phenotype and outcomes. The quality of the studies also varied. Genome-wide association studies were excluded as it was not possible to perform the standardised extraction of data or to pool outcomes. A large number of conventional genetic association studies were excluded due to insufficient data on genotype frequencies, and most of the included studies in our review had small numbers of cases. Allele frequencies for many genes differ greatly between ethnicities. This was not accounted for in our limited meta-analyses because of the paucity of data in non-Europeans.

Implications for clinical practice and future research

The identification of further genetic risk factors for complications of pre-eclampsia is an important research objective, which may lead to early identification and targeted management of high-risk pregnancies. Currently, the NICE guideline for the management of hypertension in pregnancy[38] does not recommend routinely screening for thrombophilia.The population prevalence of Factor V Leiden rs6025 is around 3-15% in Europe,[165] which may limit the clinical utility of this finding. Future work is needed to evaluate the potential benefits of integrating genetic data with clinical information to develop more accurate predictive algorithms.

There is a need for high-quality studies on a much larger scale to obtain robust and precise estimates of the association between genotypes and pre-eclampsia complications. Our study

highlights the need for evaluation of the quality of genotyping. Deviation from Hardy-Weinberg equilibrium is very rare in outbred natural populations and most often results from genotyping error. Hence studies should always state whether the genetic marker is in equilibrium and should consider excluding those that deviate from the analysis.

Furthermore, there is a need for potential confounding factors such as the use of aspirin, family history to be addressed and allowed for in the analysis of studies. None of the studies included in our review evaluated the fetal genotype that seems likely to play a part in this multifactorial disease. Recruitment methods and genotyping methodology and accuracy should be more clearly declared. Studies with adequate statistical power to investigate pre-eclampsia complications as primary outcomes will yield the most useful results for clinical practice.

Hypothesis generating studies

Genome-wide studies may be a useful tool for future work. Dissimilar to candidate gene studies, they adopt an unbiased approach to genetic hypotheses and allow investigation of many genetic polymorphisms simultaneously. This is important because the understanding of pathophysiology is incomplete so a candidate gene approach may miss an important genetic factor. Also, non-hypothesis driven genetic investigations may identify new biochemical and physiological mechanisms that might guide clinical and experimental investigations.

Linkage analysis has been helpful in the past in localising and mapping 'disease genes' to known 'genetic markers' in other conditions. Genome-wide linkage studies have pointed to several maternal pre-eclampsia susceptibility loci.[166-170] Loci at 2p13 (lod score 4.7),[166] 4q (lod score 2.9),[167] 12q (lod score 1.99),[168] 2q23 (lod score 2.58), 11q23-24 (lod score 2.02),[170] 2p25 (non-parametric linkage [NPL] score 3.74) and 9p13 (NPL score 3.74).[169] At the time of these studies, however, no candidate genes were identified in these regions, and there has been little success in replicating the results in population-based studies.

Genome-wide association studies (GWAS) have been a more promising approach and two such studies have identified candidate genes for pre-eclampsia.[171, 172] A study of 293 Caucasian women from Iowa (177 cases, 116 controls) found copy number variants consisting of an enrichment of case deletions in 19q13.31, which encompasses the pregnancy-specific glycoprotein PSG11 gene.[172] This study did not identify any associations with single nucleotide polymorphism (SNPs), possibly due to insufficient statistical power. Another GWAS for pre-eclampsia with 538 cases and 540 controls in Caucasian women based in Australia found a risk locus on 2q14.2, an intergenic region near the Inhibin, beta B (INHBB) gene.[171] Three SNPs in this region - rs7579169, rs12711941 and rs7576192 - were significant and in strong linkage disequilibrium with each other. INHBB is a subunit of both inhibin and activin, two closely related glycoproteins with opposing effects on the action of follicle stimulating hormone (FSH) and sex hormone synthesis. There is a body of substantive evidence to support the role of inhibins, activins and other members of the TGF-β family in the development of pre-eclampsia.[173-180]

To date, GWAS studies have focused on women with a predisposition to pre-eclampsia itself and not increased morbidity from significant complications of pre-eclampsia. There have been interesting findings from a recent study that identified three separate subgroups of pre-eclampsia based on expression of plasma membrane proteins involved in angiogenesis, mitogen-activated proteinase (MAP) kinase signalling and hormone biosynthesis and metabolism.[181] The genes involved in these physiological processes have not yet been examined as predictors of pre-eclampsia or its complications.

Conclusion

These findings point to a potentially causative role for thrombophilia genes in complications of pre-eclampsia responsible for substantial maternal and fetal morbidity worldwide. Further studies will be necessary to examine the full repertoire of thrombophilia genes and their polymorphisms systematically. Unfortunately at present there is insufficient evidence to justify incorporating genetic data into clinical algorithms for risk assessment but .

Since the evidence increasingly suggests that pre-eclampsia complications represent the severe end of a spectrum of disease, future genetic studies might profitably concentrate on such pregnancies. By focussing on this rich and clinically relevant phenotype, we may develop a better understanding of the underlying pathophysiology and genetic mechanisms of this disease.

My contribution to this work:

Formulation of the question, assisted clinical librarian with search, study selection in stages 1 and 2, data extraction as first reviewer, analysis, the first draft of the manuscript and all revisions.

CHAPTER 4.2 ACCURACY OF INDIVIDUAL TESTS TO PREDICT COMPLICATIONS IN WOMEN WITH PRE-ECLAMPSIA: A SYSTEMATIC REVIEW

Background

Pre-eclampsia is associated with significant maternal and fetal morbidity and mortality. The predictive values of tests such as maternal history, clinical examination and investigations for individual complications need evaluation.

Objective

To systematically review the accuracy of all routinely performed tests for predicting adverse maternal and fetal outcomes in women with pre-eclampsia.

Methods

We searched the electronic databases MEDLINE, EMBASE and Cochrane without language restrictions from inception to July 2015 for studies evaluating routinely performed tests (history, symptoms, clinical signs and haematological and biochemical investigations) for their predictive performance for development of maternal or neonatal complications in pre-eclampsia. Two independent reviewers undertook study selection, data extraction and quality assessment using the QUADAS-2 tool. Sensitivities and specificities for each test and outcome combination were pooled together and corresponding 95% confidence intervals were calculated.

Results

From 20,431 citations, 37 studies (9969 women) were included. Thirteen tests were evaluated for ten maternal complications and seven fetal complications. For maternal

outcomes, urine protein creatinine ratio (PCR), uric acid, mean arterial pressure >105 mmHg and symptoms of headache were highly sensitive (80% or more) in predicting eclampsia. The sensitivity was high for urine PCR in predicting caesarean delivery. The specificities were 80% or greater for blood pressure values greater than 160/110 mm Hg in predicting eclampsia, placental abruption, pulmonary oedema, caesarean delivery and hepatic dysfunction. Symptoms of nausea, abdominal pain and visual disturbances were highly specific in predicting eclampsia. For fetal outcomes, urine PCR was highly sensitive in predicting small for gestational age fetus, and fetal death. None of the tests were highly specific for fetal complications.

Conclusions

Individual tests vary in performance and predict maternal outcomes better than fetal outcomes. Collaborative individual patient data meta-analysis with prognostic modelling will allow us to accurately predict risks of individual complications.

Background

Pre-eclampsia, a multisystemic disorder associated with hypertension and proteinuria in pregnancy, remains one of the leading direct causes of maternal mortality.[182] Worldwide, this progressive condition is responsible for over 60,000 maternal and 500,000 perinatal deaths each year.[11, 183] The management of pre-eclampsia is underpinned by a variety of tests, which are interpreted by clinicians to decide on optimal timing of delivery, the only definitive cure of the condition. Identification of the 6% of women who develop severe pre-eclampsia with increased morbidity and mortality is needed to safely prolong gestation in the rest.[17]

Current management following a diagnosis of pre-eclampsia includes obtaining a history, assessment of clinical symptoms, examination and tests at the bedside and laboratory investigations, which are routinely done in all healthcare facilities in the developed world.[38] However, despite this comprehensive array of tests, the accuracy estimates of individual tests are imprecise due to small numbers of women who develop severe complications.[84, 86-88] Observational studies of prediction models for pre-eclampsia complications have included clinically less important outcomes such as need for blood transfusion as part of composite maternal outcomes and lack sufficient power to predict individual serious complications such as eclampsia and placental abruption.[57]

We sought to systematically review the accuracy of routinely performed individual tests including symptoms, bedside investigations, haematological and biochemical indices for individual complications, to identify a set of tests that have maximum predictive value to aid in therapeutic decision-making in the management of pre-eclampsia.

Methods

We conducted the systematic review using a prospective protocol[184] in line with current recommendations and reported according to PRISMA guidelines.[185] (Appendix 4)

Identification of studies and study selection

The initial search had been conducted in the electronic databases MEDLINE, EMBASE and Cochrane for previous systematic reviews of tests in pre-eclampsia without language restrictions from inception until December 2013. The full search strategy can be found in our published protocol.[184] The search was updated (January 2014 to July 2015)[184]. Study selection was in a two stage process with two sets of independent reviewers. The titles and abstracts were screened for relevance in the first stage and the full texts obtained in the second stage for evaluation. Any discrepancies were resolved by consensus. Authors were contacted for additional information if required.

We included studies that evaluated routinely performed tests (history, examination and investigations) and the risk of maternal or fetal complications in women with pre-eclampsia. Primary observational studies or those nested within a randomised trial were included. Studies were excluded if there was insufficient data to populate a 2 x 2 table for the test and outcome, or if the publication date was prior to 1990.

Quality Assessment and data extraction

Two independent reviewers (FC, JA) evaluated the risk of bias and the applicability of the included primary studies using the QUADAS-2 tool,[62] for patient selection, index test, reference standard, flow and timing of test. Low risk of selection bias was assigned if two or more of the following were present: consecutive or random enrolment, absence of case

control design, appropriate exclusions; medium risk of bias was assigned if one of the aforementioned criteria were present; and high risk of bias or unclear risk of bias if none of the criteria were present. Low risk of bias was assigned for the index test if one or more of the following were present: index test results interpreted without knowledge of the results of the reference standard, and pre-specified threshold for the test was used and high or unclear risk of bias if none of the criteria were present. If the conduct or interpretation of test differed from the review question, this was assessed as low risk of bias if there were no concerns, and high or unclear risk of bias if there were any.

Low risk of bias for the reference standard was assigned if one or more of the following criteria were present: the reference standard correctly classified the target condition, and the results were interpreted blindly. Low risk of bias was assigned for flow and timing of test if three or more of the following criteria were present: appropriate interval between index test and reference standard, all patients received the reference standard, all patients received the same reference standard, and all patients were included in the analysis. High risk of bias was assigned if two of the criteria were present. Unclear risk of bias was assigned if one or none of the criteria were present. Two independent researchers extracted data into 2x2 tables.

Analysis

We considered every combination of test threshold and complication of pre-eclampsia outcome. In order to avoid overlap of study constituents, the test threshold with the highest sensitivity was selected to represent that study population. Sensitivities and specificities were pooled for each test and outcome combination using a bivariate multi-level model when there were sufficient numbers to estimate all the model parameters (i.e. more than 4 studies for the

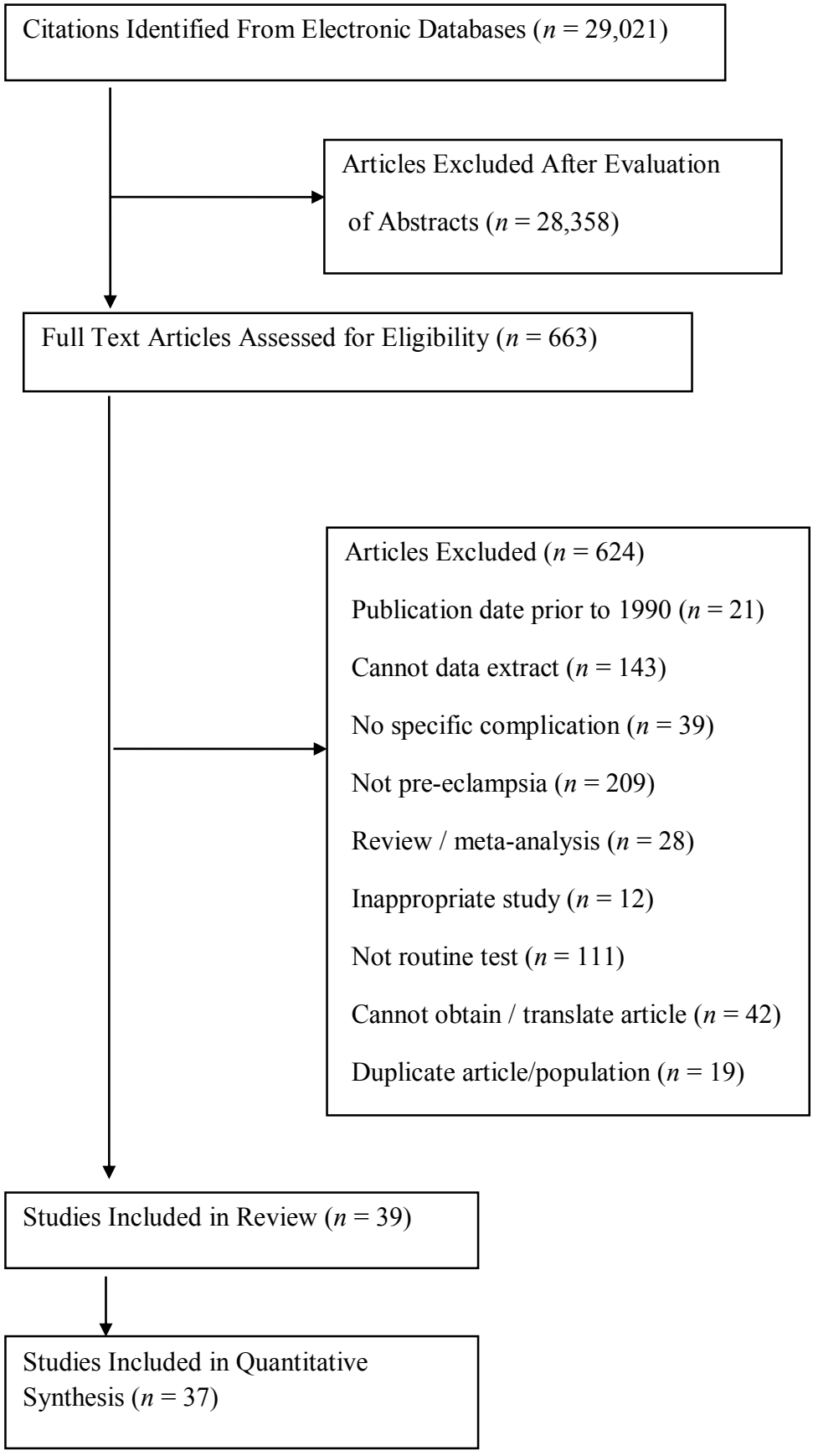
test-outcome combination). Where there were fewer than 4 studies, a univariate random effects

model was used to pool accuracy indices. Corresponding 95% confidence intervals were calculated. For each test and outcome, sensitivity and specificity were graded as high >80%, moderate 60-80% and low <60%. Although we planned to synthesise results from the individual studies to perform a meta-analysis, we encountered challenges due to the sheer heterogeneity of results arising from the different tests and test cut-off levels and the varying severity of individual maternal and fetal complications. Accurate likelihood ratios or diagnostic odds ratios were unable to be estimated. Among observational studies, there is no standardized method of assessing for publication bias and therefore we did not assess for this.[186]

Results

From 20,431 citations, we included thirty-seven studies (9969 women) in the review. There were thirty-nine studies were eligible for inclusion but two studies[187, 188] had to be excluded after data extraction as there were insufficient studies with the same test threshold and outcome combination to pool the studies with. (Figure 4.2.1). Authors from three large studies provided additional primary data.[57, 189, 190] The included studies evaluated 14 tests, 10 maternal and 7 fetal outcomes.

Figure 4.2.1 Study Selection Process in the Systematic Review of Tests to Predict Complications in Pre-eclampsia



Characteristics of included studies

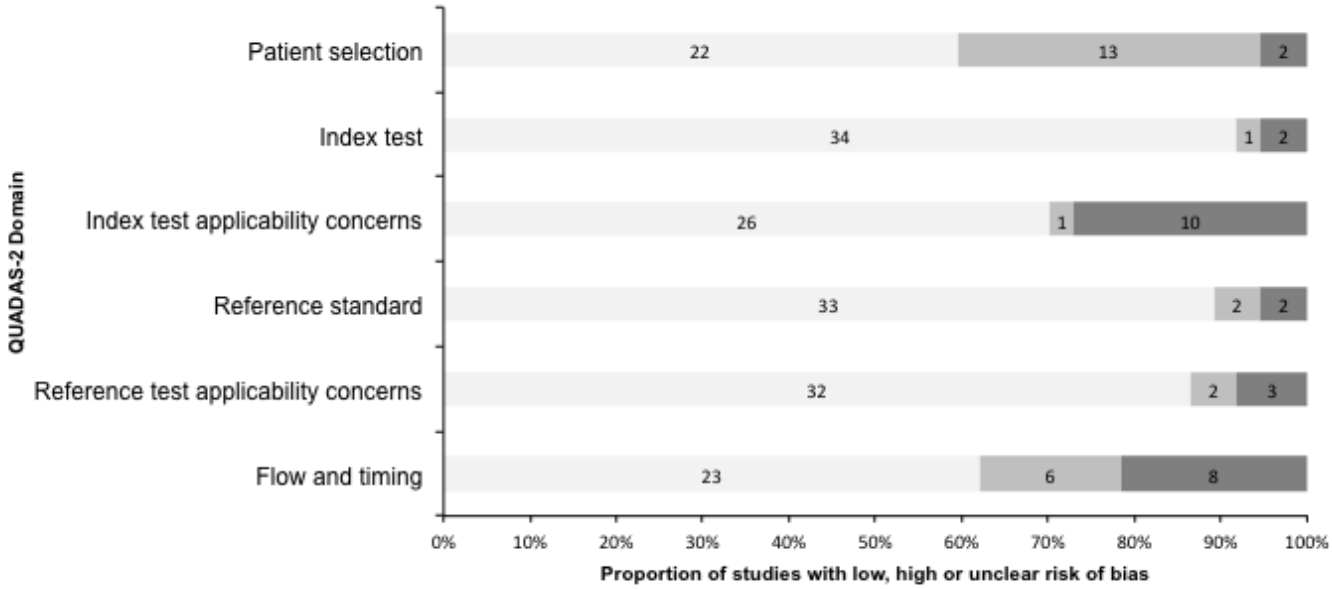
There were 29 cohort studies, one cohort nested within a randomised trial and seven case control studies. Sixteen studies were prospective and 21 were retrospective. The study population included women with pre-eclampsia and severe pre-eclampsia. The tests comprised 24 hour urinary protein level, urinary protein-creatinine ratio, serum alanine aminotransferase, serum aspartate aminotransferase, serum lactate dehydrogenase, serum uric acid, symptoms of abdominal pain, symptoms of visual disturbances, symptoms of headache, symptoms of nausea, blood pressure above 160/110mmHg, mean arterial pressure above 105mmHg, systolic blood pressure above 160mmHg and diastolic blood pressure above 110mmHg.

Adverse maternal outcomes were reported in 34 studies, and fetal and neonatal outcomes in 28 studies. Adverse maternal outcomes included eclampsia (13 studies)[57, 191-202], pulmonary oedema (3 studies)[57, 194, 198], severe hypertension (3 studies)[190, 203, 204], haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome (5 studies)[196, 197, 199, 205, 206], hepatic dysfunction (2 studies)[57, 190], renal failure (3 studies)[57, 198, 207], placental abruption (10 studies)[57, 192, 194-196, 198-200, 208, 209], and Caesarean delivery (9 studies)[57, 188, 194, 198, 202, 203, 207, 210, 211]. The adverse fetal outcomes included small for gestational age (14 studies), fetal or neonatal death (17 studies), admission to the neonatal intensive care unit (NICU) (3 studies), bronchopulmonary dysplasia (BPD) (2 studies), intraventricular haemorrhage (IVH) (3 studies), respiratory distress syndrome (RDS) (2 studies) and necrotising enterocolitis (NEC) (3 studies). Details of the full study characteristics are listed in Appendix 5.

Quality of the included studies

About two-thirds of the included studies had low risk of bias for patient selection (59%, 22/37). Most of the studies had low risk of bias for the test evaluated (91%, 34/37). 3% (1/37) had high risk of bias and 5% (2/37) unclear risk of bias) for test assessment. There was low risk of concerns regarding applicability for the index test in 70% (26/37) and unclear in the remainder. Almost 90% of the studies had low risk of bias for determination of the reference standard (89%, 33/37), with well defined adverse outcomes, and 5% (2/37) had high risk of bias. There was low risk of concerns regarding applicability for the reference test in 92% (34/37), unclear in 5% (2/37) and high risk in 3% (1/37). Evaluation of the quality of the flow and timing of the tests showed that 62% (23/37) of included studies had low risk of bias, 22% (8/37) had high risk of bias and 16% (6/37) had unclear risk of bias. There was very little information provided about the timing and gestational ages at which the tests were performed and the completeness of follow-up for the included patients. Study quality parameters according to the QUADAS 2 criteria are summarised in Figure 4.2.2.

Figure 4.2.2 Risk of bias in studies included in the systematic review on accuracy of individual tests to predict complications in women with pre-eclampsia



Key:

Low level of bias

High level of bias

Unclear

Data presented as 100% stacked bars; figures in the stacks represent number of studies.

Accuracy of tests for maternal and fetal outcomes

Maternal outcomes

Eclampsia

A high sensitivity of 80% or more was observed for urine protein creatinine ratio (PCR) (81%, 95% CI 52-95%), serum uric acid (82%, 95% CI 53-95%), a mean arterial blood pressure >105 mmHg (93%, 95% CI 82-98%) and history of headache (84%, 95% CI 50-97%) in predicting eclampsia. Clinical symptoms such as nausea (89%, 95% CI 81-94%).and an elevated alanine aminotransferase (ALT) level (90%, 95% CI 50-99%) were highly

specific for eclampsia. Both sensitivity and specificity were poor for elevated AST level (sensitivity 55%, 95% CI 29-79%; specificity 52%, 95% CI 20-83%) and systolic blood pressure >160 mmHg in predicting eclampsia (sensitivity 44%; 95% CI 4-94%; specificity 40%, 95% CI 37-43%).

Placental abruption

A mean arterial pressure >105 mmHg (92%, 95% CI 75-98%) and elevated urine PCR (81%, 95% CI 64-91%) predicted placental abruption with high sensitivity. Visual disturbances were highly specific for placental abruption (80%, 95% CI 78-82%). Both sensitivity and specificity were poor for systolic blood pressure >160 mmHg (sensitivity 59%; 95% CI 43-73%; specificity 41%, 95% CI 36-45%) and history of headache (sensitivity 51%; 95% CI 32-69%; specificity 58%, 95% CI 50-65%) predicting placental abruption.

Caesarean delivery

Urine PCR was highly sensitive for caesarean delivery (97%, 95% CI 26-100%).Sensitivity and specificity were poor for elevated AST level in predicting Caesarean delivery (sensitivity 57%, 95% CI 31-79%; specificity 35%, 95% CI 11-69%). Both sensitivity and specificity were poor for elevated AST level (sensitivity 57%, 95% CI 31-79%; specificity 35%, 95% CI 11-69%) and elevated lactate dehydrogenase (LDH) level (sensitivity 13%, 95% CI 1-68%; specificity 40%, 95% CI 11-78%) in predicting caesarean delivery.

Pulmonary oedema

Urine PCR was highly sensitive for pulmonary oedema (85%, 95% CI 71-93%).

Hepatic dysfunction

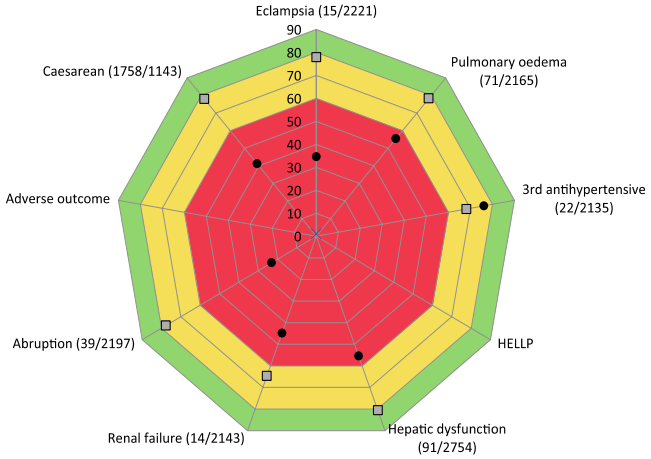
Raised blood pressure of 160/110 mm Hg showed high specificity in predicting hepatic dysfunction (81%, 95% CI 75-85%).

HELLP syndrome

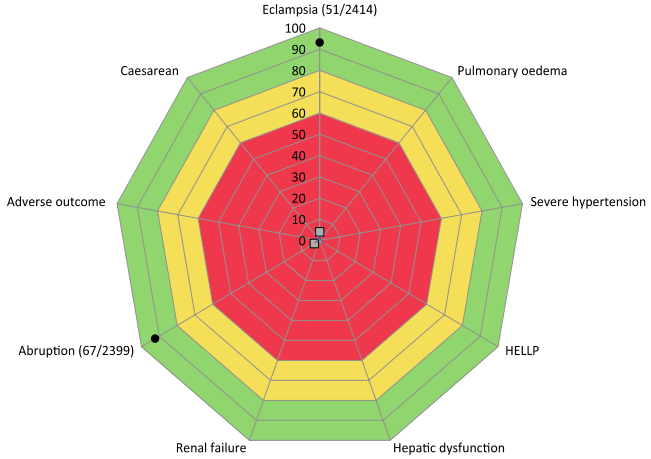
Clinical symptoms such as nausea (89%, 95% CI 79-94%) and abdominal pain (89%, 95% CI 84-93%) were highly specific for HELLP syndrome.

The radar plots in Figure 4.2.3, provide an overview of the performance of the various tests for individual maternal outcomes.

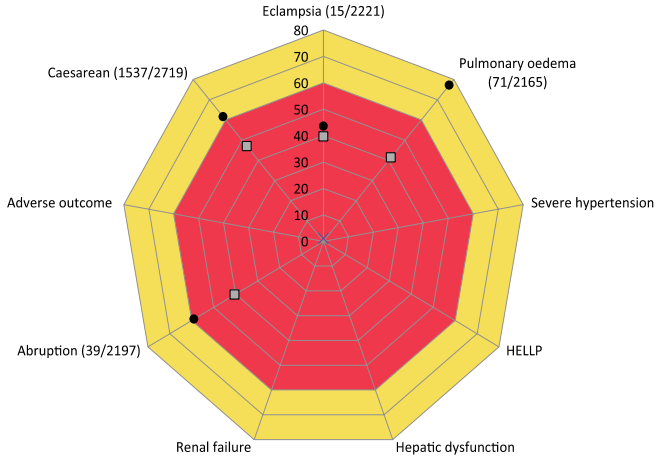
Figure 4.2.3 Radar plots of pooled sensitivities and specificities for tests to predict maternal (M) and neonatal (N) complications of pre-eclampsia (4 pages)



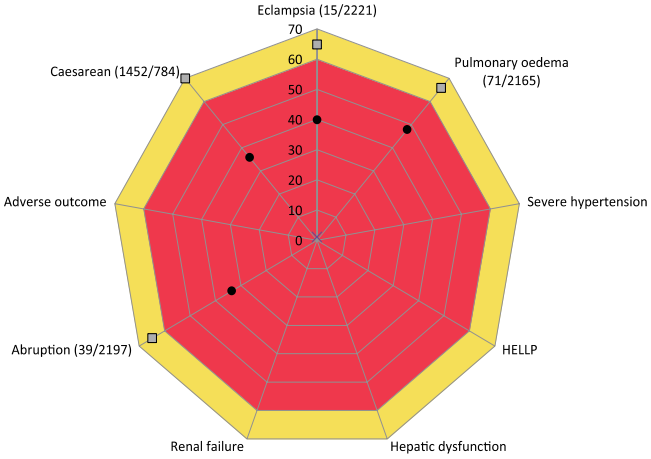
Blood pressure >160/110mmHg (M)



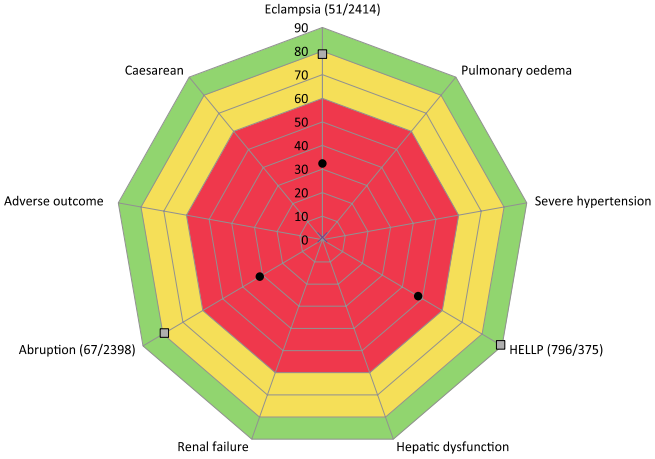
MAP>105mmHg (M)



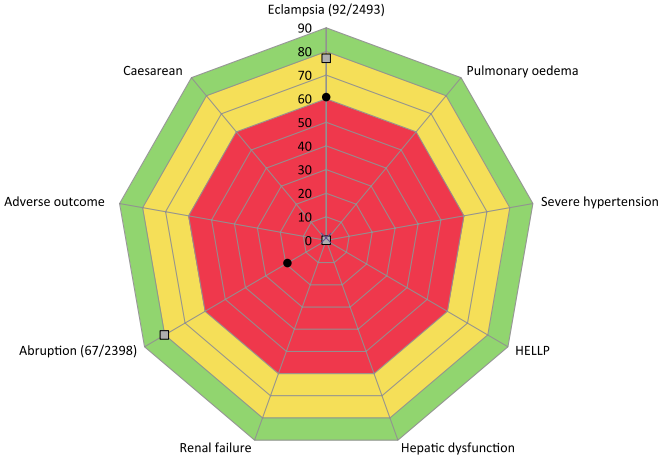
Systolic blood pressure >160mmHg (M)



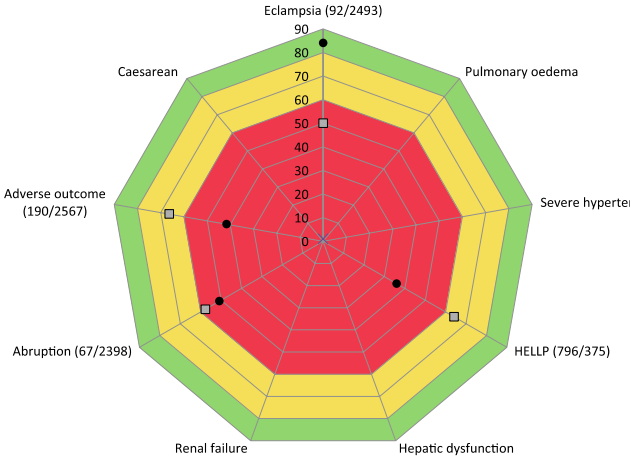
Diastolic blood pressure >110mmHg (M)



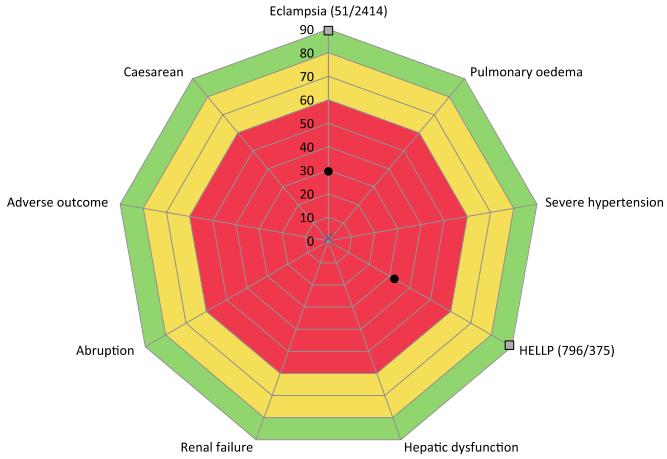
Abdominal pain (M)



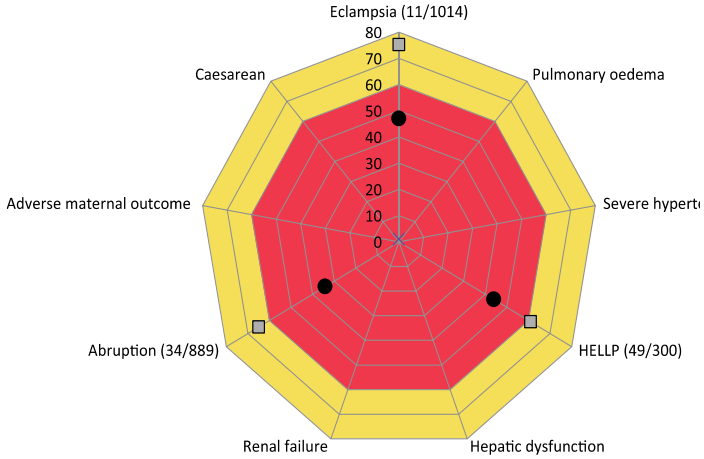
Visual disturbances (M)



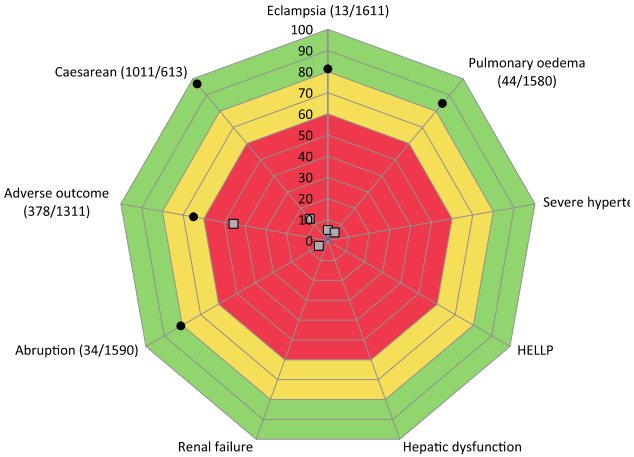
Headache (M)



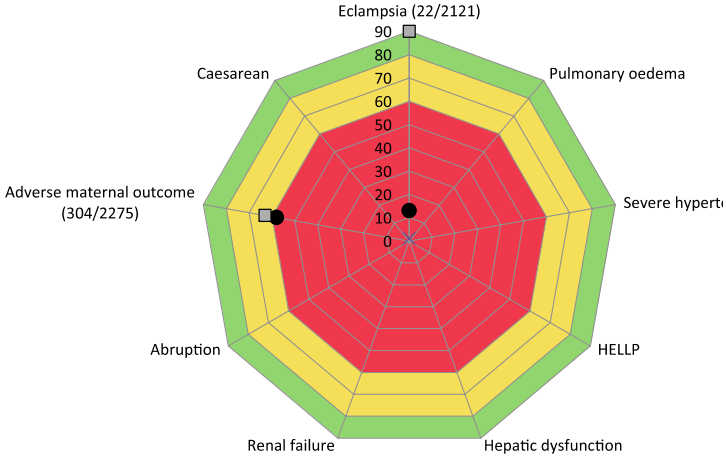
Nausea (M)



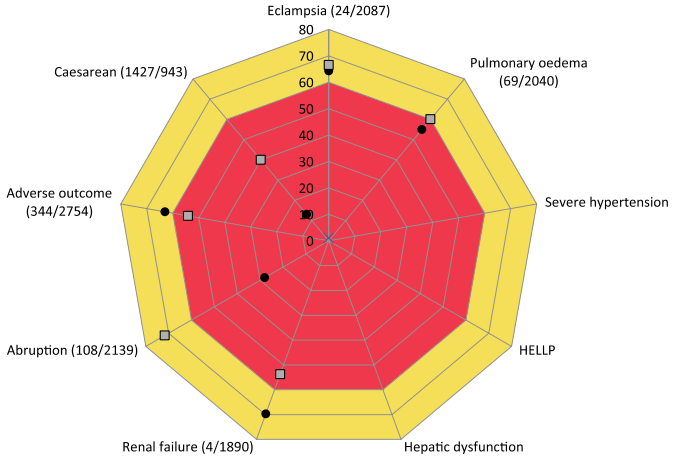
24 hour proteinuria (M)



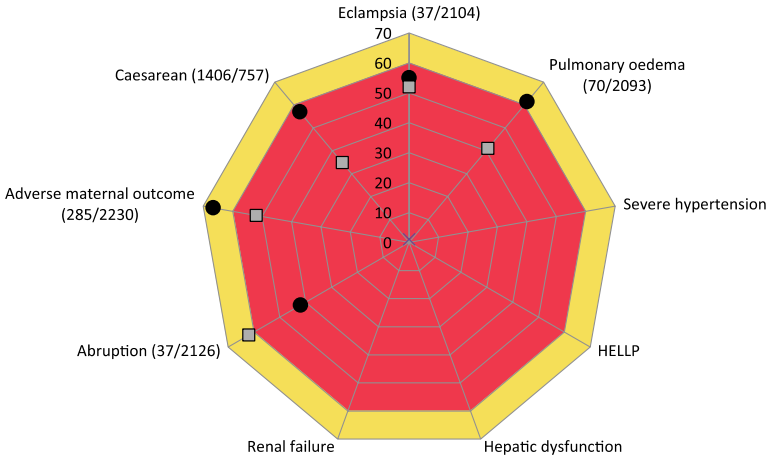
Protein creatinine ratio (M)



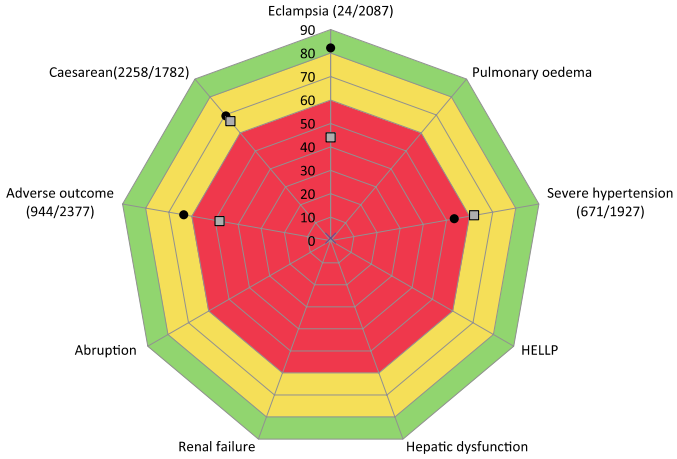
Alanine aminotransferase (M)



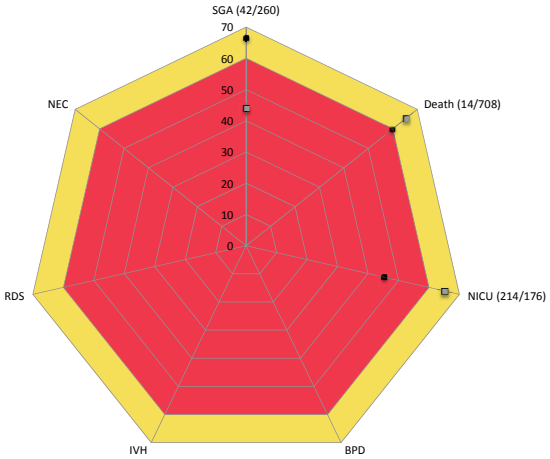
Lactate dehydrogenase (M)



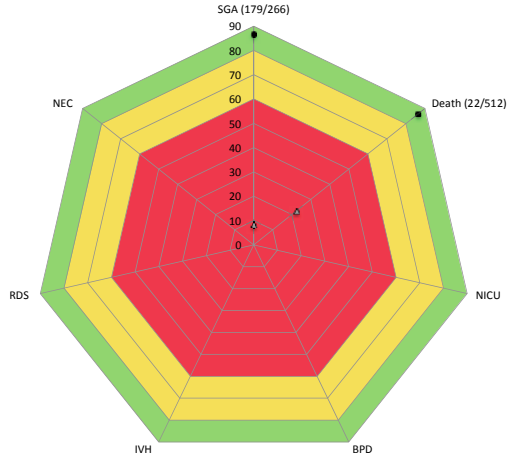
Aspartate aminotransferase (M)



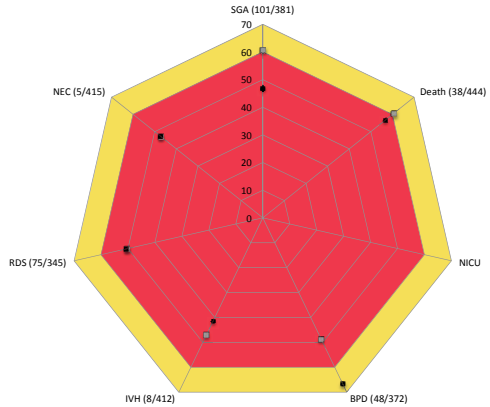
Uric acid (M)



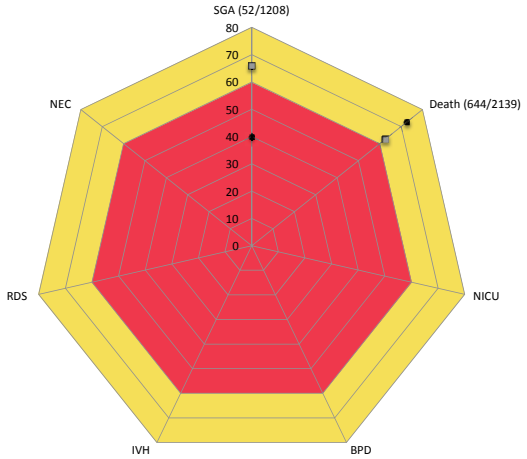
24 hour proteinuria (N)



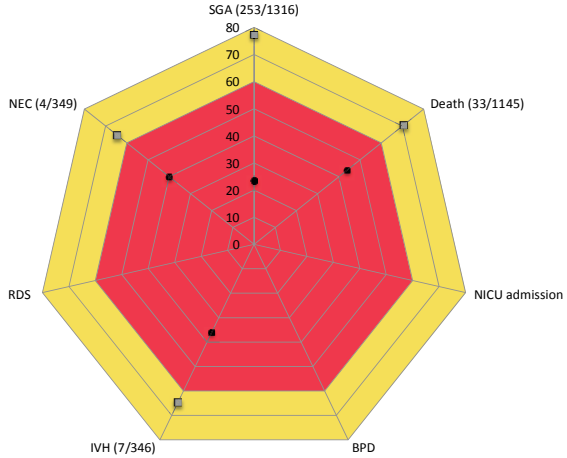
Protein creatinine ratio (N)



Aspartate aminotransferase (N)



Uric acid (N)



Blood pressure >160/110mmHg (N)

Key:□• Pooled sensitivity ■Pooled specificity (Number of patients with outcomes / Number of patients without outcomes)

Fetal outcomes

Small for gestational age

We observed a high sensitivity for urine PCR in predicting small for gestational age fetuses (87%, 95% CI 8-99%).

Perinatal death

There was a high sensitivity for urine PCR in predicting perinatal death (86%, 95% CI 14-99%).

Intraventricular haemorrhage

Both sensitivity and specificity were poor for elevated AST level in predicting intraventricular haemorrhage (sensitivity 41%, 95% CI 3-94%; specificity 47%, 95% CI 16-80%).

Respiratory distress syndrome

Sensitivity and specificity were poor for elevated ALT level in predicting respiratory distress syndrome (sensitivity 51%, 95% CI 40-62%; specificity 50%, 95% CI 12-88%).

Necrotising enterocolitis

Sensitivity and specificity were poor for elevated ALT level in predicting necrotising enterocolitis (sensitivity 47%, 95% CI 11-87%; specificity 47%; 95% CI 16-81%).

Discussion

We provide a comprehensive descriptive overview of the accuracy of routinely performed tests for the prediction of complications of pre-eclampsia.

Individual tests undertaken in women with pre-eclampsia vary widely in their accuracy for predicting maternal and fetal complications. Clinical symptoms have poor sensitivity and moderate to high specificity for complications. A blood pressure of 160/110 mmHg or more is highly specific, with poor sensitivity for maternal complications. Of the laboratory tests, urine PCR performance showed high sensitivity for complications in mother and fetus, but had very low specificity. Overall, for fetal complications, tests had moderate specificity but low sensitivity.

We performed a very comprehensive search to identify all relevant studies without any language restrictions. Since the final analysis in 2015, the search was further updated to April 2017. There have not been many published studies assessing commonly performed tests and the complications of pre-eclampsia but a relevant study that could be included in the review is the large prospective multicentre cohort study used to develop a prediction model for complications in early-onset pre-eclampsia.[212, 213] It is unlikely however for the addition of this study to significantly alter our results.

We evaluated the quality of the included studies in detail, and captured all relevant tests and outcomes. Ours is the largest evidence synthesis on predictive value of tests for complications in women with pre-eclampsia. We evaluated tests that are routinely performed in clinical practice, to aid in the generalisability of the findings. Radar plots were used to provide an overview of estimates for individual tests and complications to facilitate

interpretation. We pooled sensitivity and specificity of tests where relevant. We were able to provide robust estimates of test performance of individual complications, which were not estimated in existing prediction models.

We were limited by the paucity in reported data, with studies varying in the description of population, tests, thresholds and outcomes. The resultant heterogeneity limited our ability to combine all relevant data, and increased the heterogeneity of our findings. Despite contacting authors for raw data where possible, more than a hundred studies had to be excluded due to lack of comparative cohorts. Most studies evaluated individual tests, and we were unable to assess the impact of other tests on the overall performance. The studies were conducted in different countries and spanned temporal periods hence the differences in treatment protocols provided for pre-eclampsia might have biased the outcomes. Treatment or intervention may lead to a so-called treatment paradox with the predictive potential of a particular test in association with a specific complication inaccurately represented. The outcome or complication may not manifest as the intervention (namely delivery) may have prevented it from occurring. The decisions usually follow the clinical acumen of the attending physician as there is no standardised algorithm of management of pre-eclampsia in practice. If he or she were perceiving a particular test to be more predictive of adverse outcomes, they may be more inclined to act upon that test and therefore biasing the outcomes towards the null hypothesis.[214]

Current NICE guidelines consider platelet count, serum creatinine levels, transaminases as potential indicators of progression to severe disease in women with pre-eclampsia.[38] We did not find sufficient evidence to summarise estimates for platelet count and serum creatinine in predicting maternal or fetal complications. Our review did show that the transaminases, in

particular AST (aspartate transaminase) were moderately predictive of maternal complications including combined adverse maternal outcome, pulmonary oedema, placental abruption, eclampsia and Caesarean delivery. The predictive accuracy was less for fetal complications such as IVH, RDS and NEC but moderately predictive for BPD.

In the fullPIERS prediction model (pre-eclampsia integrated estimate of risk) which was developed and internally validated in a cohort of 2023 women with pre-eclampsia,[57] the predictors for a composite adverse maternal outcome included gestational age at diagnosis, presence of chest pain or dyspnoea, oxygen saturation level, platelet count, creatinine level and aspartate transaminase level. Similar to fullPIERS, we found AST to be most predictive and consistently so across the different maternal complications. Unfortunately we did not have enough datasets to evaluate the performance of the other predictors in their prediction model.

Relevance to clinicians

Consistent with what is already known on this subject, this review lends further support to the notion that individual test performances are very limited for accurately predicting adverse maternal and fetal outcomes in pre-eclampsia. Interestingly, we highlight that in certain tests such as the presence of symptoms of pre-eclampsia (abdominal pain, visual disturbances and headache) and elevated urinary protein creatinine ratio, their presence appears to be more likely to rule in the woman developing a complication of pre-eclampsia. Conversely, their absence is not more likely to rule out a complication. Blood pressure readings appear to be most predictive when taken as a combination of systolic and diastolic rather than individual systolic or diastolic blood pressure readings. With regard to routinely performed blood tests, individually, they have limited accuracy in predicting maternal complications. Similarly,

individual tests cannot be relied upon to predict fetal complications except for elevated PCR, which appears to be highly sensitive in predicting small for gestational age and fetal death.

Relevance to research

This review provides a comprehensive overview of individual test performances for predicting adverse maternal and fetal outcomes in pre-eclampsia. A further step would be to look at a combination of tests to women at risk such as the subset of women who develop early onset pre-eclampsia. We identified a wide variation in reporting of maternal and fetal outcomes in pre-eclampsia. This reiterates the urgent need to develop and utilise core outcome sets in future studies on pre-eclampsia.[215] An individual patient data meta-analysis (IPD) will allow us to assess the differential performance of individual in addition to combinations of tests in subgroups of women.

Biomarkers such as placental growth factor,[216] have received much interest and promise in the prediction of development of pre-eclampsia. It would be interesting to evaluate the performance of biomarkers added to the existing tests for predictive performance of developing maternal and fetal adverse outcomes associated with pre-eclampsia. The impetus behind further research in this area is to get one step nearer to identifying a set of tests that may enable us to risk stratify women with pre-eclampsia in order to significantly optimise their management and counselling for this serious condition.

Conclusions

No single test is sufficiently sensitive and specific in predicting complications in pre-eclampsia. Collaborative efforts in standardising core outcomes, IPD meta-analysis, and

prognostic modelling by including biomarkers will improve accurate prediction of risks of individual complications in pre-eclampsia.

ROLE OF FUNDING SOURCE

We received funding from the European Union made available to the EBM-CONNECT Collaboration through its Seventh Framework Programme, Marie Curie Actions, Inter-national Staff Exchange Scheme (Proposal no. 101377; Grant Agreement no. N◦ 247613). No funders played a role in the planning and execution of this work, or in drafting of the manuscript.

My contribution to this work:

Updating on search from published study protocol, study selection in stages 1 and 2, data extraction as first reviewer, quality assessment of the studies, data analysis, the first draft of the manuscript and all revisions.

CHAPTER 4.3: PRIORITISATION OF ADVERSE MATERNAL AND NEONATAL OUTCOMES IN LATE-ONSET MILD TO MODERATE PRE-ECLAMPSIA AND DEVELOPMENT OF COMPOSITE OUTCOMES

Abstract

Objective: Pre-eclampsia is a multi-systemic disorder, leading to maternal and neonatal complications; women are often delivered to avoid progression of the disease. Clinical trials vary in the reporting of outcomes. More than one outcome is important in the evaluation of interventions in women with pre-eclampsia. We developed composite maternal and neonatal outcome measures for reporting in clinical trials on interventions in women with late-onset mild and moderate pre-eclampsia.

Methods: We used a two-stage Delphi survey of experts in obstetrics and neonatology to identify the clinically important maternal and neonatal outcomes. The identified outcomes were used to develop the composite outcomes. We took into account various criteria such as importance of each outcome, their frequency of occurrence, biological plausibility and independence from the other outcomes.

Results: Eighteen (18/20, 90%) obstetricians and eighteen neonatologists (18/24, 75%) participated in the first round of the Delphi survey. In the second iteration, 100% (18/18) of the obstetricians and 94% (17/18) of the neonatologists took part. The final maternal composite outcome consisted of maternal death, eclampsia, placental abruption, major obstetric haemorrhage, pulmonary oedema, need for positive ionotropic support, stroke, reversible ischaemic neurological deficit (RIND) or HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome; and the neonatal composite outcome comprised

neonatal death, respiratory distress syndrome (RDS) needing ventilation, grade III/IV intraventricular haemorrhage or cystic periventricular leukomalacia.

Conclusion: Our work will inform trials on timing of delivery in women with mild to moderate pre-eclampsia, thereby standardising reporting of relevant outcomes.

Citation of paper published from this work

Fong F, Rogozinska E, Allotey J, Kempley S, Shah DK, Thangaratinam S. (2014) Development of Maternal and Neonatal Composite Outcomes for Trials Evaluating Management of Late-onset Pre-eclampsia. Hypertens Pregnancy. 2014 May; 33(2): 115-31. Doi: 10.3109/10641955.2013.837176.

Background

Determination of the most suitable primary outcome(s) to measure in clinical trials is of great importance to the design and credibility of clinical trials. It is often difficult to choose the primary outcome that is both clinically relevant and be adequately evaluated. This is especially so in conditions where there is more than one clinically important outcome, making where selection of one representative outcome is; and with conditions with low rates of outcomes requiring a large sample size.

When the rates of individual outcomes are low, robust evaluation could be performed by systematic reviews and meta-analyses for individual outcomes, or by the development of composite outcomes. The former relies on several trials to answer the clinical question; the latter is a more feasible option. Composite outcomes combine individual outcomes of similar importance such that the attainment of one or more of these outcomes will represent an event. Composite outcomes enable trials to answer clinical questions without the need for prohibitively huge sample sizes and enable recruitment over a shorter timeframe.

Pre-eclampsia affects 6-8% of pregnancies and can be associated with maternal, fetal and neonatal complications.[182] It can lead to various equally important maternal and fetal complications. The only known cure for pre-eclampsia is delivery. Evaluation of any intervention in pre-eclampsia will need to take into account both maternal and fetal outcomes. The incidence of individual complications of pre-eclampsia such as eclampsia, placental abruption, and stroke vary, but are generally quite low. Any clinical trial that evaluates the optimal timing of delivery before term in a high-risk women, should address the benefits of early delivery to the mother compared to prematurity-related risks to the fetus. In

view of this, composite outcomes are often used in clinical studies involving women with pre-eclampsia.[57, 217]

Clinicians have a relatively low threshold for delivery in women with late onset than early onset pre-eclampsia. However, it is increasingly evident that infants born at late preterm gestation are physiologically immature compared to their term-born counterparts with increased risk of mortality, short and long-term morbidity[218]. The neonatal and infant mortality rates are 5.5 and 3.5 fold higher respectively in infants born at late preterm gestation compared to those born at term[219, 220]. The burden in costs to the NHS is double that of infants born at 39 weeks' gestation due to increased intensive care stays and longer hospitalisations as a consequence of increased morbidity.[221] With regard to long-term neurodevelopment in infants born late preterm, there appears to be a higher incidence of neuropsychological impairment which persists into late childhood[222-224]. There is limited evidence on the morbidity of late preterm infants born to women specifically with pre-eclampsia,[225] however the increased oxidative stress state from pre-eclampsia is a known adverse effect on the neurodevelopment of the fetus.[225]

Existing composite outcomes for pre-eclampsia, particularly for late onset disease are not relevant or not developed by using robust methodological processes. We aimed to develop composite maternal and neonatal outcomes, particularly in women with mild and moderate pre-eclampsia between 34 and 37 weeks' gestation.

Materials and Methods

The development of the composite outcomes occurred in three stages. In the first stage, we performed a literature search to identify complications of pre-eclampsia reported in pre-eclampsia trials, outcomes of consensus surveys, and any composite outcomes developed in this area. In the second stage, the list of individual components identified from the search was sent to a group of experts to prioritise the clinical importance of each outcome. In the final stage, the components of the composite outcomes were chosen from those that were prioritised by the panel using pre-specified criteria.[226]

Identification of maternal and fetal components

We searched the electronic databases MEDLINE and EMBASE from inception to June 2012 for pre-eclampsia complications. This was part of our separate project on a systematic review on tests in pre-eclampsia of literature.[86, 87] Maternal and neonatal outcomes that showed a clear biological plausibility for association with pre-eclampsia or prematurity were included for consideration in the next stage.

Delphi survey to prioritise the components for clinical importance

We undertook a two-generational Delphi survey in line with published recommendations.[77, 85] This was in the form of two online questionnaire surveys (one regarding obstetric outcomes and the other neonatal outcomes) emailed out to an obstetric expert panel and a neonatal expert panel respectively. There were two rounds to the surveys such that in the first round or iteration, the initial surveys were sent out to the panels; the responses were collated and the surveys were sent out again with an anonymised summary of the initial responses by the panels, providing a chance for the panellists to revise their answers if they wished.

The Delphi panels consisted of senior clinicians and clinical academics in the UK. The obstetric expert panel included individuals who had clinical expertise, (or) were involved in studies on pre-eclampsia. The neonatal expert panel included senior clinicians from our regional research network. The panel members were informed that their contribution is crucial to the development of maternal and neonatal composite outcomes. We requested the panel members to prioritise the maternal and neonatal outcomes that they considered were clinically important in the management of women with mild and moderate pre-eclampsia between 34 and 37 weeks gestation.

We maintained anonymity throughout the process by using an online tool (www.surveymonkey.com).[227] The constituents of the panel and the individual scores were known only to the pollster (FC).

The questionnaires were administered in an online electronic format. In the first iteration, panellists were asked to grade the clinical importance of maternal or neonatal outcomes that might influence the decision to deliver mothers with mild and moderate pre-eclampsia at late preterm gestation. They were requested to grade their responses from '1' to '5' on a Likert scale with '1' denoting 'strongly disagree' to '5' denoting 'strongly agree', for an outcome to be considered important.

We sent reminders to panel members if no responses were received after 2 weeks. In the first round, the members were also given the opportunity to introduce outcomes that they considered to be important but were missing in out the initial list. Members who did not respond in the first round were excluded from the subsequent rounds. For each outcome, we calculated median scores and interquartile ranges. An interquartile range of 2 or more in the

second round was pre-specified to indicate consensus. Outcomes that generated a median score of 4 or more with consensus (IQR≤2) were selected for evaluation in the third stage for consideration in the development of the composite outcome.

Development of the composite outcome

The components of the maternal and neonatal composite outcomes were selected by a group of experts in the field of pre-eclampsia, academics and clinicians in neonatology and those with expertise in outcome development. A semi-structured discussion was undertaken to consider inclusion of each component, identified by the Delphi survey. The selection of components was based on the following pre-specified criteria: similar rates of occurrence; evidence of biological plausibility; independent of each other; evidence of same direction of the effect with the intervention.[226, 228] Components that fulfilled these criteria were included in the final maternal and neonatal composite outcomes.

Results

Identification of maternal and neonatal outcomes

Through our systematic reviews, [57, 85] randomised controlled trial,[217] and two surveys,[57, 217] we initially identified 21 maternal and 24 relevant neonatal outcomes. Appendix 6 provides the list of the outcomes. Maternal outcomes included neurological, respiratory, cardiovascular, haematological, renal, gastroenterological and other complications. Neonatal outcomes included complications related to prematurity at delivery involving neurological, respiratory and cardiovascular systems. Additionally, it included management-based outcomes such as admission to the neonatal unit, ionotropic support and use of assisted ventilation.

Prioritisation of the maternal and neonatal outcomes

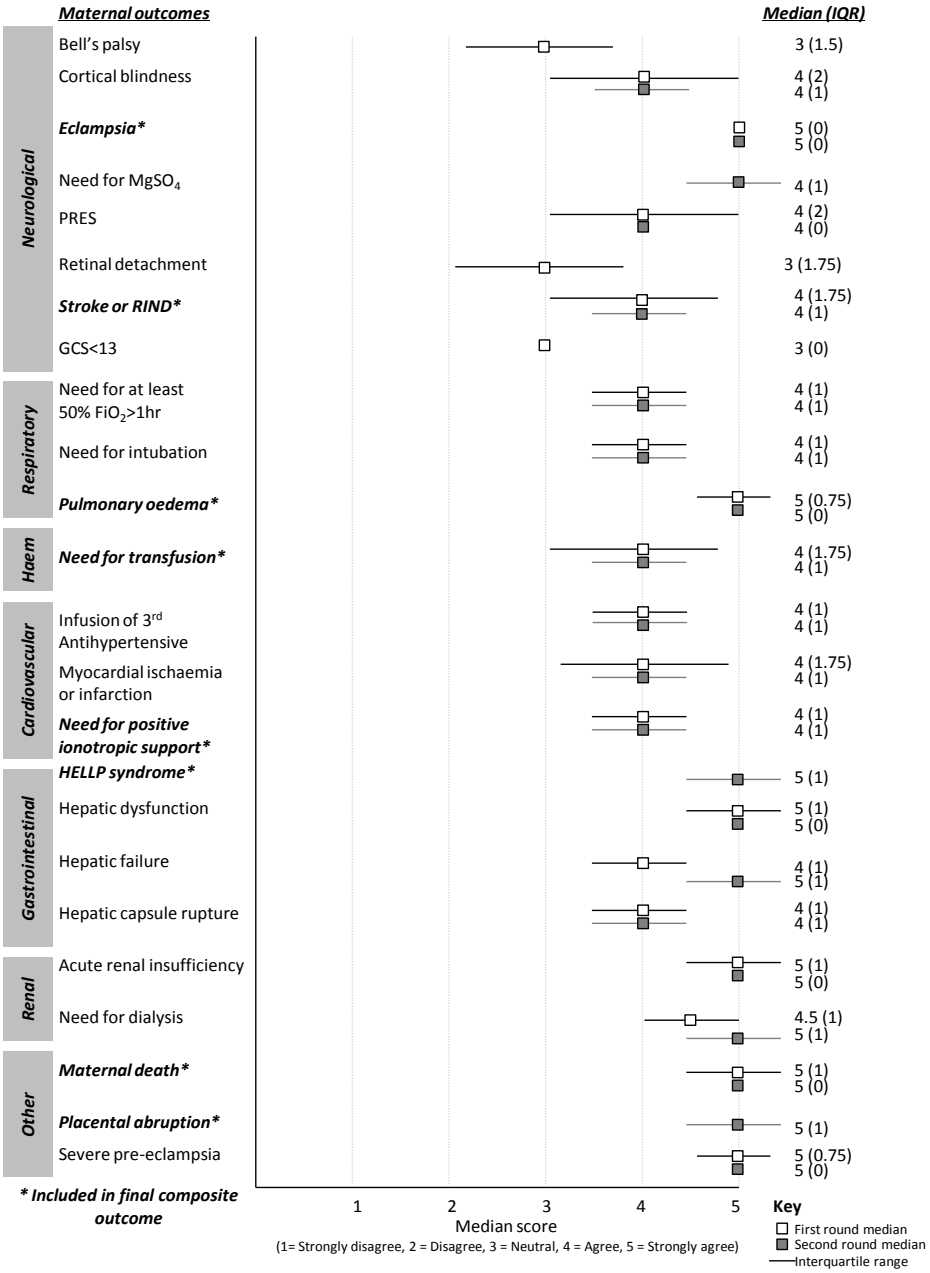
The Delphi panel consisted of 44 clinicians and clinical academics, of whom 20 were obstetricians and 24 were neonatologists.

First round

The questionnaire on the importance of individual maternal outcomes relevant to the timing of delivery in women with mild and moderate pre-eclampsia at late preterm gestations was completed by 90% (18/20) of obstetricians. Six of the 21 outcomes (29%) were scored as very important, and 12 outcomes (52%) were considered to be important. (Figure 4.3.1)

The median score was below 4 for three outcomes in the first round: Bell's palsy, Glasgow Coma Scale <13 and retinal detachment. These outcomes were excluded from the second round. Additional outcomes such as need for magnesium sulphate, placental abruption, and HELLP (Haemolysis, Elevated Liver enzymes and Low Platelets) syndrome, were suggested for consideration by the panellists, and these were added to the list for the second iteration. Six maternal outcomes were prioritised to be very important with an interquartile range (IQR) ≤1. These included eclampsia, pulmonary oedema, severe pre-eclampsia, maternal death, acute renal insufficiency and hepatic dysfunction.

Figure 4.3.1: Prioritisation of maternal outcomes relevant to the timing of delivery management in women with mild and moderate pre-eclampsia at late preterm gestations



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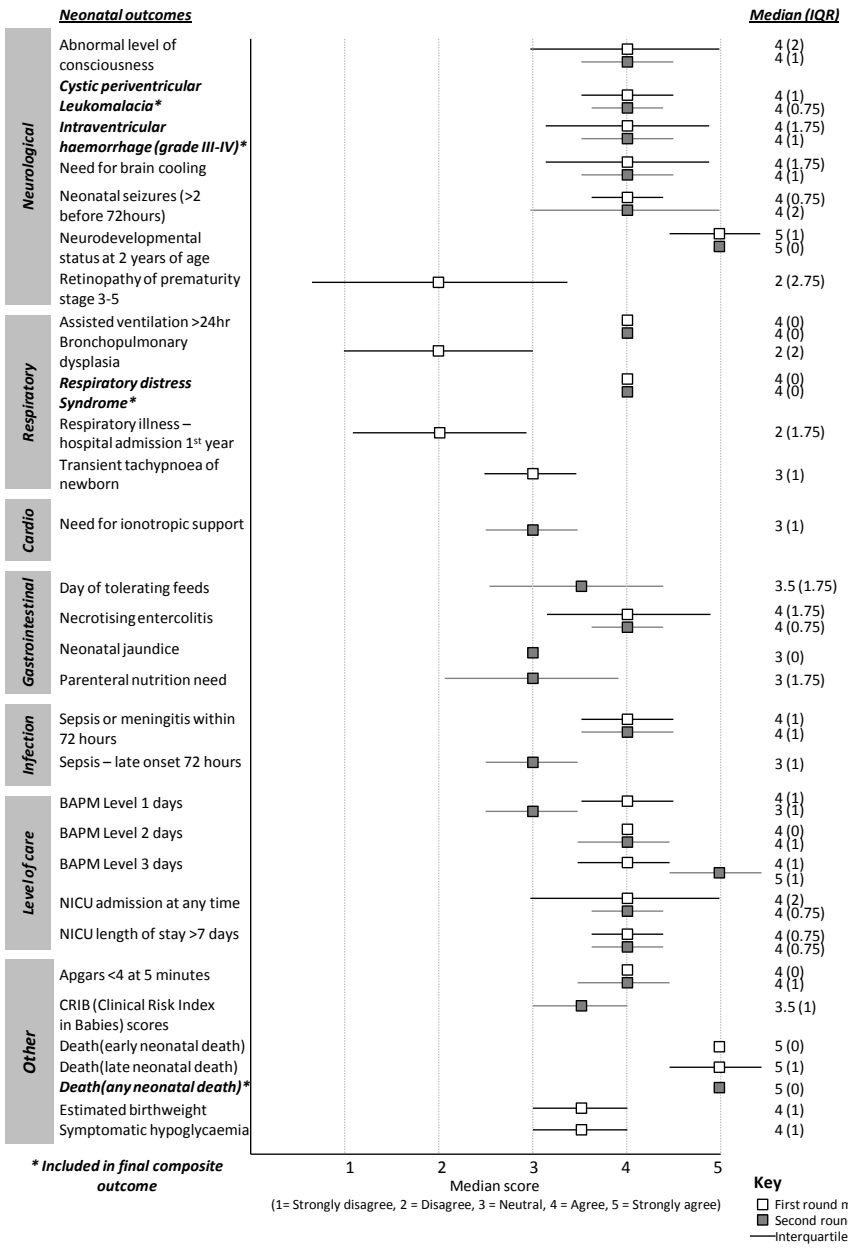
Eighteen neonatologists (18/24, 75%) prioritised neonatal outcomes in the first iteration. Three (12.5%) outcomes were scored as very important and 16 (67%) as important (Figure 2). Five outcomes including transient tachypnoea of the newborn, respiratory illness requiring admission to hospital during the first year of life, bronchopulmonary dysplasia, stage 3 to 5 retinopathy of prematurity and need for assisted ventilation more than 4 hours had a median score below 4. These were excluded from the second round of the survey.

Figure 4.3.2: Prioritisation of neonatal outcomes relevant to the time of delivery management in women with mild and moderate pre-eclampsia at late preterm gestations



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The neonatal expert panel suggested eight new items to be considered in the second round. These included estimated birth weight, Clinical Risk Index for Babies (CRIB) scores, need for ionotropic support, symptomatic hypoglycaemia, need for parenteral nutrition (number of

days), day of life tolerating enteral feeds, late onset sepsis (>72 hours) and neonatal jaundice. The outcome, hypoxic ischaemic encephalopathy was missed by the online system and did not proceed to the next round. We included this outcome in the third stage for consideration as a component in the development of composite outcomes.

Second round

During the second round, seventeen (17/18, 94%) obstetricians and 18 (18/18, 100%) neonatologists participated. Ten maternal outcomes (10/21, 48%) were considered to be very important (median score of 5); eleven maternal outcomes (11/21, 52%) were considered to be important (median score of 4). Ten maternal outcomes had a narrowing of the IQR, indicating consensus between the panellists. (Figure 4.3.1)

Three neonatal outcomes (3/25, 12%) were considered to be very important (median score of 5); they included neonatal death, neurodevelopmental status at 2 years of age and days of BAPM (British Association of Perinatal Medicine) level 3 care. Fourteen neonatal outcomes (14/25, 56%) were prioritised as important (median score of 4). The remaining eight outcomes had median scores of less than 4. Eight outcomes had narrowing of the IQR indicating consensus. (Figure 4.3.2)

Development of the composite outcome

In the final stage, we evaluated the ten maternal outcomes and seventeen neonatal outcomes prioritised by the Delphi survey, for inclusion as components of the composite outcomes.

Maternal outcomes

The final maternal composite outcome consisted of seven components: maternal death, eclampsia, pulmonary oedema, major obstetric haemorrhage with need for transfusion of blood products or need for positive ionotropic support, HELLP syndrome and placental abruption. (Table 4.3.1) We excluded outcomes with very low prevalence, such as cortical blindness, myocardial ischaemia or infarction and hepatic capsule rupture. Components that overlapped significantly with other components were excluded. Outcomes such as hepatic dysfunction and hepatic failure with HELLP syndrome; severe pre-eclampsia and the need for a 3rd antihypertensive; acute renal insufficiency and need for dialysis were excluded. Less objective and clinician-driven outcomes such as the need for magnesium sulphate were also excluded.

Neonatal outcomes

The final neonatal composite endpoint comprised of neonatal death, respiratory distress syndrome needing ventilatory support, and neurological morbidity such as cystic periventricular leukomalacia and grade III/IV intraventricular haemorrhage. (Table 4.3.2) Clinician-driven outcomes such as admission to the neonatal intensive care unit (NICU) at any time, length of stay more than seven days on the NICU and days of BAPM Level 2 care were excluded. We also excluded long-term outcomes such as 2-year follow up. The outcomes whose IQR increased in the second round, suggesting variation in consensus (neonatal seizures and Apgar <4 at 5 minutes) were not included. In many countries, including the UK, therapeutic hypothermia for neuroprotection of late preterm infants is not routinely administered to infants under 36 weeks gestation and hence it was not included. Although grade III/IV intraventricular haemorrhage and cystic periventricular leukomalacia are less common complications for neonates born at late preterm gestations, they were included in our composite outcome due to the severity and importance of these conditions.

Table 2: Criteria for developing the neonatal composite outcome

Discussion

We developed maternal and neonatal composite outcomes for clinical trials on women with mild and moderate pre-eclampsia at late preterm gestation using rigorous methodology. These composite outcomes can contribute to reducing the bias in both the design and reporting of randomised trials in this area. Studies reporting the effects of the intervention should also provide the effect of the intervention on the individual components of the composite outcome.

There are clear recommendations on the timing of delivery at early preterm gestation (<34 weeks), with the advice of delivery in women with severe pre-eclampsia, and expectant management in mild and moderate pre-eclampsia.[22, 38] However, clinical equipoise exists for the management of women in this somewhat 'grey' area of mild to moderate pre-eclampsia developing at a late preterm gestation. When the condition is mild to moderate pre-eclampsia, expectant management is usually adopted prior to 34 weeks' gestation; elective delivery at 37 weeks' gestation or thereafter but between 34 to 37 weeks' gestation, there is little guidance and the optimal management is currently unclear.

This has been identified as an area of much needed research, to determine the optimal timing of delivery of women with mild to moderate pre-eclampsia at late preterm gestations between 34 and 37 weeks. Multiple outcomes for both mother and baby need to be taken into consideration to adequately assess the effect of intervention or non-intervention of this subset of women.

Strengths and limitations

There are several strengths to this study. Firstly the Delphi survey involved clinicians and academics with expertise in the area, thereby ensuring face validity. Secondly, identification of components through systematic reviews and surveys provided content validity. Thirdly, there was minimal loss to follow up with high response rates between each iteration. Fourthly we measured each individual outcome against pre-specified and well-accepted criteria for the development of the composite outcomes.[229] We provided a clear definition for each outcome in order to minimise bias. (Appendix 7)

The Delphi technique is a consensus method commonly used to measure uncertainty in health research, enabling researchers to derive quantitative estimates through a qualitative approach.[230] Alternative consensus methods include the nominal group technique (also known as the expert panel),[231] and the consensus development conference.[230] These alternative methods are more focussed on developing consensus and are highly structured group meetings with relevant experts usually in a face-to-face setting.

The strengths of the Delphi technique in comparison to the alternative consensus methods are that it is easy and of low cost to organise, administer and analyse since there is no need for a face-to-face meeting; individuals can freely express their opinions due to the anonymous nature and a consensus is usually achieved rapidly. Its limitations are that it relies on the motivation of the panellists to respond to each round; without the face to face meeting, it is difficult to 'discuss' differing opinions or points and can be time consuming with the several rounds, awaiting responses and collating them together compared an expert panel meeting or conference.

Our selection of the components was heavily dependent on the opinions and knowledge of the panel members. It is possible that a panel of different members may have prioritised a different set of outcomes. Furthermore, despite our efforts to use stringent criteria for the development of composite endpoints, it is often difficult to identify components of absolute equal importance. Despite our efforts, the individual components of our final composite outcomes have variation in the frequency of occurrence of outcomes. These are well-recognised limitations of composite outcomes, with the effect being smallest for the most important component and largest for the least important component. The onus lies upon the researcher to ensure there is thorough and consistent reporting, and interpretation of the effect of an intervention on a composite outcome.

Use of Delphi technique

The Delphi technique provided a platform for structured group communication in order to answer a question in the absence of known consensus.[232] Pre-eclampsia is a condition with complex pathophysiology and requires intuitive interpretation of evidence. The Delphi enabled us to draw upon the experience and knowledge of a selected group of experts to reach consensus anonymously. Furthermore the two-stage process provides the opportunity for participants to acknowledge the opinions of the other panel members and modify their responses. Consensus was achieved for most outcomes.

Challenges in the development and reporting of composite outcomes

Composite outcomes have become increasingly popular in their use in clinical trials. However, the robustness of their development and the reporting of the composite outcomes have received much criticism. This is mainly due to the lack of transparency in the selection of the components and the relevance to clinical practice. We have attempted to address these

issues by undertaking a systematic search and prioritisation of the components by the Delphi technique. Another challenge is the frequency of occurrence of the individual components varies, often one component of the outcome may dominate the findings. In our example, maternal and neonatal deaths are very infrequent but we included these two components in both composite outcomes since death has a censuring effect on other components.

Certain outcomes may be more likely to be 'clinician-driven' and hence have a potential for bias, particularly in unblinded clinical trials. We therefore excluded clinician-driven outcomes such as admission to the neonatal intensive care unit (NICU) at any time with length of stay more than seven days on the NICU and days of BAPM Level 2 care. The change in the rates of all the outcomes may not be in the same direction resulting in conflicting results. The above limitations need to be acknowledged and clearly taken into account in the interpretation of results.

A recent systematic review on reporting of composite outcomes in randomised clinical trials on evaluating the highlighted that only one trial (out of 40) rationalised the selection of the individual components. About 70% of these trials had composite outcomes that included components of differing levels of importance.[228]

As identified in our searches, there have been other composite maternal and neonatal outcomes developed for pre-eclampsia.[57, 217, 233] The study by von Dadelszen also identified the individual components by the Delphi technique but the underlying clinical question differed. They focussed on maternal and neonatal outcomes in women with pre-eclampsia of any severity and development at any gestational age, to be evaluated in a prediction model.[57] In our study, the focus has been on a subset of women with the milder end of the spectrum

and late presentation of the disease. In comparison with von Dadelszen's study, we included HELLP syndrome and severe pre-eclampsia components in our study.[57] Our Delphi expert panel members were from the UK whereas their study was based in Canada. The variation in population and the panel may explain the difference in the prioritisation of outcomes.

Patient involvement

Patient and family involvement is often overlooked in the development of composite outcomes. Parents may consider a different set of outcomes to be important compared to the clinicians. There has been great success in the field of rheumatology, the development of core outcome measures has integrated patient prioritisation of outcomes at each step alongside clinician's views.[234] We were unable to obtain patient and public involvement on important outcomes for the management of women with late-onset pre-eclampsia due to time restraints.

Future recommendations

Future randomised controlled trials on women with mild or moderate pre-eclampsia, especially at late preterm gestations, should consider these composite outcomes and their components to assess the effect of intervention. Caution and acknowledgement of the limitations are needed in the interpretation of the incidence of these outcomes and components.[77] Additional input from the patient and public is needed in the development of composite outcomes.

Conclusion

The composite maternal and neonatal outcomes developed in this study provide a more realistic primary outcome measure for a feasible number of patients to be recruited to studies

attempting to answer the question of optimal timing of delivery in women with late-onset mild and moderate pre-eclampsia.

Members of the Delphi consensus

Maternal outcomes group

Joe Aquilina, Shagaf Bakour, Elizabeth Ball, Charlotte Chaliha, Arris Coomarasamy, Manish Gupta, Matthew Hogg, Khaled Ismail, Khalid Khan, Rehan Khan, Ramesan Navaratnarajah, Fidelma O'Mahony, Vincent Oon, Shakila Thangaratinam, Jason Waugh, Ling Wee, Sangeeta Agnihotri, Michele Mohajer.

Neonatal outcomes group

Narendra Aladangady, Philippa Chisholm, Paul Clarke, Sanjeev Deshpande, Rainer Ebel, Andy Ewer, Paul Fleming, Alan Gibson, John Ho, Shahid Husain, Olga Kapellou, Steve Kempley, Anne Opute, Ravi Prakash, Divyen Shah, Ajay Sinha, Zoe Smith, Caroline Sullivan.

My contribution to this work:

Literature search and Delphi survey questionnaire design, carrying out online survey and collating responses. Formulation of question and interpretation of findings. First draft of manuscript and all revisions.

SECTION C

MULTIPLE PREGNANCIES

In this section, I have undertaken a systematic review of prospective risk of stillbirth and neonatal deaths in uncomplicated monochorionic and dichorionic twin pregnancies. I have identified the optimal timing of delivery in uncomplicated monochorionic and dichorionic twin pregnancies.

CHAPTER 5.1: PROSPECTIVE RISK OF STILLBIRTH AND NEONATAL DEATHS IN UNCOMPLICATED MONOCHORIONIC AND DICHORIONIC TWIN PREGNANCIES AND OPTIMAL TIMING OF DELIVERY

Abstract

Background

The high rate of stillbirth in twins has led to a policy of planned early delivery. There is no consensus on optimal timing due to lack of robust data.

Objective

To quantify the risks of stillbirth and neonatal complications by gestational age in uncomplicated monochorionic and dichorionic twin pregnancies.

Methods

We searched major databases (Medline, Embase and Cochrane) for relevant studies (until December 2015) without language restrictions for studies of women with uncomplicated twin pregnancies, which reported rates of stillbirth and neonatal outcomes at various gestational ages. We also included unpublished data from collaborative research networks. We excluded pregnancies with unclear chorionicity, monoamnionicity and twin-to-twin transfusion syndrome. Meta-analyses of observational studies and cohorts nested within randomised studies were undertaken. We computed prospective risk of stillbirth for each study at a given week of gestation, and compared this with the risk of neonatal death amongst deliveries in the same week. We estimated the gestational age-specific risk differences for stillbirths and neonatal deaths in monochorionic and dichorionic twin pregnancies after 34 weeks of gestation.

Results

Thirty-two studies (29,685 dichorionic, 5,486 monochorionic pregnancies) were included. In dichorionic twin pregnancies beyond 34 weeks (15 studies, 17,830 pregnancies), the

prospective weekly risk of stillbirths from expectant management and the risk of neonatal death from delivery were balanced at 37 weeks' gestation (risk difference 1.2/1000; 95% CI -1.3 to 3.6, $I^2 = 0\%$). Delay in delivery by a week (until 38 weeks) led to an additional 8.8 perinatal deaths per 1000 pregnancies (95% CI 3.6 to 14.0 /1000, $I^2 = 0\%$) compared to the previous week. In monochorionic pregnancies beyond 34 weeks (13 studies, 2,149 pregnancies), there was a trend towards increase in stillbirths compared with neonatal deaths after 36 weeks, with an additional 2.5 per 1000 perinatal deaths, which was not significant (95% CI -12.4 to 17.4/1000, $I^2 = 0\%$). The rates of neonatal morbidity showed a consistent reduction with increasing gestational age in monochorionic and dichorionic pregnancies, and admission to the neonatal intensive care unit was the commonest neonatal morbidity. The actual risk of stillbirth near term may be higher than reported estimates due to the policy of planned delivery in twin pregnancies.

Conclusion

In order to minimise perinatal deaths, delivery should be considered at 37 weeks' gestation in uncomplicated dichorionic twin pregnancies, and considered at 36 weeks in monochorionic pregnancies.

Systematic review registration

PROSPERO CRD420140075382014

Citation of the paper published from this work

Cheong-See F, Schuit E, Arroyo-Manzano D, Khalil A, Barrett J, Joseph KS, Asztalos E, Lewi L, Lim A, Liem S, Norman JE, Morrison J, Combs CA, Garite TJ, Maurel K, Serra V, Perales A, Rode L, Worda K, Nassar A, Aboulghar M, Rouse D, Thom E, Breathnach F, Nakayama S, Russo FM, Robinson JN, Dodd JM, Newman RB, Bhattacharya S, Tang S, Mol

BWJ, Zamora J, Thilaganathan B, Thangaratinam S. (2016) Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. *BMJ* 2016; 354:i4353

Background

Twin pregnancies are at high risk of adverse fetal and neonatal outcomes. The risk of stillbirth is increased thirteen-fold and five-fold for monochorionic and dichorionic twin pregnancies respectively compared to singleton pregnancies.[43, 47, 235] Delivery before term predisposes to prematurity-associated neonatal mortality and morbidity.[47] Current guidelines vary in their recommendations on the timing of delivery, ranging from 34 weeks of gestation in monochorionic twins and 37 weeks in dichorionic twins.[236]

Pregnant women with twins, clinicians and policy makers need accurate and robust estimates of the stillbirth risk from continuing the pregnancy, and the neonatal risk from early delivery, to decide upon the optimal timing of delivery. Existing reviews have focused mainly on stillbirth risk without taking into account the neonatal outcomes.[237] There are no published data on gestation and chorionicity specific perinatal mortality and morbidity in twins to guide decision-making on the timing of delivery. Furthermore, randomised trials on the timing of delivery in twins are not adequately powered to provide robust estimates of benefit.[238]

Objective

We undertook a systematic review to quantify the prospective risks of stillbirth by gestational age in uncomplicated monochorionic and dichorionic twin pregnancies. We evaluated the risks to the newborn when delivered after 34 weeks' gestation and at various gestational ages in twin pregnancies.

Methods

We conducted the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Appendix 8)[65] with a prospectively registered protocol.

Study identification

We performed electronic searches on Medline, Embase and the Cochrane Library databases from inception until December 2015 for studies on twin pregnancies reporting rates of stillbirth. The search terms 'monochorionic' OR 'dichorionic' OR 'twin pregnancy' OR 'multiple pregnancy' were used to represent the population and these were combined with 'stillbirth' OR ('fetal or foetal or fetus or foetus' AND 'death or demise or mortality') for the outcome. There were no language restrictions. We supplemented this search with an added search for neonatal outcomes in twin pregnancies (Appendix 9). Reference lists of included studies were interrogated. Additionally, we contacted individual authors members of collaborative research networks such as Global Obstetric Network (GONet),[239] Evidence Based Medicine Connect (EBM Connect),[240] and the Twin pregnancies Individual Participant Data (IPD) Meta-Analysis group for relevant data.[241]

Study selection

Studies were selected in a two-step process by two independent reviewers (FC and ES). In the first stage, the titles and abstracts were screened, and in the second stage, the full texts of the identified studies were evaluated in detail.

We included studies that reported on the rates of stillbirth and neonatal outcomes in women with monochorionic and/or dichorionic twin pregnancies. Both observational cohort studies and randomised control trials with nested cohorts were included. Exclusion criteria were

unclear chorionicity, monoamnionicity, inability to exclude twin-to-twin transfusion syndrome and if the outcomes were not provided in weekly or 2-weekly gestational epochs.

We defined stillbirth as a baby born without signs of life after the viability age, or any other definition used by the authors. Neonatal mortality was defined as neonatal death up to 28 days from delivery.

For neonatal morbidity we considered the following morbidity outcomes to be clinically relevant for delivery after 34 weeks' gestation: the need for assisted ventilation, respiratory distress syndrome (RDS), septicaemia, hypoxic ischaemic encephalopathy or neonatal seizures, and the need for admission to the neonatal intensive care unit.

For moderate and extreme preterm infants, born between 26 and 33+6 weeks' gestation, we evaluated the following additional complications: bronchopulmonary dysplasia, necrotising enterocolitis, cystic periventricular leukomalacia or grade 3 or 4 intraventricular haemorrhage with a significantly abnormal cranial ultrasound scan and retinopathy of prematurity (stages 3 to 5).

Quality assessment and data extraction

We evaluated the qualities of the included studies for their internal and external validity. [12, 242, 243] Representativeness of the cohort, study design, method of sampling, adequacy of follow-up, ascertainment of the outcome and appropriate classification, such as determination of gestational age and chorionicity were assessed. Features such as prospective design, consecutive or random recruitment of patients, follow-up rates of over 80%, and use of first-trimester ultrasound signs to determine chorionicity and gestational age assessment were

considered to have high quality. We evaluated the external validity from the representativeness of the population studied. Studies that provided a clear definition of uncomplicated twin pregnancies and excluded pregnancies with fetal growth restriction and congenital abnormalities in the baby were classified as high-quality studies. Study quality assessment and data extraction were performed by two independent reviewers (FC and ES). Any discrepancies were resolved by discussion with a third reviewer (ST).

Analysis

Separate analyses were undertaken for risks of stillbirth, neonatal mortality and morbidity in monochorionic and dichorionic twin pregnancies in two periods. The first was from 34 weeks' gestation and beyond and the second, early preterm (<34 weeks) gestation.

From 34 weeks onwards, we calculated the risks by weekly gestational ages, with the 34-week period representing pregnant women entering the 34+0 to 34+6 weeks' gestation with live fetuses. For early preterm (<34 weeks) gestation, we estimated risks of outcomes by two weekly intervals.

We calculated the prospective risk of stillbirth by dividing the number of stillbirths seen that week by the number of women who were at risk in the same week. For a specific gestational age, we defined women at risk of stillbirth as those who were still pregnant at the beginning of that gestational week.

Deliveries during that week were corrected for by subtracting half the number of women who delivered that week. [244] For the risk of neonatal death, this was calculated by dividing the number of neonatal deaths in a given gestational week by the number of deliveries.

In pregnancies after 34 weeks' gestation, we assessed the competing risks of expectant management versus delivery at a given gestational age, for each study. We defined the risk of perinatal death at a given gestational week as the difference between stillbirth and neonatal death risk for deliveries in that week. This provided a direct measure of benefit or harm from expectant management vs. immediate delivery strategy. A risk difference < 0 represents a reduction in the risk of perinatal death with expectant management for the given gestational age, compared with immediate delivery.

Risk differences from individual studies were pooled together using a fixed effect model weighted by the inverse of its variance. We computed I-squared as an estimation of between-study heterogeneity and assumed values lower than 50% as little heterogeneity and I-squared greater than 75% as substantial heterogeneity.

We estimated the weekly risk of neonatal outcomes by fitting multi-level random effects logistic regression models with gestational age as the independent variable. The units of the analysis were pregnancies (at the first level) that were clustered within studies (for the second level of the analysis). We calculated point estimates of the risk of each event by the gestational period along with its corresponding 95% confidence interval (CI). We planned before analysis to restrict our evaluation up to the gestational week for which robust, unbiased data were available.

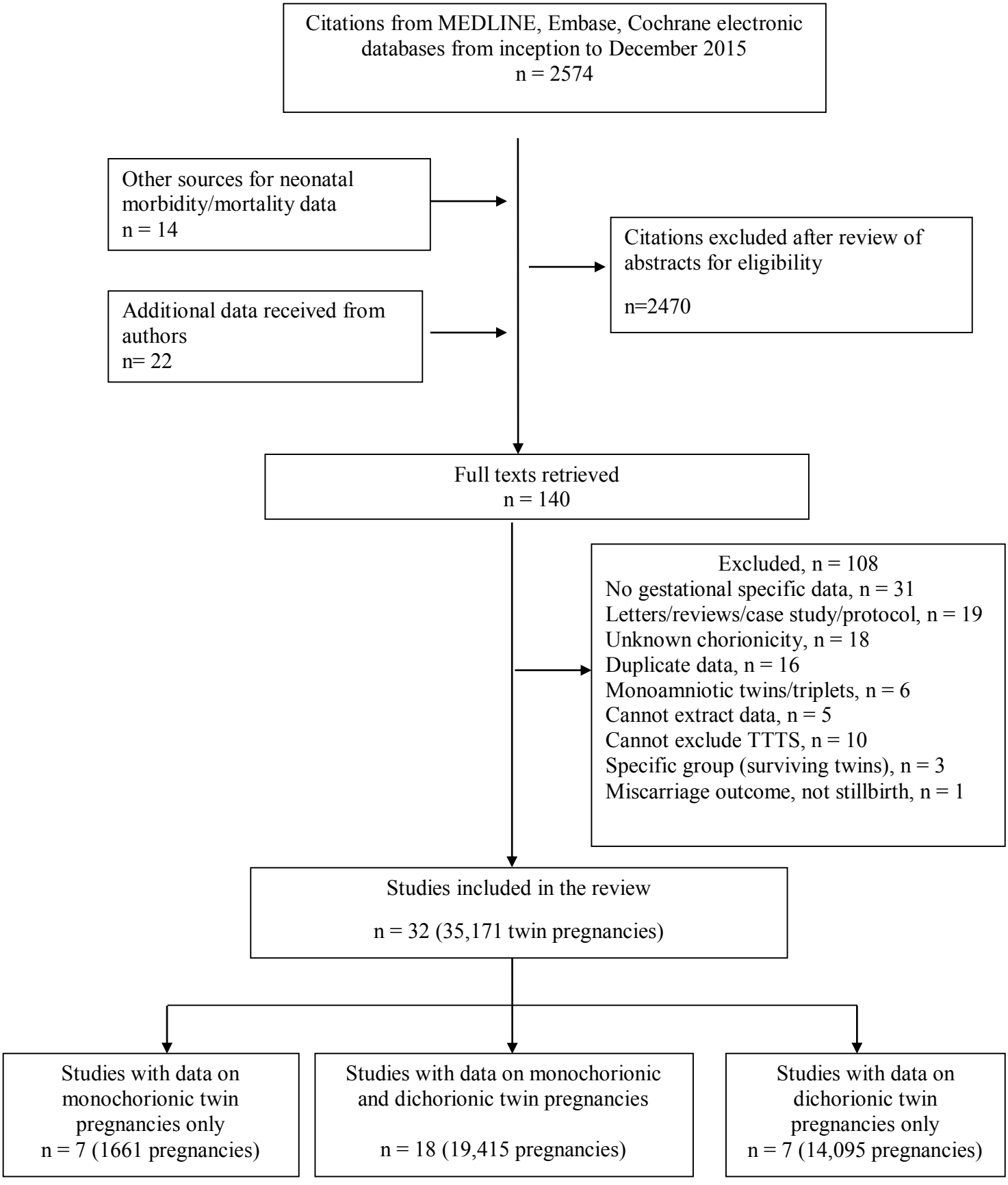
Sensitivity analysis was planned a priori to analysis to exclude studies involving pregnancies complicated by congenital abnormalities, and those with low external validity. We assessed publication bias and small study effects using funnel plots to represent the overall event rate (logit scale) versus the inverse of the sample size for each study included in main analysis.[63] .56 To evaluate publication bias, we used Peters's test, which evaluates funnel asymmetry and is advantageous for use with dichotomous outcomes due the appropriate type 1 error rates regardless of the degree of heterogeneity and the underlying effect size.[245, 246] We fitted a weighted linear regression with the logit of event rate as the dependent variable and the inverse of sample size as the independent variable. computed the weights according to the number of events and non-events.[246] We used a continuity correction for studies with zero events by adding 0.5 to the events and 1 to the total sample size.

Results

Identification of studies

From 2574 citations, we identified 32 studies reporting on 35,171 women with twin pregnancies (Figure 5.1).[43, 238, 247-273] Eighteen studies provided data on both monochorionic and dichorionic,[43, 238, 249, 251, 253, 255, 257, 259, 261-264, 267-269, 272, 274, 275] seven on monochorionic twin pregnancies only, [248, 250, 256, 258, 260, 266, 271] and seven on dichorionic twin pregnancies only. [247, 252, 254, 265, 270, 273, 276] Twenty-three authors provided additional relevant unpublished data.[43, 238, 247, 249, 251-254, 257, 258, 260-262, 266-272, 274-276]

Figure 5.1 Study selection process in the systematic review on prospective risk of stillbirth and neonatal complications in uncomplicated twin pregnancies



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Study characteristics and quality assessment

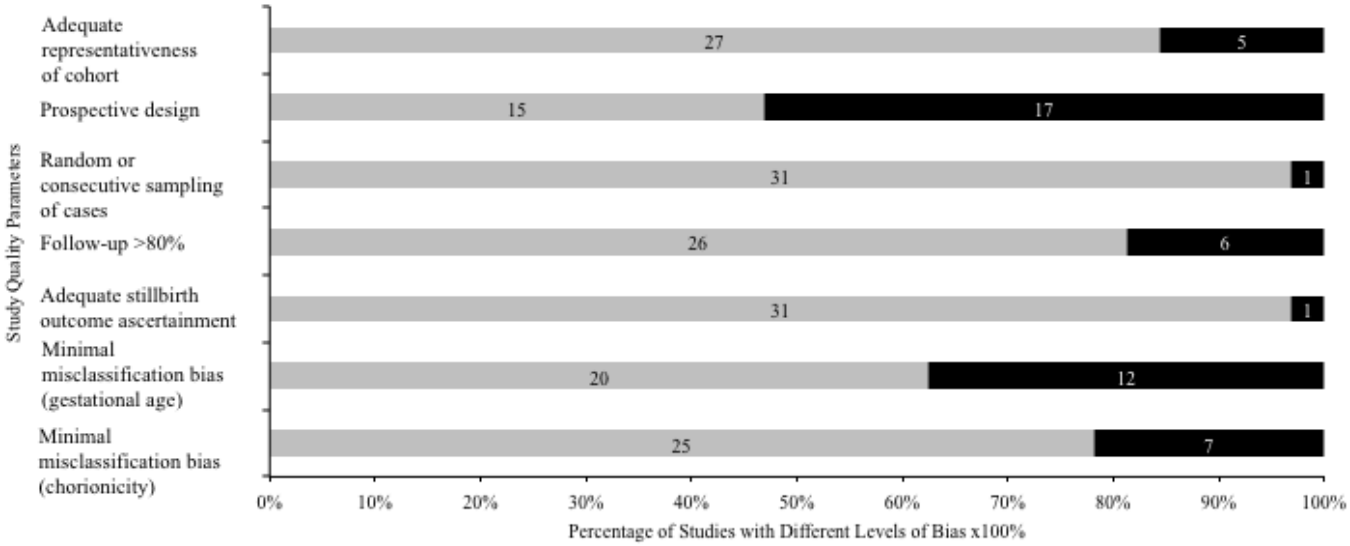
Fifteen studies on dichorionic pregnancies (17,830 women) and 13 on monochorionic pregnancies (2,149 women) provided weekly data on stillbirth after 34 weeks' gestation. The corresponding neonatal death rates were provided by 13 (n=10,333) studies for dichorionic, and 11 (n=1,461) for monochorionic pregnancies.

Overall, there were 14 studies that excluded pregnancies complicated by fetal growth restriction, and 28 studies excluded pregnancies with major congenital abnormalities. The diagnosis of fetal growth restriction and congenital abnormalities were made antenatally. The postmortem findings of the stillborn babies were reviewed for evidence of growth restriction in two studies. The definitions of stillbirths, neonatal death, and morbidity outcomes did not differ much amongst the studies (Appendix 9). The number of stillbirths and neonatal deaths from 26 to 33+6 weeks, and beyond 34 weeks of gestation in individual studies for monochorionic and dichorionic pregnancies are demonstrated in (Appendix 10).

The qualities of the studies were adequately representative in 27 (27/32, 84%), and inadequately or unclearly representative in 5 (5/32, 16%) (Figure 5.2). Fifteen of the included studies (15/32) were prospective, and of these 12 (12/32, 38%) were nested cohorts in randomised trials. The majority of studies used random or consecutive sampling methods (31/32, 97%), had achieved adequate follow-up (26/32, 81%), and we observed low levels of ascertainment bias in determining stillbirth outcome (31/32, 97%). For misclassification bias,

twenty studies had a low risk of bias for gestational age assessment (20/32, 63%), and twenty-five studies had a low risk of bias for chorionicity determination (25/32, 78%).

Figure 5.2 Risk of bias in studies included in the systematic review on prospective risk of stillbirth and neonatal complications in uncomplicated twin pregnancies



Key:

Yes

No

Data presented as 100% stacked bars; figures in the stacks represent number of studies.

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Stillbirth and neonatal mortality after 34 weeks' gestation

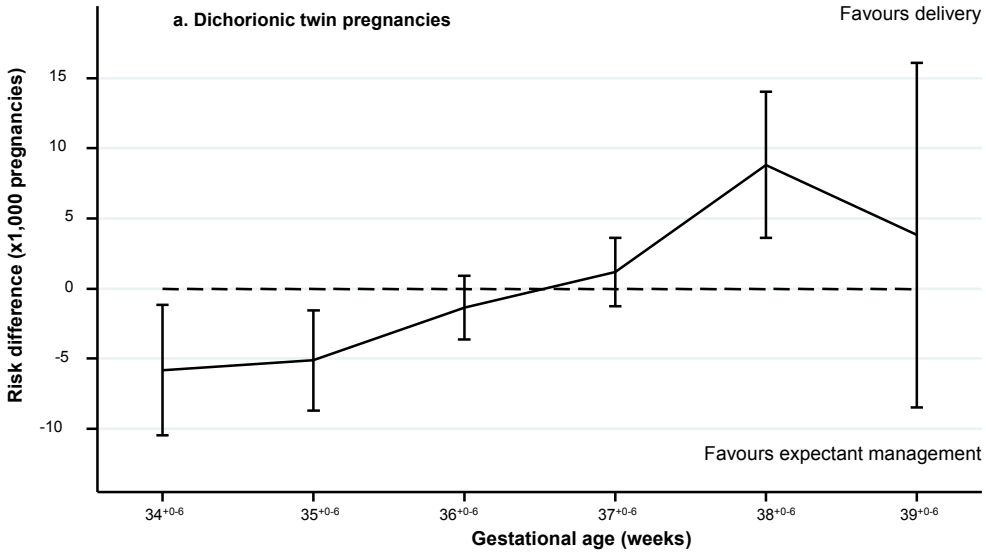
Dichorionic twin pregnancies

At 34+0-6 weeks, the prospective risk of stillbirth was 1.2 per 1000 pregnancies (95% CI 0.7-1.8) a and the corresponding risk of neonatal death was 6.7 per 1000 pregnancies (95% CI 3.3 to 13.5) (Table 5.1). The risks of stillbirth were significantly lower than the risks of neonatal deaths at 34+0-6 (risk difference -5.8/1000, 95% CI -10.4 to -1.2/1000, I2=0%), and 35+0-6 weeks' gestation (risk difference -5.1/1000, 95% CI -8.7 to -1.6/1000, I2=0%).

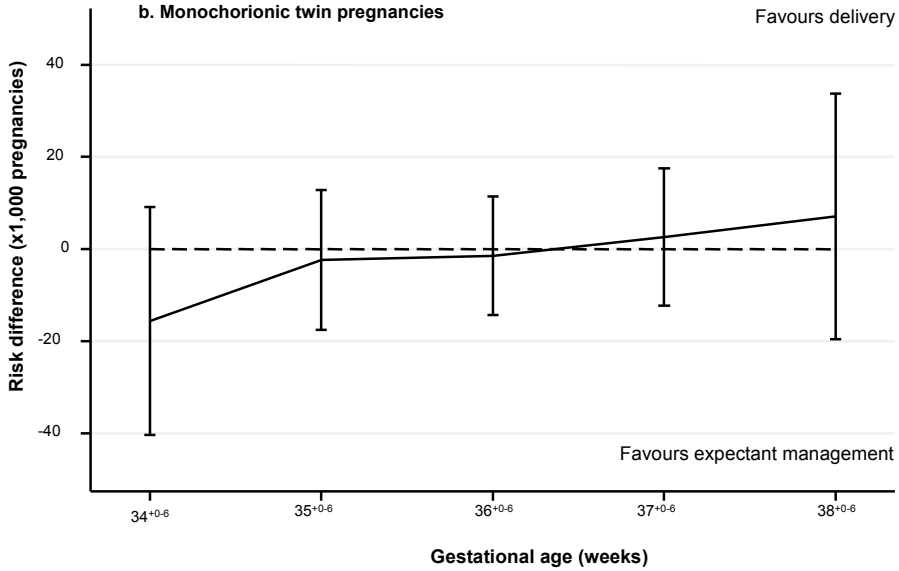
At 37+0-6 weeks, the perinatal risks were balanced with a risk difference was 1.2/1000, (95% CI -1.3 to 3.6/1000, I2=0%). After this gestational week, the risk of stillbirth increases to 10.6/1000, (95% CI 7.1 to 15.3), which significantly outweighs the neonatal death risk from delivery at 1.5/1000, (95% CI 0.7 to 3.3). The risk difference increases to 8.8/1000, (95% CI 3.6 to 14/1000, I2=0%) (Figure 5.3). Analysis by excluding fetuses with congenital abnormalities showed results similar to the main analysis (Figure 5.4).

When we excluded studies with low external validity, there was a trend towards increased stillbirth risk compared with neonatal death beyond 37+0-6 weeks, but this was not statistically significant.

Figure 5.3 Prospective risks of stillbirths from expectant management compared to neonatal mortality risks from delivery at weekly intervals from 34 week's gestation in twin pregnancies



Risk Difference (x1,000 preg.) (95% CI)	-5.8 (-10.4, -1.2)	-5.1 (-8.7, -1.6)	-1.3 (-3.6, 0.9)	1.2 (-1.3, 3.6)	8.8 (3.6, 14.0)	3.8 (-8.5,16.1)
Stillbirth	21	12	18	23	28	7
Ongoing pregnancies	17,830	15,470	11,824	6,824	2,633	752
Neonatal death	12	15	12	10	5	3
Deliveries	1,742	2,611	4,238	5,141	2,581	751



Risk Difference (x1,000 preg.) (95% CI)	-15.6 (-40.4, 9.1)	-2.4 (-17.6, 12.8)	-1.5 (-14.4, 11.4)	2.5 (-12.4, 17.4)	7.0 (-19.7, 33.7)
Stillbirth	2	5	6	7	2
Ongoing pregnancies	2,149	1,797	1,325	730	264
Neonatal death	4	2	3	4	0
Deliveries	247	367	534	532	307

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Figure 5.4 Risks of stillbirths from expectant management compared to neonatal mortality risks from delivery at weekly intervals from 34 week's gestation in studies on twin pregnancies without major congenital abnormalities

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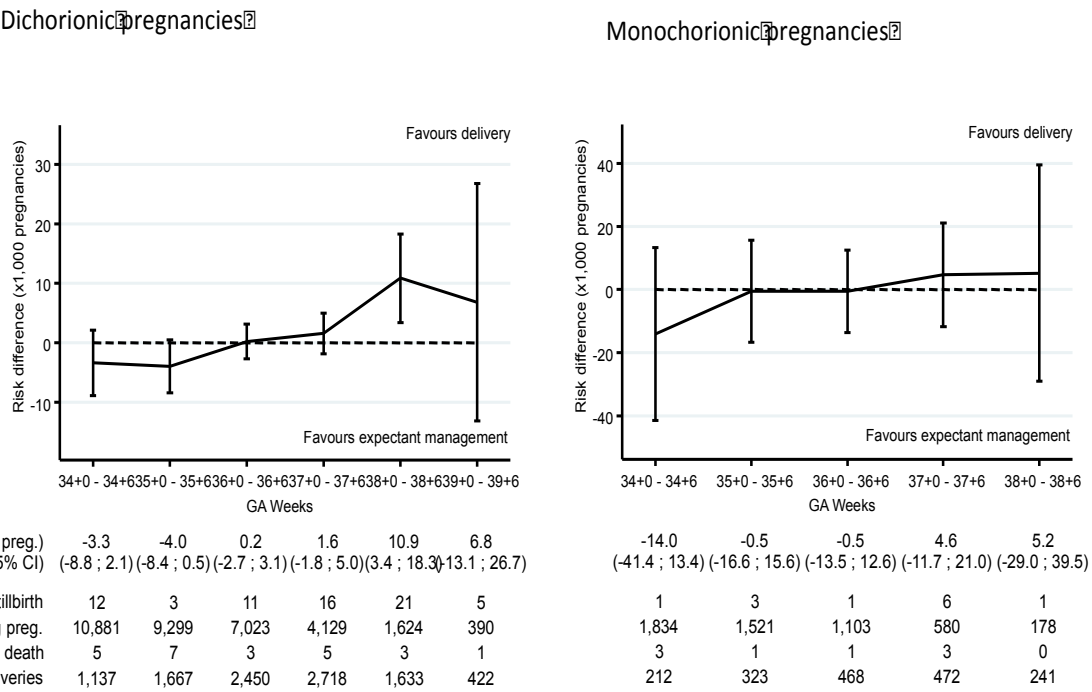


	34+0 - 34+6	35+0 - 35+6	36+0 - 36+6	37+0 - 37+6	38+0 - 38+6	39+0 - 39+6
Risk Difference (x1,000 preg.) (95% CI)	-3.3 (-8.8 ; 2.1)	-4.0 (-8.4 ; 0.5)	0.2 (-2.7 ; 3.1)	1.6 (-1.8 ; 5.0)	10.9 (3.4 ; 18.3)	6.8 (-13.1 ; 26.7)
Stillbirth	12	3	11	16	21	5
Ongoing preg.	10,881	9,299	7,023	4,129	1,624	390
Neonatal death	5	7	3	5	3	1
Deliveries	1,137	1,667	2,450	2,718	1,633	422

	34+0 - 34+6	35+0 - 35+6	36+0 - 36+6	37+0 - 37+6	38+0 - 38+6
Risk Difference (x1,000 preg.) (95% CI)	-14.0 (-41.4 ; 13.4)	-0.5 (-16.6 ; 15.6)	-0.5 (-13.5 ; 12.6)	4.6 (-11.7 ; 21.0)	5.2 (-29.0 ; 39.5)
Stillbirth	1	3	1	6	1
Ongoing preg.	1,834	1,521	1,103	580	178
Neonatal death	3	1	1	3	0
Deliveries	212	323	468	472	241

Monochorionic twin pregnancies

At 34 weeks, the prospective risks of stillbirth and neonatal mortality in monochorionic pregnancies were 0.9/1000 (95% CI 0.1 to 3.4) and 12.1/1000 (95% CI 4.2 to 34.3) respectively.

The risks of neonatal death were higher than stillbirth at 34+0-6 (risk difference -15.6/1000, 95% CI -40.4 to 9.1/1000, I2=0%) and 35+0-6 weeks (risk difference -2.4/1000, 95% CI -17.6 to 12.8/1000, I2=0%), but these were not statistically significant (Figure 3). After 36+0-6 weeks, we observed a trend where the risk of stillbirth (9.6/1000, 95% CI 3.9 to 19.7) was higher than neonatal deaths (3.6/1000, 95% CI 1.2 to 11.1) with a risk difference of 2.5/1000 (95% CI -12.4 to 17.4/1000, I2=0%). Sensitivity analysis by excluding studies with congenitally malformed fetuses (Figure 5.4) and studies with low external validity showed similar findings.

All analyses were restricted to 38 weeks for monochorionic twin pregnancies and until 39 weeks for dichorionic twin pregnancies due to the lack of robust data beyond this timeframe.

Neonatal morbidity beyond 34 weeks' gestation

The rates of need for assisted ventilation, septicaemia, respiratory distress syndrome and admission to the neonatal intensive care unit consistently reduced with increasing gestational age in babies of both monochorionic and dichorionic twin pregnancies (Table 5.2). Neonatal Intensive Care Unit (NICU) admission in the infants was the commonest complication in monochorionic and dichorionic twin pregnancies.

Stillbirth and neonatal outcomes in early preterm twin pregnancies

The cumulative risks of stillbirth and neonatal deaths by two weekly gestational periods in early preterm twin pregnancies (between 26 to 33 weeks and 6 days gestation) are provided in (Appendix 13.). Early preterm neonatal outcomes in two-weekly epochs are shown in Appendix 14. Neonatal morbidity reduced with increasing gestational age in all twin pregnancies. The commonest neonatal complications were respiratory distress syndrome, septicaemia, admission to the neonatal intensive care unit (NICU) and the need for assisted ventilation, in both monochorionic and dichorionic pregnancies.

Publication bias and small studies effect

Funnel plots found a slight asymmetry for stillbirth outcome in dichorionic pregnancies (Peter's test p-value = 0.037) consistent with the finding that smaller studies are published if they show higher stillbirth rates. We found no more significant asymmetries for neonatal death outcome.

Discussion

We observed a consistent increase in the risk of stillbirth, and a decrease in risk of neonatal deaths, with advancing gestation in both monochorionic and dichorionic twin pregnancies. In monochorionic twin pregnancies, the increase in the cumulative risk of stillbirth when awaiting delivery beyond 36^{+6} weeks gestation appears to outweigh the reduction in neonatal deaths for the same period. In dichorionic twins, this phenomenon was observed at 37^{+6} weeks. Our meta-analysis of twin pregnancies has provided comprehensive mortality and morbidity estimates required for decision-making on the timing of delivery. The rates of neonatal outcomes in twin gestations delivered early preterm provide crucial information on the prognosis.

We have undertaken the largest systematic review to-date with robust methodology, on stillbirths and neonatal outcomes in twin pregnancies. In addition to the stillbirth risk at each gestational week, we provided risk estimates of the other equally important consequence of early delivery, namely neonatal death. Furthermore, this is the first review to provide chorionicity and gestational age-specific neonatal morbidity estimates in twin pregnancies. The included studies were all published within the last ten years.

A large proportion of our data were obtained from cohorts embedded within randomised studies, thereby improving the quality of the data. The sharing of unpublished data and individual patient data by authors has allowed us to provide the mortality and morbidity estimates at weekly intervals, in comparison to the commonly available published data in two weekly epochs. We specified the gestational timeframes to reduce bias from varied lengths of follow-up. We minimised heterogeneity by excluding studies without clear details on the exclusion of twin pregnancies that were complicated by twin-to-twin transfusion syndrome. Our sensitivity analyses enabled us to assess the risks in pregnancies uncomplicated by congenital abnormalities, and fetal growth restriction.

Our findings were limited by elective delivery policy after 37 and 38 weeks gestation in most studies. This may have underestimated the risk of stillbirth in the last epoch due to the reduced available sample size near term. Although we observed an increased prospective risk of stillbirth than neonatal death beyond 36 weeks in monochorionic pregnancies, the differences were not statistically significant. This was due to the gradual decline in the number of pregnancies available for analysis, which may be attributed again to elective delivery near term. Most studies did not provide details on whether stillbirth was diagnosed antenatally or at birth. However, given the policy of regular ultrasound for fetal monitoring in

most units, we expect the interval between diagnosis and delivery to be short. Variations in the intensity of antenatal surveillance, mode and timing of delivery of twins, policies between studies and centres, may have influenced the outcomes.[277]

Exploring the small study effects that we observed for monochorionic twin pregnancies outcomes, this could be due to selective reporting, the included published studies showing good outcomes and small sample sizes. Although we included data on women from 34 weeks' gestation onwards from the randomised trials, it is possible that women who had an earlier stillbirth would not be in the analysis.

We have taken a pragmatic approach by including all twin pregnancies uncomplicated by twin-to-twin transfusion syndrome. We were unable to provide separate estimates for individual causes of neonatal mortality, or for elective and emergency deliveries. The results did not vary after excluding pregnancies complicated by fetal growth restriction, one of the main indications for emergency delivery. We only focused on short-term neonatal morbidity due to the paucity of data.[278, 279] Our analysis of risks as stillbirths per pregnancy and the neonatal outcomes per woman delivered, could not distinguish between those pregnancies with a single or double adverse outcome. This is especially relevant in monochorionic twin pregnancies when a stillbirth in one twin increases the risk to the other twin.

Primary studies,[238, 248, 258, 280, 281] systematic reviews,[237] and guideline bodies[1, 41] were limited in their interpretation of evidence on the optimal timing of delivery in twin pregnancies due to the paucity of data and methodological inadequacies. Firstly, they have compared the risks of stillbirth in twin pregnancies at various gestational epochs with those at (or) near term. These comparisons were made without considering the inherent longitudinal design with

women repeatedly observed during the pregnancy. [282] Secondly, some studies made risk estimations using survival analysis (Kaplan-Meier method) that was not appropriate. Delivery was not considered as a competing event for the outcome of stillbirth and may have overestimated the risk. [283]Thirdly, studies did not provide gestational age-specific pooled estimates for significant neonatal morbidity.[237, 284] Fourthly, the recommendations were mainly driven by the risks of fetal death.[42, 237] Finally, the risks of fetal death in twins were not assessed beyond 36 weeks gestation, and the rationale behind the choice of the gestational ages for elective delivery is unclear.[1]

Existing large epidemiological studies on perinatal outcomes in twins have been limited as population selection is broad with unclear details on chorionicity and the definition of uncomplicated monochorionic pregnancies.[285, 286]

Some current recommendations offer expectant management of uncomplicated dichorionic twin pregnancies until 38^{+0-6}.[287, 288] Based on our findings; this poses a risk of additional 8.8 perinatal deaths compared to delivery a week earlier. Although we observed a change in the direction of risk difference with more stillbirths than neonatal deaths beyond 36 weeks in monochorionic twin pregnancies, the observed difference was not statistically significant. The variation in policies for management of monochorionic twin pregnancies, with some advocating delivery as early as 34^{+0-6} weeks,[287, 288] have contributed to the fall in the number of pregnancies available for analysis in later gestation. Based on our findings, there is no clear evidence to recommend early preterm delivery routinely before 36 weeks in monochorionic pregnancies. The information on risks provided in twin pregnancies will complement the ongoing national and international efforts to reduce the rates of stillbirths[289] and unexpected neonatal complications in babies born near term.

Preterm delivery in twin pregnancies is common with about 10% delivery before 32 weeks. The estimates on early preterm neonatal mortality and morbidity from this study provides crucial information to counsel mothers on the risks of early preterm delivery.[290-292] Our work has fulfilled the unmet needs in this area, where current estimates on the predicted probability of survival of newborns, especially early preterm twins, are based on extrapolated data from small samples and do not take into account the effects of chorionicity.[293] Although we did not incorporate economic evaluation in our review, avoiding early delivery has the potential for huge savings to the healthcare system, by up to $70,000 per infant.[280]

The feasibility of a definitive randomised trial on optimal timing of delivery in twin pregnancies is low since huge numbers would be needed to assess outcomes. [228, 254]Individual patient data (IPD) meta-analysis will allow us to assess the effect of factors such as monitoring of the fetuses, the level of newborn care, and mode of delivery on outcomes. There is a need to study the effects of delivery before 37 weeks and the loss of a co-twin in monochorionic pregnancies on long-term infant neurodevelopment. [279, 294,295]

CONCLUSION

There appears to be a no additional gain in survival when pregnancy was prolonged beyond 37 weeks and 6 days in dichorionic twin pregnancies. For monochorionic twin pregnancies, the risk differences were not statistically significant at any gestational age. Decisions on the timing of delivery will need to take into account the magnitude and precision of the benefit achieved by reducing stillbirths against the risks of neonatal mortality and morbidity from planned early delivery.

ROLE OF FUNDING SOURCE

There was no funding for this review. There were no study sponsors for this review.

My contribution to this work:

Search strategy, study selection in stages 1 and 2, data extraction as first reviewer, analysis, the first draft of the manuscript and all revisions.

SECTION D

PROGNOSTIC RESEARCH IN OBSTETRICS

In this section, I have undertaken a systematic review of prediction models in obstetrics to provide an overview on the development process, performance and clinical applicability. I have provided an overview of the challenges of prognostic modelling and potential solutions.

CHAPTER 6.1: DEVELOPMENT AND CLINICAL APPLICABILITY OF PROGNOSTIC MODELS IN OBSTETRICS: A SYSTEMATIC REVIEW

Abstract

Objective: Pregnant mothers and their babies are at risk of adverse outcomes in pregnancy. The ability to predict the probability of a specified outcome empowers maternity caregivers to offer individualised risk counselling, and to target appropriate management stratified by the mother's risk status.

Methods: We searched the electronic database MEDLINE from inception until July 2012 without language restrictions, for studies reporting the development of a prediction model in obstetrics. Studies were included if the model included three or more predictors. Two independent reviewers identified full texts and selected studies for inclusion in the review; data extraction and quality assessment were performed by four independent reviewers.

Results: We included 177 studies from 10,152 citations that described the development of 263 obstetric prediction models for 40 different outcomes. The obstetric conditions for which the models were most commonly developed to predict were pre-eclampsia (69), preterm delivery (63), mode of delivery (22), and small for gestational age neonates (10). Internal and external validation was reported for 21.7% (57/263) and 8.7% (23/263) of the prediction models. Discrimination and calibration of the models were calculated in 62.7% (165/263) and 17.5% (46/263) respectively.

Conclusion: The development of obstetric prognostic research models is increasing. There is, however, a distinct lack of appropriate validation of existing models and little guidance on their clinical applicability and effect on clinical outcomes.

Introduction

Prognostic research in medicine has garnered much attention over the last decade.[296, 297] Each patient wants to know his or her own prognosis. Understanding the prognostic factors that can accurately predict the development of conditions or complications contributes towards a better understanding of each condition or disease and its pathogenesis. It empowers clinicians to move away from the one-size-fits-all counselling and treatment to providing individualised outcome prediction. Treatment strategies on health outcomes can be stratified.

Prediction models enable delivery of personalised medicine in various ways. Examples include an alert such as a screening tool to decide which patients require immediate medical care; using the model to predict outcomes (such as survival or complications) for the individual patient in order to better counsel or guide decision making; using the model on a larger scale to streamline resources so that they can be focussed more upon the 'high risk' patients.[298-301]

To date, the most widely used prediction models in obstetrics were developed back in the 1950s-1960s, and they include the Bishop score to assess cervical ripeness before and during induction of labour and the Apgar score for the need of immediate neonatal care.[49, 50] There is currently no overview of the prediction models that have been developed and published in the field of obstetrics. Recently, the PROGRESS framework[48, 296, 297, 302] highlighted standards and recommendations on the conduct of prognostic research and criticised the external validity and clinical applicability of many published models in other specialties.

We undertook a systematic review of the literature to provide an overview of the published prediction models in obstetrics, their performance and clinical applicability.

Methods

We conducted the review in compliance with PRISMA guidelines.[65] We defined a prediction model as a model that could be used to estimate risks for individual patients or to distinguish groups of patients at different risks, based on three or more predictor variables. Obstetric conditions were restricted to those that could develop from diagnosis of pregnancy to 6 weeks' postpartum.

Identification of studies and study selection

The MEDLINE database was searched using the PubMed platform from inception to July 2012 without language restrictions. The search strategy was developed to capture terms related to women, pregnancy and obstetric conditions and prognostic research modelling in all stages of development. The full search strategy is presented in Appendix 15.

Study selection

Studies were selected in a two-stage process. In the first stage, two independent reviewers identified relevant citations from 300 abstracts. The kappa-statistic was calculated for a measure of agreement. The subsequent abstracts were screened by one reviewer only. In the next stage, we reviewed full texts of selected abstracts for inclusion. The citations were divided into four groups, and four reviewers were assigned per group for data abstraction and quality assessment. Disagreements were resolved by discussion with another reviewer. Where there was more than one publication describing the same prediction model, the most recent published study was included. Authors were not contacted to provide further information.

The inclusion criteria were: a) the primary or secondary aim of the study was to develop a prediction model from identified predictor variables; b) the prediction model consisted of at least 3 predictor variables; c) the development process of the prediction model was described, and d) the prediction model was designed to predict a future outcome. Studies were excluded if they involved animal research only; non-obstetric conditions and if they were non-original publications such as case reports, case series, reviews, comments, letters, editorials, protocols and conference abstracts.

Data were abstracted from each study to assess the study characteristics in addition to concepts identified to be important in the development and validation of clinical prediction models.[303] These included discrimination, calibration, internal validity, external validity, prediction rule or score and guidance for the use of the model in practice. (Box 1)

Box 1 Explanation of important concepts in prediction model development and evaluation

Concept	Description
Discrimination	How well a model discriminates between different patients, commonly presented as the area under the receiver operating characteristics curve (AUC) or the concordance index (C-index). Both the AUC and the C-index provide the probability that the model will give a higher probability of the outcome to a patient with the outcome than a randomly chosen patient without the outcome, or that the patient with the higher probability will have the outcome sooner.
Calibration	The agreement between observed outcomes and prediction.
Internal validity	The process of determining internal validity, or "reproducibility" of the prediction model for the underlying population, the setting where the development data originated from. Techniques include apparent validation (model performance is directly assessed in the development data), split-sample validation or cross-validation (the sample is (randomly) divided, part of the data is used to develop the model and the part that was not used for development is used to evaluate performance) and bootstrapping (bootstrap samples are drawn with replacement from the original study sample, reflecting the drawing of study samples from the underlying population. Each sample is used to develop and evaluate the model, the difference in performance of the model between the bootstrap sample and the

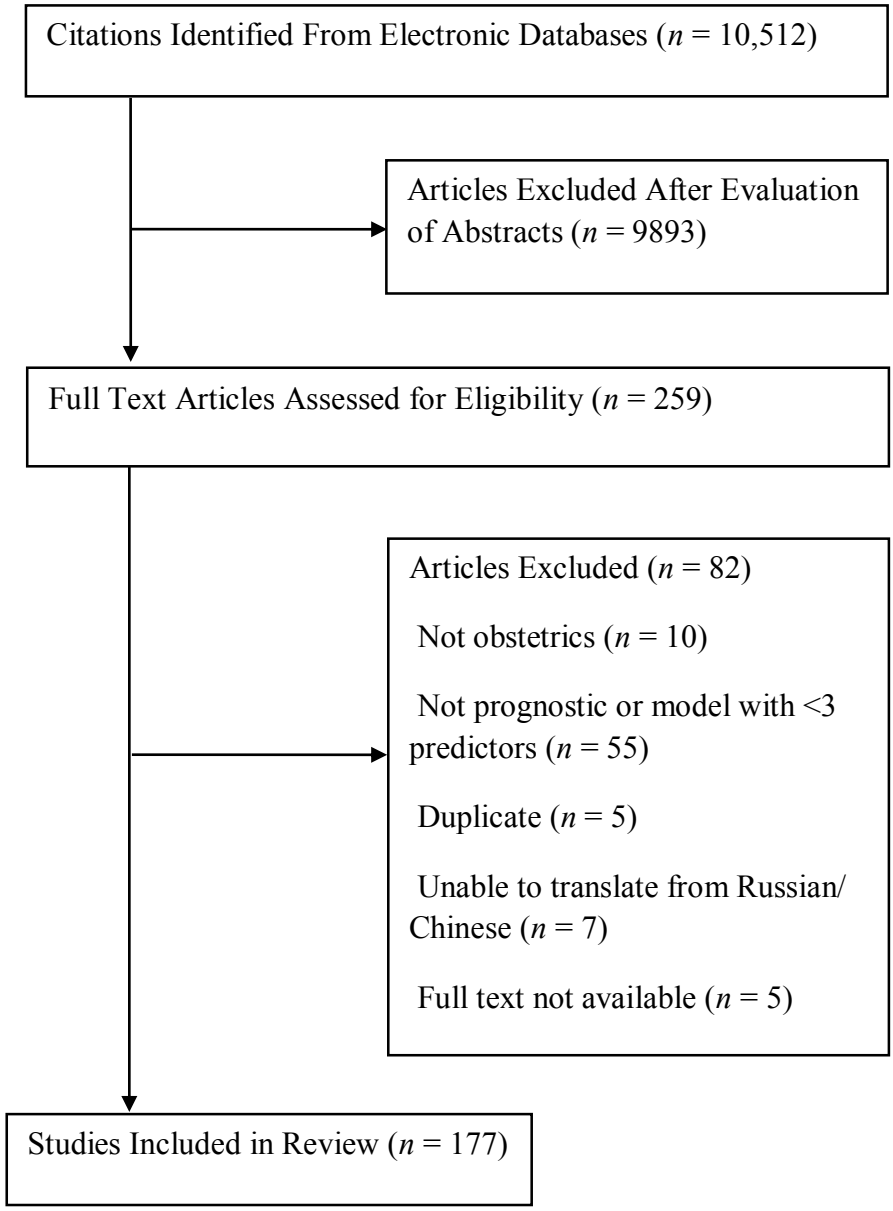
	original sample indicates the 'optimism' of the model that arises since model parameters are optimized for the sample).
External validity	The process of determining external validity, or "generalizability" of the prediction model for populations that are similar to, or related to, the development sample population. External validation can be performed by the same investigators who developed the model, for example in patients more recently attending for care (temporal) or in another hospital or centre (geographical) but is preferably done by other, fully independent investigators.
Prediction rule or score	The format in which the prediction model is presented and that can be used to calculate risks for individual patients or groups of patients. Ideally, for a logistic regression model the intercept and regression coefficients would be reported, and for a Cox model the baseline survival and regression coefficients (regression formula). Alternatives include a nomogram (a graphical presentation of the model with lines for scoring points for each predictor and a line to obtain risk from the sum of points), a score chart, and a table with predictions for certain groups based on combinations of predictor variables.

Results

Study identification

From 10,152 citations, we included 177 studies describing the development of one or more obstetric prediction models in this systematic review.[57, 304-474] A flowchart of the study selection process is presented in Figure 6.1.

Figure 6.1 Study Selection Process



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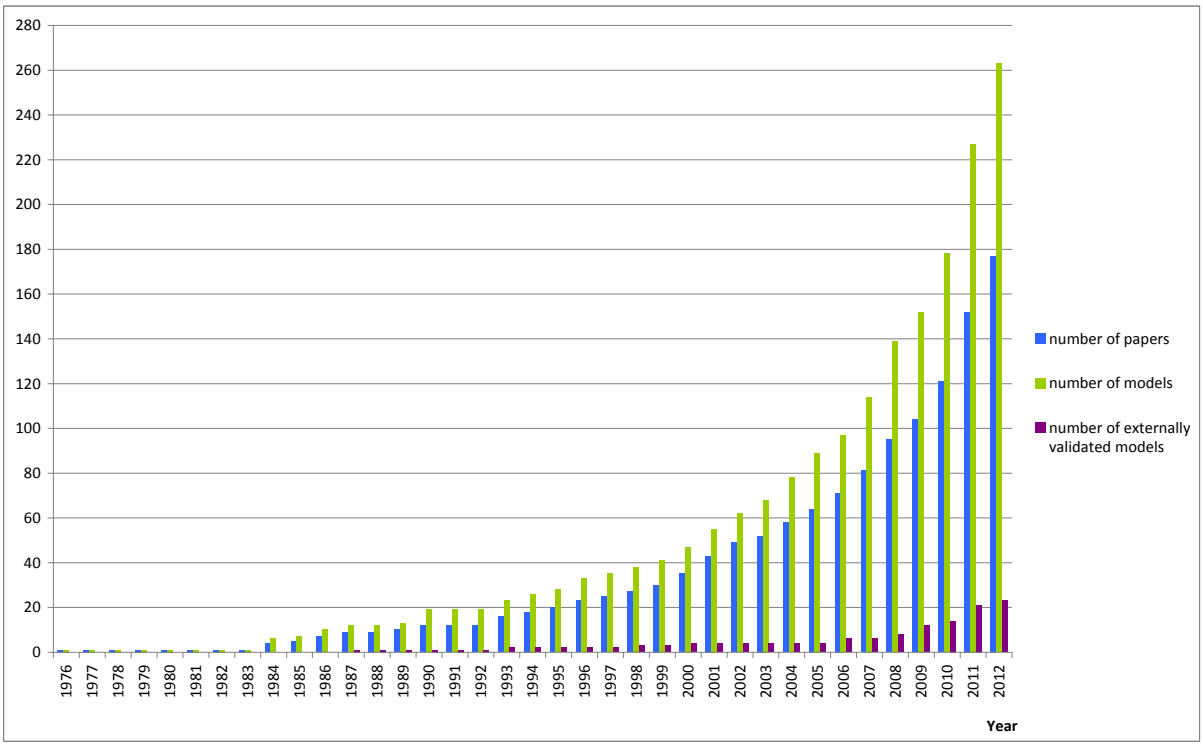
There were 263 models for 40 different outcomes and the years of publication ranged from 1976 to 2012. The number of obstetric prediction models that have been published has increased steadily over the years, particularly over the last decade. (Figure 6.2)

Figure 6.2 Cumulative number of published papers describing prediction models and externally validated models



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Prediction Model Development

The 263 obstetric prediction models were developed to predict 40 different outcomes. These included hypertensive disorders in pregnancy, preterm delivery, gestational diabetes mellitus, fetal growth and birthweight, labour and delivery, breech to cephalic presentation, fetal loss, complications of pregnancy and delivery (placenta praevia, placental abruption, postpartum haemorrhage, shoulder dystocia, birth trauma, anal sphincter injury, thrombosis) and combined adverse maternal outcome. Study characteristics including study design, population, type of model, statistical power, discrimination and calibration of the model, and type of prediction rule are provided in detail in Appendix 16.

The most common conditions or outcomes the models were developed to predict were: pre-eclampsia (69/263, 26%), preterm delivery (63/293, 24%), mode of delivery (22/263, 8%), gestational hypertension (11/263, 4%) and small for gestational age neonate (10/293, 3%). For the remaining 35 outcomes, fifteen outcomes had one published prediction model; fourteen outcomes had two or three prediction models developed, and six outcomes had between four to ten models developed each. (Table 6.1.1)

Internal validation of the prediction model was performed in 57 models (21.7%) and external validation in only 23 models (8.7%). Details of model calibration were presented for 46 models (17.5%) and details of discrimination for 165 models (62.7%). A prediction formula, rule or score that could be used by others was reported for 164 models (62.4%) and guidance for clinical use was discussed for 29 (11.0%).

For the five most prevalent outcomes, detailed characteristics of the developed models are presented in Table 6.1.2. The most common study design was a prospective cohort study (50-70%); a multivariable logistic regression model was used to develop the majority of models (54-69%) and the number of events per variable in the model (an indication of study sample size) was ≥10 for 49-82% of models for the five outcomes.

There were very few models that had been externally validated, with only 7.2% (5/69) for predicting pre-eclampsia and 6.3% (4/63) for predicting preterm delivery and none for the other outcomes. Of those models that presented discrimination values in the development phase, the area under the receiving operator curve (AUC) was high (0.90-1.00) for 25% of the pre-eclampsia prediction models and 24% of the preterm delivery prediction models. At

the external validation phase, the AUC of models ranged between 0.70 to 0.85 for pre-eclampsia prediction models and 0.65 to 0.72 for preterm delivery prediction models. The newer prediction models published more recently did not have better performance than the older models for predicting pre-eclampsia and preterm delivery. None of these models is currently in wide clinical practice.

Discussion

Main findings

The number of prediction models in obstetrics has significantly increased over the past decade. Recognised standards for prognostic research studies are not universally followed in study design, conduct, analysis and reporting in the development of obstetric prediction models. Despite the abundance of published obstetric prediction models, only a handful has been externally validated, and none are in clinical practice.

There are many possible reasons as to why prediction models are not in use. Firstly very few prediction models progress beyond the stage of development and hence the evidence for improvement in clinical outcomes with the use of these models is lacking. Prior to external validation, these models are only specific to the population that they were developed in. External validation is important to verify the robustness and generalizability of the developed model before the model can undergo impact studies to see if they improve clinical outcomes.

The obstetric conditions that have received the most attention in the development of prediction models are pre-eclampsia and preterm delivery. This may well be explained by the high prevalence of these two conditions in the pregnant population and the significant associated burdens each condition carries towards maternal and perinatal morbidity worldwide.

The ability to predict pregnant women most at risk of these conditions enables potential preventative strategies, such as aspirin in pre-eclampsia and elective cerclage or progestogens to prevent preterm delivery; timely intervention to optimise outcomes such as administration of steroids and transfer to an appropriate unit when delivery is anticipated and expediting delivery in pre-eclampsia; and streamlining resources to focus intensive surveillance on the pregnant women most at risk.

Strengths and limitations

This is the first systematic review of prediction models in obstetrics, providing a comprehensive overview of the quality of these models by assessing the development process, validation, reporting and clinical applicability. We used recent recommendations to robustly assess each prediction model.[51] We limited our search to one online database and as such may have missed studies.

Obstetric prediction models in practice

The lack of prediction models in wide clinical practice may be due to multiple reasons. Firstly many of the models were extremely complex and may not be suitable for daily clinical use without computer support as may often be the case in clinical practice.[475] Secondly, external validation of the prediction models is crucial to confirm that the model is clinically applicable and has face validity.[476] Thirdly our review highlighted the poor reporting of prediction models regarding methodology and guidance on clinical applicability.[477-480]

Obstetric prediction models that are based on routinely measured indices are more likely to be incorporated into clinical use, as long as they demonstrate acceptable performance. A few

of the models identified in our review incorporated additional biomarkers and expensive tests[370, 402, 407] which may deter from routine clinical use.

With regard to external validation of the prediction model, this is of crucial importance; prediction models should, ideally, be externally validated by independent investigators and compared to competing models. Surprisingly only 10% of the prediction models that we identified were external validated. For the remaining 90%, nearly half of the studies did not present sufficient data (prediction rule or score) to enable future researchers to perform external validation.

There should be clear recommendations for how the models should be used in practice. Only 10% of the identified models discussed guidance for future use. Also, the sheer number of prediction models on the same outcomes suggests a lack of awareness of other prediction models. Researchers should check if there is an existing prediction model for that specific outcome with acceptable performance.

The quality of reporting on all stages of model development was poor (62%) with a consistent lack of transparency and detail, rendering it difficult for the clinician or researcher to fully appreciate the potential of the model. The advent of the PROGRESS framework that provides a consensus on reporting guidelines hopes to improve the quality and robustness of the underlying methodology in prognostic research. Although methodological quality is of less importance when a model shows good performance at external validation, the likelihood of developing a generalizable model (which is not overfit) is higher when recommended statistical methods have been used.[303]

Prediction model development is costly and can be complex. There is a huge amount of potential in this area but it is still unclear whether the obstetric prediction models identified in this review will be able to impact upon clinical practice and improve patient outcomes.

Researchers with an interest in this area, should appreciate that developing the prediction model is only one of the steps. External validation, transparent reporting, clear guidance on the use of the model in practice, comparing the model to existing models and assessing the impact of the prediction model on health outcomes are crucial steps that need to be taken.

Accurate prognostication and timely intervention have great potential to improve patient outcomes. We have identified pitfalls through this systematic review and hope that future obstetric prediction models may focus more on building on the previous efforts, collaboration with other research groups, without ignoring the next important steps of validity assessment and clinical impact.

My contribution to this work:

Study selection in stages 1 and 2, data extraction as second reviewer, analysis, first draft of the manuscript and all revisions.

CHAPTER 6.2: AN OVERVIEW OF CHALLENGES IN DEVELOPING OBSTETRIC PROGNOSTIC MODELS IN PRE-ECLAMPSIA AND POTENTIAL SOLUTIONS

Abstract

Objective: Prognostic models in obstetrics are often developed from large observational studies. The precision in selecting the 'best' predictors for a prognostic model is affected by many factors, in particular by a phenomenon called 'treatment paradox'. The aim of this review is to provide an overview of prognostic modelling challenges in obstetrics with potential solutions.

Methods: Using an example of developing a prognostic model for predicting complications of early-onset pre-eclampsia (PREP), a symposium was convened of experts in prognosis medicine and obstetrics to discuss and propose potential solutions for treatment paradox and other prognostic modelling challenges.

Results: For treatment paradox, seven potential solutions are proposed: standardisation of treatment, removal of factors that influence treatment decisions, inclusion of interaction between 'decision to treat' as a predictor, use of treatment as a modifying factor, treatment becoming an outcome, use of a propensity score and inverse probability weighting.

Conclusion: Prognostic models have the potential to be powerful tools but much caution is needed in each part of the development process.

Citation from work:

Cheong-See F, Allotey J, Marlin N, Mol BW, Schuit E, Ter Riet G, Riley RD, Moons K, Khan KS, Thangaratinam S. (2016) Prediction models in obstetrics: understanding the

treatment paradox and potential solutions to the threat it poses. BJOG 2016,doi 10.1111/1471-0528.13859.

Background

Prognostication in obstetrics can be complex with both maternal and fetal outcomes to consider. From the first encounter taking the booking history from the pregnant woman, we predict the probability of a pregnancy being low or high-risk and dictate the level of antenatal surveillance and need for further tests or intervention. For example, we use prognostic research to predict the probability of developing maternal conditions such as gestational diabetes mellitus, the probability of developing adverse maternal and fetal outcomes in such conditions and to provide estimates of long-term outcomes in the baby according to the timing of delivery.

In many obstetric situations, the prognostic factors undergo changes due to the advancing pregnancy or as a result of an intervention that cannot be ethically withheld. An effective treatment may prevent a certain proportion of adverse outcomes from occurring, making a good prognostic factor and factors associated with it (that triggered the treatment in the first place) look poorer in their predictive performance, a phenomenon that can be described as 'treatment paradox'.[53, 481] These pose significant challenges in the development of prediction models in pregnancy-specific conditions such as pre-eclampsia.

Prediction of complications in women with pre-eclampsia:

Numerous models for prediction of pre-eclampsia have been developed, but very few for prediction of complications.[57] Early-onset pre-eclampsia is a pregnancy-specific condition characterised by hypertension and proteinuria before 34 weeks of gestation. Currently, the only cure for pre-eclampsia is delivery. In women with early onset pre-eclampsia, the mainstay of management is to make the best balance between preventing maternal

complications by expediting delivery compared to increasing the risk of neonatal complications from early delivery. An accurate prediction model will help identify women and babies most at risk of adverse outcomes to guide clinical treatment decisions and outcomes.

PREP study: an example

PREP is an ongoing study, funded by National Institute of Health Research, Health Technology Assessment (NIHR HTA) for the development and validation of a prediction model in women admitted with early onset pre-eclampsia (PREP).[482] The primary objectives are twofold: firstly to develop and internally validate a prediction model to assess the risk of any adverse maternal outcome at 48 hours and at any time until discharge, and secondly to externally validate the model through two external datasets of patients diagnosed with early onset pre-eclampsia. The secondary objective is to assess the risk of adverse fetal and neonatal outcomes at birth and at any time until discharge and to summarise the unadjusted and adjusted prognostic ability of a set of candidate predictor variables.

The candidate predictor variables consist of patient symptoms, signs and investigations performed in clinical practice and pre-selected based on previous research and expert consensuss.[57, 84, 86-88, 184] These include symptoms of a headache, epigastric pain, chest pain, vomiting, visual disturbance; signs such as hyperreflexia, papilloedema; history of pre-existing medical conditions; maternal age; and results from investigations such as uterine artery Doppler flow, umbilical artery Doppler flow, cardiotocography, estimated fetal weight by ultrasound, blood pressure, serum uric acid, level of proteinuria, liver function tests, renal function tests, pulse oximetry, and the gestational age at which early onset pre-eclampsia was diagnosed.

The maternal outcomes include mortality, Glasgow Coma Scale <13, eclampsia, stroke, cortical blindness, posterior reversible encephalopathy syndrome, reversible ischaemic neurological deficit (RIND), retinal detachment, need for positive inotropic support, myocardial infarction, acute renal impairment, need for renal dialysis, hepatic dysfunction, hepatic haematoma or rupture, platelet count <50,000 without blood transfusion, need for transfusion of blood products, need for >50% oxygen for more than one hour or intubation and pulmonary oedema.

The study is designed to examine ten candidate predictor variables for inclusion into the prediction model. We convened a meeting of experts in the field of prognosis and obstetricians to deal with the unique challenges in the development of the model.

Currently, in clinical practice, interventions such as anti-hypertensives are usually given based on blood pressure readings that are also evaluated as a predictor in the model performance. If the predictor (blood pressure) is accurate in prediction of high(er) risk, this will lead to underestimation of how informative this particular (and correlated) prognostic indicators will be, as the intervention it triggers leads to non-occurrence of the outcome in some patients. This weakens the predictor-outcome association and natural outcome (prevalence). This is often the case when the decision to treat, is based on the levels of one or more (candidate) prognostic factors that are also being considered for the prediction model.

Interventions that contribute to treatment paradox in pre-eclampsia prediction modelling

Women with a diagnosis of pre-eclampsia have varied management depending on the clinical findings. Mothers with mild disease routinely do not receive any treatment. Interventions such as oral antihypertensives are given for moderate hypertension and women with severe

hypertension receive parenteral antihypertensives and magnesium sulphate anticonvulsant to prevent or to treat eclampsia. Delivery is often expedited at a preterm gestation in the latter group.[38]

Solutions for treatment paradox

The PREP prognostic group discussed in detail the various options to overcome the bias in the estimates of the prediction model for complications in pre-eclampsia due to treatment paradox.

Standardisation of treatment

By ensuring that the predictor in question is collinear with treatment and this is standardised across all patients, either the test or treatment can be chosen as a predictor. By incorporating treatment into the care plan, this renders the study similar to that of an observational effectiveness study where we are not interested in the treatment effect parameter but the linear predictor.

For example, the prediction model developed to predict postoperative nausea and vomiting has included the intervention into the prediction model.[483] In the PREP study, although the commencement of antihypertensives and magnesium sulphate anti-convulsant are standardised by NICE guidelines in the UK, the decision to deliver an early preterm baby is influenced primarily by the clinician. This phenomenon, therefore, limits the applicability of this model.

Remove all factors that influence treatment decisions

The bias due to treatment effect can be minimised by removing all the prognostic factors on which the decision to intervene is based, and substitute these for an alternative prognostic factor. This may be possible in certain settings, for example, Cukjati et al. substituted wound, patient and treatment attributes by weekly follow-ups of the wound healing process to predict wound healing rate.[484] However, in women with pre-eclampsia, this poses a problem, as clinicians rely on more that one predictor such as blood pressure, symptoms, haematological and biochemical indices to decide on treatment. Removal of these will severely restrict our ability to include any meaningful predictors in the model. This means that at the baseline, we cannot predict anything. There are also too many factors associated with the decision to treat to identify a single alternative prognostic factor.

Include interaction between decision to treat factors as a predictor

The decision to treat can, by itself, be considered a prognostic factor itself. The variable 'decision to treat' is not an independent prognostic factor, but is often based on a combination of one, or more of the other prognostic factors, and carries a risk of false treatment effect. By accounting for the interaction between 'decision to treat' as a predictor and each of the other prognostic factors, these biases can be overcome. When more interactions are involved, the more complex this approach becomes, and a larger sample size is needed.

Use treatment as a modifying factor for the prognostic factor

If the treatment is specific for one prognostic factor, e.g., high blood pressure and administration of antihypertensive medication, we can combine the two as a single prognostic factor. There needs to be standardised care, however with no variation in the treatment, i.e., the same antihypertensive medication and the same threshold before treatment is given.

Treatment becomes an outcome

If treatment may likely have led to avoidance of an outcome, those who received treatment can be regarded as having had an outcome. In this situation, we decided to include decision for delivery prior to 34 weeks as an outcome.

For example, in a prediction model to predict the risk of exacerbations in chronic obstructive pulmonary disease, the focus was not on mortality as an outcome but instead need for hospitalisation and 'treatment, ' i.e., symptomatic deterioration requiring pulsed oral steroid use.[485]

Propensity score

The propensity score is the probability of treatment being assigned to an individual based on observed pre-treatment variables.[485] We can designate propensity scores to each individual in the study taking into account the interactions with other prognostic factors (on which the decision to treat was based):

P (probability of receiving treatment) = $\alpha + \beta a X_1 BP + \beta b X_2 proteinuria + ...$

= Propensity Score

This can be fitted into the prediction model by logistic regression:

$$\ln (p/1-p) = \alpha + \beta_1 BP + \beta_2 proteinuria + \beta_3 Propensity\ Score + \beta_4 treatment$$

This prediction model will not, however, be clinically helpful as the decision to treat was not based on prior knowledge of the propensity score.

Inverse Probability Weighting

We can use the propensity scoring and take it one step further with inverse probability weighting. By taking into account each patient's propensity score, we can assign a different weight for the contribution of that particular patient towards the logistic model analysis and development of the prognostic model. Patients who received little or no treatment (and hence less treatment effect) should carry more weighting compared to the patients who had a high probability of being treated. An example of the use of this method was in determining the effectiveness of potent antiretroviral therapy (HAART) in preventing AIDS and death.[486] Sterne et al. used weighted Cox proportional hazards models to create a statistical population in which the probability of being treated was unrelated to prognostic factors (i.e., the placebo) compared to the population who received HAART.

Clinical interpretation of prediction models in women with pre-eclampsia

There is currently an internally validated prediction model for adverse maternal outcomes in pre-eclampsia known as PIERS (Pre-eclampsia Integrated Estimate of Risk).[57] The model uses six prognostic indicators: gestational age at diagnosis, maternal symptoms of chest pain or dyspnoea, oxygen saturation on air, platelet count, serum creatinine level and aspartate transaminase level. Although it is well known that severe high blood pressure is associated with adverse maternal outcomes, this was surprisingly not found to be a predictor in the

PIERS final model. This may be due to dilution of the predictive accuracy by treatment paradox. Those with higher blood pressure are given treatment X, and this causes a reduction in outcome risk: thus there may be little or no observed association between blood pressure and outcome, but only as treatment has removed this association. The issue is that if a prediction model that did not include blood pressure was used to decide treatment decisions, it might overlook patients with high blood pressure.

The consensus views were limited to the specific topic of prognostic modeling for complications in pre-eclampsia. Although many of these proposed solutions to overcome treatment paradox were unsuitable for the PREP model, they have been used in other prediction models as mentioned and may be useful in the design of other clinical prediction models.

There are however many clinical conditions similar to pre-eclampsia, with the same difficulty of a multiplicity of different managements and the different timings of those managements, combined with the fact that management choice is not independent of the other predictors in the model. It is therefore very difficult to control for this treatment paradox.

Another option to consider is to incorporate the clinician's decision-making process into the prognostic modeling, by prospectively gathering data when a management decision is made about the specific predictors that resulted in the clinician's decision to 'treat. This can give us a better understanding and insight into which variables are less informative as predictors, given that they were already used to avert the outcome.

Conclusion

Obstetric prognostic research modelling faces many challenges. Any models developed in the circumstances outlined above would offer rules that might benefit from assessment of their impact in future research.

PREP Prognostic Meeting Expert Panel

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Project/Obstetric Lead, WHRU QMUL; Richard Riley, Reader in Biostatistics, PREP Study Senior Statistician, Birmingham

My contribution to the work

Invited the experts and convened the meeting, set the discussion points to address with the panel. Wrote the initial draft and all revisions with input from all panel members.

CHAPTER 7: CONCLUSION

Summary of findings

This chapter provides an overview of the results of the individual chapters. Detailed results are included in the individual chapters. I have addressed the objectives pre-specified in my thesis. In collaboration with my co-reviewers listed in Chapter 4, we have quantified the strength of association of genetic and clinical predictors of complications in pre-eclampsia; we have estimated the level of increasing fetal and neonatal risks with advancing gestation in mothers with multiple pregnancy (uncomplicated monochorionic and dichorionic twin pregnancies). We have identified the components of maternal and fetal composite outcomes for reporting in primary studies on pre-eclampsia management and we have provided an overview of methodological deficiencies in prognostic research in obstetrics, and explored methods to address the challenges.

The table below summarises the objectives of my thesis and a column of findings from the chapters of this thesis.

Chapter Number	Population	Intervention or Test	Outcome(s)	Research Design	Results
Objective A: In women with pre-eclampsia: - *What maternal genetic factors predispose women with pre-eclampsia to complications in pregnancy?* - *How accurate are the routinely performed tests in women with pre-eclampsia to predict maternal and fetal complications?* - *What outcomes are clinically relevant for evaluation in clinical trials on late onset pre-eclampsia?*					
4	Women with pre-eclampsia	Maternal genotype	Adverse maternal and neonatal outcomes	HuGENet systematic review of observational studies and meta-analysis	I found an increased risk of severe pre-eclampsia with thrombophilic genes (F5 rs6025 and MTHFR rs1801133). Individual genotypes showed positive associations with severe pre-eclampsia for F5 (rs6025) (OR 1.90, 95% CI 1.42, 2.54), F2 mutation G20210A (rs1799963) (OR 2.01, 95% CI 1.14, 3.55) and

					leptin receptor (LEPR) polymorphism (rs1137100) (OR 1.87, 95% CI 1.43, 2.45).
4	Women with pre-eclampsia	Tests including clinical history, examination and investigations	Adverse maternal and neonatal outcomes	Systematic review	Urine protein creatinine ratio is sensitive for many maternal and fetal outcomes (eclampsia. 81%, 95% CI 52-95%; placental abruption 81%, 95% CI 64-91%; caesarean delivery 97%, 95% CI 26-100% and pulmonary oedema 85%, 95% CI 71-93%). No single test showed high sensitivity and specificity.
3	Women with late-onset pre-eclampsia	Pregnancy complications	Composite maternal and neonatal adverse outcomes	Delphi survey	The final maternal composite outcome included maternal death, eclampsia, stroke, reversible ischaemic neurological deficit, pulmonary oedema, major obstetric haemorrhage or need for positive inotropic support, HELLP syndrome and placental abruption. The final neonatal composite outcomes included neonatal death, respiratory distress syndrome needing ventilator support and neurological outcomes such as cystic periventricular leukomalacia and grade III/IV intraventricular haemorrhage.
Objective B: In women with multiple pregnancy - *What are the prospective risks of stillbirth, neonatal morbidity and mortality associated with delivery at different gestational ages in monochorionic and dichorionic twin pregnancies?* - *What is the optimal timing of delivery with the lowest stillbirth risk and serious neonatal adverse outcomes in uncomplicated monochorionic and dichorionic twin pregnancies?*					
5	Women with uncomplicated twin pregnancies	Monochorionicity or dichorionicity	Risk of stillbirth, neonatal morbidity and mortality	Systematic review	In dichorionic twin pregnancies, the delay in delivery by a week (until 38 weeks) led to an additional 8.8 perinatal deaths per 1000 pregnancies (95% CI 3.6 to 14.0 /1000) compared to the previous week. In monochorionic pregnancies, there was a trend towards increase in stillbirths compared

					with neonatal deaths after 36 weeks, with an additional 2.5 per 1000 perinatal deaths, which was not significant (95% CI -12.4 to 17.4/1000,).
Objective C: In the field of prognostic research in obstetrics - *What is the quality of published obstetric prognostic models and what is their clinical usefulness?* - *What are the methodological challenges of developing and applying an obstetric prognostic model and how can they be overcome?*					
3	Pregnant women	Prognostic models	Quality and clinical applicability of models	Systematic review	177 studies reported the development of 263 prediction models for 40 different outcomes. Internal and external validation was reported for 21.7% and 8.7% of the prediction models. The assessment of discrimination and calibration was carried out for 62.7% and 17.5% of the models respectively. The clinical applicability of the model was discussed in 11%.
3	Women with early-onset pre-eclampsia	Risk factors for complications	Prognostic model	Consensus	Methods to minimise bias from treatment paradox where it is not possible or unethical to withhold treatment include, standardisation of treatment, predictor substitution, treatment as a predictor, treatment as an outcome and use of propensity scores.

Predictors for adverse outcomes in pre-eclampsia

In pre-eclampsia, my systematic review showed that maternal thrombophilic genes are associated with an increased risk of severe pre-eclampsia. The review of accuracy of tests to predict complications in pre-eclampsia demonstrated that no single test is adequately sensitive or specific enough to predict pre-eclampsia complications. Urine PCR, uric acid, mean arterial pressure >105mmHg and symptoms of headache were highly sensitive in predicting eclampsia. The sensitivity was high for urine PCR in predicting Caesarean

delivery. The specificities were highest for blood pressure greater than 160/110mmHg in predicting eclampsia, placental abruption, pulmonary oedema, Caesarean delivery and hepatic dysfunction. Symptoms of nausea, abdominal pain and visual disturbances were highly specific in predicting eclampsia. For fetal outcomes, urine PCR was highly sensitive in predicting small for gestational age fetus and fetal death. I identified and prioritised the complications associated with pre-eclampsia that are considered to be useful outcomes to address in trials involving women with late onset pre-eclampsia and developed composite maternal and neonatal outcomes for this purpose. The composite outcomes consisted of maternal death, eclampsia, placental abruption, major obstetric haemorrhage, pulmonary oedema, need for positive ionotropic support, stroke, reversible ischaemic neurological deficit (RIND) or HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome for the maternal components; neonatal death, respiratory distress syndrome (RDS) needing ventilation, grade III/IV intraventricular haemorrhage or cystic periventricular leukomalacia for the neonatal components.

Risks of stillbirth and neonatal deaths in women with multiple pregnancy

I undertook the largest systematic review to-date on the prospective risks of stillbirth, neonatal morbidity and mortality by gestational week of delivery in uncomplicated monochorionic and dichorionic twin pregnancies. The risks of stillbirth significantly outweighed the risk of neonatal death by 38 weeks in dichorionic pregnancies. My work also provided estimates of neonatal morbidity and mortality before 37 weeks gestation to inform mothers expecting or experienced early preterm birth involving twin pregnancies.

Prognostic research in obstetrics

My work assessed the the quality of reporting in published obstetric prognostic models. The systematic review assessed characteristics in model development and validation and found areas of methodological deficiency. There was little guidance on their clinical applicability.

The methodological challenge of dealing with treatment paradox in the context developing and applying a prognostic model in early onset pre-eclampsia was addressed and solutions proposed through expert consensus.

Strengths and limitations

The questions set in this thesis were addressed through systematic reviews, Delphi survey and expert consensus. For the systematic reviews, these were performed with robust methodology as appropriate. For the systematic review of maternal genotype and severe pre-eclampsia, I adhered to the HuGENet systematic review criteria specific to genetic association studies. The reviews were prospectively registered, sensitivity analyses were planned a priori and extensive literature searches were done in the relevant databases without language restrictions to avoid missing studies. Study selection, data extraction and study quality assessments were all done in duplicate to minimise bias. Meta-analyses was performed where appropriate, assessing for heterogeneity.

For the systematic review of prospective risk of stillbirth, we took a new statistical approach to consider delivery as a competing event to avoid the methodological inaccuracies of

overestimating risk as done in previously published papers on this subject. Publication bias was assessed and explanations sought.

Limitations were based mainly on heterogeneity of data. For the HuGENet review, there was inconsistent and poor reporting of genotyping methods, success rates, blinding of staff, any deviation from the Hardy Weinberg equilibrium and unclear exclusion criteria for adequate quality assessment. Furthermore there was a lack of consistency in definition of the phenotype of pre-eclampsia and severe pre-eclampsia.

There was also paucity in reported data for the studies assessing accuracy of tests to predict pre-eclampsia complications, studies varied in the description of populations, tests, thresholds and outcomes. This heterogeneity rendered it difficult to combine all relevant data and therefore meta-analysis was not possible.

Implications for clinical practice

There is sufficient evidence now to justify incorporating genetic data into clinical algorithms for risk assessment for pre-eclampsia and evaluation of this approach in clinical trials to improve accuracy of screening programmes. Clinicians should be aware that the individual test performances are very limited for accurately predicting adverse maternal and fetal outcomes in pre-eclampsia. Elevated PCR was sensitive for predicting small for gestational age and fetal death. Women with uncomplicated dichorionic pregnancies should be offered delivery by 37 weeks, and delivery considered for monochorionic pregnancies by 36 weeks to prevent stillbirth.

Clinicians should be aware of the limitations in published prognostic models. External validation of models is required before they could be introduced to clinical practice. There should be clear recommendations for how prognostic models should be used in practice. Only 10% of the identified models from the systematic review of obstetric prognostic models discussed guidance for future use. Also, the sheer number of prognostic models on the same outcomes suggests a lack of awareness of other prognostic models. Researchers should check if there is an existing prognostic model for that specific outcome with acceptable performance.

Implications for research

The identification of further genetic risk factors for complications of pre-eclampsia is an important research objective, which may lead to early identification and targeted management of high-risk pregnancies. Future work is needed to evaluate the potential benefits of integrating genetic data with clinical information to develop more accurate predictive algorithms. Future randomised controlled trials on women with mild or moderate pre-eclampsia, especially at late preterm gestations, should consider the maternal and neonatal composite outcomes we developed and their components to assess the effect of intervention. Additional input from the patient and public is needed in the development of composite outcomes.

The feasibility of a definitive randomised trial on optimal timing of delivery in twin pregnancies is limited, given the huge numbers needed to assess outcomes. Individual patient data (IPD) meta-analysis will allow us to assess the effect of factors such as monitoring of the fetuses, level of newborn care, and mode of delivery on outcomes. There is a need to study

the effects of delivery before 37 weeks and the loss of a co-twin in monochorionic pregnancies on long-term infant neurodevelopment.

Researchers with an interest in prognostic research in the field of obstetrics should appreciate that developing the prediction model is only one of the steps. External validation, transparent reporting, clear guidance on use of the model in practice, comparing the model to existing models and assessing the impact of the prediction model on health outcomes are crucial steps that need to be taken.

TABLES

Table 4.1.1 Genotype by function or system involved of the studies included in the meta-analysis of relationships between maternal genotype and severe pre-eclampsia

Function/system involved	Gene	Genotype	rs number
Immune related	CD28	(+17TC)	rs3116496
	Cytotoxic T lymphocyte antigen 4 (CTLA-4)	(+49AG)	rs231775
	Inducible costimulator (ICOS)	(-1564TC)	rs4675378
		Intron+1	
	Interferon gamma (IFNγ)	874A/T	rs2430561
	Interleukin 10 (IL-10)	592C/A;	rs1800872
		819C/T;	rs1800871
		1082A/G	rs1800896
	Interleukin 6 (IL-6)	174G/C	rs1800795
	Intracellular Adhesion Molecule-1 (ICAM-1)	K469E	rs5498
	Killer immunoglobulin like receptor	A52G	unknown
	(KIR3DL2)	C32T	unknown
	Mannose Binding Lectin (MBL2)	Codon 54	rs1800450
	Transforming growth factor β1 (TGFβ1)	Codon 10	rs1982073
		+869T/C	
		Codon 25	rs1800471
		+915G/C	
	Tumour necrosis factor α	G308A	rs1800629
		C850T	rs1799895
Vasoactive genes	Aldosterone synthase gene	C344T	rs1799998
	Angiotensin converting enzyme (ACE)	DD	rs4646994
	Angiotensinogen gene	M253T	rs699
	Angiopoietin 1 (ANGPT1)	TT	rs2507800
	Angiotension II receptor type 1 (AGTR1	A116C	rs5186
Thrombotic	Factor V Leiden	G1691A; +/-	rs6025
	Methylenetetrahydrofolate (MTHFR)	C677T	rs1801133
	Prothrombin	G20210A	rs1799963
Cell signalling pathways	CX3CR1 (CX3 chemokine receptor 1)	T280M	rs3732378
		V249I	rs3732379
	E-selectin	Ser128Arg	unknown
	Guanine nucleotide binding protein (GNB3)	C825T	rs4606
	NADPH*/NADH oxidase† gene	C242T	unknown
	P-Selectin	Thr715Pro	unknown
	Regulator of G-protein signalling 2 (RGS2)	C1114G	rs5443
Metabolic processes	Adiponectin	276G/T	rs1501299
		45T/G	rs2241766
	Apolipoprotein E	E2E3; E2E4	unknown
	Catechol-O-methyltransferase (COMT)	Val158Met	rs4680
	Cytochrome P450c17α (CYP 17A1)	C785T	unknown
	Deiodinase D1	Asp727Glu	unknown
	Leptin	TTTCn	(TTTC)
	Leptin Receptor	c.1968G/C,	rs8179183
		A223G/R223Q	rs1137101
		c.3024A/G	rs6413506
		(S1008);	
		c.326A/G	rs1137100
		(K109);	
		G1019A;	unknown
		PPAR γ2	rs1801282
Other	Dopamine B hydroxylase (DBH)	589G/A	rs5320
	Epithelial sodium channel β subunit	T594	unknown
	Estrogen Receptor α (ESR1)	PvuII	rs2234693
		Xbal	rs9340799
	Fas	TNFRSF6 A/G	unknown
	Superoxide dismutase (SOD3)	G172A	rs1799895

Table 4.1.2 Subgroup analysis for F5 (Factor V Leiden) rs6025

Subgroup analysis	Detail	Cases	Controls	Odds Ratio (95% CI)	p-value (subgroup differences)
Study design	Case-control (19)	1458	3503	2.04 (1.45, 2.86, 34%)	0.40
	Cohort (4)	366	598	1.56 (0.92, 2.64, 2%)	
Ethnicity	Caucasian (15)	1186	2740	1.91 (1.34, 2.73, 17%)	0.87
	Other/mixed (8)	638	1361	1.81 (1.07, 3.08, 51%)	
Sample size	<100 cases (19)	1213	2452	1.97 (1.35, 2.85, 40%)	0.70
	>100 cases (4)	605	1434	1.75 (1.11, 2.75, 0%)	

Table 4.1.3 Subgroup analysis for F2 (Factor 2 Prothrombin G20210A) rs1799963

Subgroup analysis	Detail (no of studies)	Cases	Controls	Odds Ratio (95% CI, heterogeneity)	p-value (subgroup differences)
Study design	Case-control (8)	459	1431	2.18 (1.22, 3.91, 0%)	0.24
	Cohort (1)	50	50	0.49 (0.04, 5.58, 0%)	
Ethnicity	Caucasian (5)	292	1058	2.77 (1.36, 5.65, 2%)	0.13
	Other/mixed (4)	217	423	1.09 (0.42, 2.86, 0%)	
Sample size	<100 cases (9)	509	1481	2.01 (1.14, 3.55, 0%)	N/A

Table 4.1.4 Epidemiologic credibility based on Venice criteria

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Criteria	Amount of evidence	Replication	Protection from bias	Credibility of cumulative epidemiological evidence
F5 rs6025	A	B	C	Weak evidence
F2 rs1799963	B	A	C	Weak evidence
LEPR rs1137100	B	C	C	Weak evidence

Table 4.3.1 Criteria for developing maternal composite outcome

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Outcome	Rate	Biological plausibility	Clinically important	Equal importance to other components	Independent of each other	Affected to a similar degree by intervention and same direction of effect
Maternal death *Maternal death occurring within six weeks of pregnancy or if later, attributable to complications of pre-eclampsia*	0-0.01%	Pre-eclampsia is one of the major contributors to maternal death from organ dysfunction	Yes	No	No	Yes
Neurological						
Eclampsia *Occurrence of a seizure in association with pre-eclampsia*	0.5-1.8%	Cerebral vasospasm and vasoconstriction associated with increased blood pressure, cerebral oedema or infarction	Yes	Yes	Yes	Yes
Respiratory						
Pulmonary oedema	0.5-1.9%	Endothelial dysfunction in severe pre-eclampsia leads to leaky capillaries resulting in pulmonary oedema with increased the risk of maternal mortality	Yes	Yes	Yes	Yes
Haematological						
Major obstetric haemorrhage with need for transfusion of blood products	2-3.1%	Pre-eclampsia is a risk factor for major obstetric haemorrhage, mainly postpartum haemorrhage from consumptive coagulopthy and endothelial dysfunction	Yes	Yes	Yes	Yes
Cardiovascular						

Cardiac morbidity - infusion of 3rd anti-hypertensive or positive ionotropic support	0.1-0.5%	Severe hypertension due to vasoconstriction may be difficult to control with parenteral anti hypertensives. Cardiac failure in severe pre-eclampsia necessitates ionotropic support	Yes	Yes	Yes	Yes
Other						
HELLP syndrome	1-2%	Microangiopathic haemolysis and platelet consumption, and hepatocellular damage from periportal or focal parenchymal necrosis result in HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) Associated with major maternal morbidity in worsening pre-eclampsia	Yes	Yes	Yes	Yes
Placental abruption	1.5-2.3%	Inadequate placentation due to absence of spiral artery remodelling leads to abruption placentae resulting in increased maternal morbidity	Yes	No	Yes	Yes

Table 4.3.2 Criteria for developing neonatal composite outcome

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Outcome	Rate	Biological plausibility	Clinically important	Equal importance to other components	Independent of each other	Affected to a similar degree by intervention and same direction of effect
Neonatal death	0.7%	Late preterm newborns are at higher risk of mortality during the neonatal period and later	Yes	No	No	Yes
Respiratory						
Respiratory distress syndrome (RDS) needing ventilator support	5.3-6.4%	Delayed lung fluid clearance and relative deficiency of surfactant can result in increased incidence of RDS.	Yes	Yes	Yes	Yes
Neurological						
Cystic periventricular leukomalacia (PVL) or intraventricular haemorrhage	0.5%	Prematurity is a risk factor for brain injury as the last part of fetal development is an intensive period for cerebral growth and development. PVL and IVH can be associated with neurodevelopmental disability.	Yes	Yes	Yes	Yes

Table 5.1 Prospective risk of stillbirth and neonatal death risk in weekly intervals in uncomplicated dichorionic and monochorionic twin pregnancies from 34 weeks' gestation

Gestational age (weeks)	No. of stillbirths /No. of ongoing pregnancies	Crude stillbirth risk (x1,000) (95% CI)	No. of neonatal deaths /No. of women delivered	Neonatal death risk[a] (x1,000) (95% CI)	Pooled Risk Difference[b] (x1,000) (95% CI)
Dichorionic twin pregnancies (15 studies)					
34^{+0-6}	21/17,830	1.2 (0.7, 1.8)	12/1,742	6.7 (3.3, 13.5)	-5.8 (-10.4, -1.2)
35^{+0-6}	12/15,470	0.8 (0.4, 1.4)	15/2,611	4.6 (2.4, 8.7)	-5.1 (-8.7, -1.6)
36^{+0-6}	18/11,824	1.5 (0.9, 2.4)	12/4,238	3.2 (1.7, 5.9)	-1.3 (-3.6, 0.9)
37^{+0-6}	23/6,824	3.4 (2.1, 5.1)	10/5,141	2.2 (1.1, 4.3)	1.2 (-1.3, 3.6)
38^{+0-6}	28/2,633	10.6 (7.1, 15.3)	5/2,581	1.5 (0.7, 3.3)	8.8 (3.6, 14.0)
39^{+0-6}	7/752	9.3 (3.8, 19.1)	3/751	1.1 (0.4, 2.6)	3.8 (-8.5, 16.1)
Monochorionic twin pregnancies (13 studies)					
34^{+0-6}	2/2,149	0.9 (0.1, 3.4)	4/247	12.1 (4.2, 34.3)	-15.6 (-40.4, 9.1)
35^{+0-6}	5/1,797	2.8 (0.9, 6.5)	2/367	8.1 (3.4, 19.3)	-2.4 (-17.6, 12.8)
36^{+0-6}	6/1,325	4.5 (1.7, 9.8)	3/534	5.4 (2.2, 13.3)	-1.5 (-14.4, 11.4)
37^{+0-6}	7/730	9.6 (3.9, 19.7)	4/532	3.6 (1.2, 11.1)	2.5 (-12.4, 17.4)
38^{+0-6}	2/264	7.6 (0.9, 27.1)	0/307	2.4 (0.6, 10.3)	7.0 (-19.7, 33.7)

[a] Risk of neonatal death was computed by multilevel logistic regression model (see text).

[b] Individual studies risk differences were pooled by a fixed-effect model meta-analysis (see text).

Table 5.2 Individual neonatal morbidity outcomes in monochorionic and dichorionic twin pregnancies after 34 weeks gestation

Gestational age	Assisted ventilation		Hypoxic Ischaemic Encephalopathy or neonatal seizures		Respiratory distress syndrome (RDS)		Septicaemia		NICU admission	
	n/N	Risk (95% CI)	n/N	Risk (95% CI)	n/N	Risk (95% CI)	n/N	Risk (95% CI)	n/N	Risk (95% CI)
Monochorionic		7 studies		3 studies		10 studies		11 studies		9 studies
34^{+0}-34^{+6}	23/143	112.9 (49.2-238.3)	0/101	N/A	38/178	176.7 (105.2-281.5)	9/196	54.3 (23.9-118.8)	61/157	501.6 (306.1-696.6)
35^{+0}-35^{+6}	17/206	61.3 (26.9-133.3)	0/144	N/A	22/261	74.2 (43.6-123.7)	7/283	24.4 (11.7-50.5)	61/229	316.8 (173.2-506.6)
36^{+0}-36^{+6}	14/289	32.4 (13.7-74.3)	1/238	N/A	13/365	29.1 (15.9-52.5)	3/406	10.8 (4.6-24.9)	44/319	176.1 (88.0-321.4)
37^{+0}-37^{+6}	7/308	16.9 (6.6-42.5)	0/242	N/A	9/424	11.1 (5.3-22.8)	3/452	4.7 (1.6-14.1)	34/345	89.7 (41.3-183.9)
38^{+0}-38^{+6}	2/163	8.7 (3.0-25.0)	0/137	N/A	0/225	4.2 (1.7-10.2)	0/237	2.1 (0.5-8.5)	5/168	43.4 (18.4-99.3)
Dichorionic		9 studies		2 studies		13 studies		11 studies		11 studies
34^{+0}-34^{+6}	75/372	97.3 (36.4-235.4)	1/190	3.6 (0.7-19.7)	94/490	130.1 (77.8-209.6)	11/465	9.5 (2.4-36.1)	181/401	492.6 (317.4-669.6)
35^{+0}-35^{+6}	72/518	56.8 (20.9-145.6)	1/304	2.8 (0.9-9.2)	63/695	69.3 (40.9-114.9)	6/659	6.4 (1.7-23.5)	179/577	315.4 (182.3-487.8)
36^{+0}-36^{+6}	69/779	32.6 (11.8-86.9)	1/530	2.2 (0.9-5.3)	49/1013	35.7 (20.8-60.8)	10/943	4.3 (1.2-15.7)	152/853	179.5 (95.9-310.9)
37^{+0}-37^{+6}	41/1146	18.5 (6.5-51.0)	1/820	1.7 (0.6-4.8)	46/1563	18.1 (10.2-31.8)	8/1447	2.9 (0.8-10.9)	154/1296	94.1 (47.7-177.2)
38^{+0}-38^{+6}	21/834	10.4 (3.6-29.7)	0/601	1.3 (0.3-5.9)	17/1120	9.1 (4.9-16.7)	7/1081	2.0 (0.5-7.8)	77/932	47.0 (22.9-94.0)
39^{+0}-39^{+6}	2/103	5.8 (2.0-17.3)	1/63	1.1 (0.1-8.2)	1/258	4.5 (2.3-8.8)	1/235	1.3 (0.3-5.8)	5/134	22.9 (10.8-47.9)

Risks are per thousand deliveries.
n = number of adverse outcomes
N = number of women delivered in that 1 weekly gestational epoch

Table 6.1.1 Overview of obstetric prediction models

Outcome	Number of models	Internal validation	External validation	Calibration	Discrimination	Prediction rule	Decision recommended
Total	**262**	**57 (21.8%)**	**23 (8.8%)**	**46 (17.6%)**	**165 (63.0%)**	**164 (62.6%)**	**29 (11.1%)**
Pre-eclampsia	69	14	5	8	60	45	9
Eclampsia	1	1	0	0	1	0	0
Gestational hypertension	11	0	0	0	7	9	0
Preterm delivery	62	15	4	7	34	33	7
Gestational diabetes	9	2	1	1	8	3	2
Insulin treatment for gestational diabetes	1	0	0	1	0	0	0
Abnormal glucose challange test	1	0	1	0	1	1	0
Congenital malformations	3	0	0	0	3	0	0
Small for gestational age neonate	10	3	0	2	6	5	0
Intra-uterine growth restriction	4	2	0	1	1	4	1
Birthweight	3	1	2	0	1	3	1
Low birthweight	1	1	0	1	0	1	0
Vaginal birth after caesarean	9	4	2	3	4	6	0
Induction of labour	1	0	0	0	1	1	0
Successful induction of labour	8	0	0	0	2	4	0
Mode of delivery	22	3	5	10	14	18	4
Time to delivery	1	0	0	0	0	0	0
Successful external cephalic version	4	3	3	3	1	4	3
Vaginal delivery after external cephalic version	1	1	0	0	1	1	0
Mode of delivery in breech presentation	1	0	0	0	0	0	0
Intra-amniotic infection and/or inflammation	2	0	0	2	2	2	0
Clinical infection	1	1	0	0	1	1	0
Histologic signs of infection	1	0	0	0	1	0	0
Miscarriage or early fetal loss	2	0	0	0	1	1	0
Stillbirth	3	0	0	0	2	2	0
Perinatal mortality or survival	2	1	0	1	0	2	0
Poor perinatal outcome	2	0	0	0	0	1	0
Hypertensive disorders (combined) or placenta-related complications	3	1	0	0	3	1	0
Placenta praevia	1	0	0	0	1	0	0
Shoulder dystocia	3	1	0	1	2	1	0
Birth trauma	3	0	0	0	0	3	0
Placental abruption	4	0	0	0	1	3	0
Postpartum haemorrhage	3	1	0	1	1	2	0
Anal sphincter injury	1	0	0	0	0	1	0
Thrombosis	2	0	0	0	0	2	2
Maternal complications of attempted VBAC	2	0	0	0	2	0	0
Maternal complications of pre-eclampsia	2	2	0	2	2	1	0
Combined adverse pregnancy outcome	1	0	0	0	0	1	0
Short cervix	1	0	0	1	1	1	0
Higher CRH levels	1	0	0	1	0	1	0

Table 6.1.2: Characteristics of prediction models for the five most frequently predicted outcomes

	Pre-eclampsia	Preterm delivery	Mode of delivery	Gestational hypertension	Small for gestational age neonate
Number of models	69	63	22	11	10
Study design					
- prospective cohort	39 (56.5)	44 (69.8)	12 (54.5)	6 (54.5)	5 (50.0)
- retrospective cohort	5 (7.2)	15 (23.8)	6 (27.3)	2 (18.2)	0
- crossectional cohort	0	0	1 (4.5)	0	0
- case-control	21 (30.4)	11 (17.5)	2 (9.1)	3 (27.3)	3 (30.0)
- randomized trial	3 (4.3)	0	1 (4.5)	0	2 (20.0)
- unclear	1 (14.5)	3 (4.8)	0	0	0
Type of model					
- logistic	65 (94.2)	50 (79.4)	21 (95.5)	8 (72.7)	9 (90.0)
- multinomial regression	0	1 (1.6)	1 (4.5)	0	0
- bayesian	3 (4.3)	4 (6.3)	0	1 (9.1)	1 (10.0)
- linear regression	0	1 (1.6)	0	2 (18.2)	0
- artificial neural network	0	3 (4.8)	0	0	0
- other	1 (1.4)	1 (1.6)	0	0	0
- no multivariable model	0	1 (1.6)	0	0	0
- unclear	0	2 (3.2)	0	0	0
Sample size: number of events per variable					
- ≥10	34 (49.3)	35 (55.6)	18 (81.8)	9 (81.8)	7 (70.0)
- 7 – 9	8 (11.6)	6 (9.5)	2 (9.1)	0	0
- ≤6	22 (31.9)	11 (17.5)	0	1 (9.1)	0
- unclear	5 (7.2)	11 (17.5)	2 (9.1)	1 (9.1)	3 (30.0)
Internal validation presented					
- bootstrapping	2 (2.9)	3 (4.8)	2 (9.1)	0	0
- split sample	5 (7.2)	12 (19.0)	1 (4.5)	0	2 (20.0)
- crossvalidation	2 (2.9)	0	0	0	0
- Monte Carlo simulations	3 (4.3)	0	0	0	1 (10.0)
- jackknifing/leave-one-out procedure	2 (2.9)	0	0	0	0
- none	55 (79.7)	48 (76.2)	19 (86.3)	11 (100)	7 (70.0)
External validation presented					
- in the same paper	0	4 (6.3)	2 (9.1)	0	0
- by others	5 (7.2)	0	2 (9.1)	0	0
- none	64 (92.8)	59 (93.7)	18 (81.8)	11 (100)	10 (100)
Calibration of the model presented					
- calibration plot	0	1 (1.6)	1 (4.5)	0	0
- calibration table	2 (2.9)	0	2 (9.1)	0	2 (20.0)
- p-value Hosmer-Lemeshow test	6 (8.7)	6 (9.5)	7 (31.8)	0	0
- none	61 (88.4)	56 (88.9)	12 (54.5)	11 (100)	8 (80.0)
Discrimination with the model (AUC)					
- 0.90 – 1.00	15 (21.7)	8 (12.7)	0	0	0
- 0.80 – 0.90	28 (40.6)	8 (12.7)	4 (18.2)	2 (18.2)	0
- 0.70 – 0.80	13 (18.8)	9 (14.3)	7 (31.8)	5 (45.5)	1 (10.0)
- 0.60 – 0.70	4 (5.8)	8 (12.7)	3 (13.6)	0	4 (40.0)
- < 0.60	0	1 (1.6)	0	0	1 (10.0)
- Not reported	9 (13.1)	29 (46.0)	8 (36.4)	4 (36.4)	4 (40.0)
Prediction rule presented					
- regression formula	46 (66.7)	25 (39.7)	13 (59.1)	9 (81.8)	4 (40.0)
- risk score	5 (7.2)	6 (9.5)	3 (13.6)	0	0
- risk table or curve	0	1 (1.6)	1 (4.5)	0	1 (10.0)
- nomogram	0	0	1 (4.5)	0	0
- risk for risk groups	1 (1.4)	1 (1.6)	1 (4.5)	0	0
- none	24 (34.8)	30 (47.6)	4 (18.2)	2 (18.2)	5 (50.0)
Clinical guidance: treatment or decision recommended for certain risk					
- yes	9 (13.0)	7 (11.1)	4 (18.1)	0	0
- no	60 (87.0)	56 (88.9)	18 (81.8)	11 (100)	10 (100)

APPENDICES

Appendix 1 Search strategy for maternal genotype on complications of pre-eclampsia (Medline) *Permission granted to reproduce this supplementary file from American Journal of Epidemiology, Oxford University Press. Licence number 3998150855655*

Pre-eclampsia and genotype

1. pre-eclampsia.mp. or exp Pre-Eclampsia/
2. (pre-eclampsia or preeclampsia or pre eclampsia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. 1 or 2
4. exp Genes/
5. exp Genetics/
6. exp Alleles/
7. allel*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. exp Polymorphism, Genetic/
9. polymorph*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. 4 or 5 or 6 or 7 or 8 or 9
11. 3 and 10

Complications

1. cardiovascular disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. exp Cardiovascular Diseases/
3. hypertension.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. exp Hypertension/
5. high blood pressure.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. exp Pre-Eclampsia/
7. exp Recurrence/
8. 6 and 7
9. (recurren* and (pre-eclampsia or pre eclampsia or preeclampsia)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. **1 or 2 or 3 or 4 or 5 or 8 or 9**
11. exp Fetal Growth Retardation/
12. ((fetus or foetus or foetal or fetal or intrauterine) and growth and (restrict* or retard*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
13. (infant, small for gestational age or small for gestational age).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14. (small for date infant or small for date baby or small for date newborn or small for date neonate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
15. **11 or 12 or 13 or 14**
16. exp Abortion, Spontaneous/
17. exp Abortion, Habitual/

18. (miscarriage or spontaneous abortion or pregnancy loss).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
19. exp Fetal Death/
20. ((fetal or foetal or fetus or foetus or intrauterine) and (death or loss)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
21. exp Infant Mortality/
22. exp Stillbirth/
23. ((newborn or neonat*) and death).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
24. stillbirth.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25. **or/16-24**
26. limit 25 to humans
27. exp Infant, Premature/
28. exp Obstetric Labor, Premature/
29. exp Premature Birth/
30. ((preterm or pre-term or pre term or premature) and (delivery or birth or labour or labor)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
31. or/27-30
32. **limit 31 to humans**
33. venous thromboembolism.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
34. exp Venous Thromboembolism/
35. deep vein thrombosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
36. exp Venous Thrombosis/
37. dvt.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
38. exp Pulmonary Embolism/
39. pe.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
40. or/33-39
41. **limit 40 to humans**
42. **10 or 15 or 25 or 32 or 41**

Appendix 2 Study characteristics of the included studies for meta-analysis of relationships between maternal genotype and severe pre-eclampsia (8 pages) *Permission granted to reproduce this figure from American Journal of Epidemiology, Oxford University Press. Licence number 3998150855655*

Author (year)	Study design	Country/ ethnicity	Complication	Number of cases of complications/ pre-eclampsia/ controls	Mean maternal age for cases of complications/ pre-eclampsia/ controls (years)	Nulliparity (% or mean no of pregnancies) for cases of complications/ pre-eclampsia/ controls	Mean gestational age (weeks)at delivery for cases of complications/ pre-eclampsia / controls	Definition(s) of complications	Language
Aggarwal (2011)	Case-control	India/ Indian	Severe PE	90 (severe PE) 110 (mild PE) 200 (controls)	25.8 (severe PE) 26.1 (mild PE) 25 (controls)	54.5% (severe PE) 64.5% (mild PE) 49% (controls)	32 (severe PE) 35 (mild) 38 (controls)	BP >160/110mmHg Proteinuria: >5g/24hour Other: Oliguria, cerebral or visual disturbances, pulmonary oedema, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia. Criteria: PE plus ≥1 above criteria and diagnosis after 20 weeks gestation.	English
Agorastos (2002)	Case-control	Greece	Severe PE	16 (severe PE) 100 (controls)	No details	No details	No details	BP>160/110mmHg Proteinuria: >5g/24hour Criteria: Above BP and proteinuria.	English
Ahmadi (2012)	Case-control	Iran	Severe PE	70 (severe PE) 128 (mild PE) 101 (controls)	29.3 (severe PE) 29 (mild PE) 27.4 (controls)	No details	No details	BP>160/110mmHg Proteineuria:> 3+ protein Headache, visual disturbance, upper abdominal pain, elevated serum creatinine, transaminase; thrombocytopenia and fetal growth restriction. Criteria: Combination of clinical signs and laboratory tests (not specified how).	English
Alfirevic (2001)	Case-control	UK/ White (88%)	Severe PE (including eclampsia)	63 (severe PE and eclampsia) 44 (controls)	29 (severe PE and eclampsia) 33 (controls)	66% (severe PE and eclampsia) 41% (controls)	No details	BP and proteinuria as per Davey and MacGillivray criteria. Criteria: Above and requiring obstetric intensive care or placental abruption, FGR requiring delivery before 36 weeks, unexplained stillbirth after 23 weeks.	English
Andraweera (2012)	Nested case-control	Australia and New Zealand	Small for gestational age	46 (SGA) 105(PE) 989 (controls)	27.3 (PE) 28.2 (controls)	No details	37.6 (PE) 39.7 (controls)	BP ≥140/90mmHg Proteinuria:>300mg/24hr, PCR≥30mg/mmol or ≥ 2+ dipstick SGA: Birthweight <10th customized centile adjusted for maternal height, weight, parity, ethnicity, gestational age at delivery and infant sex.	English
Barbosa de Lima (2009)	Case-control	Brazil / Mulatto	Eclampsia	73 (eclampsia) 92 (PE)	18 (eclampsia) 23 (PE)	No details	37 (eclampsia) 37 (mild PE)	Criteria of report of National High Blood Pressure Education Program.	English

				101 (controls)	26 (controls)		39 (controls)	BP >140/90mmHg Proteinuria: ≥0.3g protein in 24 hours. Eclampsia defined as occurrence in a woman with pre-eclampsia of seizures that cannot be attributed to other causes.	
Benedetto (2002)	Case-control	Italy/ Caucasian white	HELLP	32 (HELLP) 111 (controls)	31.6 (controls)	66% (controls)	39.3 (controls)	HELLP: LDH>600iu/l or serum bilirubin >1.2mg/dl or schistocytes in peripheral blood; AST≥70iu/l; platelets <100,000/mm^3.	English
Currie (2002)	Prospective cohort study	Australia/ Caucasian (95.8% cases and 93.5% controls)	Severe PE (including eclampsia)	48 (severe PE) 46 (controls)	29 (severe PE) 29 (controls)	76% (severe PE) 79% (controls)	34.1 (severe PE) 40.1 (controls)	BP: SBP≥170mmHg or DBP≥110mmHg Proteinuria:≥300mg/24h or 2+ dipstick Other: ALT≥55iu/l); FGR<3rd centile; visual disturbances; persistent headaches; epigastric pain; eclampsia; elevated creatinine (≥0.09mml/l); hyperreflexia; clonus; thrombocytopenia (≤100,000cels/uL); disseminated intravascular coagulation Criteria: PE plus >1 of the above	English
de Groot (1999)	Case-control	Netherlands / Caucasian 96%	Severe PE Eclampsia	37 (severe PE) 11 (eclampsia) 163 (controls)	28 (controls)	No details	No details	BP: DBP ≥110mmHg Proteinuria: ≥2+ dipstick Criteria: Above.	English
Derzbach (2007)	Case-control	Hungary/ Caucasian	Severe PE	126 (severe PE) 106 (controls)	28 (severe PE) 27 (controls)	75% (severe PE) 46% (controls)	33 (severe PE) 40 (controls)	BP≥ 160/110mmHg Proteinuria: 3+ or 4+ protein or ≥5g/24 hr. Criteria: Above only.	English
Deveer (2012)	Cross-sectional	Turkey	Severe PE	50 (severe PE) 50 (controls)	28.8 (severe PE) 27.2 (controls)	Mean gravid 2 (severe PE) 2 (control)	34.4 (severe PE) 38.1 (controls)	ACOG definition BP: ≥160 systolic or ≥110 diastolic Proteinuria: ≥5g/24 hr or ≥3+ Other: Oliguria, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, fetal growth restriction.	English
Dizon-Townson (1996)	Case-control	USA/ Caucasian 94% Hispanic 3% Asian 2% Black 0.8% Native American 0.4%	Severe PE	158 (severe PE) 403 (controls)	No details	No details	No details	BP: ≥160/110mmHg Proteinuria: 3+/ 4+ dipstick or ≥5g/24 hr Other: Oliguria, cerebral or visual disturbances, pulmonary oedema or cyanosis, epigastric or right upper quadrant pain, impaired liver function of unclear etiology, thrombocytopenia. Criteria: Above and ≥1 of other features.	English
Gerhardt (2005)	Case-control	Germany	Severe PE (including eclampsia and HELLP)	97 (severe PE) 277 (controls)	29.3 (severe PE) 24.3 (controls)	89.7% (severe PE)	33.6 (severe PE) 39.8 (controls)	BP: >160/110mmHg Proteinuria: >5g/24hr Other: platelets <100,000mm^3; HELLP (hemolysis, high AST and platelets <100,000mm^3); eclampsia defined by ACOG bulletin no 219 as pre-eclampsia with central nervous system involvement leading to seizures.	English

								Criteria: ≥1 of the above	
Guan (2011)	Case-control	China / Asian	Severe PE	207 (severe PE) 252 (controls)	26.8 (severe PE) 27.1 (controls)	All primigravida	34.8 (severe PE) 35.3 (controls)	Criteria from Obstetrics & Gynaecology 6th edition, Beijing.	Chinese
Hiltunen (2008)	Nested case-control	Finland/ Caucasian	Severe PE Fetal growth restriction	168 (severe PE) 53 (FGR) 679 (controls)	29.0 (All cases) 28.9 (controls)	1.9 (All cases) 2.4 (controls)	36 (all cases) 38.9 (controls)	BP >160/110mmHg Proteinuria: >3g/24 hr Other: Eclampsia, epigastric pain, visual symptoms, oliguria, dyspnoea. Criteria: BP and proteinuria above with or without other features. FGR: Birthweight minus ≥ 2SD for gestational age (customised for sex and Finland)	English
Kaiser (2004)	Case-control	Australia / Caucasian	Eclampsia	51 (eclampsia) 122 (PE) 100 (controls)	No details	No details	No details	BP ≥ 140/90mmHg or SBP≥25mmHg rise or DBP ≥15mmHg rise above baseline Proteinuria: ≥2+ or ≥0.3g in 24 hours Eclampsia – Above BP and proteinuria with convulsions or unconsciousness in perinatal period	English
Kaur (2005)	Prospective case control	India/ Asian	Eclampsia	3 (eclampsia) 9 (PE) 50 (controls)	24.9 (eclampsia) 31.9 (PE) 23.7 (controls)	All primigravida	35.9 (all cases) 35.8 (controls)	BP ≥140/90mmHg Proteinuria: >0.3g/l Eclampsia – Above BP and proteinuria and presence of convulsions.	English
Kim (2001)	Case-control	USA/ White	Severe PE HELLP	169 (severe PE) 18 (HELLP) 253 (controls)	No details	No details	No details	BP: SBP>160mmHg or DBP >110mmHg Proteinuria: >5g/24hr or 4+ dipstick Other: platelets<100,000/ml; oliguria <400ml/24h; pulmonary edema, elevated AST or ALT Criteria: ≥1 of the above HELLP: platelets <100,000/ml; AST and ALT >70iu/l; total bilirubin >1.2mg/dl, LDH≥600u/l and evidence of microangiopathic hemolytic anemia on smear.	English
Kim (2010)	Cohort	Korea/ Asian	Severe PE Fetal growth restriction	117 (severe PE) 57 (FGR) 47 (PE) 182 (controls)	30.8 (All cases) 33.1 (controls)	78.1% (All cases) 54.4% (controls)	36.4 (All cases) 39.1 (controls)	BP: DBP>110mmHg Proteinuria: >5g.24 hr or ≥3+ dipstick Other: pulmonary oedema, seizures, oliguria, thrombocytopenia or severe central nervous system symptoms Criteria: Above BP and proteinuria and ≥1 other features.	English
Kobashi (2000)	Case-control	Japan/ Asian	Severe PE	73 (All cases) 215 (controls)	30.4 (All cases) 29.8 (controls)	53.4 % (All cases) 48.4% (controls)	36.3 (All cases) 39.1 (controls)	BP ≥160/110mmHg Proteinuria: ≥2g/24hr Criteria: Above BP and proteinuria only.	English
Kupferminc (1999)	Case-control	Israel/ Ashkenazi 48%	Severe PE	34 (severe PE) 110 (controls)	29 (all cases) 28 (controls)	92% (all cases) 62% (controls)	32.2 (all cases) 39.5 (controls)	BP: >160/110mmHg Proteinuria: >5g/24 hr Other: platelets <100,000/mm3, combination	English

		Non Ashkenazi 58% Mixed 4%						of haemolysis, high serum aminotransferase concentrations and platelet count of <100,000; eclampsia defined by ACOG bulletin no 219 as pre-eclampsia with central nervous involvement leading to seizures. Criteria: ≥1 of the above	
Kupferminc (2000)	Case-control	Israel/ Ashkenazi Non Ashkenazi	Severe PE	63 (severe PE) 126 (controls)	26 (severe PE) 28.5 (controls)	79.4% (severe PE) 54% (controls)	32.0 (severe PE) 39.5 (controls)	BP: >160/110mmHg Proteinuria: >5g/24hr Other: platelets<100,000mm3; HELLP (hemolysis, elevated enzymes and low platelets); eclampsia defined by ACOG bulletin no 219 as pre-eclampsia with central nervous involvement leading to seizures. Criteria: ≥1 of above	English
Kvehaugen (2012)	Case-control	Norway	Eclampsia	43 (eclampsia) 1130 (PE) 2290 (controls)	31 (eclampsia) 26.6 (PE) 29.6 (controls)	No details	37 (eclampsia) 38.7 (PE) 39.7 (controls)	Eclampsia: Occurrence of convulsions during pregnancy or in first 10 days postpartum with at least two (within 24 hours after convulsions) thrombocytopenia, increased aspartate aminotransferase concentration.	English
Kwon (2012)	Case-control	Korea/ Asian	Severe PE	27 (severe PE) 15 (PE) 138 (controls)	32.1 (All cases) 34.7 (controls)	76.2% (All cases) 0% (controls)	35.6 (all cases) 38.9 (controls)	BP: DBP ≥110mmHg Proteinuria: ≥2+ dipstick Other: headache, visual disturbances, upper abdominal pain, oliguria, convulsion, elevated creatinine, thrombocytopenia, marked liver enzyme elevation and pulmonary oedema. Criteria: BP or proteinuria above (in context of pre-eclampsia) and ≥ 1of other features.	English
Lim (2010)	Case-control	Korea/ Asian	Severe PE Fetal growth restriction	108 (severe PE) 58 (FGR) 182 (controls)	%<35yrs 81.7% (All cases) 81.9% (controls)	85.4% (All cases) 61.5% (controls)	%<37 weeks 43.9%(All cases) 6% (controls)	BP: DBP≥110 ≥5g/24h Proteinuria: ≥3+ dipstick Other: severe central nervous system symptoms, pulmonary oedema, seizures, oliguria, thrombocytopenia. Criteria: BP or proteinuria and ≥1 other feature. FGR – birthweight below 10th percentile (population based)	English
Livingston (2001)	Cross-sectional study	USA / African-American 57.2% (cases) 63.9% (controls)	Severe PE	110 (severe PE) 97 (controls)	24.5 (severe PE) 24.4 (controls)	Mean parity 1 (severe PE) 1.3 (controls)	34.3 (severe PE) 35.6 (controls)	BP: SBP ≥160mmHg or DBP ≥110mmHg Proteinuria: >300mg/24hr Criteria: Above and/or HELLP syndrome or eclampsia.	English
Malek-Khosravi (2012)	Case-control	Iran/Other	Severe PE	70 (severe PE 128 (PE) 101 (controls)	29.3 (severe PE) 29 (PE) 27.4 (controls)	No details	30-39 (severe PE) 36-39 (controls)	BP >160/110mmHg Proteinuria: >3+ dipstick Other: headache, visual disturbances, upper abdominal pain, elevated serum creatinine	English

								and transaminase, thrombocytopenia, fetal growth restriction Criteria: ≥1 of the above in the context of pre-eclampsia.	
Mando (2009)	Case-control	Italy / Caucasian	Severe PE	119 (severe PE) 81 (PE) 412 (controls)	33.4(All cases) 33.2 (controls)	No details	33.9 (All cases) 38.9 (controls)	BP ≥160/110mmHg Proteinuria: ≥5g/24h Other: multi organ involvement eg FGR or HELLP syndrome (platelet count <100,000mm^3, serum aminotransferase level ≥70IU/l, total bilirubin <1.2mg/dL or LDH ≥600IU/l. Criteria: Above BP and/or proteinuria or BP above and ≥1 other feature.	English
Molvarec (2007)	Case-control	Hungary/ Caucasian	Severe PE	119 (severe PE) 103 (controls)	28 (severe PE) 28 (controls)	73.9% (severe PE) 47.6% (controls)	33 (severe PE) 40 (controls)	BP ≥160/110mmHg Proteinuria: ≥5g/24h Criteria: BP and proteinuria above after 20 weeks and resolving by 12 weeks postpartum.	English
Molvarec (2008)	Case-control	Hungary/ Caucasian	Fetal growth restriction HELLP	69(HELLP) 62(FGR) 140 (PE) 144 (controls)	29.0 (HELLP) 28.4 (PE) 29.1 (controls)	66.7% (HELLP) 69.3% (PE) 53.5% (controls)	31 (HELLP) 33.3 (PE) 39.6 (controls)	PE: BP ≥140/90 and proteinuria: ≥0.3g/24h HELLP– serum AST >70 U/l, LDH >600 U/l, platelets <150,000/uL FGR – birthweight <10th centile (population based)	English
Muetze (2008)	Case-control	Germany/ Caucasian	HELLP	71 (HELLP) 79 (controls)	30 (HELLP) 30.9 (controls)	88.7% (HELLP) 65.8% (controls)	33 (HELLP) 39.7 (controls)	Serum haptoglobin <0.3g/l or LDH >300iu/l, elevated AST/ALT over norm and platelets <100,000/ul.	English
Nagy (1998)	Case-control	Hungary/ Caucasian	Severe PE	69 (severe PE) 71 (controls)	27.9 (severe PE) 26 (controls)	No details	39.4 (controls)	BP: ≥160/90mmHg Proteinuria: ≥1g/24h Criteria: BP and proteinuria above.	English
Nagy (2009)	Case-control	Hungary/ Caucasian	HELLP Severe PE	77 (HELLP) 79 (severe PE) 88 (controls)	28.5 (HELLP) 29.0 (severe PE) 28.1 (controls)	53.2% (HELLP) 48.1% (severe PE) 47.7% (controls)	32 (HELLP) 32(severe PE) 40 (controls)	BP: ≥160/110mmHg Proteinuria: ≥1g/24h Criteria: Above BP and proteinuria after 20 weeks gestation. HELLP – AST or ALT >70 IU/l, LDH>600 IU/l, platelets ≤100x10^^{9}/l	English
Pazarbasi (2007)	Case-control	Turkey/ Caucasian	Eclampsia	40 (eclampsia) 113 (PE) 80 (controls)	31.9 (severe PE) 30.1 (PE) 28.5 (controls)	No details	33.7 (severe PE) 34.7 (PE) 38.7 (controls)	Eclampsia – Pre-eclampsia (BP ≥140/90mmHg and proteinuria ≥0.3g/24h) and convulsions or unconsciousness in perinatal period	English
Pegoraro (2004)	Case-control	South Africa/ Afro-caribbean	Eclampsia	120 (eclampsia) 204 (PE) 338 (controls)	No details	No details	No details	Eclampsia – Pre-eclampsia (BP ≥140/90 and proteinuria ≥1+ dipstick) and seizures occurring for the first time in pregnancy	English
Pendeloski (2011)	Case-control	Brazil/ Latin American	Severe PE	76 (severe PE) 1580 (controls)	25.79 (All cases) 30.72 (controls)	1.9 (All cases) 2.51 (controls)	No details	BP >160/110mmhg Proteinuria: ≥0.3g/24h Other: abnormal platelet count, abnormal liver enzymes, maternal symptoms Criteria: Above proteinuria and BP or ≥1	English

								other feature.	
Percin (2006)	Case-control	Turkish/ Other	Eclampsia HELLP	36 (eclampsia) 55 (HELLP) 143 (PE) 147 (controls)	24.3 (eclampsia) 28.6 (HELLP) 29.2 (PE) 30 (controls)	1.3 (eclampsia) 2.2 (HELLP) 2.4 (PE) 2.4 (controls)	34 (eclampsia) 33.6 (HELLP) 34.9 (PE)	Eclampsia – Tonic-clonic seizures occurring in a hypertensive pregnancy (BP>140/90mmHg), with or without proteinuria. HELLP – haemolysis (LDH>600 U/l or serum total bilirubin 1.2mg/dl), elevated liver enzymes (AST and/or ALT >40 U/l) and low platelet counts (<100,000/mm^3).	English
Procopciuc (2002)	Case-control	Romania/ Caucasian	Severe PE	5 (severe PE) 8 (PE) 6 (controls)	29.2 (severe PE) 22.88 (PE) 28.83 (controls)	No details	No details	BP >160/110mmHg Proteinuria: ≥0.3g/24h Other: renal disease, hepatic abnormalities, neurological and haematological modifications, persistent headaches, thrombocytopenia. Criteria: Above BP and proteinuria and ≥1 of other features.	English
Procopciuc (2012)	Case-control	Romania/ Caucasian	Severe PE†	11 (severe PE) 39 (PE) 50 (controls)	28.58 (All cases) 28.04 (controls)	72% (All cases) 56% (controls)	35.36 (All cases) 38.64 (controls)	ACOG definition BP: ≥160 systolic or ≥110 diastolic Proteinuria: ≥5g/24 hr or ≥3+ Other: Oliguria, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, fetal growth restriction.	English
Raijmakers (2002)	Case-control	Netherlands/ Caucasian	HELLP	55 (HELLP) 40 (PE) 78 (controls)	30 (HELLP) 32 (PE) 32 (controls)	No details	30 (HELLP) 33 (PE)	HELLP – haemolysis LDH>600iu/l, elevated liver enzymes, AST and ALT >70IU/l and low platelet count <100 x 10^9/l.	English
Rigo (2000)	Case-control	Hungary/ Caucasian	Severe PE Eclampsia HELLP Fetal growth restriction	120 (severe PE) 6 (eclampsia) 18 (HELLP) 65 (FGR) 101(controls)	27.3 (severe PE) 26.5 (controls)	1.41 (severe PE) 1.55 (controls)	No details	BP ≥160/100mmHg Proteinuria ≥0.3g/24h Other: persistent headache, visual disturbance, epigastric pain, platelet count <100 x10^9/l, serum glutamicoxaloacetic acid transaminase >50u/l, oliguria, hyperreflexia. Criteria: BP and proteinuria above and ≥1 of other features.	English
Rigo (2006)	Case-control	Hungary/ Caucasian	Severe PE	124 (severe PE) 104 (controls)	28 (severe PE) 27 (controls)	74% (severe PE) 57% (controls)	33 (severe PE) 40 (controls)	BP ≥160/100mmHg Proteinuria ≥1g/24h Criteria: BP and proteinuria above, no urinary tract infection and new onset hypertension after 20 weeks.	English
Roberts (2004)	Case-control	South Africa/ Afro-caribbean	Eclampsia	120 (eclampsia) 204 (PE) 338 (controls)	26.3(All cases) 25.0 (controls)	1 (All cases) 1 (controls)	34.4 (All cases) 38.8 (controls)	BP ≥140/90mmHg Proteinuria: ≥1+ protein Eclampsia defined as presence of seizures for the first time in pregnancy together with associated pre-eclampsia or early onset pre-eclampsia.	English
Rosta (2009)	Case-control	Hungary/	FGR	47 (FGR)	28.0 (All cases)	48.4% (All	32.5(All cases)	BP ≥140/90mmHg	English

		Caucasian		112 (PE) 114 (controls)	29.1 (controls)	cases) 49.1% (controls)	39.5 (controls)	Proteinuria: ≥0.3g/24h FGR defined as birthweight below 10th percentile for gestation age and gender (Hungarian birthweight percentiles)	
Schlembach (2003)	Case-control	Germany/ Caucasian White	HELLP	36 (HELLP) 27 (controls)	29.5 (HELLP) 29.8 (controls)	77.8% (HELLP) 56.3% (controls)	33.4 (HELLP) 39 (controls)	Working Group on High Blood Pressure in Pregnancy definition. HELLP defined as after 20 weeks gestation platelet <100,000 cells/uL, evidence of microangiopathic haemolytic anemia (with increased LDH >200 units/l), elevated hepatic enzymes (ALT and AST >20 units/l) and persistent epigastric pain.	English
Seremak-Mrozikiewicz (2010)	Case-control	Poland/ Caucasian	Severe PE	68 (severe PE) 41 (PE) 400 (controls)	28.5 (severe PE) 28.3 (PE) 27.5 (controls)	66.2% (severe PE) 63.4% (PE) 54.3% (controls)	34.3 (severe PE) 37.4 (PE) 39.2 (controls)	BP >160/110mmHg Proteinuria: ≥1g/24h or ≥2+ Other: biochemical, haematological disturbances (thrombocytopenia, elevated liver enzyme level) or clinical signs (epigastric pain, visual disturbances). Criteria: BP and ≥1 of other features or severe proteinuria.	English
Stepanian (2009)	Case-control	France/ Caucasian or Maghrebian	Severe PE	148 (severe PE) 36 (PE) 185 (controls)	31.1 (All cases) 31.2 (controls)	11% (All cases) 5.5% (controls)	No details	BP ≥160/110mmHg Proteinuria ≥5g/24h Other: oliguria, cerebral or visual disturbances, pulmonary oedema or cyanosis, epigastric pain, impaired liver function AST≥70iu/l, thrombocytopenia platelets <100 x 10^9/l, fetal growth restriction Z-score <-1.88. Criteria: ≥1 of above in context of pre-eclampsia (≥140/90mmHg after 20 weeks and proteinuria ≥0.3g/24hr)	English
Sziller (2005)	Case-control	Hungary/ Caucasian	FGR	14 (FGR) 24 (PE) 89 (controls)	29.8 (All cases) 30.0 (controls)	57% (All cases) 46% (controls)	33.1(All cases) 39.0 (controls)	BP ≥140/90mmHg Proteinuria: ≥0.3g/24h FGR defined as birthweight below 10th percentile for gestation in context of pre-eclampsia.	English
Sziller (2007)	Case-control	Hungary/ Caucasian	HELLP	81 (HELLP) 51 (PE) 184 (controls)	30.7 (HELLP) 29.7 (PE) 29.2 (controls)	54.3% (HELLP) 56.8% (PE) 41.8% (controls)	31.9 (HELLP) 33.7 (PE) 38.6 (controls)	BP ≥140/90mmHg Proteinuria ≥0.3g/24h HELLP defined as thrombocytopenia (<150,000 cells/uL^{-1}), hepatic dysfunction (AST or ALT >70iu/l), LDH>600iu/l), haemolysis (serum bilirubin >1.2mg/dl).	English
Tempfer (2004)	Case-control	Austria/ White	Severe PE	24 (severe) 24 (controls)	29 (severe PE) 29 (controls)	0 (severe PE) 0 (controls)	38 (severe PE) 40 (controls)	BP >160/110mmHg Proteinuria: ≥5g/24hr or ≥3+ on dipstick (two random samples 4hr apart) Other: oliguria, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain,	English

								impaired livere function, thrombocytopenia and fetal growth restriction. Criteria: ≥1 of above features in context of pre-eclampsia (SBP≥140mmHg and/or DBP≥90mmHg and ≥300mg/24hr proteinuria).	
van Pampus (1999)	Case-control	Netherlands/	Severe PE HELLP Eclampsia	284 (Combined severe PE, HELLP, eclampsia) 67 (controls)	No details	No details	No details	DBP ≥110mmHg Proteinuria: ≥0.5g/l Criteria: Above BP and proteinuria before 34 weeks and delivery before 36 weeks or with HELLP (LDH>600 U/L, AST or ALT >50 U/L and platelet count <100 x 10^9/L) or eclampsia irrespective of gestational age of fetus.	English
Varkonyi (2010)	Case-control	Hungary/ Caucasian	HELLP	75 (HELLP) 83 (controls)	30.08 (HELLP) 31.76 (controls)	40% (HELLP) 57% (controls)	31.2 (HELLP) 39.63 (controls)	HELLP defined as haemolysis (LDH>600iu/l), elevated liver enzymes (AST and ALT >70iu/l), thrombocytopenia ≤100 x 10^9/l.	English
Von Tempelhoff (2000)	Case-control	Germany/ Caucasian	Severe PE HELLP	29 (severe PE) 32 (HELLP) 61 (controls)	No details	All primiparous	29 (severe PE) 39 (controls)	BP >160/110mmHg Proteinuria: ≥5g/24hr HELLP defined as hemolysis, elevated liver enzymes, low platelets.	English
Wang (2011)	Cross-sectional study	China/ Asian	Severe PE	88 (severe PE) 17 (PE) 103 (controls)	No details	No details	No details	BP >140/90mmHg Proteinuria: ≥0.3g/24h No details for 'severe' pre-eclampsia definition although separate subset.	English
Wiedemann (2009)	Case-control	Germany/ Caucasian	Eclampsia HELLP	5 (Eclampsia) 32 (HELLP) 27 (PE) 100 (controls)	32.5 (All cases) 46.7 (controls)	1.4 (All cases) 2.03 (controls)	34.7 (All cases) No details	No definitions given or referenced.	English
Youpeng (2010)	Case-control	China/ Asian	Severe PE	87 (severe PE) 20 (PE) 81 (controls)	30.9 (severe PE) 30.9 (PE) 20.1 (controls)	80.5 (severe PE) 80.5 (PE) 81.5 (controls)	No details	BP >140/90mmHg or single DBP ≥110mmHg Proteinuria ≥0.3g/24h No definition given for severe PE although separate analysis.	English
Zhu (2006)	Case-control	China/ Asian	Eclampsia Severe PE	19 (Eclampsia) 49 (severe PE) 95 (controls)	26.3 (All cases) 27.1 (controls)	No details	38.2 (All cases) 39.5 (controls)	No definitions of PE or severe PE.	Chinese

Appendix 3 Methodological quality assessment for included studies

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First author, Year	Study design	Newcastle Ottawa Score (risk of bias)			Ethnicity	Exclusion criteria	Genotyping accuracy reporting	Blinding or negative control used	Hardy Weinberg Equilibrium (HWE) reporting for genotypes	HWE	Sample size estimation
		Selection	Comparability	Outcome							
Aggarwal, 2011[123]	Case-control	Low	Medium	Medium	Asian (Indian) (homogenous)	Pre-existing chronic hypertension, gestational hypertension.	No	No	AGT ACE DD MTHFR *FVL (<5 in group)*	0.00 0.06 0.59 *0.58*	Yes (PE)
Agorastos, 2002	Case-control	Medium	Medium	Medium	Caucasian (Greek) (homogenous)	None for cases.	No	Yes	Not done		No
Ahmadi, 2012	Case-control	Medium	Low	Medium	Caucasian (Kurdish) (homogenous)	Family history of chronic hypertension, diabetes mellitus, renal disease or any collagen diseases.	No	No	Not done		No
Alfirevic, 2001	Case-control	Low	Low	Medium	Caucasian (British) 88%	Congenital anomalies or history of thromboembolism.	No	No	Not done		Yes (severe PE)
Andraweera, 2012	Nested case-control	Low	Medium	Medium	No data	Multiple pregnancy, multiparous. High risk of pre-eclampsia, small for gestational age infants or preterm birth because of	No	No	ANGPT1 rs2507800	0.66	No

						underlying medical, obstetric or gynaecological conditions.					
Barbosa de Lima, 2009	Case-control	Low	High	Medium	Mixed (Brazil) No stratification.	Fetal death, autoimmune disease, diabetes, uterine malformation, IVF, placental abruption, any infection, cancer or systemic disease including pre-existing hypertension.	Yes 71-87% success for cases 94-96% for controls.	No	TNFα rs1800629 IL6 rs1800795 IFN gamma rs2430561 IL10-1082A rs1800896, IL10-819C rs1800871, IL10-592C rs1800872, TGF β1 codon 10 rs1982073, *TGF β1 codon 25 rs1800471,(<5 in group)*	0.99 0.55 0.32 0.32 0.07 0.07 0.1 *0.45*	Yes (PE and severe PE cases)
Benedetto, 2002	Case-control	Medium	Low	Medium	Caucasian (Italy) (homogenous)	Chronic hypertension, chronic nephropathy, major systemic diseases.	No	No	Not done		Yes (PE)
Currie, 2002	Prospective cohort study	Medium	Low	Medium	Caucasian (Australian) (95.8% cases, 93.5% controls)	None for cases.	No	No	Not done		No
de Groot, 1999	Case-control	Medium	Medium	Low	Caucasian (Netherlands) 96% (homogenous)	Multiple pregnancies, chronic hypertension, renal disease, diabetes, collagen vascular diseases, cancer, or thrombosis before first pregnancy.	No	Yes	Not done		No

Derzbach, 2007	Case-control	Low	Low	Medium	Caucasian (Hungarian) (homogenous)	Chronic hypertension and pregestational diabetes.	No	No	*P selectin Thr715Pro (<5 in group),* *E selectin Ser128Arg (<5 in group)*	*0.88* *0.23*	Yes (Severe PE)
Deveer, 2012	Cross-sectional	Low	Medium	Medium	Caucasian (Hungarian) (homogenous)	Malformed fetuses, multiple pregnancies.	No	No	*FVL (rs6025)* *FVR2* *Prothrombin (rs1799963)* *MTHFR C677T (rs1801133)* *MTHFR 1298* (all <5 per group)	*0.02* *0.16* *0.16* *0.0033* *0.00003*	No
Dizon-Townson, 1996	Case-control	Medium	High	Low	Caucasian USA 94% Hispanic 3% Asian 2% Black 0.8% Native America 0.4%	Pre-existing hypertension, renal disease, HELLP syndrome.	No	No	Not done		No
Gerhardt, 2005	Case-control	High	Medium	Medium	Caucasian (German) (homogenous)	Previous history of venous or arterial thromboembolic disease. Cases - recurrent fetal loss, diabetes mellitus, chronic hypertension, chronic kidney disease, systemic lupus	No	No	Not done		Yes (Severe PE)

						erythematosus. Antiphospholipid syndrome. Anticoagulation with heparin or antiplatelet using aspirin during pregnancy.					
Guan, 2011	Case-control	Medium	Low	Medium	Asian (China) (homogenous)	No blood relationship, diabetes mellitus, hypertension, renal disease, heart disease, autoimmune disease.	No	No	LEPR G1019A, Leptin PPAR gamma A223G (rs1137101)	0.000349 0.08	No
Hiltunen, 2008	Nested case-control	Medium	Low	Medium	Caucasian (Finland) (homogenous)	Controls: stillbirth, miscarriage, preterm delivery, small for gestational age, venous or arterial thrombosis in index pregnancy. No history of hypertension, stillbirth, pre-eclampsia, thrombosis.	No	Yes	*Factor V Leiden (rs6025) (<5 in group)*	*0.75*	No
Kaiser, 2004	Case-control	Medium	High	High	Caucasian (Australia) (homogenous)	Pre-existing hypertension, chronic renal disease or autoimmune disorders.	No	No	TNFα 307 (rs1800629)	0.70	No
Kaur, 2005	Prospective case control	High	Medium	High	Asian (India) (homogenous)	Chronic medical disorders – diabetes, hyperthyroidism, sarcoidosis, chronic hypertension, chronic renal	No	No	ACE DD (rs4646994)	0.70	No

						disorders, collagen disorders, cardiovascular disease, family history of hypertension, multiple pregnancy.					
Kim, 2001	Case-control	Medium	High	Medium	Caucasian (USA) (homogenous)	None for cases.	No	No	*Not done* *Factor V Leiden rs6025* *(<5 in group)*	 *0.70*	Yes (PE)
Kim, 2010	Cohort	Medium	Low	High	Asian (Korea) (homogenous)	Major congenital anomalies, prior pre-eclampsia, drugs, alcohol, smoking, pre-existing conditions (chronic hypertension, diabetes, renal insufficiency, congenital anomalies, fetal growth restriction, fetal demise)	No	No	TGF β1 (rs1982073) c869TC	0.47	Yes (PE)
Kobashi, 2000	Case-control	Low	Low	High	Asian (Japan) (homogenous)	HELLP, renal disease, diabetes mellitus, amniotic volume abnormality, fetal abnormalities.	No	No	MTHFR C677T (rs1801133)	0.70	No
Kupferminc, 1999	Case-control	Low	Low	Medium	Other (Israel)	None specified for cases	No	No	Not done Unable to calculate		No
Kupferminc, 2000	Case-control	Medium	Medium	Medium	Other (Israel)	None specified for cases	No	No	Not done Unable to calculate		No

Kvehaugen, 2012	Case-control	Medium	High	Medium	Caucasian (Norway) (homogenous)	Chronic hypertension, chronic renal disease, heart disease, diabetes mellitus, registered non	Yes rs5443 98.6%; rs5186 99.1%; rs4606 98.4%	No	GNB3 C825T (rs5443) AGTR1 A1166C (rs5186) RGS2 C1114G (rs4606)	0.51 0.50 0.50	No
Kwon, 2012	Case-control	Medium	High	High	Asian (Korea) (homogenous)	Chronic hypertension, diabetes, chronic renal disease or autoimmune disorders.	No	No	ICAM-1 K469E (rs5498)	0.89	No
Lim, 2010	Case-control	Medium	Low	Medium	Asian (Korea) (homogenous)	Gestational hypertension. Abnormal fetal karyotype, chromosomal abnormalities, chronic hypertension, diabetes, renal disease.	No	No (but each sample ran 3 times to confirm accuracy)	COMT (rs4680) CYP17A1 (rs11206244)	0.47 0.28	Yes (PE)
Livingston, 2001	Cross-sectional study	Low	Low	Low	Mixed (USA) 57.2% African American, 42.8% White	Chronic hypertension, diabetes mellitus, pre-existing renal disease, history of thromboembolism, multiple gestation, major fetal congenital anomaly.	No	No	MTHFR C677T (rs1801133) FVL rs6025 *(<5 in group)*	0.14 0.00	Yes (severe PE)
Malek-Khosravi, 2012	Case-control	Medium	Low	High	Other (Iran) (homogenous)	Multiple pregnancy, previous hypertension, diabetes, cardiac	No	No	Factor V Leiden (rs6025) Prothrombin	0.17	No

						disease, renal disease.			(rs1799963)	0.02	
Mando, 2009	Case-control	Low	Medium	Medium	Caucasian (Italy) No stratification	Multiple pregnancy, abnormal karyotype, malformations, infection	>95% success	No	ACE (rs4646994)	0.29	Yes (PE)
Molvarec, 2007	Case-control	Low	Medium	Medium	Caucasian (Hungary) (homogenous)	Multiple pregnancy, chronic hypertension, diabetes mellitus, autoimmune disease and renal disease.	No	No	Estrogen receptor PvuII (rs2234693) Estrogen receptor XbaI (rs9340799)	0.62 0.01	Yes (Severe PE)
Molvarec, 2008	Case-control	High	Low	High	Caucasian (Hungary) (homogenous)	Multiple pregnancy, chronic hypertension, diabetes mellitus, autoimmune disease and renal disease.	No	No	TNF-α G-308A (rs1800629)	0.46	Yes (Severe PE – PE with SGA)
Muetze, 2008	Case-control	Medium	Low	Medium	Caucasian (Germany) (homogenous)	No exclusion criteria.	No	No	MTHFR C677T (rs1801133) FVL (rs6025) (<5 in group) Prothrombin (rs1799963) (<5 in group)	0.06 0.00 0.00	No (post hoc analysis (HELLP)
Nagy, 1998	Case-control	High	Medium	Medium	Caucasian (Hungary) (homogenous)	No exclusion criteria	No	No	Unable to calculate		No
Nagy, 2009	Case-control	High	Low	High	Caucasian Hungarian (homogenous)	Controls were excluded if they developed hypertensive disorder	No	No	Leptin (TTTC)n	0.03	No

Pazarbasi, 2007	Case-control	Medium	Medium	High	Caucasian (Turkey) (homogenous)	Pre-existing hypertension, chronic renal disease, or autoimmune disorders	No.	No	TNF-α G308A (rs1800629) TNF-α C850 (rs1799895)	0.81 0.64	No
Pegoraro, 2004	Case-control	High	Low	Medium	Afro-caribbean (Africa) (homogenous)	No exclusion criteria	No	No	*Epithelial sodium channel beta subunit gene T594M (<5 in group)*	*0.74*	No
Pendeloski, 2011	Case-control	Low	High	High	Mixed (Brazil) No stratification	Multiple gestation, fetal death, autoimmune diseases, diabetes, uterine malformation, in vitro fertilization treatment, placental abruption, infection and cancer or any other systemic disease, including pre-existing hypertension.	No.	Yes Repeated positive sample testing policy	CTLA-4 (rs231775), CD28, ICOS (rs4675378)	0.30 0.47 0.10	Yes (severe PE)
Percin, 2006	Case-control	High	Medium	High	Caucasian Turkish (homogenous)	<20 weeks gestation or significant medical condition, including renal, hepatic or cardiovascular diseases and diabetes mellitus.	No	No	Aldosterone synthase CYP11B2 (rs1799998)	0.59	No
Procopciuc, 2002	Case-control	High	High	High	Caucasian Romanian	No exclusion criteria	No	No	Angiotensinogen gene M235T (rs699) (<5 in	0.54	No

					(homogenous)				group)		
Procopciuc, 2012	Case-control	High	Low	High	Caucasian Romanian (homogenous)	History of chronic hypertension, renal disease, metabolic disorder or medication known to affect thyroid function.	No	No	Deiodinase D1 C785T	0.39	No
Raijmakers, 2002	Case-control	High	Medium	High	Caucasian Dutch (homogenous)	No exclusion criteria	No	No	Unable to calculate		No
Rigo, 2000	Case-control	High	Low	High	Caucasian Hungarian (homogenous)	Multiple pregnancy, diabetes, chronic renal disease, or autoimmune disorders	No	No	Unable to calculate		No
Rigo, 2006	Case-control	Low	Low	Medium	Caucasian Hungarian (homogenous)	Multiple pregnancy, chronic hypertension, renal disease, gestational diabetes mellitus and autoimmune disease.	No	No	LEPR A109G 0.62 LEPR A223G (rs1137101)	0.07	No
Roberts, 2004	Case-control	High	Low	Medium	Afro-caribbean Black Africa Zulu (homogenous)	Hypertension in a previous pregnancy for controls.	No	No	ACE (rs4646994) Unable to calculate for ATR, *AGT (rs699) (One group n<5)*	0.81 *0.61*	No
Rosta, 2009	Case-control	Medium	High	High	Caucasian Hungarian (homogenous)	Multiple pregnancy, chronic hypertension, diabetes mellitus, autoimmune disease	No	No	SOD3 G172A (rs1799895)	0.68	Yes (severe PE) (PE with

						and renal disorder.					SGA)
Schlembach, 2003	Case-control	Medium	Low	Medium	Caucasian German (homogenous)	No exclusion criteria.	No	No	Unable to calculate		No
Seremak-Mrozikiewicz, 2010	Case-control	Medium	Medium	High	Caucasian Polish (homogenous)	Fetal abnormalities, chronic hypertension, chronic nephropathy, diabetes mellitus, cardiovascular disease, multiple pregnancy, chronic hypertension persisting 12 weeks after delivery.	No	No	Factor V Leiden G1691A (rs6025), *Prothrombin G20210A (rs1799963) (<5 in group)*	0.9 *0.7*	No
Stepanian, 2009	Case-control	Low	Medium	Medium	Maghreb (40 pairs) Mixed European/Maghreb (3 pairs) Accounted for ethnicity	< 20 weeks	No	No	CX3CR1 V249I (rs3732379), CX3CR1 T280M (rs3732378)	0.57 0.42	Yes (PE)
Sziller, 2005	Case-control	Medium	Medium	High	Caucasian Hungarian (homogenous)	Multiple pregnancy or pregnancy-induced diabetes mellitus were excluded	No	Yes (negative controls)	Fas gene TNFRSF62 at 670G>A	0.164	No
Sziller, 2007	Case-control	Low	Medium	High	Caucasian Hungarian (homogenous)	No exclusion criteria	No	Yes (blinding and negative controls)	*Mannose Binding lectin codon 54 (rs1800450) (<5 in group)*	*0.471*	No

Tempfer, 2004	Case-control	Low	Medium	Medium	Caucasian (Austrian)	Multiple pregnancy, essential hypertension, diabetes, chronic renal disease, platelet disorders, maternal or fetal infection, autoimmune disorders, epilepsy and a history of recurrent miscarriage, intrauterine fetal death and cardiovascular disease.	No	No	Unable to calculate as no individual genotype frequencies		No
van Pampus, 1999	Case-control	Medium	Medium	Medium	Caucasian from Netherlands (homogenous)	Pre-existing hypertension, vascular or renal disease or diabetes.	No	No	Unable to calculate as no individual genotype frequencies		No
Varkonyi, 2010	Case-control	Medium	Low	High	Caucasian Hungarian (homogenous)	No exclusion criteria	No	Yes (blinding)	LEPR c326AG (rs6413506), LEPR c668AG (rs1137101) *LEPR C1968GC (rs8179183) (<5 in group)*, LEPR G3024A-G (rs6413506)	0.004 0.1 *0.1* 0.43	Yes (severe PE) (HELLP)
Von Tempelhoff, 2000	Case-control	Medium	High	Medium	Caucasian German (homogenous)	Arterial or venous thrombosis, diabetes or vascular disease.	No	No	Unable to calculate as no individual genotype frequencies		No

Wang, 2011	Cross-sectional study	Low	Low	High	Asian Chinese (homogenous)	Chronic hypertension, pregestational diabetes and chronic renal disease	No	No	Killer Immunoglobulin-like Receptor 3DL2	0.00	No
Wiedemann, 2009	Case-control	High	High	High	Caucasian German (homogenous)	Diabetes and chronic hypertension.	No	No	Leptin TTTCn, LEPR R223Q (rs1137101), Leptin PPARγ2 P12A (rs1801282)	0.00 0.13 0.37	Yes (no details)
Youpeng, 2010	Case-control	Medium	Low	High	Asian Chinese (homogenous)	Multiple pregnancy, diabetes, heart disease, chronic hypertension, fetal malformation, chronic nephritis	No	No	*Adiponectin +45T/G (rs2241766) (<5 in group),* Adiponectin +276G/T (rs1501299)	0.23 0.05	No
Zhu, 2006	Case-control	High	Medium	High	Asian Chinese (homogenous)	History of hypertension, heart disease, kidney disease, diabetes mellitus and no blood transfusions or immunotherapy.	No	No	Dopamine β Hydroxylase (DBH) G589A (rs5320)	0.53	No

Appendix 4 PRISMA checklist for the systematic review of accuracy of individual tests to predict complications in women with pre-eclampsia (Part 1/2)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	79
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	79-80
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	81
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	81
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	69 (82)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	82
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	82
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Reference 184
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	82
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	82
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	82
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	82-83
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	83-84
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	83-84

Appendix 4 PRISMA checklist for the systematic review of accuracy of individual tests to predict complications in women with pre-eclampsia (Part 2/2)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	84
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	84 Figure 4.2.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 4.2.2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 4.2.3 88-95
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 4.2.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	88 Figure 4.2.2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	96
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	96-97
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	99-100
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	100

Appendix 5 Study Characteristics of Included Studies for tests to predict maternal and neonatal complications of pre-eclampsia (10 pages)

Study author, year	Language, country	Study design, years recruited	Number of patients	Inclusion criteria	Exclusion criteria	Timing of test and frequency	Test and cut-off level	Maternal complications	Fetal complications
Aali, 2004	English, Iran	Prospective, cross-sectional, 2001-2002	200	Pre-eclampsia (ACOG)	None specified	Unknown gestational age, multiple testing	Liver function ALT 300, AST 500	Eclampsia	
Abramovici, 1999	English, USA	Retrospective cross-sectional, 1993-1996	269	Severe pre-eclampsia	History of renal, liver or haematological abnormalities, multiple pregnancies	24 to 36 weeks, frequency not known	Liver function LDH 600, AST 70	Caesarean delivery	IUGR, NND, RDS, NEC Grade 2-3, BPD, Mechanical ventilation, IVH Grade 3-4
Abroug, 1992	English, Tunisia	Prospective cohort, 1989	62	Pre-eclampsia and eclampsia (ACOG)	None specified	37 weeks (mean gestation at admission), testing on admission	Liver function ALT 30, AST 35	Death, Eclampsia, Severe hypertension, Acute renal failure, Caesarean section	IUFD; Fetal distress; IUGR, NND, Neonatal thrombocytopenia, Neonatal leucopenia
Audibert, 1996	English, USA	Retrospective cohort, 1992-1995	327	Severe pre-eclampsia or HELLP (ACOG)	Laboratory abnormalities from other disorders	Unclear	Liver function LDH 600, ALT 70, AST 70	Eclampsia, Caesarean section, Blood transfusion, Disseminated intravascular coagulation, Pleural effusion, Wound haematoma/ infection, Acute renal failure, Abruption, Pulmonary oedema,	

								Intracerebral haemorrhage, Death	
Ben Salem 2003	French, Tunisia	Case-control, 1994-2000	120	Pre-eclampsia and eclampsia (WHO)	Other causes of convulsions, epilepsy, meningitis, cerebral haemorrhage, cerebral tumours	Not known	Symptoms: headache, visual disturbances	Eclampsia	
Black 2007	English, USA	Case-control, 8 months, year unknown	100	Pre-eclampsia (ACOG)	None specified	Not known	Symptoms: Vertigo, epigastric pain, headache, blurred vision, scotoma, inability to concentrate	Severe pre-eclampsia (BP>160 or 110 for 2 or more readings, proteinuria >/=5g/24h or worsening pre-eclampsia BP >/150 or 100 but <160 or 110 for 2 or more readings; proteinuria >/=100mg/l but <5g/24h)	
Brown, 1996	English, Australia	Prospective cross-sectional, 1987-1997	825	Pre-eclampsia (Australasian Society for study of Hypertension in Pregnancy)	None specified	Unknown gestation, testing twice weekly	Uric acid, 350umol/l (6mg/dl)	Severe hypertension (SBP >/=170 or DBP >/=110)	SGA (<10th centile birthweight) corrected for sex) Perinatal mortality
Buchbinder 2002	English, USA	Prospective cross-sectional, 1991-1995	107	Previous history of pre-eclampsia (defined as BP≥140/90 on 2 occasions 4 hours apart or 1	Multiple pregnancy, diabetes mellitus, chronic hypertension, baseline proteinuria	Unclear	Urinary protein, 5g/24 hr	Abruption	Preterm delivery, Fetal death, Neonatal death, NICU admission, IVH, RDS, SGA

				DBP>=110 mm Hg, proteinuria ≥300mg/24h or 2 dipstick ≥2+ (100mg/dl) 4h apart with no evidence of urinary tract infection) singleton pregnancy					
Chan 2005	English, Australia	Retrospective cross-sectional, 1998-2001	321	Pre-eclampsia (ISSHP definition)	Pre-eclampsia superimposed on pre-existing hypertension, unavailable spot PCR, booking BP >/=140/90mmHg, postpartum dx	Unclear	Urinary protein, spot PCR 500mg/mmol, 900mg/mmol	Adverse maternal outcome (severe hypertension, renal insufficiency, cerebral irritation and thrombocytopenia)	Adverse fetal outcome (perinatal mortality, SGA <10th centile corrected for sex)
D'Anna 2000	English, Italy	Retrospective cross-sectional, 1990-1998	94	Pre-eclampsia (National Working Group on Hypertension in Pregnancy)	Chronic medical disease	Unclear	Uric acid, 340umol/l		IUGR
Dukler, 2000	English, Israel	Retrospective cohort, 1978-1981	380	Pre-eclampsia >140/90mmHg and ≥1+ proteinuria on 2 occasions in 2nd trimester)	Lack of prenatal care, missing data	2nd trimester, multiple testing	BP, DBP 90-110mmHg, DBP >100mmHg	CS	Spontaneous preterm labour and delivery
Furukawa, 2006	English, Japan	Retrospective cross-sectional, 1994-2002	79	Pre-eclampsia (National High Blood Pressure Program)	Multiple pregnancy, renal disease, diabetes mellitus	At delivery	Urinary protein, 3+ dipstick		SGA<10th centile
Ganzevoort, 2005*	English, Netherlands	Prospective randomised	216	HELLP syndrome,		24-34 weeks,	BP, LDH, PCR, BMI,	Abruption, CS, Eclampsia, Liver	BPD, CPL, IUFD, IVH, NEC, NND,

		control trial, 2000-2003		Pregnancy induced hypertension and FGR, Severe pre-eclampsia		multiple testing	AST, Umbilical artery PI	haematoma, Pulmonary oedema	RDS, ROP, SGA
Girling, 1997	English, UK	Prospective cross-sectional, year unknown	430	Pre-eclampsia (2 consecutive measurements of DBP >90mmHg 4 or more hours apart or a single reading >110mmHg with proteinuria >0.3g/24h or >2+ on dipstick testing	Liver pathology, hypertension or multiple pregnancy.	Unknown gestation, multiple testing	Liver function, gestation specific 95% reference range – 3rd trimester ALT 32, AST 30, Bilirubin 14, GGT 41	Maternal complications (medical complications due to pre-eclampsia) Caesarean section	Neonatal death, Preterm delivery
Gowri, 2010	English, Oman	Retrospective cross-sectional, 2006-2007	94	Pre-eclampsia - mild and severe	None specified	Unknown gestation, on admission	Uric acid, >0.35mmol	Caesarean delivery	
Haddad, 2000	English, USA	Retrospective case control, 1992-1999	64	Severe pre-eclampsia (ACOG)	History of haematological or liver diseases, gestation >28 weeks at admission	<28 weeks	Liver function, LDH 600, AST 70	Eclampsia, abruption, DIC, Ascites, Pulmonary oedema, Pleural effusion, Acute renal failure, Transfusion of blood products, Caesarean section	Neonatal death, Intraventricular haemorrhage, Respiratory distress syndrome
Hall, 2002	English, South Africa	Prospective cross-sectional, 1992-1997	340	Pre-eclampsia (ISSHP), singleton with early-onset severe PE (24-	None specified	24-34 weeks, twice weekly	Urinary protein, increase by 2g/24hr in two samples	Eclampsia, Abruption, HELLP, Caesarean section, Pulmonary oedema, ITU	Fetal death, Low Apgar, NICU admission

				34 weeks) with heavy proteinuria ≥5g/24 hr				admission, Ascites	
Harms, 1991	German, Germany	Retrospective cohort, 1983-1990	201	Pre-eclampsia (≥140/90mmHg within 6 hrs of each other)	None specified		Symptoms - Headache, visual disturbances, epigastric pain, nausea and vomiting	HELLP syndrome	
Hawkins, 2012*	English, Australia	Retrospective cohort, 2000-2008	993 (with PE - data from authors)	Pre-eclampsia (ISSHP)	Hypertension, renal disease or systemic disease eg diabetes, receiving medication during pregnancy apart from iron supplements, active labour or rupture of membranes.		Uric acid, >0.35mmol/l	Adverse maternal outcome (composite); Caesarean, severe hypertension, transaminitis, thrombocytopenia, renal dysfunction, neurotoxicity, magnesium sulphate	Adverse fetal outcome (composite), SGA, premature delivery <34/40, NICU admission
Jaiswar, 2011	English, India	Case-control, 1 year (not specified when)	107	Pre-eclampsia (mild, severe, eclampsia)	Hypertension <20 weeks, pre-existing diabetes, renal disease, liver disorder, thyroid disorder, epilepsy	3rd trimester, testing on one occasion	Liver function, LDH 600-800 iu/l, >800iu/l	Severe hypertension (SBP >/=160 or DBP >/=110)	Perinatal death
Martin, 1999	English, USA	Retrospective cohort, 1981-1997	568	Severe pre-eclampsia with or without HELLP syndrome (ACOG)	Eclampsia	Test on admission	Liver function: LDH 1000-1400, AST 50-150, ALT 30-100; Urinary protein: 2+	Combined maternal adverse outcome (renal, hepatic and/or gastrointestinal morbidity)	

							3+. Uric acid ≥380 and ≥460 umol/l; Symptoms: Headache, nausea and vomiting, epigastric pain		
Martins-Costa, 2011	English, Brazil	Retrospective cohort, 1999-2004	278	Pre-eclampsia subgroup taken (140/90mmHg in pregnancy, live fetus at admission and at least 1 random PCR >0.3)	Nephropathy previous to pregnancy, twin pregnancies, missing data	Unknown	Urinary protein, ≥2.0mg/mg protein creatinine	Composite (Severe hypertension SBP≥160, DBP ≥110, plt <100,000mm^3, LDH >600, DIC, abruption, HELLP, eclampsia)	Composite (Perinatal death, cerebral haemorrhage of the newborn, RDS, sepsis, SGA <10th centile) SGA and NICU separately
Newman, 2002	English, USA	Retrospective cross-sectional, 1997-2001	209	Pre-eclampsia (ACOG)	Multiple pregnancy, renal disease	Unknown, test within 48 hours of admission	Urinary protein: ≥5g/24hr, ≥10g/24hr	Eclampsia, severe hypertension, HELLP syndrome	5 min Apgar score <7, NND, NICU admission, Delivery <32 weeks, RDS, IVH, NEC
Odegard, 2000	English, Norway	Retrospective cross-sectional, 1993-1995	307	Pre-eclampsia (Increase in DBP of 25mmHg to ≥90mmHg and proteinuria after 20 weeks	Multiple pregnancy, unknown gestational age	Unknown	Urinary protein: 2+, 3+ dipstick, ≥500mg/24hr)		SGA (2SD below EFW or >24% lower than expected BW or 840g reduced in BW for term infant)
Odendaal, 1996	English, South Africa	Prospective cross-sectional, year unknown	229	Severe pre-eclampsia		28-31 weeks (mean gestation)	Uric acid: ≥520µmol/l	Caesarean delivery	SGA, IUGR, Neonatal death, Perinatal mortality (within 7 days), Preterm delivery
Odendaal, 2000	English, South	Case-control, 1992-1997	340	Early severe pre-eclampsia,			Liver function:	Placental abruption	

	Africa			singleton			LDH ≥350µmol/l		
Peek, 1995	English, Australia	Prospective cohort, 1993-1994	137	Pre-eclampsia – mild and severe	Chronic hypertension, diabetes, multiple gestation	3rd trimester	BP: > 130/90 and <160/110 with proteinuria 1+ and 2+, severe hypertension	Spontaneous labour, delivery, admission, forceps delivery, Caesarean section	Perinatal mortality, NICU admission, IVH, NEC
Qublan, 2005	English, Jordan	Case-control, 2002	62	Pre-eclampsia – mild and severe	Hypertension before 20 weeks, diabetes mellitus, renal disease, thyroid disease, liver disease	Unknown	Liver function: LDH 600-800iu/l, >800iu/l	Eclampsia, abruption, intracranial haemorrhage, HELLP, acute renal failure, pulmonary oedema, DIC, Caesarean	Perinatal death
Schiff, 1996	English, USA	Retrospective cohort, 1990-1994	66	Severe pre-eclampsia (new onset persistent hypertension SBP>140mmHg or diastolic >90mmHg, proteinuria >/=300mg/24 hours and hyperuricemia (>5mg/dl) and one of SBP >160mmHg or DBP >110mmHG, proteinuria (>5g/24h) or serum AST >72 iu/L.	Chronic hypertension	26 to 32 weeks, on admission 2 tests ≥4days apart	Urinary protein: increase in 24 hour proteinuria by ≥2g	HELLP syndrome, Caesarean delivery for fetal distress, placental abruption, eclampsia	Stillbirth, Apgar ≤6 at 5 min

von Dadelszen, 2010*	English, Canada	Prospective cohort	594	Pre-eclampsia * data from authors specifically for patients with pre-eclampsia	Spontaneous labour. Maternal outcome achieved before fulfilling eligibility criteria.	BP, LDH, ALT, AST, uric acid, 24 hour urinary protein, urine PCR, symptoms: nausea, visual disturbances, abdominal pain, headache.	Adverse maternal outcome (death or complication involving hepatic or CNS or renal or respiratory or haematological systems). * data given for individual outcomes	
Waugh, 2005	English, UK	Prospective cross-sectional, year unknown	195	Sustained DBP >/=90mmHg or systolic BP >/=140mmHg on 2 occasions or a single DBP >110mmHg or SBP>160mmHg over 20 weeks (only included pre-eclampsia)	Less than 20 weeks' gestation	Urinary protein: 0.3g/24hr, 0.5g/24hr		SGA<10^{th} percentile
Williams, 2002	English, USA	Prospective cross-sectional, 1992-1996	194	Pre-eclampsia (National High Blood Pressure education Program Working Group)		Uric acid: ≥450µmol/l, ≥540µmol/l	HELLP syndrome, severe hypertension	SGA <10^{th} centile

Witlin, 1999	English, USA	Prospective cohort, 1992-1997	445	Severe pre-eclampsia and eclampsia (ACOG)	Indication for immediate delivery (non reassuring fetal status, vaginal bleeding, eclampsia, uncontrolled severe hypertension, pulmonary oedema, compromised renal function, persistent severe headache or visual changes, platelet count <100,000/mm^3 or AST or ALT more than twice the upper limit of normal with epigastric pain or RUQ pain)	Symptoms: Nausea and vomiting, epigastric pain, headache, visual symptoms	Placental abruption, eclampsia
Woldesellasie, 2005	English, Namibia	Retrospective cross-sectional, 2003-2004	230	Pre-eclampsia (Canadian Hypertension Society Conference)		Liver function: ALT>60iu/l, AST >43iu/l, LDH>181iu/l	Eclampsia, severe pre-eclampsia (HELLP syndrome)

Yassaee, 2003	English, Iran	Prospective cohort, 1986-2001	103	Severe pre-eclampsia (no specified definition)	None specified	Unknown	Uric acid: ≥6mg/dl	Eclampsia, maternal death, Caesarean delivery	Intrauterine death, IUGR
Yucesoy, 2005	English, Turkey	Retrospective cross-sectional, 1997-2004	255	Pre-eclampsia (mild and severe) (National High Blood Pressure Education Program Working Group)	None specified	20 weeks, multiple testing	Liver function: Increase in AST or ALT or LDH	Placental abruption, acute renal failure, DIC, pulmonary oedema, adult RDS, retinal detachment, intracranial bleed, death	
Xiong, 1999	English, Canada	Retrospective cohort, 1989-1990	428	Pre-eclampsia	Chronic cardiovascular disease, chronic hypertension, history of hypertension, chronic renal disease, diabetes, multiple gestation	3rd trimester, multiple testing	BP: >160/110 mmHg	Caesarean delivery	

* These authors provided additional primary data.

Appendix 6 List of maternal and neonatal outcomes considered to be relevant in the management of women with mild and moderate pre-eclampsia between 34 and 37 weeks of gestation

a. Maternal outcomes
Maternal death
Severe pre-eclampsia
Eclampsia
GCS <13
Stroke or RIND (Reversible Ischaemic Neurological Deficit)
Cortical blindness
Retinal detachment
Bell's palsy
Posterior reversible encephalopathy
Haematological - need for transfusion of any blood product
Hepatic - dysfunction
Hepatic - capsule rupture
Hepatic – failure
HELLP syndrome
Cardiac - need for positive ionotrope support
Cardiac - myocardial ischaemia or infarction
Cardiac - infusion of any third parenteral antihypertensive
Respiratory - need for intubation
Respiratory - need for at least 50% FIO_2 for >1hr
Respiratory - pulmonary oedema
Renal - acute renal insufficiency (creatinine >200uM)
Renal - need for dialysis
Need for Magnesium sulphate
Placental abruption

b. Neonatal outcomes
Abnormal level of consciousness (coma/stupor)
Apgars (<4 at 5 min)
Assessment of neurodevelopmental status at follow-up
Assisted ventilation (needed for >4hr)
Assisted ventilation (needed for >24hr)
Birthweight
CRIB score (Clinical Risk Index for Babies)
Special Care - no of days at this level
High Dependency Care and short term Intensive Care - no of days at this level
Maximal Intensive Care - no of days at this level
Death - Early neonatal (within 7 days)
Death - Late neonatal (within 28 days)
Feeding – need for parenteral feeding
Feeding – day of life tolerating feeds

Gastrointestinal - Necrotising enterocolitis
Hypoglycaemia (symptomatic)
Infection - (sepsis, meningitis) within 72hrs
Infection – late onset sepsis
Inotropic support
Neurological - Cystic periventricular leukomalacia
Neurological - Grade III/IV intraventricular haemorrhage
Neurological - Hypoxic ischaemic encephalopathy
Neurological - Need for brain cooling
Neurological - Neonatal seizures (>2 before 72hrs regardless of cause)
NICU - admission at any time
NICU - length of stay >7 days
Opthalmological - Stage 3-5 retinopathy of prematurity
Respiratory - Bronchopulmonary dysplasia
Respiratory - Respiratory illness requiring admission to hospital during the first year of life
Respiratory - Respiratory Distress Syndrome
Respiratory - Transient Tachypnoea of the Newborn

Appendix 7 Definitions of components of maternal and neonatal composite outcomes

a. Maternal outcomes	
Maternal death	Maternal death occurring within six weeks of pregnancy or if later, attributable to complications of pre-eclampsia
Eclampsia	Occurrence of a seizure in association with pre-eclampsia
Pulmonary oedema	Clinical diagnosis with X-ray confirmation or requirement of diuretic treatment and oxygen saturations on air (SpO2 <95%)
Need for at least 50% FiO2 for more than 1 hour	Oxygen given at greater than 50% concentration based on local criteria for longer than 1 hour
Need for intubation	Intubation may be by ventilation, electric impedance tomography (EIT) or continuous positive airways pressure (CPAP).
Major obstetric haemorrhage	Loss of more than 1000ml of blood before or after delivery necessitating transfusion of blood or blood products
Cardiac morbidity - positive inotropic support	The use of vasopressors to maintain a sBP > 90 mmHg or mean arterial pressure > 70 mmHg (inotropic support)
HELLP syndrome	Haemolysis, elevated liver enzymes, low platelet count. Defined as new onset of elevated liver enzymes (serum aspartate aminotransferase (AST) ≥70 U/L or gamma-glutamyltransferase (γGT) ≥70 U/L or alanine aminotransferase (ALT) ≥70 U/L and low platelets defined as platelet count < 100 x 10^9/L and either haemolysis, defined by abnormal peripheral blood smear or serum lactate dehydrogenase levels (LDH) ≥600 U/L or total bilirubin level ≥20.5μmol/L
Placental abruption	Premature separation of a normally located placenta from the uterine wall occurring before delivery of the fetus. Diagnosed clinically by evidence of retroplacental clot, sonographic visualisation of abruption or vaginal bleeding accompanied by non-reassuring fetal status or uterine hypertonicity and signs of hypovolaemic shock in the mother.

b. Neonatal outcomes	
Neonatal death	Death before 28 completed days following live birth.
Respiratory distress syndrome	Clinical presentation of neonatal acute respiratory distress with cyanosis, grunting, retractions and tachypnoea, supplemental oxygen requirement and admission to the neonatal unit for further respiratory support with the diagnosis verified by chest radiograph findings of reticulogranular patterns and air bronchograms.
Cystic periventricular leukomalacia; Grade III/IV intraventricular haemorrhage	Ischaemic brain injury. Diagnosed by periventricular echodensities or cysts on cranial ultrasound or MRI scan. (PVL) Grade III IVH is subependymal haemorrhage with extension into lateral ventricules with ventricular enlargement. Grade IV is intraparenchymal

haemorrhage. (IVH)

Appendix 8 PRISMA checklist for the systematic review of stillbirth and neonatal complications in uncomplicated twin pregnancies (Part 1/3)

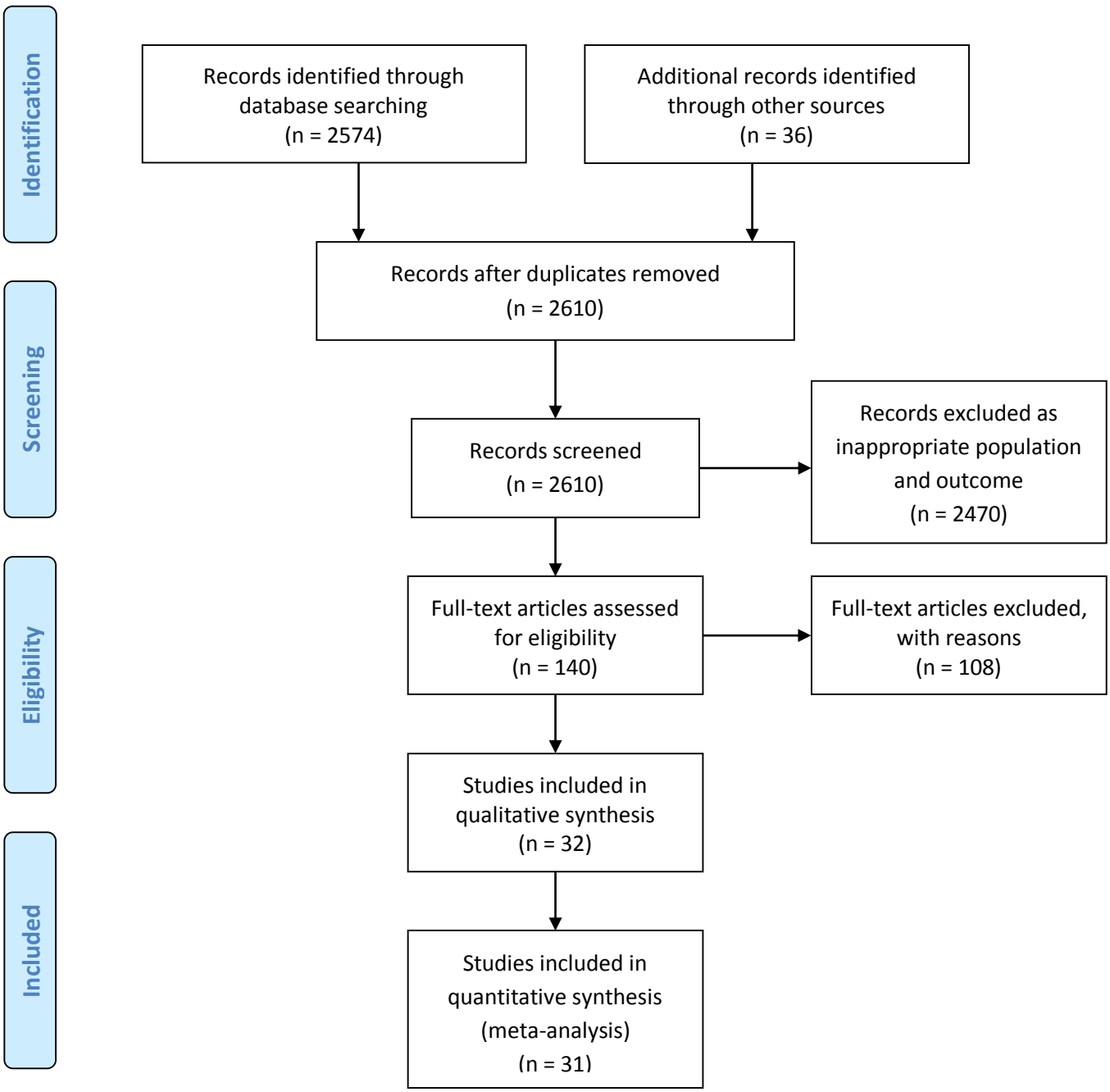
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	124
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	121-122
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	124
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	124-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	125
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	126
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	126
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	127
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	127
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	127
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	128
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	129-131
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	129-131

Appendix 8 PRISMA checklist for the systematic review of stillbirth and neonatal complications in uncomplicated twin pregnancies (Part 2/3)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	131
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	131
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	131, Figure 5.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 5.2 Appendix 11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 5.3, 5.4, Table 5.1, App 12, 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 5.3, 5.4 Table 5.1, App 12, 13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 5.2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	134, Figure 5.4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	139-143
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	140-141
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	142-144
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	144

Appendix 8 PRISMA checklist for the systematic review of stillbirth and neonatal complications in uncomplicated twin pregnancies (Part 3/3)

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Appendix 9 Search strategy in Medline for the systematic review on prospective risk of stillbirth and neonatal complications in uncomplicated twin pregnancies

a. Stillbirth outcome

1. Pregnancy.ti.ab
2. Twin.ti.ab
3. (Monochorionic or dichorionic).ti.ab
4. (Fetal or foetal or fetus or foetus).ti.ab
5. Multiple.ti.ab
6. 1 and 2
7. 1 and 5
8. 3 or 6 or 7
9. (Death or Demise or Mortality).ti.ab
10. Stillbirth.ti.ab
11. 4 and 9
12. 10 or 11
13. 8 and 12

b. Neonatal outcomes

1. Pregnancy.ti.ab
2. Twin.ti.ab
3. (Monochorionic or dichorionic).ti.ab
4. Multiple.ti.ab
5. Twins
6. 1 and 2
7. 1 and 4
8. 3 or 5 or 6 or 7
9. Neonatal death.ti.ab
10. Neonatal morbidity.ti.ab
11. Neonatal mortality.ti.ab
12. Neonatal outcome*.ti.ab
13. /or 9-12
14. Bronchopulmonary dysplasia.ti.ab
15. Assisted ventilation.ti.ab
16. Retinopathy of prematurity.ti.ab
17. Hypoxic ischaemic encephalopathy.ti.ab
18. Neonatal sepsis.ti.ab
19. Neonatal meningitis.ti.ab
20. /or 14-19
21. 13 or 20
22. 8 and 21
23. 8 and 12

Appendix 10: Study characteristics of included studies in the systematic review on prospective risk of stillbirth and neonatal complications in uncomplicated twin pregnancies (12 pages)

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Author, Year (Country)	Study Quality	Population Centre	Inclusion criteria	Exclusion criteria	Duration of follow-Up	Monitoring and Delivery Policy	Fetal and Neonatal Outcomes
Aboulghar, 2012 (Egypt) *	Low risk of bias for representativeness Prospective RCT Random sampling 100% follow-up Low risk of ascertainment bias Low risk of misclassification bias	DC twins (88) Single centre 2008-2010	Healthy pregnant women who conceived after IVF/ICSI between 18-24 weeks with a first pregnancy, singleton or dichorionic twins (we only included DC twin data)	Excluded serious fetal anomalies for which termination may be considered, IUGR (<10^{th} percentile), monochorionic twins, uterine anomalies, cervical cerclage	20 weeks to delivery	Scans every 4 weeks for growth and Doppler (DC twins). Delivery: 37 weeks (Elective Caesarean delivery for all patients)	Stillbirth Neonatal death Assisted Ventilation NICU RDS
Barigye, 2005 (UK)	Low risk of bias for representativeness Retrospective cohort Consecutive sampling 96.2% follow-up Low risk of ascertainment bias Medium risk of misclassification bias	MC twins (151) Single centre 1992-2004	MC twins with appropriate and concordant fetal growth	Excluded TTTS, IUGR, structural abnormalities, TRAP.	24 to >36 weeks	Scans every 2 weeks for growth, amniotic fluid and Doppler (umbilical artery, vein). Ductus venosus Doppler (after 1999). Chorionic plate Doppler (after 1995). Delivery: 36-37 weeks (MC)	Stillbirth
Barrett, 2012 (25 countries) *	Low risk of bias for representativeness Prospective RCT Consecutive sampling 99.3% follow-up Random sampling Low risk of ascertainment bias Low risk of misclassification bias	MC twins (660) DC twins (1930) Multicentre (106) 2003-2011	Twin pregnancy between 32^{+0} and 38^{+6} weeks, first twin in cephalic presentation, both fetuses alive with an estimated weight between 1500g and 4000g confirmed by ultrasound within 7 days before randomisation.	Excluded monoamniotic twins, lethal fetal anomaly, contraindication to labour or vaginal delivery (fetal compromise, first twin substantially larger than second twin, fetal condition that may cause mechanical problems at delivery, previous vertical uterine incision or more than	32 to >40 weeks	Scans at least every 4 weeks for growth. Non-stress or biophysical profiles twice weekly if needed. Delivery: 37^{+5}-38^{+6} weeks (MC and DC)	Stillbirth Neonatal death Assisted ventilation BPD PVL HIE^ (broad definition) IVH NEC^ (diagnosis by x-ray, surgery or autopsy) Neonatal seizures^ (before 72 hours of age)

				one lower segment Caesarean delivery). * Authors provided data excluding cases of TTTS and/or fetal growth restriction			NICU^ (ventilator and parenteral nutrition support) RDS SCBU Sepsis
Berezowsky, 2014 (Israel)	Low risk of bias for representativeness Prospective cohort Consecutive sampling Unclear follow-up rate Low risk of ascertainment bias Unclear risk of misclassification bias	MC twins (332) Single centre Unclear years of recruitment	Uncomplicated monochorionic diamniotic twin pregnancies who delivered between 34 and 37 weeks of gestation.	Excluded TTTS, selective IUGR, major malformations or chromosomal abnormalities in either twin.	34 weeks until delivery	Scans every 2 weeks for biometry and Doppler evaluation. Delivery policy: Unclear	Stillbirth Neonatal death IVH^ (no details of staging) NEC^ NICU ^ RDS^ SCBU Sepsis^ ^ no details of definitions
Bhattachary a 2015 (UK)	High risk of bias for representativeness Retrospective cohort Consecutive sampling Unclear follow-up rate Low risk of ascertainment bias Low risk of misclassification bias	MC twins (422) DC twins (2081) Single centre Unclear years of recruitment (databank on twins from 1968 to present day)	Authors provided data on twin pregnancies uncomplicated by TTTS and deliveries between 26 to >40 weeks	Excluded TTTS	26 weeks until delivery	Scans every 2 weeks for growth (MC); scans every 4 weeks for growth (DC) Delivery: 36 weeks (MC); 38 weeks (DC)	Stillbirth Neonatal death
Breathnach, 2011 (Ireland) *	Low risk of bias for representativeness Prospective cohort Consecutive sampling 97.4% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (185) DC twins (781) Multicentre (8) 2007-2009	Twin pregnancies with fetal growth appropriate for gestational age >10th centile, normal amniotic fluid and normal umbilical artery Doppler evaluation at 34/40 (MC) and 36/40 (DC).	Excluded major structural abnormality in either twin, fetal aneuploidy, prenatally identified TTTS cases from MC cohort, fetal growth <10th centile and intertwin growth discordance >20%.	26 weeks to delivery	Scans every 2 weeks for growth, amniotic fluid, Doppler (umbilical artery and middle cerebral artery) from 16 weeks (MC) and from 24 weeks (DC). Ductus venosus Doppler if abnormal umbilical or middle cerebral artery Doppler or intertwin growth discordance exceeded 20%. Delivery: No detailed policy but all delivery by 37 weeks	Stillbirth Neonatal death Assisted ventilation PVL HIE IVH NEC^ (all stages) RDS ROP SCBU Sepsis

						(MC) and 40 weeks (DC).	
Briery, 2009 (USA) *	Low risk of bias for representativeness Prospective RCT Random sampling 100% follow-up Low risk of ascertainment bias Low risk of misclassification bias	DC twins (25) Single centre	Women with twin gestations cared for by the centre.	Excluded IUGR <10th percentile, growth discordancy ≥20%, severe medical disorders eg sickle cell disease, insulin dependent diabetes mellitus, chronic hypertension, cervical dilatation ≥1cm, cerclage, uterine abnormalities) * Authors provided data excluding major congenital abnormalities.	20 weeks until delivery or maternal discharge	Scans every 3 weeks for growth after 20 weeks. Doppler only performed for complications. No delivery policy.	Stillbirth Neonatal death BPD Assisted ventilation NEC RDS^ (>24 hours and diagnosis by x-ray) NICU IVH Sepsis
Burgess, 2014 (USA)	Moderate risk of bias for representativeness Retrospective Consecutive sampling Unclear response rate. Low risk of ascertainment bias Low risk of misclassification bias	MC twins (167) DC twins (601) Single centre 1987-2010	MC and DC twins delivered at Medical University of South Carolina from 1987-2010.	Gestational age <34 weeks, monoamnionicity, aneuploidy, fetal anomalies that require prolonged hospitalisation or immediate surgery, co-twin death at <34 weeks' gestation, unknown chorionicity.	34 to ≥39 weeks	Scans every 4 weeks for growth and amniotic fluid. (MC and DC) Scans at least 3 weekly (MC twins after 2005). Weekly non-stress testing from 32 weeks (MC) and 34 weeks (DC). Delivery: 36-37 weeks (MC) and 37-38 weeks (DC).	Stillbirth Neonatal death Assisted ventilation NICU RDS SCBU Sepsis
Combs, 2011 (USA) *	Moderate risk of bias for representativeness Prospective RCT Random sampling 99.9% follow up Low risk of ascertainment bias Low risk of misclassification bias	DC twins (236) 18 centres 2004-2009	DCDA twin pregnancy at 15-23 weeks' gestation and detailed ultrasound showing no major fetal anomalies.	Excluded <18 years old, women who had taken any progestins >15 weeks gestation, symptomatic uterine contractions, rupture of membranes, contraindications to prolonging the pregnancy, any pre-existing condition that might be worsened by progesterone or a pre-existing medical	From enrolment to post delivery	No scanning policy, authors advise clinical care as per ACOG Educational Bulletin on multiple gestations. Delivery: No policy, left entirely to managing clinicians.	Stillbirth Neonatal death Assisted ventilation^ (broad definition) BPD^ (within 28 days of life) PVL^ (local neonatologist) IVH^ (local neonatologist) NEC NICU

				condition carrying a high risk of preterm delivery) * Authors provided data where IUGR and twin growth discordance excluded.			RDS^ (broad definition) ROP^ (no staging) Sepsis^ (no time limit)
Dodd, 2012 (Australia, New Zealand) *	Moderate risk of bias for representativeness Prospective RCT Random sampling 100% follow up Low risk of ascertainment bias Moderate risk of misclassification bias	MC twins (40), DC twins (195) 13 centres 2003-2010	Twin pregnancy at $\geq 36^{+6}$ weeks' gestation with no contraindication to continuing the pregnancy, presenting to a collaborating centre.	Excluded fetal demise of one or both twins at time of trial entry, active labour, evidence of a non-reassuring fetal heart rate tracing or maternal or fetal compromise precluding continued antenatal surveillance. * Authors confirmed that cases of TTTS, congenital abnormalities/ structural malformations were excluded.	36^{+6} weeks to over 39^{+} weeks. Women and babies followed up til 4 months postpartum and babies at 18 months postpartum.	Scan policy as per recruiting centre management. Not specified for study as women were randomised at 36^{+6} weeks. Delivery policy: Elective Birth Group (37 weeks); Standard Care Group (continued expectant management with birth planned from 38 weeks)	Stillbirth Neonatal deaths Assisted ventilation^ (within birth admission) HIE^ (grades 3 or 4 Sarnat neonatal encephalopathy) NEC Neonatal seizures^ ($\leq$24 hours, requiring $\geq$2 drugs to control) NICU RDS^ (severe with MAP $\geq$10mmHg and $FiO_2 \geq 0.8$) Sepsis^ (within 48 hours)
Domingues, 2009 (Portugal)	Moderate risk of bias for representativeness Retrospective cohort Consecutive sampling 100% follow-up Low risk of ascertainment bias Medium risk of misclassification bias	MC twins (111) DC twins (290) Single centre 1996-2007	All completed multiple pregnancies managed in the centre during the timeframe, uncomplicated MCDA twin pregnancies who delivered after 24 weeks' gestation selected, DCDA twin pregnancies also selected.	Excluded TTTS, IUGR, discordant growth ($\geq$20% difference in estimated fetal weight), structural abnormalities, TRAP, IUFD of one fetus before 24^{th} week' gestation.	24 to 35^{+6} weeks	Scans every 2 weeks for growth, amniotic fluid and Doppler until 32/40 then weekly thereafter (MC and DC). Delivery: 36-37 weeks (MC and DC)	Stillbirth
Farah, 2011 (Ireland)	Low risk of bias for representativeness Retrospective cohort Consecutive sampling	MC twins (144) Single centre 1999-2007	Appropriate growth (fetal weight $>5^{th}$ percentile)	Excluded TTTS, IUGR, discordant fetal growth ($\geq$25% difference in EFW), structural	24 to 39^{+6} weeks	Scans every 2 weeks (no details on which parameters were assessed). Delivery: 38-40 weeks (MC)	Stillbirth

	100% follow-up Low risk of ascertainment bias Medium risk of misclassification bias			abnormalities, TRAP.			
Hack, 2008 (Netherlands) *	Low risk of bias for representativeness Retrospective cohort Consecutive sampling 100% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (119) DC twins (952) 2 centres 1995-2004	All twin pregnancies from the electronical database who delivered in the timeframe.	Excluded TTTS, fetal growth restriction, major lethal chromosomal and/or congenital malformations.	26 to >40 weeks (MC and DC)	Scans every 2 weeks for growth, amniotic fluid and 'Doppler assessments' after 20/40. Delivery at 37-38 weeks (MC); Await spontaneous delivery if uncomplicated (DC)	Stillbirth Neonatal death IVH^ (all stages) NEC^ (all stages, conservative and surgical) RDS Sepsis
Hack, 2011 (Netherlands) *	Low risk of bias for representativeness Retrospective cohort Consecutive sampling 100% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (466) Multicentre (10) 2000-2005	Monochorionic twin pregnancies delivering in the participating centres in the timeframe.	Excluded TTTS, fetal growth restriction, major lethal chromosomal and congenital malformations. Authors contacted and provided further data so that population did not overlap with Hack 2008.	32 to >40 weeks	Scans at least at 20, 24, 28 weeks and 2 weekly after for growth, amniotic fluid, umbilical artery Doppler. If 'nonreassuring fetal findings' or maternal complications, twice weekly evaluations of amniotic fluid volume, umbilical artery Doppler and proceeding to middle cerebral artery and Ductus venosus Doppler. Delivery: 37 weeks (local policy in 7/10 centres) In the other centres, no specific policy other than delivery undertaken in the case of fetal or maternal complications. (MC)	Stillbirth Neonatal death IVH^ (all stages) NEC^ (all stages, conservative and surgical) RDS Sepsis
Lee, 2008 (USA)	Low risk of bias for representativeness Retrospective cohort Consecutive sampling	MC twins (130) DC twins (641) Single centre 2000-2007	All twin pregnancies who delivered at the centre in the timeframe identified from a departmental	Excluded monoamniotic twins, twin sets within triplets or higher order multiples, IUGR (EFW <10th	24 to >38 weeks	Scans every 3-4 weeks for growth. Frequency of scans increased if IUGR or growth	Stillbirth

	100% follow-up Low risk of ascertainment bias Low risk of misclassification bias		perinatal database.	centile for gestational age), significant inter-twin discordance (≥20% difference in EFW), major anomaly or TTTS. No cases of TRAP or conjoined twins.		discordance discovered. Weekly biophysical profile with amniotic fluid in 3rd trimester. (MC) Delivery: 34-35 weeks (MC)	
Lewi, 2008 (2 countries - Belgium and Germany) *	Low risk of bias for representativeness Prospective cohort Consecutive sampling 100% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (149) 2 centres 2002-2007	Monochorionic twin pregnancies diagnosed between 11-14 weeks' by first trimester ultrasound.	Excluded TRAP, triplets containing a monochorionic pair or monochorionic twin pregnancies resulting from reduction of a higher order multiple pregnancy. * Authors contacted and provided data excluding TTTS cases and prenatally detected fetal growth restriction or >25% fetal growth discordance at 26 weeks gestation.	12 weeks until delivery	Scans at 12, 16 weeks and then 2 weekly until 32 weeks and weekly from 32 to 36 weeks for growth, signs of TTTS and Doppler (ductus venosus, umbilical artery, middle cerebral artery). Delivery: Recommended at 36-37 weeks (MC)	Stillbirth Neonatal death Assisted ventilation BPD HIE IVH NEC Neonatal seizures NICU ROP Sepsis^ (no time limit, any septicaemia in neonatal period)
Liem, 2013 (Netherlands) *	Moderate risk of bias for representativeness Prospective RCT Random sampling 99.4% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (173) DC twins (588) 40 centres 2009-2012	Multiple pregnancy between 12 and 20 weeks' gestation.	Excluded serious congenital defects, TTTS, known placenta praevia.	26 to 39^{+6} weeks (MC) 26 to >40 weeks (DC)	Scans for growth, amniotic fluid, umbilical artery Doppler every 2 weekly from 14 weeks for MC twins. No routine ultrasound for DC twins. (Nationwide guidelines) Delivery – no protocol, adhered to nationwide guidelines: 36-37 weeks (MC), before 40 weeks (DC)	Stillbirth Neonatal death BPD NEC IVH^ (grade II and above) PVL^ (all stages) RDS^ (grade II and above) NICU Sepsis
Lim, 2011 (Netherlands) *	Moderate risk of bias for representativeness	MC twins (109) DC twins	Multiple pregnancy between 15 and	Excluded serious congenital	15-19 weeks until 6	Scans according to local protocol.	Stillbirth Neonatal death

	Prospective RCT Random sampling 99.4% follow-up Low risk of ascertainment bias Unclear risk of misclassification bias	(518) 55 centres 2006-2009	19 weeks' gestation, accurate determination of chorionicity by ultrasonography before inclusion.	defects, early signs of TTTS, women with previous spontaneous preterm birth before 34 weeks, death of one or more fetuses or primary cerclage.	weeks after delivery (MC & DC)	No delivery policy – by local protocol	BPD^ NEC^ RDS^ NICU IVH^ Sepsis^ ^ all based on local neonatologist's diagnosis
Mahony, 2011 (Ireland)	Low risk of bias for representativeness Retrospective cohort Consecutive sampling 100% follow-up Low risk of ascertainment bias Unclear risk of misclassification bias	MC twins (194) DC twins (569) Single centre 1997-2006	All twin pregnancies delivered at the centre within the timeframe, identified by the hospital perinatal database, twins with two viable foetuses at 23^{+6} week and delivery at 24^{+0} weeks or later.	Excluded fetal malformation, IUGR (<5^{th} centile for gestational age on standardised growth chart), significant inter-twin discordance (≥20% difference in EFW) and TTTS (in separate table)	24 to >38 weeks	Scans every 4 weeks (MC and DC prior to 2002) Scans at least every 2 weeks for fetal weight, biophysical profile, umbilical artery Doppler. (MC after 2002) Scans every 4 weeks until 28 weeks then 2 weekly after for fetal weight, biophysical profile, umbilical artery Doppler (DC after 2002) Delivery: 38 weeks (MC and DC)	Stillbirth
McPherson, 2012 (USA)	High risk of bias for representativeness Retrospective cohort Consecutive sampling 92.6% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (471) DC twins (1619) Single centre 1990-2008	All twin pregnancies undergoing routine sonographic anatomic survey at 17-22 weeks at the centre in the timeframe.	Excluded monoamniotic pregnancies, TTTS, single.	20 to >38 weeks.	2 weekly scans to check for TTTS (MC) Scans for growth every 3-4 weeks growth scans (MC and DC) Twice weekly non-stress tests or biophysical profiles from 32 weeks if clinically indicated. No details of delivery policy but mean delivery gestation was 33.9 (SD 4.8) for MC and 34.8 (SD 4.2) for DC	Stillbirth
Morikawa, 2012 (Japan)	High risk of bias for representativeness Retrospective	DC (6467) 120 centres 2005-2008	Twin pregnancies registered on the JSOG	Excluded unknown chorionicity, monchorionic	26 to >40 weeks.	No details regarding scanning policy. No details of	Stillbirth Neonatal death

	cohort Consecutive sampling Response rate unclear Unclear risk of ascertainment bias Moderate risk of misclassification bias		Successive Pregnancy Birth Registry system, deliveries occurred ≥22 weeks in the specified centres.	monoamniotic twin pregnancies.		delivery policy	
Nakayama, 2012 (Japan) *	Moderate risk of bias for representativeness Retrospective cohort Consecutive sampling 100% follow-up Unclear risk of ascertainment bias Moderate risk of misclassification bias	MC twins (187) Single centre 2004-2010	Monochorionic diamniotic twin pregnancies delivered at the centre, received prenatal care before 14 weeks' gestation, delivered at the centre.	Excluded single or double fetal demise before 14 weeks' gestation, TRAP, triplets containing a monochorionic pair and major anomalies diagnosed before 14 weeks. *Authors provided data excluding TTTS cases	26 to >40 weeks	Scans for growth, amniotic fluid weekly from 16 weeks' gestation. Detailed scan at 20 and 30 weeks' gestation. Delivery at 38 weeks (MC)	Stillbirth Neonatal death
Awwad, 2014 (Lebanon)	Moderate risk of bias for representativeness Prospective RCT Random sampling 98.3% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (39) DC twins (212) Single centre 2006-2012	Twin pregnancy diagnosed by ultrasound and maternal age ≥18 years.	Excluded known fetal anomaly, elective cerclage prior to 14 weeks' gestation, hypertension, diabetes mellitus, asthma, history of deep vein thrombosis, history of hepatic disease or abnormal liver enzymes, pre-existing renal disease or abnormal kidney function and seizure disorders. * Authors confirmed TTTS excluded	20 weeks until delivery and discharge of babies from hospital (MC & DC)	Scans every 2 weeks for fetal wellbeing and TTTS features (MC) and weekly or semi-weekly non-stress tests from 32-34 weeks. Scans every 4 weeks for fetal wellbeing (DC). Delivery: 36-37 weeks (MC unless complicated), 37-38 weeks (DC)	Stillbirth Neonatal death Assisted ventilation BPD PVL IVH NEC Neonatal seizures NICU RDS ROP Sepsis
Norman, 2009 (UK) *	Moderate risk of bias for representativeness Prospective RCT Random sampling 97.6% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (89) DC twins (390) 9 centres 2004-2008	Twin pregnancy with gestation and chorionicity established by scan before 20 weeks and attending ANC during recruitment period.	Excluded TTTS (if occurring before 24 weeks), recognised structural or chromosomal fetal abnormality (contraindications to	20 weeks until delivery	No specific scanning policy. Delivery policy – anticipate vaginal delivery, no policy for gestational age for delivery.	Stillbirth Neonatal death Assisted ventilation^ BPD^ PVL^ IVH^ NEC^ NICU ROP

				progesterone, planned cervical suture, planned elective delivery before 34 weeks)			RDS^ Sepsis^ ^ all based on local neonatologist's diagnosis)
Rode, 2011 (2 countries – Denmark & Austria) *	Low risk of bias for representativeness Prospective RCT Random sampling 99.7% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (99) DC twins (567) multicentre (17) 2006-2008	Women with a live diamniotic twin pregnancy and chorionicity assessed by ultrasound before 16 weeks' gestation.	Excluded treatment for or signs of TTTS, known major structural or chromosomal fetal abnormality (<18 years old, known allergy to progesterone or peanuts, history of hormone associated thromboembolic disorders, rupture of membranes, intentional fetal reduction, known or suspected malignancy in genitals or breasts, known liver disease) * Authors provided data excluding fetal growth restriction if suspected or present at inclusion	18 to 24 weeks until delivery (infants until 18 months post EDD) (MC and DC)	Denmark - scans every 2 weeks from 18 weeks (MC); scans every 4 weeks from 20 weeks (DC). Delivery - No protocol, adhered to nationwide guidelines. Denmark – 38 weeks (MC and DC); Austria – 36-37 weeks (MC); 37-38 weeks (DC)	Stillbirth Neonatal death Assisted ventilation IVH NEC NICU RDS ROP Sepsis
Rouse, 2007 (USA) *	Low risk of bias for representativeness Prospective RCT Random sampling 99.1% follow-up Low risk of ascertainment bias Unclear risk of misclassification bias	MC twins (92) DC twins (531) 14 centres 2004-2006	Women with twin pregnancies between 16 to 20+3 weeks' gestation.	Excluded serious fetal anomalies, spontaneous death of a fetus after 12 weeks, presumed monoamniotic placenta, suspected TTTS, marked ultrasonographic growth discordance (>3 weeks of estimated gestational age between fetuses), planned non study progesterone	16 weeks til delivery	Scans at 12 and 20+6 weeks, adhered to local guidelines Delivery policy: No protocol, adhered to nationwide guidelines	Stillbirth Neonatal death Assisted ventilation BPD PVL IVH NEC Neonatal seizures NICU ROP RDS Sepsis

				therapy after 16 weeks, in-place or planned cervical cerclage, major uterine anomaly (bicornuate uterus), treatment with 10,000 or more units of unfractionated heparin per day, treatment with low molecular weight heparin at any dose and major chronic medical disease (eg insulin requiring diabetes mellitus or pharmacologically treated hypertension), twin gestations that were the result of intentional fetal reduction.			
Russo, 2013 (Italy) *	Moderate risk of bias for representativeness Retrospective 100% follow-up Low risk of ascertainment bias Low risk of misclassification bias	MC twins (207) DC twins (532) Single centre 1995-2011	Singleton and twin pregnancies delivered in the centre in the timeframe.	Excluded triplets or higher order multiple gestations, monoamniotic pregnancies and pregnancies with fetal death at <22 weeks. Authors provided data excluding TTTS cases and fetal abnormalities.	26 to >40 weeks (MC and DC)	Scans to check for TTTS features 2 weekly from 16/40 (MC) Scans for growth every 4 weeks from 20/40 (DC) Delivery – await until 40 weeks unless developed complications (MC and DC) Complications included premature rupture of membranes, maternal or obstetric complications, abnormal umbilical artery Doppler, abnormal biophysical profile, oligohydramnios of either twin, arrest of fetal growth in either	Stillbirth

						twin.	
Serra, 2012 (Spain) *	Moderate risk of bias for representativeness Prospective RCT 98.6% follow-up Low risk of ascertainment bias Low risk of misclassification bias	DC twins (283) 5 centres 2005-2008	DCDA twin pregnancies diagnosed by ultrasound and maternal age >/=18 years	Excluded fetal anomalies, singleton pregnancies, monochorionic pregnancies, triplets or higher order multiple pregnancies, elective cervical cerclage prior to 14 weeks, history of hepatic problems or gestational cholestasis, abnormal liver enzymes, abnormal kidney function, local allergy to micronized natural progesterone, allergy to peanuts, recurrent vaginal bleeding, recurrent vaginal infections, alcohol or illicit drug consumption, smoking ≥10 cigarettes/day).	20 weeks until delivery	Scans at 12, 20, 24, 28, 32-34 and 36-38 weeks. Delivery policy – according to local protocols at 5 centres.	Stillbirth Neonatal death Assisted ventilation BPD PVL IVH NEC Neonatal seizures NICU RDS ROP Sepsis
Smith, 2010 (USA)	Low risk of bias for representativeness Retrospective cohort Consecutive sampling 96.8% follow-up Low risk of ascertainment bias Unclear risk of misclassification bias	MC twins (232) Single centre 2001-2008	Women with viable MCDA twin pregnancy identified by ultrasound at the centre in the timeframe, ≥14 weeks' gestation.	Excluded TRAP, twins from selective reduction of higher order multiples. * Authors provided data on 'uncomplicated twins' (excluding TTTS, anomalies, growth discordance)	26 to >40 weeks.	Scans to check for growth and amniotic fluid volume 2 weekly. Umbilical artery Doppler if growth or amniotic fluid discordance identified. Non-stress test or biophysical profile weekly from 32 weeks. Delivery at 35-37 weeks (MC)	Stillbirth
STORK, 2012 (UK)	Moderate risk of bias for representativeness Retrospective cohort Consecutive sampling 100% follow-up	MC twins (527) DC twins (2456) 9 centres 2000-2009	Women registering for routine antenatal care by 11 weeks' gestation with confirmed diamniotic twin pregnancy.	Excluded stillbirth with birthweight <500g. * Authors provided data excluding TTTS and congenital	26 to >40 weeks	Scans for growth every 3-4 weeks from 28 weeks or more frequently if clinically indicated. Additional scans	Stillbirth

	Low risk of ascertainment bias Low risk of misclassification bias			abnormalities.		at 17 and 19 weeks for TTTS (MC) Delivery at 36 weeks CS (MC) 37 weeks CS (DC if presenting twin non cephalic) 38 weeks planned vaginal birth (DC). Policy may vary among different centres and over timeframe.	
Suzuki, 2010 (Japan)	High risk of bias for representativeness Retrospective cohort Consecutive sampling Unclear response rate Low risk of ascertainment bias Medium risk of misclassification bias	DC twins (274) Single centre 2004-2008	All women who delivered singleton and dichorionic twin pregnancies at 34 to 40 weeks' at the centre in the timeframe.	Monochorionic twin pregnancies.	26 to >40 weeks	No details of scanning policy. No details of delivery policy	Stillbirth IVH ^ (no details of staging) RDS^ (clinical and radiological signs)
Wood 2015 (Canada)	High risk of bias for representativeness Retrospective cohort Consecutive sampling 100% follow-up Low risk of ascertainment bias High risk of misclassification bias (chorionicity only)	DC twins (6722) 81 centres 1992-2007	All twin pregnancies in which the fetuses survived until ≥23 weeks of gestation.	Triplet pregnancies, twin pregnancies for which siblings could not be matched, unknown gestational age. * Authors provided data excluding congenital abnormalities	23 to >40 weeks	Data on frequency of ultrasound surveillance and adequacy of prenatal care not available. No details of delivery policy.	Stillbirth Neonatal death

Key

* Authors sent additional data

Quality assessment: Quality of representativeness reflects the representativeness of an uncomplicated twin population (high quality if excluded congenital abnormalities/major structural malformations, intrauterine fetal growth restriction and/or significant intertwin growth discordance >25%). Level of ascertainment bias reflects the accuracy of definition of stillbirth (>24 weeks' gestation or >500g birthweight). Level of misclassification bias reflects the accuracy of the chorionicity determination and of gestational age assessment.

^ The neonatal morbidity outcome definition deviated from our standard definitions detailed :Bronchopulmonary dysplasia – need for oxygen at a postnatal gestational age of 36 completed weeks and an x-ray compatible with bronchopulmonary dysplasia; Need for assisted ventilation – for more than 24 hours within 72 hours of birth; Necrotising enterocolitis (NEC) – Bell's staging 2 or 3 (ie definite or severe NEC) radiological signs of significant intestinal dilatation, pneumatosis intestinalis, portal vein gas, with or without ascites, persistently abnormal gas pattern, with or without pneumoperitoneum; Septicaemia – confirmed by positive blood cultures within 72 hours of birth.; Intraventricular haemorrhage – grade 3 or 4 – ventricular enlargement due accumulated blood and/or bleeding extends into brain tissue around the ventricles.; Cystic periventricular leukomalacia – periventricular cystic changes in the white matter excluding subependymal and choroid plexus cysts); Retinopathy of prematurity (stages 3, 4 or 5); Hypoxic ischaemic encephalopathy (clinical or laboratory evidence of subacute brain injury due to asphyxia); Respiratory distress syndrome (requiring ventilation); Neonatal seizures (seizures that occur from birth until the end of the neonatal period); NICU admission (any admission to the neonatal intensive care unit).

Appendix 11: Individual study data for stillbirths and neonatal deaths for monochorionic and dichorionic twin pregnancies

		Monochorionic pregnancy (13 studies)			Dichorionic pregnancy (15 studies)		
Study		**No. of neonatal death**	**No. of stillbirth**	**No. of pregnancies**	**No. of neonatal death**	**No. of stillbirth**	**No. of pregnancies**
Aboulghar 2013	Early preterm	-	-	-	2	1	91
	34 weeks and after				0	2	
Awwad 2014	Early preterm	0	0	39	1	4	220
	34 weeks and after	0	0		0	4	
Barrett 2013	Early preterm	0	1	656	3	0	1925
	34 weeks and after	4	3		9	9	
Bhattacharya 2015	Early preterm	10	11	443	41	19	2098
	34 weeks and after	6	13		16	12	
Breathnach 2011	Early preterm	0	4	193	0	2	785
	34 weeks and after	0	2		0	0	
Burgess 2014	Early preterm	0	0	151	0	0	547
	34 weeks and after	0	0		4	1	
Coombs 2011	Early preterm	-	-	-	1	0	236
	34 weeks and after				0	0	
Hack 2008	Early preterm	9	7	126	16	7	955
	34 weeks and after	0	2		1	3	
Hack 2011	Early preterm	16	6	469	-	-	-
	34 weeks and after	2	1				
Lewi 2008	Early preterm	1	1	151	-	-	-
	34 weeks and after	0	1				
Liem 2013	Early preterm	2	2	175	1	2	591
	34 weeks and after	0	3		0	4	
Lim 2011	Early preterm	0	1	108	1	1	525
	34 weeks and after	0	0		3	7	
Morikawa 2012	Early preterm	-	-	-	21	31	6514
	34 weeks and after				20	34	
Nakayama 2012	Early preterm	2	1	192			
	34 weeks and after	1	3				
Norman 2009	Early preterm	0	1	90	2	3	394
	34 weeks and after	1	0		1	2	

Rode 2011	Early preterm	0	1	100	0	2	570
	34 weeks and after	0	0		1	2	
Serra 2013	Early preterm				1	1	286
	34 weeks and after	-	-	-	0	2	
Wood 2015	Early preterm				20	21	6704
	34 weeks and after	-	-	-	5	33	
N=13 studies					**N=15 studies**		

*****Early preterm: $26^{+0} – 33^{+6}$ weeks gestation*

Appendix 13 Risks of stillbirths and neonatal deaths in dichorionic and monochorionic twin pregnancies between 26^{+0} weeks and 33^{+6} weeks

Gestational age (weeks)	No. of stillbirths /No. of ongoing pregnancies n/N	Stillbirth crude rate x 1000 pregnancies (95% CI)	No. of neonatal deaths /No. of women delivered n/N	Neonatal death weekly risk x 1000 women delivered (95% CI)
Dichorionic pregnancies				
26^{+0} - 27^{+6}	20/26685	0.7 (0.5-1.2)	40/316	195.5 (92.8-365.9)
28^{+0} - 29^{+6}	38/26247	1.4 (1.0-2.0)	40/513	72.0 (32.7-151.0)
30^{+0} - 31^{+6}	40/25511	1.6 (1.1-2.1)	17/905	24.2 (10.5-54.6)
32^{+0} - 33^{+6}	49/24178	2.0 (1.5-2.7)	9/1514	7.8 (3.2-19.3)
Monochorionic pregnancies				
26^{+0} - 27^{+6}	21/4115	5.1 (3.2-7.8)	12/44	203.4 (66.3-478.5)
28^{+0} - 29^{+6}	18/3998	4.5 (2.7-7.1)	12/79	84.5 (26.6-237.6)
30^{+0} - 31^{+6}	15/3830	3.9 (2.2-6.5)	11/132	32.3 (9.4-105.1)
32^{+0} - 33^{+6}	16/3546	4.5 (2.6-7.3)	3/202	11.9 (3.02-46.5)

Appendix 14 Rates of neonatal complications for monochorionic and dichorionic twin pregnancies delivered at various gestational ages between 26^{+0} weeks and 33^{+6} weeks *Permission granted to reproduce this table from The BMJ, BMJ Publishing Group. Licence number 3998160881661*

Gestational age (weeks)	Necrotising enterocolitis		Respiratory distress syndrome		Retinopathy of prematurity		Neonatal seizures		Septicaemia	
	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)
Monochorionic		8 studies		7 studies		4 studies		3 studies		8 studies
26^{+0}-27^{+6}	4/35	99.7 (43.3-212.9)	32/35	902 (795.5-956.1)	0/1	N/A	0/0	N/A	14/35	522.4 (385.4-656.1)
28^{+0}-29^{+6}	3/62	67 (38.8-113.1)	48/61	752.9 (609.4-856.1)	0/6	N/A	0/1	N/A	30/62	375.6 (290.8-468.7)
30^{+0}-31^{+6}	5/95	44.5 (26.4-73.9)	46/86	501.9 (360.9-642.6)	0/12	N/A	0/11	N/A	21/95	248.5 (192.1-315)
32^{+0}-33^{+6}	4/141	29.3 (13.1-64.4)	38/124	250 (150.1-386.2)	0/24	N/A	0/19	N/A	21/141	153.9 (104.7-220.5)
Dichorionic		9 studies		10 studies		4 studies		3 studies		9 studies
26^{+0}-27^{+6}	5/45	156.2 (84.6-270.7)	43/46	919.3 (831.9-963.2)	1/5	236.3 (58.4-606.8)	0/0	N/A	25/45	571.1 (405.5-722.2)
28^{+0}-29^{+6}	8/73	75.1 (48.6-114.2)	53/74	798.6 (669.6-885.8)	1/16	104 (40.1-243.8)	1/5	N/A	35/73	377 (259.3-511.3)
30^{+0}-31^{+6}	6/144	34.3 (20.5-57)	90/146	580 (436.1-711.6)	3/27	41.7 (15.3-108.5)	0/10	N/A	48/144	215.7 (143.2-311.5)
32^{+0}-33^{+6}	2/231	15.3 (6.8-34.4)	79/231	324.8 (209.8-465.7)	0/64	16.1 (3.2-76.2)	0/20	N/A	25/231	111.1 (67.9-176.7)

Gestational age (weeks)	Need for assisted ventilation		Bronchopulmonary dysplasia		Cystic periventricular leukomalacia		NICU admission		Intraventricular haemorrhage	
	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)	n/N	Risk x1000 (95% CI)
Monochorionic		5 studies		4 studies		3 studies		6 studies		8 studies
26^{+0}-27^{+6}	5/9	524.7 (121.1-898.4)	2/4	456.8 (65.4-909.9)	0/8	N/A	11/11	990.4 (566.1-999.9)	14/35	170.8 (34.8-540.4)
28^{+0}-29^{+6}	8/13	352.4 (75.7-783.4)	0/2	172.3 (27.3-607.3)	1/7	N/A	12/13	976.3 (550.6-999.3)	13/62	76.5 (15.1-308.6)
30^{+0}-31^{+6}	16/30	211.5 (40.7-629.3)	2/15	49.0 (6.5-290.2)	0/20	N/A	30/32	942.5 (464.4-996.8)	12/95	32.3 (6.1-154.2)
32^{+0}-33^{+6}	17/59	116.8 (18.6-480.4)	0/36	12.6 (0.9-152.0)	0/37	N/A	57/68	867.2 (278.8-991.0)	5/141	13.2 (2.2-74.1)
Dichorionic		8 studies		7 studies		7 studies		9 studies		9 studies
26^{+0}-27^{+6}	9/13	805.6 (378.1-965.8)	2/8	246.9 (77.7-560.5)	1/13	66.8 (12.3-291.2)	14/15	985.3 (831.6-998.9)	26/45	360.8 (182.9-587.5)
28^{+0}-29^{+6}	20/30	552.7 (176.2-877.1)	3/19	116.8 (49.9-250.0)	1/32	38.5 (11.3-123.7)	30/33	957.8 (722.3-995.0)	14/73	152.0 (73.1-289.7)
30^{+0}-31^{+6}	29/59	269.2 (62.6-670.3)	1/47	50.7 (22.2-111.7)	2/70	22.0 (7.0-67.1)	68/74	885.1 (532.6-981.2)	19/144	53.9 (24.4-115.0)
32^{+0}-33^{+6}	32/129	99.0 (18.0-397.1)	3/104	21.1 (6.3-67.9)	2/154	12.4 (2.7-55.3)	124/158	723.1 (277.9-946.6)	5/231	17.8 (7.1-44.0)

n = number of adverse outcomes; N = number of women delivered in that 2 weekly gestational epoch

Appendix 15 Search strategy for the systematic review of prognostic models in obstetrics (Medline)

MEDLINE search strategy	
1	Validat*(ti.ab) OR predict*(ti.ab) OR rule*(ti.ab)
2	Predict*(ti.ab) AND (outcome*(ti.ab) OR risk*(ti.ab) OR model*(ti.ab))
3	(History(ti.ab) OR variable*(ti.ab) OR criteria(ti.ab) OR scor* (ti.ab) OR characteristic*(ti.ab) OR finding*(ti.ab) OR factor*(ti.ab)) AND (predict*(ti.ab) OR model*(ti.ab) OR decision*(ti.ab) OR identif*(ti.ab) OR prognos*(ti.ab))
4	Decision*(ti.ab) AND (model*(ti.ab) OR clinical*(ti.ab) OR logistic model*(ti.ab)
5	Prognostic(ti.ab) AND (History(ti.ab) OR Variable*(ti.ab) OR Criteria(ti.ab) OR Scor*(ti.ab) OR Characteristic*(ti.ab) OR Finding*(ti.ab) OR Factor*(ti.ab) OR Model*(ti.ab)
6	"risk score"[All fields] OR "prediction model"[All fields] OR "prediction rule"[All fields] OR "risk assessment"[All fields] OR "algorithm"[All fields]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	pregnan*(ti.ab) OR obstetric*(ti.ab) OR woman(ti.ab) OR women(ti.ab) VBAC(ti.ab) OR anal sphincter rupture(ti.ab) OR post partum haemorrhage(ti.ab) OR vacuum extraction(ti.ab) OR forceps extraction (ti.ab) OR caesarean (ti.ab) OR casarean (ti.ab) OR caesarian (ti.ab) OR cesarian (ti.ab) OR shoulder dystocia(ti.ab) OR manual placenta removal(ti.ab) OR gestational diabetes(ti.ab) OR placenta praevia(ti.ab) OR abruption (ti.ab) OR cervical incompetence(ti.ab) OR cervical length (ti.ab) OR growth restrict* OR external cephalic version(ti.ab) OR breech OR rupture of membranes(ti.ab) OR PROM(ti.ab) OR PPROM (ti.ab) OR preeclampsia(ti.ab) OR pre-eclampsia (ti.ab) OR pregnancy induced hypertension(ti.ab) OR HELLP(ti.ab) OR vaginal deliver* (ti.ab) OR preterm deliver* (ti.ab) OR preterm labour (ti.ab) OR preterm labor (ti.ab) OR preterm birth (ti.ab)
9	#7 or #8
10	#9 NOT (Animals[MeSH] NOT Humans[MeSH)]

Appendix 16 Details of all prognostic models included in systematic review, organised by predicted outcome (43 pages)

Hypertensive disorders

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Pre-eclampsia											
Di Lorenzo 2012	Pre-eclampsia	Women with singleton pregnancies	Prospective cohort	2218 (25; 3)	Logistic	None	None	None	None	Regression formula	No
Khalil 2012	Pre-eclampsia	Women with live singleton pregnancies	Prospective cohort	7084 (181; unclear)	Logistic	None	None	None	0.85	None	No
Myatt 2012	Pre-eclampsia	Nulliparous women at low risk to develop pre-eclampsia	Nested case-control	683 (174; 7)	Logistic	None	None	None	0.73	None	No (low sensitivity and therefore do not recommend use of model)
Zhou 2012	Pre-eclampsia	Pregnant women	Prospective cohort	1000 (61; 5)	Logistic	None	None	None	0.77	None	Yes
Hoirisch-Clapauch 2011	Pre-eclampsia	Women with third trimester fetal loss or preterm delivery	Retrospective cohort	133 (79; 3)	Logistic	Bootstrapping	None	None	0.81	Score chart	No
North 2011	Pre-eclampsia	Nulliparous women with singleton pregnancies without a recognised high risk for pre-eclampsia, small for gestational age baby or spontaneous preterm birth	Prospective cohort	3347 (186; 12) (model A) 3347 (186; 13) (model B)	Logistic	Crossvalidation	None	"Reasonable" (as stated in paper)	0.71 (internal validation for models A and B)	Regression formula, probability table	Yes
Odibo 2011-a	Pre-eclampsia	Women with singleton pregnancies	Nested case-control	82 (41; 7) (model A) and 82 (41; unclear) (model B)	Logistic	None	None	None	0.82 (model A) and 0.81 (model B)	None	No
Odibo 2011-b	Pre-eclampsia	Women with singleton pregnancies	Prospective cohort	452 (42; 6)	Logistic	None	None	None	0.77	Regression formula	No
Seed 2011	Pre-eclampsia	Women with clinical risk factors for developing pre-	Randomized trial	1121 (190; 6) (development sample)	Logistic	Split-sample	None	Fair (based on table), less in validation sample	0.70 (development); 0.66 (validation)	Regression formula	No (performance not good enough for use in practice)

	eclampsia

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Pre-eclampsia											
Audibert 2010	Pre-eclampsia	Nulliparous women with singleton pregnancies without major fetal anomalies	Prospective cohort	893 (40; unclear)	Logistic	None	None	None	0.82	None	No
Farina 2010	Pre-eclampsia	Women who were scheduled for chorionic villous sampling or amniocentesis at 11-14 weeks in which no major fetal defects were detected	Case-control	99 (11; 4)	Logistic	None	None	None	0.95	None	No
Goetzinger 2010	Pre-eclampsia	Women with singleton pregnancies	Retrospective cohort	3716 (293; 5)	Logistic	None	None	None	0.69	Regression formula, score chart	No
Kenny 2010	Pre-eclampsia	Healthy nulliparous women with singleton pregnancies not considered at high risk of PE, SGA or PTB due to underlying conditions	Nested case-control	120 (60; 14)	PLS-DA (partial least squares - discriminant analysis)	Crossvalidation and permutation testing; incorporation of validation sample for development of final model	None	None	0.94 (discovery); 0.92 (validation)	None	No
Sekizawa 2010	Pre-eclampsia	Singleton pregnant women without any pre-existent medical diseases	Nested case-control	372 (62; 4)	Logistic	None	None	None	0.88	None	No
Phaloprakarn 2009-a	Pre-eclampsia	Women with gestational diabetes mellitus	Prospective cohort	813 (78; 3)	Logistic	None	None	P=0.79	0.91	Risk score, number of risk factors vs risk	Yes

Poon 2009-c	Pre-eclampsia	Women with singleton pregnancies	Prospective cohort	8051 (156; unclear)	Logistic	None	None	None	0.81	No	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Pre-eclampsia											
Emonts 2008	Pre-eclampsia	Women hospitalized with severe PE and women with a successful term delivery after a normotensive pregnancy	Unclear	151 (101; 14)	Logistic	None	None	None	None	Regression formula	No
Khaw 2008	Pre-eclampsia	Nulliparous women with singleton pregnancies	Prospective cohort	534 (8; 3)	Logistic	None	None	None	Only ROC curve, AUC not reported	None	No
de Paco 2008	Pre-eclampsia	Women with singleton pregnancies	Prospective cohort	4376 (83; 5)	Logistic	None	None	None	0.81	Regression formula	No
de Paco 2008	Pre-eclampsia without SGA	Women with singleton pregnancies	Prospective cohort	4376 (46; 5)	Logistic	None	None	None	0.83	Regression formula	No
Poon 2008	Pre-eclampsia	Pregnant women	Prospective cohort	4619 (104; 5)	Logistic	None	None	None	0.85	Regression formula	No
Plasencia 2007	Pre-eclampsia	Women with singleton pregnancies	Prospective cohort	6015 (107; 5)	Bayesian and logistic	None	None	None	0.85	Regression formula	No
Papageorghiou 2005	Pre-eclampsia	Unselected women with singleton pregnancies	Prospective cohort	16806 (369; 9)	Bayesian	None	None	None	0.79	None	Yes
Yu 2005	Pre-eclampsia	Unselected women with singleton pregnancies	Prospective cohort	15392 (315; 3) (development sample)	Logistic	Split sample	None	P=0.76	0.83 (development and internal validation)	Regression formula	Yes
August 2004	Superimposed pre-eclampsia	Women with chronic hypertension	Randomized trial	110 (37; 3)	Logistic	Jackknifing procedure	None	P=0.40	0.69	Probability table (no of risk factors vs risk)	No
Mello 2002	Pre-eclampsia	White normotensive pregnant women with singleton pregnancies with a history of pre-eclampsia	Prospective cohort	187 (47; 8) (development sample)	Logistic	Leave-one-out method	None	None	0.98	None	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Pre-eclampsia											
Lambert-Messerlian 2000	Pre-eclampsia	Women with pre-eclampsia matched to controls for gestational age and date blood sampling. Women with chronic hypertension or diabetes were excluded	Case-control	360 (60; 3)	Logistic	None	None	None	0.75	None	No
Harrington 1997	Pre-eclampsia	Women with singleton pregnancies	Prospective cohort	626 (44; 7) (model A) and 626 (44; 3) (model B)	Logistic	None	None	None	Only ROC curve, AUC not reported	Regression formula	No
Early-onset pre-eclampsia											
Abdelaziz 2012	Early-onset pre-eclampsia	Women with singleton pregnancies without a priori high risk of pregnancy-induced hypertensive complications	Nested case-control	267 (16; 3)	Logistic	None	None	None	0.86	None	No
Bahado-Singh 2012	Early-onset pre-eclampsia	Pregnant women attending in the first trimester	Case-control	90 (30; 6) (model A), 90 (30; 7) (model B), 90 (30; 7) (model C), 90 (30; 9) (model D)	Logistic	None	None	None	0.90 (model A), 0.98 (model B), 0.84 (model C), 0.94 (model D)	None	No
Di Lorenzo 2012	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	2218 (12; 3)	Logistic	None	None	None	0.89	Regression formula	No
Akolekar 2011	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort, nested case-control	33602 (112; 17)	Logistic	Monte Carlo simulations	None	None	Only ROC curve, AUC not reported	Algorithm on website	No

Publication	Outcome	Population	Study design	Women (events;	Type of model	Internal validation	External validation	Calibration (p-value	Discrimination (AUC)	Prediction rule	Decision recommended

				predictors) *n*				Hosmer-Lesmeshow test or appearance calibration plot)			
Early-onset pre-eclampsia											
van Kuijk 2011	Recurrent early-onset pre-eclampsia	Women with early onset pre-eclampsia in their first singleton pregnancy (including HELLP) resulting in delivery <34 weeks, having a singleton pregnancy following the index pregnancy	Retrospective cohort	407 (28; 5)	Logistic	Bootstrapping	None	P=0.11	0.65 (internal validation)	Regression formula	No
Odibo 2011-a	Early-onset pre-eclampsia	Women with singleton pregnancies	Nested case-control	82 (unclear; 7)	Logistic	None	None	None	0.85	None	No
Odibo 2011-b	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	452 (12; 4)	Logistic	None	None	Not reported, only "goodness of fit was evaluated"	0.85	Regression formula	No
Seed 2011	Early-onset pre-eclampsia	Women with clinical risk factors for developing pre-eclampsia	Randomized trial	1121 (34; 5) (development sample)	Logistic	Split-sample	None	Fair (based on table), less in validation sample	0.85 (development); 0.81 (validation)	Regression formula	No (performance not good enough for use in practice)
Audibert 2010	Early-onset pre-eclampsia	Nulliparous women with singleton pregnancies without major fetal anomalies	Prospective cohort	893 (9; unclear)	Logistic	None	None	None	0.99	None	No
Poon 2010-a	Early-onset pre-eclampsia	Women with singleton pregnancies	Nested case-control	402 (26; 4)	Logistic	None	None	None	0.91	Regression formula	No
Poon 2010-b	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	8366 (37; 4)	Logistic	None	None	None	0.79	Regression formula	No
Akolekar 2009	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	234 (26; 7)	Logistic	None	None	None	0.94	None	No
Poon 2009-a	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	8366 (37; 3)	Logistic	None	None	None	0.95	Regression formula	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-	Discrimination (AUC)	Prediction rule	Decision recommended

								Lesmeshow test or appearance calibration plot)			
Early-onset pre-eclampsia											
Poon 2009-b	Early-onset pre-eclampsia	Women with singleton pregnancies	Nested case-control	627 (29; 6)	Logistic	None	None	None	Only ROC curves, AUC not reported	Regression formula	No
Poon 2009-c	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	8051 (32; 5)	Logistic	None	None	None	0.91	Regression formula, risk table	Yes
Akolekar 2008	Early-onset pre-eclampsia	Pregnant women attending for routine assessment	Case-control	824 (29; 5)	Logistic	None	None	None	0.94	Regression formula	No
Onwudiwe 2008	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	2829 (23; 3)	Logistic	None	None	None	0.996	Regression formula	No
Plasencia 2008	Early-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	3107 (22; 5)	Logistic	None	None	None	0.98	Regression formula	No
Yu 2005	Early-onset pre-eclampsia	Unselected women with singleton pregnancies	Prospective cohort	15392 (72; 3) (development sample)	Logistic	Split-sample	None	P=0.98	0.95 (development and internal validation)	Regression formula	Yes
Masse 1993	Early-onset pre-eclampsia	Nulliparous women	Prospective cohort	1366 (109; 9) (model A), 1366 (109; 5) (model B), 1366 (109; 11) (model C) and 1366 (109; 7) (model D)	Logistic	None	None	None	None	Regression formula	No
Intermediate-onset pre-eclampsia											
Akolekar 2011	Intermediate-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort, nested case-control	33602 (187; 17)	Logistic	Monte Carlo simulations	None	None	Only ROC curve, AUC not reported	Algorithm on website	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Late-onset pre-eclampsia											

Poon 2009-b	Late-onset pre-eclampsia	Women with singleton pregnancies	Nested case-control	627 (89; 6)	Logistic	None	By Farina et al., 2011[1]	None	Only ROC curves, AUC not reported (development); 0.74-0.75 (external validation)	Regression formula	No
Poon 2009-c	Late-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	8051 (124; 5)	Logistic	None	By Farina et al., 2011[1]	None	0.79 (development); 0.70 (external validation)	Regression formula	No
Akolekar 2008	Late-onset pre-eclampsia	Pregnant women attending for routine assessment	Case-control	824 (98; 6)	Logistic	None	None	None	0.817	Regression formula	No
Onwudiwe 2008	Late-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	2884 (78; 5)	Logistic	None	By Farina et al., 2011[1]	None	0.83 (development); 0.85 (external validation)	Regression formula	No
Plasencia 2008	Late-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	3107 (71; 6) (model A); 3107 (71; 7 (model B)	Logistic	None	By Farina et al., 2011[1]	None	0.78 (model A); 0.78 (model B) 0.76 on external validation	Regression formula	No
Plasencia 2007	Late-onset pre-eclampsia	Women with singleton pregnancies	Prospective cohort	6015 (unclear; 4)	Bayesian and logistic	None	By Farina et al., 2011[1] and by Herraiz et al., 2009[2]	None	0.84 (development); 0.72 (external validation by Farina); 0.64 (external validation by Herraiz)	Regression formula	No
Yu 2005	Late-onset pre-eclampsia	Unselected women with singleton pregnancies	Prospective cohort	15392 (243; 3) (development sample)	Logistic	Split-sample	None	P=0.83	0.80 (development and internal validation)	Regression formula	Yes

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Severe pre-eclampsia											
Myatt 2012	Severe pre-eclampsia (including eclampsia and HELLP syndrome)	Nulliparous women at low risk to develop pre-eclampsia	Nested case-control	683 (72; 5)	Logistic	None	None	None	0.75	None	No (low sensitivity and therefore do not recommend use of model)
Audibert 2010	Severe pre-eclampsia	Nulliparous women with singleton pregnancies without major fetal anomalies	Prospective cohort	893 (16; unclear)	Logistic	None	None	None	0.89	None	No
Lee 2000	Severe pre-eclampsia	Women with singleton pregnancies	Retrospective cohort	1052 (56; 4)	Logistic	None	None	None	0.77	Risk score	No
Stamilio 2000	Severe pre-eclampsia	Women with singleton pregnancies	Retrospective cohort	1998 (49; 4)	Logistic	None	None	"good fit", statistics not reported	0.75	Risk score	Yes
Eclampsia											
Koopmans 2011	Eclampsia	Women with mild PE or PIH ≥ 36 weeks (controls) and women who developed eclampsia >36 weeks (cases)	Nested case-control	1225 (76; 12)	Logistic	Bootstrapping	None	None	0.92 (development); 0.88-0.89 (internal validation)	None	No
Gestational hypertension											
Abdelaziz 2012	Gestational hypertension	Women with singleton pregnancies without a priori high risk of pregnancy-induced hypertensive complications	Nested case-control	267 (13; 3)	Logistic	None	None	None	0.73	None	No
Di Lorenzo 2012	Gestational hypertension	Women with singleton pregnancies	Prospective cohort	2218 (46; 4)	Logistic	None	None	None	None	Regression formula	No
Khalil 2012	Gestational hypertension	Women with live singleton pregnancies	Prospective cohort	7084 (137; unclear)	Logistic	None	None	None	0.85	None	No
Poon 2010-a	Gestational hypertension	Women with singleton pregnancies	Nested case-control	402 (85; 3)	Logistic	None	None	None	0.72	Regression formula	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Gestational hypertension											
Poon 2010-b	Gestational hypertension	Women with singleton pregnancies	Prospective cohort	8366 (140; 4)	Logistic	None	None	None	0.72	Regression formula	No
Poon 2009-a	Gestational hypertension	Women with singleton pregnancies	Prospective cohort	8366 (140; 3)	Logistic	None	None	None	0.79	Regression formula	No
Poon 2009-b	Gestational hypertension	Women with singleton pregnancies	Nested case-control	627 (82; 4)	Logistic	None	None	None	Only ROC curves, AUC not reported	Regression formula	No
Onwudiwe 2008	Gestational hypertension	Women with singleton pregnancies	Prospective cohort	2880 (74; 5)	Logistic	None	None	None	0.84	Regression formula	No
Plasencia 2007	Gestational hypertension	Women with singleton pregnancies	Prospective cohort	6015 (107; 3)	Bayesian and logistic	None	None	None	0.71	Regression formula	No
Tomoda 1996	Gestational hypertension	Nulliparous women that delivered a singleton without major anomalies after 32 weeks	Retrospective cohort	1189 (305; 4)	Linear regression (4 grades of hypertension as continuous variable)	None	None	None	None	Regression formula	No
Tomoda 1996	Gestational hypertension	Multiparous women that delivered a singleton without major anomalies after 32 weeks	Retrospective cohort	957 (192; 4)	Linear regression (4 grades of hypertension as continuous variable)	None	None	None	None	Regression formula	No

Preterm delivery

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Preterm delivery <28 weeks in asymptomatic women											
Celik 2008	Preterm delivery <28 weeks	Women attending for routine care	Prospective cohort	58807 (139; 3)	Logistic	None	None	P=0.49	0.90	Regression formula	No
Preterm delivery <30 weeks in asymptomatic women											
Celik 2008	Preterm delivery 28-30 weeks	Women attending for routine care	Prospective cohort	58807 (215; 3)	Logistic	None	None	P=0.97	0.82	Regression formula	No
Preterm delivery <32 weeks in asymptomatic women											
Fuchs 2012	Preterm delivery <32 weeks	Women with a singleton pregnancy receiving emergency cervical cerclage	Retrospective cohort	85 (37; 4)	Logistic	None	None	None	0.85 (0.88 for score chart)	Score chart	No
Lee 2011	Preterm delivery <32 weeks	Asymptomatic women who delivered singleton live newborns at ≥ 24 weeks gestation	Prospective cohort	522 (14; 13) (total sample)	Bayesian	Split-sample	None	None	None	None	No
Tan 2007	Preterm delivery <32 weeks	Women with singleton pregnancies	Retrospective cohort	2391480 (unclear; 9) (development sample)	Logistic	Split-sample	None	None	0.73	Regression formula	No
Tan 2007	Preterm delivery <32 weeks	Women with twin pregnancies	Retrospective cohort	83673 (unclear; 9) (development sample)	Logistic	Split-sample	None	None	0.65	Regression formula	No
Tan 2007	Preterm delivery <32 weeks	Women with triplet pregnancies	Retrospective cohort	3110 (unclear; 9) (development sample)	Logistic	Split-sample	None	None	0.65	Regression formula	No
To 2006	Preterm delivery <32 weeks	Women with singleton pregnancies	Prospective cohort	40995 (223; 7)	Logistic	None	None	None	0.67	Regression formula, probability table	Yes
Odibo 2003	Spontaneous preterm delivery <32 weeks	High-risk patients who received cerclage at 10-24 weeks based on history	Retrospective cohort	256 (51; 3)	Logistic	None	None	None	0.91	Score chart	Yes

Publication	**Outcome**	**Population**	**Study design**	**Women (events;**	**Type of model**	**Internal validation**	**External validation**	**Calibration (p-value**	**Discrimination (AUC)**	**Prediction rule**	**Decision recommended**

				predictors) *n*							
Preterm delivery <32 weeks in asymptomatic women											
Goldenberg 2001	Spontaneous preterm delivery <32 weeks	Asymptomatic women with singleton pregnancies with ≤3 cm (multiparous women) or ≤2 com (nulliparous women) cervix dilation	Nested case-control	100 (50; 6)	Logistic	None	None	None	None (authors feel this is not appropriate because of case-control design)	None	No
Preterm delivery <34 weeks in asymptomatic women											
Greco 2012	Preterm delivery <34 weeks	Women with singleton pregnancies	Prospective cohort	9974 (104; 5)	Logistic	None	None	None	0.84	None	No
Kiefer 2012	Preterm delivery <34 weeks (with a score for amniotic inflammation)	Women with singleton pregnancies with risk factors for preterm birth	Prospective cohort	44 (unclear; 14)	None (univariable analysis only)	None	In same paper	None	None	Score chart (for amniotic inflammation)	No
Beta 2011	Spontaneous preterm delivery <34 weeks	Women with singleton pregnancies	Prospective cohort, nested case-control	33370 (353; 6)	Logistic	None	None	None	0.67	None	No
Lee 2011	Preterm delivery <34 weeks	Asymptomatic women who delivered singleton live newborns at ≥ 24 weeks gestation	Prospective cohort	522 (28; 13) (total sample)	Bayesian	Split-sample	None	None	None	None	No
Celik 2008	Preterm delivery 31-33 weeks	Women attending for routine care	Prospective cohort	58807 (526; 3)	Logistic	None	None	P=0.20	0.78	Regression formula	No
Preterm delivery <35 weeks in asymptomatic women											
de Oliveira 2012	Spontaneous preterm delivery <35 weeks	Women with singleton pregnancy between 22 and 34 weeks gestation	Prospective cohort	70 (unclear; 9)	Logistic	Bootstrapping	None	None	0.91	Probability table	No

Publication	Outcome	Population	Study design	Women (events;	Type of model	Internal validation	External validation	Calibration (p-value	Discrimination (AUC)	Prediction rule	Decision recommended

				predictors) *n*				Hosmer-Lesmeshow test or appearance calibration plot)			
Preterm delivery <35 weeks in asymptomatic women											
Esplin 2011	Preterm delivery <35 weeks	Asymptomatic pregnant women	Nested case-control	160 (80; 3)	Logistic	None	None	None	0.89	None	No
Goldenberg 2001	Spontaneous preterm delivery <35 weeks	Asymptomatic women with singleton pregnancies with ≤3 cm (multiparous women) or ≤2 com (nulliparous women) cervix dilation	Nested case-control	254 (127; 7)	Logistic	None	None	None	None (authors feel this is not appropriate because of case-control design)	None	No
Preterm delivery <36 weeks in asymptomatic women											
Celik 2008	Preterm delivery 34-36 weeks	Women attending for routine care	Prospective cohort	58807 (2356; 3)	Logistic	None	None	P=0.20	0.62	Regression formula	No
Grzymala-Busse 1994	Preterm delivery <36 weeks	Unclear	Unclear	9480 (unclear; unclear) (development sample)	Logistic, machine learning	Split-sample	None	None	None	None	No
Preterm delivery <37 weeks in asymptomatic women											
Greco 2012	Preterm delivery 34-36 weeks	Women with singleton pregnancies	Prospective cohort	9974 (213; 5)	Logistic	None	None	None	0.58	None	No
Elaveyini 2011	Preterm delivery <37 weeks	Women with a pregnancy complicated by first-trimester intra-uterine hematoma	Retrospective cohort	50 (6; unclear) (total sample)	Artificial neural network	Split-sample	None	None	None	None	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Preterm delivery <37 weeks in asymptomatic women											
Goodwin 2011	Preterm delivery <37 weeks	Ethnically diverse sample of pregnant women	Retrospective cohort	19970 (4433; 7)	An experimental classifier software program based on statistical, case-based, and CART algorithms, using only demographic variables	None	None	None	0.72	None	No
Lee 2011	Preterm delivery <37 weeks	Asymptomatic women who delivered singleton live newborns at ≥ 24 weeks gestation	Prospective cohort	522 (96; 13) (total sample)	Bayesian	Split-sample	None	None	None	None	No
van Ravenswaaij 2011	Spontaneous preterm delivery 16-37 weeks	Women who underwent first trimester screening	Retrospective cohort	28566 (1503; 4)	Logistic	None	None	None	0.65	Regression formula	No
Pearce 2010	Idiopathic preterm delivery <37 weeks	Pregnant women	Nested case-control	183 (60; 6)	Logistic	None	None	None	3 top ranked models 0.81; 0.78; 0.75	None	No
Esplin 2008	Preterm delivery <34 and <37 weeks	Women with a first live birth and at least one subsequent live birth	Retrospective cohort	98724 (395; 20)	Multinomial regression	None	In same paper	None	0.72 (in validation sample)	None	No
Catley 2006	Preterm delivery <37 weeks	Births in the Canadian province of Ontario	Retrospective cohort	48000 (4128; 8)	Artificial neural network	None	In same paper	None	0.65	None	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Preterm delivery <37 weeks in asymptomatic women											
Catley 2006	"High-risk preterm delivery" (delivery <33 weeks or delivery 33-36 weeks with low Apgar score, low birthweight, NICU admission and/or neonatal resuscitation)	Births in the Canadian province of Ontario	Retrospective cohort	10864 (2173; 7)	Artificial neural network	None	In same paper	None	0.71	None	No
Smith 2006	Preterm delivery <37 weeks	Women having first pregnancies in West of Scotland	Retrospective cohort	84391 (5275; 10)	Logistic	None	None	None	0.67 for delivery 24–28 weeks, 0.65 for delivery 29–32 weeks, and 0.62 for delivery 33-36 weeks	None	No
Onderdonk 2003	Preterm delivery <37 weeks	Women with a previous preterm delivery	Prospective cohort	32 (11; 7)	Logistic	None	None	None	0.82	Regression formula	Yes
Onderdonk 2003	Preterm delivery <37 weeks	Women with a previous preterm delivery and without vaginal bleeding	Prospective cohort	28 (9; 4)	Logistic	None	None	None	0.91	Regression formula	Yes
Onderdonk 2003	Preterm delivery <37 weeks	Women without a previous preterm birth with H2O2 positive lactobacilli present	Prospective cohort	139 (15; 6)	Logistic	None	None	None	0.74	Regression formula	Yes

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Preterm delivery <37 weeks in asymptomatic women											
Onderdonk 2003	Preterm delivery <37 weeks	Women without a previous preterm birth with H2O2 positive lactobacilli absent	Prospective cohort	35 (2; 3)	Logistic	None	None	None	0.94	Regression formula	Yes
Mara 2002	Preterm delivery <37 weeks	Unselected women with singleton pregnancies without fetal anomalies	Prospective cohort	314 (38; 5)	Logistic	None	None	None	None	None	No
Ruiz 2002	Gestational age at delivery (preterm delivery defined as <37 weeks)	Women with singleton pregnancies	Prospective cohort	76 (6; 4)	Linear regression	None	None	None	None	None	No
Maclean 1999	Preterm delivery <37 weeks	unselected pregnant women who did not use systemic corticosteroids	Prospective cohort	819 (unclear; 3)	Bayesian	None	None	None	Only ROC curve, AUC not reported	Risk groups and risk	No
Mercer 1996	Spontaneous preterm delivery <37 weeks	Nulliparous women with singleton pregnancies	Prospective cohort	1218 (100; 7) (total sample)	Logistic	Split-sample	None	None	None	Regression formula	No
Mercer 1996	Spontaneous preterm delivery <37 weeks	Multiparous women with singleton pregnancies	Prospective cohort	1711 (204; 4) (total sample)	Logistic	Split-sample	None	None	None	Regression formula	No
de Caunes 1990	Preterm delivery <37 weeks	Singleton deliveries	Case-control	746 (unclear; 9) (total sample)	Unclear	Split-sample	None	Calibration plot: no clear interpretation	None	Score chart	No
Blondel 1990	Preterm delivery <37 weeks	Nulliparous women with singleton pregnancies	Retrospective cohort	4025 (201; 9)	Logistic	None	None	None	None	Regression formula	No
Blondel 1990	Preterm delivery <37 weeks	Multiparous women with singleton pregnancies	Retrospective cohort	2884 (153; 9)	Logistic	None	None	None	None	Regression formula	No
Ross 1986	Preterm delivery <37 weeks	Pregnant women	Retrospective cohort	8240 (530; 22)	Unclear	None	None	None	None	Regression formula, score chart	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Preterm delivery <37 weeks in asymptomatic women											
Onderdonk 2003	Preterm delivery <37 weeks	Women without a previous preterm birth with H2O2 positive lactobacilli absent	Prospective cohort	35 (2; 3)	Logistic	None	None	None	0.94	Regression formula	Yes
Mara 2002	Preterm delivery <37 weeks	Unselected women with singleton pregnancies without fetal anomalies	Prospective cohort	314 (38; 5)	Logistic	None	None	None	None	None	No
Ruiz 2002	Gestational age at delivery (preterm delivery defined as <37 weeks)	Women with singleton pregnancies	Prospective cohort	76 (6; 4)	Linear regression	None	None	None	None	None	No
Maclean 1999	Preterm delivery <37 weeks	unselected pregnant women who did not use systemic corticosteroids	Prospective cohort	819 (unclear; 3)	Bayesian	None	None	None	Only ROC curve, AUC not reported	Risk groups and risk	No
Mercer 1996	Spontaneous preterm delivery <37 weeks	Nulliparous women with singleton pregnancies	Prospective cohort	1218 (100; 7) (total sample)	Logistic	Split-sample	None	None	None	Regression formula	No
Mercer 1996	Spontaneous preterm delivery <37 weeks	Multiparous women with singleton pregnancies	Prospective cohort	1711 (204; 4) (total sample)	Logistic	Split-sample	None	None	None	Regression formula	No
de Caunes 1990	Preterm delivery <37 weeks	Singleton deliveries	Case-control	746 (unclear; 9) (total sample)	Unclear	Split-sample	None	Calibration plot: no clear interpretation	None	Score chart	No
Blondel 1990	Preterm delivery <37 weeks	Nulliparous women with singleton pregnancies	Retrospective cohort	4025 (201; 9)	Logistic	None	None	None	None	Regression formula	No
Blondel 1990	Preterm delivery <37 weeks	Multiparous women with singleton pregnancies	Retrospective cohort	2884 (153; 9)	Logistic	None	None	None	None	Regression formula	No
Ross 1986	Preterm delivery <37 weeks	Pregnant women	Retrospective cohort	8240 (530; 22)	Unclear	None	None	None	None	Regression formula, score chart	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Preterm delivery <37 weeks in symptomatic women											
Hueston 1998	Preterm delivery <37 weeks	women with preterm contractions in level I and level II facilities	Retrospective cohort	239 (78; 4)	Logistic	None	None	None	None	None	No
Woolery 1995	Preterm delivery <37 weeks	high- and low-risk pregnant women in a level III perinatal center	Unclear	9480 (unclear; unclear) (development sample)	Logistic, machine learning	Split-sample	None	None	None	None	No
Preterm delivery <48 hours in symptomatic women											
Park 2011	Preterm delivery <48 hours	women diagnosed with PPROM with live singleton with GA 23-34, dilatation < 3 cm	Prospective cohort	102 (24; 3) (model A) and 102 (24; 3) (model B)	Logistic	None	None	P=0.18 (model A) and P= 0.11 (model B)	0.80 (model A) and 0.83 (model B)	Regression formula	No
Macones 1999-b	Preterm delivery <48 hours	Women with idiopathic preterm labour without ruptured membranes and treated with magnesium sulfate between 24 and 34 completed weeks of gestation	Case-control	200 (50; 6)	Logistic	None	None	None	None	None	No
Besinger 1987	Preterm delivery <48 hours	Women with preterm labour pregnant between 26 and 34 weeks gestation	Prospective cohort	50 (20; 3) (model A), 50 (20; 4) model B. 50 (20; 5) model C	Logistic	None	None	None	None	None	No
Preterm delivery <7 days in symptomatic women											
Giannella 2012	Delivery within 7 days	Women with spontaneous preterm labour between 24 and 34 weeks	Prospective cohort	730 (110; 3)	Logistic	None	None	None	0.95	None	No
Tsiartas 2012	Delivery within 7 days	Women with a singleton pregnancy with threatened preterm labour between 22-34 weeks	Prospective cohort	142 (57; 3)	Logistic	None	None	P=0.91	0.88	Regression formula	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Preterm delivery <7 days in symptomatic women											
Park 2011	Delivery within 7 days	Women diagnosed with PPROM with live singleton with GA 23-34, dilatation < 3 cm	Prospective cohort	91 (51; 3)	Logistic	None	None	None	0.77	Regression formula	No
Holst 2009	Spontaneous preterm delivery within 7 days	Healthy women with singleton pregnancies who were in preterm labour (22-33 weeks) with intact membranes	Prospective cohort	89 (34; 4) (model A) and 89 (34; 3) (model B)	Logistic	None	None	None	0.91 (model A); 0.91 (model B)	None	No
Macones 1999-a	Preterm delivery within 7 days	Women between 24 and 34 weeks' gestation who sought treatment for uterine contractions with cervical dilatation ≤2 cm, received tocolysis with magnesium sulfate, without spontaneous rupture of membranes on admission	Case-control	200 (50; 3)	Logistic	None	None	None	None	None	No ("because of the modest performance we do not believe that our clinical rule could be used alone")
Hueston 1998	Preterm delivery within 7 days (and <34 weeks)	Women with preterm contractions in level I and level II facilities	Retrospective cohort	239 (26; 5)	Logistic	None	None	None	None	None	Yes
Faber 1995	Delivery within 7 days	Women with preterm labour	Prospective cohort	114 (unclear; 5)	Logistic	None	None	None	None	Regression formula	No
Preterm delivery <10 days in symptomatic women											
Bastek 2012	Delivery within 10 days	Women with a singleton pregnancy at 22-33+6/7 weeks with symptoms of preterm labour	Prospective cohort	583 (90; 3)	Logistic	Bootstrapping	None	None	0.75 (0.76 for score chart)	Score chart	No

Gestational diabetes mellitus

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Gestational diabetes mellitus											
Ramos-Levi 2012	Gestational diabetes mellitus	Women without a previous history of diabetes mellitus	Cross-sectional cohort	2194 (213; 6)	Logistic	None	None	None	None	Regression formula	No
Zhou 2012	Gestational diabetes mellitus	Pregnant women	Prospective cohort	1000 (100; 5)	Logistic	None	None	None	0.71	None	Yes
Nanda 2011	Gestational diabetes mellitus	Women without pre-pregnancy diabetes mellitus type 1 or 2 with singleton pregnancies delivering a phenotypically normal neonate at or after 30 weeks of gestation, attending for their routine first hospital visit	Prospective cohort, nested case-control	11464 (297; 6)	Logistic	None	None	None	0.84	None	No
Nanda 2011	Gestational diabetes mellitus	Women with previous gestational diabetes but without pre-pregnancy diabetes mellitus type 1 or 2 with singleton pregnancies delivering a phenotypically normal neonate at or after 30 weeks of gestation, attending for their routine first hospital visit	Prospective cohort, nested case-control	107 (63; 6)	Logistic	None	None	None	0.87	None	No
Nanda 2011	Gestational diabetes mellitus	Women without previous gestational diabetes and without pre-pregnancy diabetes mellitus type 1 or 2 with singleton pregnancies delivering a phenotypically normal neonate at or after 30 weeks of gestation, attending for their routine first hospital visit	Prospective cohort, nested case-control	11357 (234; 6)	Logistic	None	None	None	0.81	None	No
Teede 2011	Gestational diabetes mellitus	Women with singleton pregnancies	Retrospective cohort	2880 (250; 5)	Logistic	None	In same paper	None	0.70 (external validation)	Score chart	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Gestational diabetes mellitus											
Savvidou 2010	Gestational diabetes mellitus	Women with singleton pregnancies, without pre-existing diabetes mellitus	Nested case-control	372 (124; 11) (model A) and 372 (124; 5) (model B)	Logistic	Bootstrapping	None	None	0.82 (model A) and 0.86 (model B)	None	No
Savvidou 2010	Gestational diabetes mellitus	Women with singleton pregnancies, without pre-existing diabetes mellitus or previous gestational diabetes	Nested case-control	202 (44; 11) (model A) and 202 (44; 5) (model B)	Logistic	Bootstrapping	None	None	0.75 (model A) and 0.81 (model B)	None	No
van Leeuwen 2010	Gestational diabetes mellitus	Women with singleton pregnancies without pregestational diabetes mellitus	Prospective cohort	995 (24; 5)	Logistic	None	None	P=0.25	0.77	Regression formula, nomogram	Yes
Insulin treatment for gestational diabetes											
Pertot 2011	Need for insuline treatment in gestational diabetes mellitus	Women with gestational diabetes mellitus	Prospective cohort	3009 (1535; 7)	Logistic	None	None	Calibration table: good calibration	None	None	No
Abnormal glucose challange test											
Phaloprakarn 2009-b	Abnormal glucose challenge test	Singleton pregnant women without overt diabetes	Retrospective cohort	1876 (586; 5)	Logistic	None	In same paper	None	0.80 (development); 0.75 (validation)	Prognostic index	No
Congenital malformations											
Garcia-Patterson 2004	Any major congenital malformations (one or more)	Infants of mothers with gestational diabetes	Prospective cohort	983 (unclear; 3)	Logistic	None	None	None	0.65	None	No

Congenital malformations

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Congenital malformations											
Garcia-Patterson 2004	Any minor congenital malformations (one or more)	Infants of mothers with gestational diabetes	Prospective cohort	983 (unclear; 3)	Logistic	None	None	None	0.60	None	No
Garcia-Patterson 2004	Major congenital malformations of the heart	Infants of mothers with gestational diabetes	Prospective cohort	983 (unclear; 4)	Logistic	None	None	None	0.81	None	No

Fetal growth and weight

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Small for gestational age neonate											
Karagiannis 2011	Small for gestational age neonate in absence of pre-eclampsia	Women with singleton pregnancies who did not develop pre-eclampsia	Prospective cohort, nested case-control	32850 (1536; unclear)	Logistic	Monte Carlo simulations	None	None	Only ROC curve, AUC not reported	None	No
Karagiannis 2011	Small for gestational age neonate in absence of pre-eclampsia with delivery indicated <37 weeks	Women with singleton pregnancies who did not develop pre-eclampsia	Prospective cohort, nested case-control	32850 (163; unclear)	Logistic	Unclear	None	None	None	None	No
Karagiannis 2011	Small for gestational age neonate in absence of pre-eclampsia with delivery >37 weeks	Women with singleton pregnancies who did not develop pre-eclampsia	Prospective cohort, nested case-control	32850 (1373; unclear)	Logistic	Unclear	None	None	None	None	No
725 Poon 2011	Small for gestational age neonate in absence of pre-eclampsia	Women with singleton pregnancies who did not develop pre-eclampsia	Prospective cohort	32850 (1536; 11)	Logistic	None	None	None	0.75	Risk curve	No
Seed 2011	Small for gestational age neonate	Women with clinical risk factors for developing pre-eclampsia	Randomized trial	1121 (255; 6) (development sample)	Logistic	Split-sample	None	Fair (based on table), less in validation sample	0.65 (development); 0.57 (validation)	Regression formula	No (performance not good enough for use in practice)
Seed 2011	Small for gestational age neonate with severe advere perinatal outcome	Women with clinical risk factors for developing pre-eclampsia	Randomized trial	1121 (104; 4) (development sample)	Logistic	Split-sample	None	Fair (based on table), less in validation sample	0.73 (development); 0.66 (validation)	Regression formula	No (performance not good enough for use in practice)

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Small for gestational age neonate											
Onwudiwe 2008	Small for gestational age neonate	Women with singleton pregnancies	Prospective cohort	3172 (366; 5)	Logistic	None	None	None	0.65	Regression formula	No
de Paco 2008	Small for gestational age neonate	Women with singleton pregnancies	Prospective cohort	4376 (532; 5)	Logistic	None	None	None	0.63	None	No
Pilalis 2007	Small for gestational age neonate	Women with singleton pregnancies	Prospective cohort	878 (94; 4)	Logistic	None	None	None	None	None	No
Plasencia 2007	Small for gestational age neonate	Women with singleton pregnancies	Prospective cohort	6015 (760; 7)	Bayesian and logistic	None	None	None	0.66	Regression formula	No
Intra-uterine growth restriction											
Bachman 2003	Intra-uterine growth restriction	Women with singleton pregnancies	Prospective cohort	260 (22; 3)	Logistic	None	None	None	0.83	Number of risk factors vs risk	No
Doherty 2002	Intra-uterine growth restriction (birthweight <p10)	Sample of unselected pregnancies with oversampling of cases with abnormal outcomes	RCT	114 (43; 4) (model A); 114 (43; 7) (model B) (development sample)	None	Split-sample	None	None	Only ROC curve, AUC not reported	Regression formula	No
de Caunes 1990	Intra-uterine growth restriction	Singleton deliveries	Case-control	746 (unclear; 12) (total sample)	Unclear	Split-sample	None	Calibration plot: no clear interpretation	None	Score chart	No
Snidvongs 1989	Intra-uterine growth restriction	Pregnant women	Prospective cohort	766 (71; 6)	Logistic	None	None	None	Only ROC curve, AUC not reported	Score chart	Yes
Birthweight											
Liu 2008	Birthweight	Women with pre-eclampsia or gestational hypertension	Retrospective cohort	661 (NA; 6) (model A) and 661 (NA; 5) (model B)	Linear regression	None	In same paper	None	0.94 (model A); 0.78 (model B); when cut-off of 2555 g was used	Regression formula	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Birthweight											
Liu 2008	Birthweight	Women with pre-eclampsia or gestational hypertension	Retrospective cohort	661 (NA; 6) (model A) and 661 (NA; 5) (model B)	Linear regression	None	In same paper	None	0.94 (model A); 0.78 (model B); when cut-off of 2555 g was used	Regression formula	No
Mamelle 2001	Individualized birth weight limit of an infant (taking into account genetic growth potential, in order to distinguish 'fetal growth-restricted' infants and 'constitutionally small' infants)	Live born singletons in maternity hospitals located in various regions of France and in Belgium	Retrospective cohort	71778 (NA; 6)	Linear regression	None	None	None	None	Regression formula	Yes
Weiner 1985	Birthweight	Pregnant women likely to deliver preterm (<34 weeks) within 48 hours	Prospective cohort	33 (NA; 3) (development sample)	Linear regression	Split-sample	By Pielet et al., 1987[3]	None	None	Regression formula	No
Low birthweight											
de Caunes 1990	Low birthweight	Women with singleton deliveries	Case-control	746 (unclear; 10) (total sample)	Unclear	Split-sample	None	Calibration plot: no clear interpretation	None	Score chart	No

Labour and delivery

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Vaginal birth after caesarean											
Grobman 2009	Vaginal birth after caesarean	Women who underwent a trial of labour at ≥37 weeks with 1 previous low-transverse CS and vertex singleton	Retrospective cohort	9616 (7066; 12) (total sample)	Logistic	Split-sample	By Costantine et al., 2011[4]	"Adequate" based on calibration plot Adequate on external validation	0.77 0.76 on external validation	Regression formula, nomogram	No
Grobman 2007	Vaginal birth after caesarean	Women with one prior low transverse caesarean who underwent a trial of labor at term with a vertex singleton gestation	Prospective cohort	11856 (8659; 6) (total sample)	Logistic	Split-sample	By Costantine et al., 2009[5]	None Fair on external validation (curve)	0.75 (for formula and nomogram in internal validation sample) 0.70 on external validation	Regression formula, nomogram	No
Hashima 2007	Vaginal birth after caesarean	Primiparous women with 1 prior caesarean	Retrospective cohort	10828 (unclear; 3) (total sample)	Logistic	Split-sample	None	None	None	Scoring system	No
Srinivas 2007	Vaginal birth after caesarean	Women with a previous caesarean delivery	Retrospective cohort	13706 (10340; 6)	Logistic	None	None	None	0.72	None	No
Kraiem 2006	Vaginal birth after caesarean	Women with a prior uterine scar (Caesarean or myomectomy)	Retrospective cohort	581 (268; 5)	Logistic	None	None	None	None	Score chart	No
Smith 2005	Failed vaginal birth after caesarean (emergency cesaerean)	Women with singletons with one prior Caesarean delivery who attempted vaginal birth at or after 40 weeks gestation	Retrospective cohort	11643 (3067; 6) (development sample)	Logistic	Split sample	None	P=0.95	0.71	Regression formula	No
Gonen 2004	Vaginal birth after caesarean	Women with history of 1 low tranverse Caesarean delivery	Retrospective cohort	339 (279; 4)	Logistic	None	None	None	None	None	No
Weinstein 1996	Vaginal birth after caesarean	Women with a prior caesarean who attempted vaginal birth	Retrospective cohort	471 (368; 4)	Logistic	None	None	None	None	Score chart	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Vaginal birth after caesarean											
Jakobi 1993	Vaginal birth after caesarean	Women with a previous caesarean who were allowed to trial of labour	Unclear	261 (147; 6)	Logistic	None	None	None	None	None	No
Induction of labour											
Rao 2008	Induction of labour	Singleton pregnancies with a live fetus at 40+4 to 41+6 weeks of gestation	Prospective cohort	1864 (328; 4)	Logistic	None	None	None	0.76	Regression formula	No
Vaginal delivery within 24 hours after induction of labour											
Pitarello 2013	successful vaginal delivery within 24 hours	Women with singleton live term fetus in cephalic presentation	Prospective cohort	190 (119; 4)	Logistic	None	None	None	0.81	Regression formula	No
Mbele 2007	successful vaginal delivery within 24 hours	Women with singleton pregnancy who underwent an induction of labour with oral misoprostol	Prospective cohort	558 (53; 4)	Logistic	None	None	None	None	Scoring system	No
Bueno 2007	successful vaginal delivery within 24 hours	Women admitted for induction of labour	Unclear	196 (144; 5)	Logistic	None	None	None	None	None	No
Rane 2005	successful vaginal delivery within 24 hours	Women with singleton live pregnancies in cephalic presentation undergoing induction of labour at 35 to 42+6 weeks for a variety of indications	Prospective cohort	822 (530; 3)	Logistic	None	None	None	None	Regression formula	No
Rane 2004	successful vaginal delivery within 24 hours	Women with singleton live pregnancies in cephalic presentation (occiput posterior position) undergoing induction of labour at 35 to 42+6 weeks gestation for a variety of indications	Prospective cohort	604 (388; 4)	Logistic	None	None	None	0.89	Regression formula	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Vaginal delivery within 24 hours after induction of labour											
Wing 2002	successful vaginal delivery within 24 hours	Women with intact membranes and minimal uterine activity, who underwent induction of labour with misoprostol (maximum duration of 24 hours)	Retrospective cohort	1373 (657; unclear)	Logistic	None	None	None	None	None	No
Pandis 2001	successful vaginal delivery within 24 hours	Singleton pregnancies with live fetus in cephalic presentation undergoing induction of labor with Dinoprostone Gel at 37– 42 weeks, mainly for prolonged pregnancy	Prospective cohort	240 (142; 3)	Cox	None	None	None	None	None	No
Vaginal delivery within 12 hours after induction of labour											
Riboni 2012	Delivery within 12 hours	Women who underwent induction of labour at term with dinoprostone gel	Prospective cohort	115 (42; 6)	Logistic	None	None	None	None	None	No
Mode of delivery (vaginal or caesarean) after induction of labour											
Gomez-Laencina 2012	Caesarean section	Women undergoing induction of labour	Prospective cohort	177 (63; 5)	Logistic	None	None	None	None	Regression formula	No
Isono 2011	Emergency caesarean section	Low-risk nulliparous women with premature rupture of membranes who underwent induction of labour	Retrospective cohort	392 (56; 3) (development sample)	Logistic	Split-sample and crossvalidation	None	Calibration table: fair	0.73 (internal validation)	Regression formula	No
Laughon 2011	Vaginal delivery	Nulliparous women with vertex singleton undergoing induction of labour at term and delivering between 37-42 weeks	Retrospective cohort	5610 (4224; 4)	Logistic	Bootstrapping	In same paper	None	None	Risk score	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Mode of delivery (vaginal or caesarean) after induction of labour											
Robinson 2010	Caesarean section	Women undergoing labour induction for pre-eclampsia with euploid singletons in vertex position	Retrospective cohort	608 (195; 11)	Logistic, artificial neural network	None	None	P=0.50	0.74 (logistic); 0.75 (neural network)	None	No
Rane 2005	Caesarean section for failure to progress	Singleton live pregnancies in cephalic presentation undergoing induction of labour at 35 to 42+6 weeks for variety of indications	Prospective cohort	822 (91; 5)	Logistic	None	None	None	None	Regression formula	No
Rane 2005	Caesarean section (all indications)	Singleton live pregnancies in cephalic presentation undergoing induction of labour at 35 to 42+6 weeks for variety of indications	Prospective cohort	822 (161; 5)	Logistic	None	By Verhoeven et al., 2009[6]	P=0.11 (external validation)	0.67 (external validation)	Regression formula	No
Rane 2004	Caesarean section	Women with singleton live pregnancies in cephalic presentation (occiput posterior position) undergoing induction of labour at 35 to 42+6 weeks gestation for a variety of indications	Prospective cohort	604 (120; 3)	Logistic	None	None	None	0.81	Regression formula	No
Rane 2004	Caesarean section	Women with singleton live pregnancies in cephalic presentation (occiput posterior position) undergoing induction of labour at 35 to 42+6 weeks gestation for a variety of indications	Prospective cohort	604 (120; 3)	Logistic	None	None	None	0.81	Regression formula	No
Herman 1993	Caesarean section	Pregnant women undergoing induction of labour	Retrospective cohort	401 (46; 4)	Logistic	None	None	Calibration table shows fair calibration	None	Regression formula, score chart	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Mode of delivery											
Benjamin 2012	Caesarean section for cephalopelvic disproportion	Women with a first term singleton pregnancy	Prospective cohort	249 (27; 3)	Logistic	None	None	None	None	None	No
Pitarello 2013	successful vaginal delivery	Women with singleton live term fetus in cephalic presentation	Prospective cohort	190 (130; 4)	Logistic	None	None	None	0.80	Regression formula	No
Schuit 2012	Operative delivery (instrumental vaginal (IVD) or caesarean (CS)) for fetal distress (FD) or failure to progress (FTP)	Labouring women with high-risk vertex singleton pregnancies >36 weeks gestation	Randomized trial	5667 (375 + 212 + 433 + 571; 7) (model A), 5667 (375 + 212 + 433 + 571; 14) (model B),	Multinomial logistic	Bootstrapping	None	Calibration plot shows good calibration	IVD-FD: 0.72 (model A) and 0.73 (modelB2); CS-FD: 0.70 (model A) and 0.73 (model B); IVD-FTP: 0.78 (model A) and 0.80 (model B); CS-FTP: 0.78 (model A) and 0.81 (model B)	Nomogram in online appendix	No
Kambale 2011	Caesarean section	Pregnant Italian women	Retrospective cohort	5812 (2102; unclear)	Logistic	None	None	P=0.87	0.65	None	No
Kim 2011	Caesarean delivery performed during labour	Nulliparous women with singletons in vertex position, no pregnancy complications, ≥ 37 weeks, intact membranes, no labour, with planned vaginal delivery	Prospective cohort	453 (57; 3)	Logistic	None	None	P=0.47, plot fair	0.76	Regression formula	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Mode of delivery											
Nader 2010	Vaginal delivery	Nulliparous women with singleton pregnancies between 36 and 38 weeks gestation aiming for a vaginal delivery	Prospective cohort	473 (unclear; 5)	Logistic	None	In same paper	P=0.12 (external validation)	0.70 (external validation)	Regression formula	No
Rao 2008	Caesarean section	Singleton pregnancies with a live fetus at 40+4 to 41+6 weeks of gestation	Prospective cohort	1536 (233; 5)	Logistic	None	None	None	0.75	Regression formula	No
Roman 2008	Caesarean delivery performed during labour	Women with planned vaginal delivery	Retrospective cohort	2478 (705; 9)	Logistic	None	None	None	0.72	Scoring system	No
Dietz 2006	Normal vaginal delivery (vs operative vaginal or CS)	Nulliparous women with an uncomplicated singleton pregnancy and planned for a vaginal delivery	Prospective cohort	202 (124; 4)	Logistic	None	None	P=0.48	0.85	Regression formula	Yes
Dietz 2006	Vaginal delivery (normal or operative, vs CS)	Nulliparous women with an uncomplicated singleton pregnancy and planned for a vaginal delivery	Prospective cohort	202 (149; 5)	Logistic	None	By Nader et al., 2010[7]	P=0.79 P<0.0001 on external validation	0.87 (development); 0.62 (external validation)	Regression formula	Yes
Akmal 2004	Caesarean section	Women with singleton pregnancies in cephalic presentation in the early stage of active labour between 37-42 weeks gestation	Cross-sectional cohort	601 (87; 9)	Logistic	None	None	None	None	Probability table	Yes
Dulitzki 1998	Caesarean section	women ≥44 years old who delivered singleton infants; the control group included the women 20–29 years old who delivered singleton infants at immediately after each study subject	Case-control	418 (56; 3)	Logistic	None	In same paper	None	None	Number of risk factors vs risk	Yes

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Time to delivery											
Pascual-Ramirez 2012	Time to vaginal delivery	Women undergoing childbirth who received epidural or combined spinal-epidural analgesia	Randomized trial	144 (NA; 4)	Cox	None	None	None	None	None	No

Breech presentation

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Successful external cephalic version											
Kok 2011	Successful external cephalic version	Women with singletons in breech presentation ≥36 weeks	Randomized trial	310 (122;4)	Logistic	Bootstrapping	By de Hundt et al., 2012[8]	P=0.66, calibration plot shows good fit P=0.30 on external validation	0.71 (development); 0.66 (external validation)	Regression formula	Yes
Wong 2000	Successful external cephalic version	Women with a fetus in breech presentation at ≥36 weeks who underwent external cephalic version with the use of tocolytics	Prospective cohort	53 (34; 4)	None (univariable analysis only)	None	In same paper	Calibration table shows good calibration	None	Risk score	Yes
Lau 1997	Successful external cephalic version	Women that underwent an external cephalic version for breech presentation at ≥36 weeks of gestation	Prospective cohort	243 (169; 3) (total sample)	Logistic	Split-sample	None	None	None	Regression formula, risk groups	No
Newman 1993	Successful external cephalic version	Women that underwent an external cephalic version for breech presentation	Retrospective cohort	108 (unclear; 5) (development sample)	Linear regression	Split-sample	In same paper	Calibration plot shows reasonable fit	None	Score chart	Yes

Publication	Outcome	Population	Study design	Women (events;	Type of model	Internal validation	External validation	Calibration (p-value	Discrimination (AUC)	Prediction rule	Decision recommended

				predictors) *n*				Hosmer-Lesmeshow test or appearance calibration plot)			
Successful vaginal delivery after external cephalic version											
Chan 2004	Successful vaginal delivery after external cephalic version	Women with singleton pregnancies who had a single attempt of external cephalic version at or after 36 weeks of gestation	Prospective cohort	192 (unclear; 5) (development sample)	Logistic	Split-sample	None	None	0.71	Regression formula	No (authors acknowledge model not effective enough for routine use)
Mode of delivery											
Broche 2008	Mode of delivery (vaginal birth or caesarean section)	Women with singletons in breech presentation > 37 weeks indexed for vaginal birth trial	Retrospective cohort	376 (80; 5)	Logistic	None	None	None	None	None	No

Infection and inflammation

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Intra-amniotic infection and/or inflammation											
Park 2012	Intra-amniotic infection and/or inflammation	Pregnant women with PPROM	Partly prospective, partly retrospective cohort	171 (63; 4)	Logistic	None	None	P=0.52	0.85	Regression formula	No
Jung 2011	Intra-amniotic inflammation	Women admitted with preterm labour and intact membranes between 21 and 35 weeks gestation, with a singleton live fetus without major congenital anomalies, ≤3 cm cervical dilatation	Cross-sectional cohort	153 (30; 3)	Logistic	None	None	P=0.75	0.724	Regression formula	No
Clinical infection											
Kayem 2009	Clinical infection	Women hospitalised for preterm labour	Prospective cohort	371 (21; 5)	Logistic	Crossvalidation	None	None	0.82 (development)	Risk score	No
Histologic signs of infection											
Cobo 2012	Histological funisitis	Pregnant women with diagnosed PPROM	Prospective cohort	107 (19; 3)	Logistic	None	None	None	0.89	None	No

Fetal health and survival

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Miscarriage or early fetal loss											
van Ravenswaaij 2011	Miscarriage <16 weeks	Women who underwent first trimester screening	Retrospective cohort	28566 (150; 3)	Logistic	None	None	None	0.78	Regression formula	No
Dugoff 2008	Early fetal loss	Women with singleton pregnancies	Randomized trial	35253 (318; 7)	Unclear	None	None	None	None	None	No
Stillbirth											
Reddy 2010	Antepartum stillbirth	Singleton deliveries ≥ 23 weeks gestation	Retrospective cohort	174809 (712; unclear)	Cox	None	None	None	None	None	No
Smith 2007	Stillbirth ≤ 33 weeks	Pregnant women at 22-24 weeks of gestation	Retrospective cohort	30519 (unclear; 4)	Logistic	None	None	None	0.87	Regression formula	No
Smith 2007	Stillbirth ≥ 34 weeks	Pregnant women at 22-24 weeks of gestation	Retrospective cohort	30519 (unclear; 3)	Logistic	None	None	None	0.67	Regression formula	No
Perinatal mortality or survival											
de Caunes 1990	Perinatal mortality (fetal death with birthweight >500 g or death within 7 days of live birth)	Singleton deliveries	Case-control	746 (208; 10) (total sample)	Unclear	Split-sample	None	Calibration plot: no clear interpretation	None	Score chart	No
Block 1976	Perinatal survival	Women undergoing cerclage beyond 12 weeks	Retrospective cohort	31 (unclear; 5)	None	None	None	None	None	Score chart	No
Poor perinatal outcome											
Romero 2001	Fetal wellbeing (1 minute Apgar score <6 or admission to NICU)	Hypertensive pregnancies at 36-42 weeks	Prospective cohort	171 (8; 5)	Logistic	None	None	None	None	Regression formula	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Poor perinatal outcome											
Weenink 1984	Unfavourable fetal outcome (perinatal death or prolonged NICU stay)	Women with pregnancy-induced or aggravated hypertension	Prospective cohort	57 (27; 3)	Logistic	None	None	None	None	None	No

Complications of pregnancy and delivery

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Hypertensive disorders (combined) or placenta-related complications											
Abdelaziz 2012	Hypertensive disorders (PE and PIH)	Women with singleton pregnancies without a priori high risk of pregnancy-induced hypertensive complications	Nested case-control	267 (89; 3)	Logistic	None	None	None	0.79	None	No
van Ravenswaaij 2011	Placenta-related complications (low birthweight, stillbirth, PIH, PE, HELLP)	Women who underwent first trimester screening	Retrospective cohort	28566 (1074; 4)	Logistic	None	None	None	0.56	Regression formula	No
Mello 2001	Pregnancy induced hypertensive disorders (PE and IUGR)	Normotensive white women with singleton pregnancies at high risk for PE and IUGR (insulin-dependent DM, previous PE, recurrent abortions or previous stillbirth)	Prospective cohort	187 (47; 9) (models A and B) (development sample)	Artificial neural network	Split sample	None	None	0.95 (model A) and 0.85 (model B)	None	No
Placenta praevia											
Odibo 2007	Placenta praevia	Women with a previous caesarean delivery	Retrospective cohort	25076 (361; 7)	Logistic	None	None	None	0.59	None	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Shoulder dystocia											
Dodd 2012	Shoulder dystocia	Pregnant women	Retrospective cohort	114827 (1303; 4)	Logistic	None	None	P=0.04	0.73	None	No
Gupta 2010	Shoulder dystocia	Women without pre-existing or gestational diabetes or previous shoulder dystocia with singleton vaginal live cephalic deliveries at ≥36 weeks	Retrospective cohort	20142 (120; 3) (model A) and 20142 (120; 7) (model B) (development sample)	Logistic	Split-sample	None	results not reported but "no strong evidence of poor fit"	0.90 (model A and 0.69 (model B)	Regression formula	No
Gross 1987	Shoulder dystocia (with and without trauma)	Women delivering neonates with birth weights ≥ 4000 g	Unclear	394 (29+20; 3)	Three-way discriminant analysis	None	None	None	None	None	No
Birth trauma											
Levine 1984	Birth trauma: brachial plexus injury	Women with a singleton term live birth	Retrospective cohort	13870 (36; 5)	Logistic	None	None	None	None	Score chart	No
Levine 1984	Birth trauma: clavicular fracture	Women with a singleton term live birth	Retrospective cohort	13870 (28; 6)	Logistic	None	None	None	None	Score chart	No
Levine 1984	Birth trauma: facial nerve injury	Women with a singleton term live birth	Retrospective cohort	13870 (104; 6)	Logistic	None	None	None	None	Score chart	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Placental abruption											
Odibo 2007	Placental abruption	Women with a previous caesarean delivery	Retrospective cohort	25076 (309; 7)	Logistic	None	None	"good fit" but statistics not reported	0.61	None	No
Lindqvist 2005	Placental abruption	Unselected pregnant women	Case-control	2483 (112; 10)	None (only univariable analysis)	None	None	None	None	Risk score	No
Baumann 2000	Placental abruption	Primiparous women with singleton pregnancies	Retrospective cohort	80336 (382; 10)	Logistic	None	None	None	None	Regression formula	No
Baumann 2000	Placental abruption	Multiparous women with singleton pregnancies	Retrospective cohort	89889 (492; 12)	Logistic	None	None	None	None	Regression formula	No
Postpartum haemorrhage											
Biguzzi 2012	Postpartum haemorrhage	Women with a singleton vaginal delivery ≥ 37 weeks	Unclear	6011 (1435; 6)	Logistic	Bootstrapping	None	Based on calibration plot: good fit	0.70	Nomogram	No
Prata 2011	Postpartum haemorrhage	Women expecting a singleton vaginal delivery	Prospective cohort	2510 (93; 20)	Logistic	None	None	None	None	Number of risk factors vs risk	No
Tsu 1994	Postpartum haemorrhage	Women with singleton pregnancies and spontaneous onset of labour	Case-control	653 (151; 5)	Logistic	None	None	None	Only ROC curve, AUC not reported	None	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Anal sphincter injury											
Williams 2005	Anal sphincter injury	Women with term singleton deliveries	Case-control	246 (123; unclear)	Logistic	None	None	None	Not shown but "ROC curve approximated to a straight line demonstrating very poor discrimination"	Risk score	No
Thrombosis											
Lindqvist 2002	Thrombosis in pregnancy (deep venous thrombosis, pulmonary embolism, or cerebral thromboembolism)	Unselected pregnancies	Prospective cohort	2384 (3; 8)	Logistic	None	None	None	None	Internet-based risk calculator (not available anymore)	Yes
Lindqvist 2002	Thrombosis within 3 months postpartum (deep venous thrombosis, pulmonary embolism, or cerebral thromboembolism)	Unselected pregnancies	Prospective cohort	2384 (3; 10)	Logistic	None	None	None	None	Internet-based risk calculator (not available anymore)	Yes
Maternal complications of attempted VBAC											
Scifres 2011	Major maternal morbidity after attempted VBAC (any of the following): uterine rupture, bladder or ureteral injury, bowel injury, or uterine artery laceration	Women with prior caesarean sections who attempted VBAC	Retrospective cohort	13706 (300; 6)	Logistic	None	None	None	0.65	None	No (performance too poor for use in practice)
Macones 2006	Uterine rupture after attempted VBAC	Women with prior caesarean sections who attempted VBAC	Nested case-control	799 (134; 4) (model A) and 799 (134; 6) (model B)	Logistic	None	None	None	0.68 (model A) and 0.71 (model B)	None	No

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Maternal complications of pre-eclampsia											
von Dadelszen 2011	Maternal mortality or one or more serious CNS, cardiorespiratory, hepatic, renal, or haematological morbidity in women with pre-eclampsia	women who were admitted with pre-eclampsia or had developed pre-eclampsia after admission	Prospective cohort	1935 (106; 6)	Logistic	Bootstrapping	None	Good calibration (based on table)	0.88	Regression formula	No
van der Tuuk 2011	Progression to a high risk situation (any of the following: diastolic blood pressure ≥ 110 mmHg, systolic blood pressure ≥ 170 mmHg and/or proteinuria ≥5 g in 24 h, eclampsia, HELLP syndrome or maternal mortality)	women with asingleton in cephalic presentation between 36-41 weeks and gestational hypertension or mild pre-eclampsia managed expectantly	Randomized trial	730 (244; 12)	Logistic	Bootstrapping	None	P=0.40	0.71	None	No
Combined adverse pregnancy outcome											
Magann 2011	At least one of the following adverse outcomes: pre-eclampsia, gestational diabetes, induction of labor, caesarean delivery, postpartum haemorrhage, postterm delivery, endometritis, wound infection, neonate born LGA, perinatal death, and neural tube defects	Women with singleton pregnancies	Retrospective cohort	4500 (2308; 4)	Recursive partitioning followed by logistic	None	None	None	None	Risk for specified risk groups	No

Other

Publication	Outcome	Population	Study design	Women (events; predictors) *n*	Type of model	Internal validation	External validation	Calibration (p-value Hosmer-Lesmeshow test or appearance calibration plot)	Discrimination (AUC)	Prediction rule	Decision recommended
Short cervix											
Souka 2011	Short cervix (≤15 mm) at 20-24 weeks of gestation	women with viable singleton pregnancies presenting at 11-14 weeks	Prospective study	800 (12; 3) (model A); 800 (12; 4) (model B)	Logistic	None	None	P=0.22 (model A); P>0.05 (model B)	0.81 (model A); 0.88 (model B)	Probability curve	No
Higher CRH levels											
Latendresse 2010	Higher CRH levels (>= 15 pcg/mL) at 14-20 weeks	Women with "healthy" singleton pregnancies	Cross-sectional cohort	84 (16; 3)	Logistic	None	None	P=0.071	None	Regression formula	No

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