HEALTH TECHNOLOGY ASSESSMENT IN MATERNAL AND PERINATAL MEDICINE

Delphi survey of practice, Systematic reviews of evidence and Meta analyses

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A thesis submitted to the Faculty of Medicine and Dentistry of the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

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May 2010

SYNOPSIS

This thesis systematically reviewed published literature on tests and treatments and surveyed practice patterns in high-risk conditions in maternal and perinatal medicine.

DEDICATION

To Arun, Shivanii, Shalu, Mum and Dad

ACKNOWLEDGEMENTS

This work was submitted during my post as Clinical Lecturer at Birmingham Women's Hospital, University of Birmingham. I am greatly indebted to my supervisor and friend Prof Khalid Khan, for his constant invaluable guidance and support at all stages of this work. I would like to thank my friend and colleague Arri Coomarasamy for introducing me to the world of systematic reviews and meta analyses and for his unfailing encouragement over the years. Many thanks to Prof Mark Kilby for his input as my supervisor. My thanks to Mr Khaled Ismail who was instrumental in starting my academic career as a Clinical Research Fellow at Keele University, Stoke-on Trent. I would like to thank my friend Javier Zamora for his crucial statistical input and for his fantastic software, MetaDisc.

Thanks to Jane Daniels, my colleague sharing the office, for patiently listening to my occasional exasperated bursts. Thanks to my parents-in-law for their support throughout and to Sally for being there for the kids. I would like to acknowledge the contributions of Prof Shaughn O'Brien, Mr Harry Gee, Prof Ben WJ Mol, Dr Fidelma O'Mahony, Mr Steven Sharp, Miss Manjo Doug and my co reviewers on the various included reviews for their help in the completion and publication of the papers arising from the thesis. Finally I would like to offer my thanks to Mrs Ann Daly, Miss Sandra Harrison and Mr Derick Yates, information specialists at Birmingham Women's Hospital.

EXECUTIVE ABSTRACT

Aim

This thesis performed Health Technology Assessments for a range of tests and interventions in the field of maternal and perinatal medicine. The main objectives were

A. To perform Delphi survey of experts to prioritise the tests in pre eclampsia where there was a perceived need for evidence to inform practice and to plan further research

B. To review the methodological quality of existing reviews in maternal and fetal medicine

C. To undertake systematic reviews and meta analyses of therapy studies in areas like epilepsy and pre term labour, conditions that have significant influence on maternal and perinatal mortality and morbidity

D. To conduct diagnostic reviews and meta analyses of test accuracy studies in pre eclampsia and congenital heart disease, conditions that have significant influence on maternal and perinatal mortality and morbidity

Methods

The work undertaken in this thesis was based on prospective study protocols using the following research methodologies:

- Delphi survey of tests in pre eclampsia
- Review of quality of reviews in maternal and fetal medicine
- Systematic reviews and meta-analyses of tests and treatment in maternal (pre eclampsia, epilepsy, pre term labour) and perinatal (congenital heart disease in newborn) medicine

To achieve the aims of this thesis the work undertaken has been divided in four sections:

- Section A - Delphi survey:

  Delphi survey to prioritise the accuracy of tests in predicting complications in women with pre eclampsia (Chapters 2, 3).

- Section B - Review of Reviews

  Systematic review of quality of existing reviews in the field of maternal and fetal medicine (Chapters 4, 5).

- Section C - Systematic review of therapy studies

  Systematic quantitative overviews of relevant therapy studies to obtain summary estimates of effectiveness of interventions a) anti epileptic drug lamotrigine management in pregnant women with epilepsy (Chapter 6) and b) progesterone in women at risk of pre term labour (Chapter 7).

- Section D - Systematic review of test accuracy studies

  In maternal medicine, systematic quantitative overviews of relevant test accuracy studies to obtain summary estimates of accuracy of the tests for predicting maternal and fetal complications in pre-eclampsia (Chapters 8, 9, 10, 11, 12, 13). In perinatal medicine, systematic review of accuracy of pulse oximetry in screening for congenital heart disease in newborns (Chapter 14).

Results

Section A: Delphi Survey

- The Delphi survey of experts in the field of high risk obstetrics in UK and Australia considered blood pressure to be the best predictor of complications with mean score (SD) of (4.7 ± 0.47), followed by proteinuria (4.6 ± 0.5) and liver function tests (4.5 ± 0.52) (scale x to y anchored between 0 -5).

Section B: Review of reviews in maternal and fetal medicine

- A total of 3523 relevant citations were identified from the detailed search in major databases. Of these, 336 articles were evaluated in detail and 152 review articles were included in the final reviews.

- Majority of the reviews in maternal medicine (62/68, 91%) specified the question and 54/68 (79%) had a focussed question with clearly defined population and outcome measures. Cochrane reviews specified the questions more often than non-Cochrane reviews ($p<0.04$) and also framed more narrowly focussed questions ($p<0.001$). Cochrane reviews attempted more often to include unpublished data in the literature search ($p<0.002$). The meta analysis technique ($p<0.02$) and assessment for heterogeneity ($p<0.01$) was found to be employed significantly more often by Cochrane reviews.

- The majority of reviews in fetal medicine (58/84, 69%) specified the question to be answered and only 52% (44/84) had a narrow focus. Fetal growth reviews performed significantly better than reviews in other areas in question specification ($p<0.03$), search

without language restriction ($p<0.004$), assessment of risk of missing studies ($p<0.006$) and study quality assessment ($p<0.002$). There was no difference in other quality items.

Section C: Systematic review and meta analyses of therapy studies

- A comprehensive search of major databases identified 1819 relevant citations. Full manuscripts of 103 papers were retrieved for detailed evaluation and 14 studies with 1149 patients were included in the reviews evaluating the effectiveness of progesterone and lamotrigine in women at risk of pre term labour and pregnant women with epilepsy respectively.

- A significant benefit of progestational agents was observed in reducing preterm delivery before 37 weeks (Odds ratio OR 0.42, 95% confidence interval CI 0.31 to 0.57) and before 34 weeks (OR 0.51, 95% CI 0.34 to 0.77). No heterogeneity was identified for either results.

- The combined rate of seizure deterioration was 0.40 (95% CI 0.26 to 0.55) in pregnant women with epilepsy on lamotrigine treatment managed by serum drug levels compared to 0.73 (95% CI 0.56 to 0.86) in those managed by clinical monitoring alone.

Section D: Systematic review and meta analyses of test accuracy studies

- The abstracts of 20,058 citations were reviewed to identify the studies to be included in the review of accuracy of tests in pre eclampsia including proteinuria, uric acid, liver function tests, symptoms and blood pressure and pulse oximetry to detect congenital heart disease in the newborns.

- Sixteen primary articles with a total of 6749 women met the selection criteria with levels of proteinuria estimated by urine dipstick, 24-hour urine proteinuria or urine protein : creatinine ratio as a predictor of complications of pre-eclampsia. The area under the curve (AUC) for adverse maternal and fetal outcomes are 0.63 (95% CI 0.22, 0.91) and 0.59 (95% CI 0.36, 0.79) respectively.

- There were 18 primary articles that met the selection criteria, including a total of 3675 women evaluating the accuracy of uric acid in predicting adverse maternal and fetal outcomes. The AUC for adverse maternal and fetal outcomes were 0.75 (95% CI 0.46, 0.92) and 0.69 (95% CI 0.39, 0.86) respectively.

- Thirteen primary articles were selected including a total of 2813 women to assess the accuracy of liver function tests in predicting complications in pre eclampsia. For predicting adverse maternal outcome, the AUC was 0.79 (95% CI 0.51, 0.93). For predicting adverse fetal outcomes the AUC was 0.65 (95% CI 0.26, 0.9). The sensitivity of the test was poor for both maternal and fetal outcomes.

- Six primary articles with 2573 women were included in the review of symptoms in pre eclampsia. The AUC for predicting maternal complications with symptoms of headache, epigastric pain and visual disturbances were 0.58 (95% CI 0.24, 0.86), 0.70 (95% CI 0.3, 0.93) and 0.74 (95% CI 0.33, 0.94) respectively.

- Eight articles with 2304 women evaluated the accuracy of blood pressure in predicting adverse outcomes. For the prediction of eclampsia, abruption, renal, neurological and liver impairment, mean arterial pressure (MAP) $\geq$ 140 mmHg or BP $\geq$ 170/110 had high specificity (more than 80%) and low sensitivity (<50%). The area under the curve (AUC) for any adverse maternal outcome was 0.68 (95% CI 0.29, 0.92). The specificity for adverse

fetal outcomes was more than 70% in 11/15 (73.3%) studies and sensitivity was more than 70% in 6/15 (40%) studies.

- Eight studies with 35,960 newborns were included in the review of accuracy of pulse oximetry in detecting congenital heart disease. The summary estimates of sensitivity and specificity were 0.63 (95% CI 0.39, 0.83) and 0.998% (95% CI, 0.99, 1.00) respectively, yielding a false positive rate of 0.2% (95% CI, 0% to 1%).

Conclusion

This thesis has identified and prioritised the tests that are considered to be useful in the management of women with pre eclampsia by a Delphi survey of experts in this field. The systematic reviews of the diagnostic value of these prioritised tests have quantified the accuracy in predicting adverse maternal and fetal outcomes and been referenced by international guidelines. The review on the effectiveness of progesterone in preterm labour has demonstrated its beneficial effect in reducing preterm births with significance for clinical practice. The review on the accuracy of pulse oximetry has reinforced the role of abnormal pulse oximetry in accurately identifying babies with congenital heart disease. The magnitude of proteinuria in women with pre-eclampsia is a poor predictor of the major maternal and fetal complications. Although uric acid as a marker may be of value in detecting pre-eclampsia, it has been identified as a poor predictor of any complications of pre-eclampsia. In women with preeclampsia, liver function tests had at best moderate prediction of maternal and fetal complications. The test specificity, however, was better than sensitivity. Among women with pre-eclampsia, symptoms of visual disturbance and epigastric pain were moderately good predictors of maternal complications with better accuracy than headache. The presence of symptoms is clinically more useful for *ruling in* complications in

comparison to their absence for *ruling out* complications. Blood pressure was a better predictor of adverse fetal than maternal outcomes.

The implications for future research are that maternal and fetal medicine specialties need further good quality research. The systematic review of tests in pre eclampsia has provided the evidence to justify a large prospective study in this area. This has led the successful NIHR (National Institute for Health Research) grant to conduct a large multicentre prospective study, Prediction of Risks in Early onset Pre eclampsia (PREP). The pulse oximetry review generated results that needed to confirm the value of pulse oximetry as a screening test, in isolation or in combination with antenatal ultrasound to obtain precise estimates of its sensitivity. This led to the successful NIHR grant for the multicentre Pulse Ox study. The review of optimal monitoring regimen of anti epileptic drugs (AED) in pregnant women with epilepsy established the poor quality small studies in this area. Based on these findings, funding for a pilot randomised controlled trial, SOAP (Study of Optimal Anti epileptic Drugs in Pregnancy) has been provided by the Research and Development (R & D) department of the Birmingham Women's Hospital. Recently, the findings have been instrumental in the successful NIHR funding for a multicentre randomised controlled trial in this area, EMPIRE - Anti Epileptic drug (AED) Management in PREgnancy: An evaluation of effectiveness, cost effectiveness and acceptability of dose adjustment strategies.

PUBLICATIONS IN PEER REVIEWED JOURNALS FROM THE THESIS

1. **Thangaratinam S**, Coomarasamy A, O'Mahony F, Sharp S, Zamora J, Khan KS, Ismail KM. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med 2009;7:10

2. **Thangaratinam S**, Coomarasamy A, Sharp S, Ismail KMK, Khan KS for the TIPPS (Tests in Prediction of Pre-eclampsia's Severity) review group Tests for predicting complications of pre-eclampsia: A protocol for systematic reviews of the literature BMC Pregnancy Childbirth. 2008;8:38

3. Knox E, **Thangaratinam S**, Kilby MD, Khan KS. A review of the methodological features of systematic reviews in fetal medicine. Eur J Obstet Gynecol Reprod Biol 2009;146: 121-128

4. Sheikh L, Johnston S, **Thangaratinam S**, Kilby MD, Khan KS. A review of the methodological features of systematic reviews in maternal medicine. BMC Med. 2007;5:10.

5. **Thangaratinam S**, Ismail K, Sharp S, Coomarasamy A, O'Mahony F, Khan KS, O'Brien S; TIPPS (Tests in Prediction of Preeclamsia's Severity) Review Group.Prioritisation of tests for the prediction of preeclampsia complications: a Delphi survey.Hypertens Pregnancy. 2007;26:131-8.

6. **Thangaratinam S**, Daniels J, Ewer AK, Zamora J, Khan KS.Accuracy of pulse oximetry in screening for congenital heart disease in asymptomatic newborns: a systematic review.Arch Dis Child Fetal Neonatal Ed. 2007;92:F176-80

7. Coomarasamy A, **Thangaratinam S**, Gee H, Khan KS.Progesterone for the prevention of preterm birth: a critical evaluation of evidence.Eur J Obstet Gynecol Reprod Biol. 2006;129:111-8.

8. **Thangaratinam S**, Ismail KM, Sharp S, Coomarasamy A, Khan KS; Tests in Prediction of Pre-eclampsia Severity review group.Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG. 2006;113:369-78.

9.**Thangaratinam S**, Gallos I, Meah N, Usman S, Ismail KMK, Khan KS. How accurate are maternal symptoms in predicting impending complications in women with pre-eclampsia? A systematic review. (Acta Obstet et Gynecol in print)

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CHAPTER 1: INTRODUCTION

1.1 Health technology assessment

The term 'health technology' encompasses a range of methods used to improve health, prevent and treat disease and improve rehabilitation and long term care.[1] Health technology assessment (HTA) is the systematic appraisal of properties, effects or other impacts of health technology. The main role of HTA is to inform health care decisions at the individual or patient level, the level of the health care provider or institution, or at the regional, national and international levels. HTA evaluates the direct and intended results of technologies as well as their indirect and unintended results. It improves existing knowledge base for improving the quality of health care, especially to support development and updating of a wide spectrum of standards, guidelines, and other health care policies.

1.1.1 HTA for therapeutic effectiveness

Effective therapeutic interventions that reduce maternal and fetal mortality and morbidity are needed in addition to accurate diagnostic tests or strategies to improve clinical care and prognosis. The purpose of treatment is to improve or maintain health status, avoid further deterioration, or provide palliation. Evaluation of therapy includes assessment of efficacy and effectiveness of intervention, investigation of the technology and its safety, economic attributes, social, legal or ethical impact of the intervention studied. Efficacy and effectiveness both refer to how well an intervention or technology improves patient outcome. Efficacy refers to the added value of using a technology for a particular clinical problem in an ideal situation like a randomised trial conducted as per protocol in a tertiary unit. Effectiveness refers to the added value of using a technology for a

particular problem under general or routine conditions like primary or secondary hospitals involving a wide range of patients.

1.1.2 HTA for diagnostic technologies

One of the important medical interventions in the quest for preventing or reducing maternal and fetal mortality and morbidity is the prediction or diagnosis of the high risk maternal, fetal or neonatal status. This will help to offer appropriate and timely management aimed at reducing maternal and fetal complications. Clinical prediction of disease complications using a combination of patients' characteristics, symptoms, physical signs and investigations all of which we consider tests, forms the basis of clinical care in these situations. Therefore, there is a need for guidance about the best testing strategies with which to predict development of complications. As well as allowing clinicians to avoid unnecessary interventions in low risk groups, this will allow high-risk groups to benefit from monitoring of disease severity and use of appropriate treatment. Diagnostic accuracy studies provide information on the discriminatory power of the tests in identifying the disease. The impact of the individual diagnostic tests and diagnostic strategies studied by randomised controlled trials depend on the accuracy of the tests as well as the treatment protocol based on the test results.

1.2 Conduct of Health Technology Assessment

There is wide variation in the methods, scope and conduct of HTA. Widely they involve the following steps (Fig 1.1).

1. Specify the problem and its importance to patient and health services: Surveys of clinicians and patients

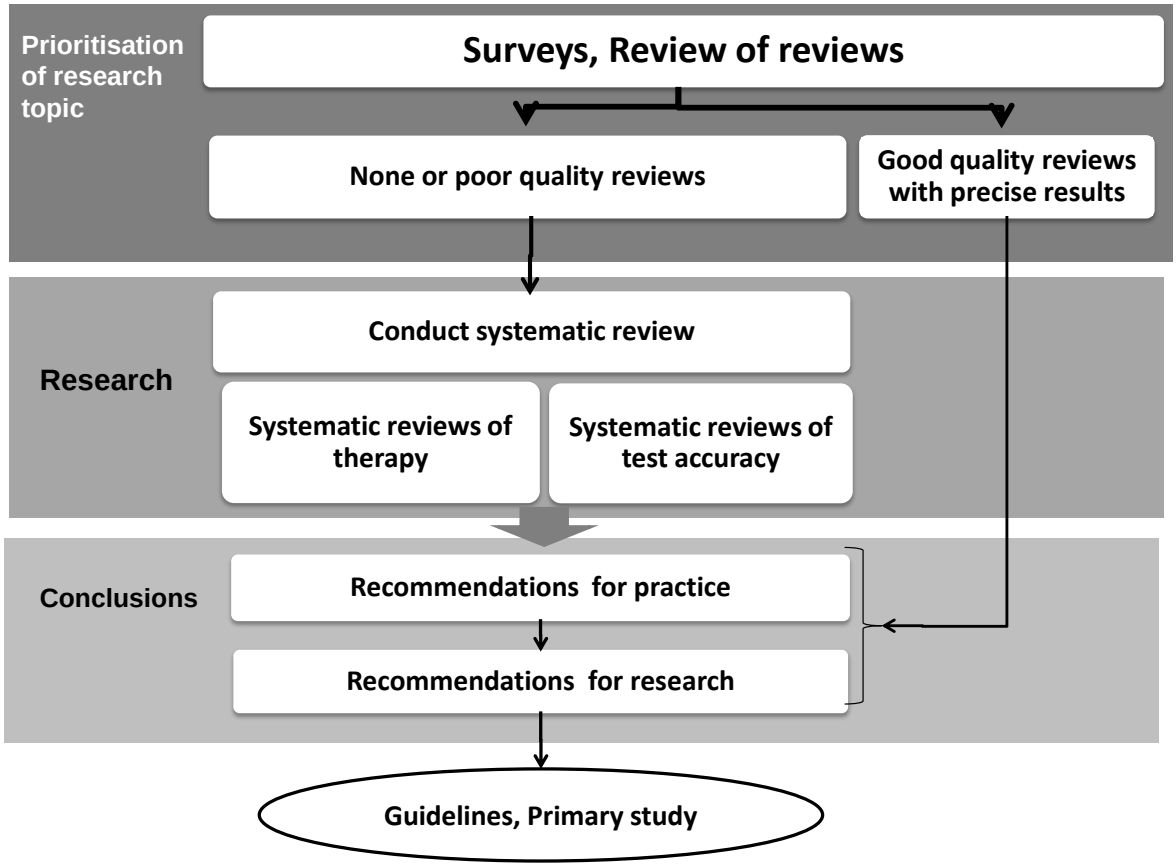
2. Search and retrieve appropriate evidence, appraise the retrieved evidence, collate or synthesise evidence: Systematic reviews of primary studies

3. Collect new primary data if insufficient or poor quality evidence: primary research

4. Generate the results and recommendations: Appropriate interpretation of findings

5. Disseminate the findings and integrate into clinical practice

Fig 1.1 Health Technology Assessment of tests and treatment



Systematic review provides a key methodology for HTA. It synthesises the best available evidence to provide an overall assessment. Furthermore, it identifies variation in effect or performance between various studies. Recently there has been a proliferation of systematic reviews as one of the key tools for evidence-based medicine.[2] In the field of fetal medicine, although the number of primary studies has exponentially increased over the last 30 years, their systematic reviews are relatively sparse in comparison (Appendix 2). By collating all the available evidence, reviews often

highlight the paucity in quality and number of existing studies and provide justification for new well defined prospective studies.

1.3 Maternal and perinatal medicine topics reviewed in this thesis

Maternal medicine is defined as specialised services provided to women with pre-existing or pregnancy related disease. Perinatal medicine deals with the care of the fetus and premature or ill newborns. It is difficult to separately define the various components of maternal and perinatal medicine as the care of women in high risk pregnancies considerably overlaps and closely links with the care and outcome of the fetus and neonate. When assessing health technologies aimed at improving reducing maternal and neonatal mortality and morbidity, these links need serious attention. The following areas that have a significant impact on maternal and perinatal morbidity and mortality have been included in this thesis.

a. Pre eclampsia

Pre eclampsia is a multisystem disorder in pregnancy associated with hypertension and proteinuria.[3-5] Hypertension is defined as systolic blood pressure of 140 mm Hg or more and diastolic blood pressure of 90 mm Hg or more on two occasions 4-6 hours apart.[3-5] Proteinuria is defined as 300 mg or more in 24 hour urine collection or urine dipstick of 1+ or more in 2 samples 6 hours apart or a spot urine protein/creatinine ratio of at least 30 mg/mmol.[4-6] Hypertensive diseases in pregnancy remain one of the leading causes of direct maternal deaths in the UK and account for 20% of all stillbirths.[7] In 1% of pregnant women pre eclampsia occurs before 34 weeks, so called early onset pre eclampsia.[8;9]

Early onset pre eclampsia is considered to be a pathophysiologically different disease than late onset pre eclampsia with considerably increased risk of maternal complications with 20-fold higher maternal mortality.[10-12] The only known cure in this condition is delivery of the baby and placenta. In women with early onset pre eclampsia, the decision about when is the best time to deliver can be difficult, as fetal and neonatal benefits from prolongation of pregnancy needs to be balanced against the risk of multisystem dysfunction in the mother. Preterm delivery accounts for 65% of neonatal deaths and 50% of neurological disability in childhood.[13] Current practice guidelines do not consider gestational age at presentation as a criterion for diagnosis, severity, or sub classification to stratify risk in women with pre eclampsia.[4;14] Pre eclampsia is considered to manifest as two syndromes: Maternal, associated with hypertension and proteinuria, and fetal, manifested by intrauterine growth restriction (IUGR). The maternal syndrome the disease, may persist, often worsening briefly, following delivery of the imperfectly implanted placenta.[15]

Although the proportion of women with early onset pre eclampsia is only 1% of all pregnancies, the complexity of the treatment gives rise to large health care costs.[8;9] Patients are often admitted in a tertiary care facility and 30% experience complications, which may necessitate an intensive care facility.[16] Infants usually need prolonged intensive care treatment for management of complications including lifelong handicaps arising as a result of pre maturity.

One of the key recommendations in the last CEMACH (Confidential Enquiries into Maternal and Child Health) report for policy makers, service commissioners and providers, and healthcare professionals is the need to adopt an early warning system to help in the timely recognition, treatment and referral of treatment of women who have or are developing critical conditions.[7] This applies to women with severe pre eclampsia where early recognition of women at risk of adverse outcomes can be transferred early from secondary to tertiary unit to enable care in a high dependency unit or neonatal intensive care unit if needed. Timely prediction of complications in

women with pre-eclampsia involves the use of a combination of patients' characteristics, symptoms, physical signs and investigations[17] these 'tests' are performed routinely in all units, but, in the absence of a structured approach, somewhat haphazardly.

b. Epilepsy In Pregnancy

Epilepsy affects 0.5-1% of general population.[18] Approximately one third of people receiving anti epileptic drugs (AED) are of reproductive age.[19;20] There is a 10-fold increase in mortality among pregnant women with epilepsy which greatly exceeds the two to three-fold mortality rate observed in all people with epilepsy.[21] In 2000-2002, 13 maternal deaths in the UK were attributed to epilepsy.[22] These were invariably a direct consequence of seizures. There is one in 250 pregnancies exposed to AEDs .[23;24] AED exposure in-utero is associated with congenital malformations.[25] Fetal risk is related to the number of AEDs, AED type and probably AED dose. Furthermore, there are concerns about the long-term neurological development of children exposed to AEDs in-utero. There is a general consensus that the risks of uncontrolled convulsive seizures in the mother outweigh the potential teratogenic risk of the medication, and most women with active epilepsy are advised to continue with medication during pregnancy.[18] The effect of seizures extend into daily living resulting in loss of driving license, a negative impact on employment and relationships, and reduced Quality of Life (QoL).[26] The triennial Confidential Enquiries into Maternal Deaths in the UK reported concerns about epilepsy management during pregnancy.[22]

Seizure control is important during pregnancy. Uncontrolled epilepsy with generalised tonic-clonic convulsions, carry risk of harm including miscarriage, fetal hypoxia and acidosis and fetal loss.[27-29] The reasons for fetal loss are not entirely understood but are more likely to be related to

maternal seizures than to fetal exposure to AEDs.[29;30] This is supported by the finding of fetal heart rate decelerations during maternal seizures.[31]

Data from pregnancy registers and from Study of Standard Versus New Antiepileptic Drugs (SANAD), have increasingly influenced clinicians to favour the newer AEDs, with lamotrigine (LTG) being the first choice for women of child-bearing age.[32] Prescription of newer AEDs has been increasing in NHS with associated drug costs (£99m of £142m).[33] There are additional costs of monitoring in antenatal clinics and admission in hospitals if significant seizure deterioration occurs. Congenital malformations and the adverse effects on the neurodevelopment of children exposed to AEDs in utero have added morbidity and long-term costs.

c. Pre-term labour

Pre-term birth, i.e. delivery at less than 37 completed weeks' of gestation, is a heterogeneous condition. Spontaneous pre-term birth prior to 37 weeks' gestation occurs in 7-11% of pregnancies and occurs in 3-7% of pregnancies before 34 weeks' gestation.[34] Pre-term delivery particularly that before 34 weeks' gestation, accounts for three-quarters of neonatal mortality and one-half of long term neurological impairment in children. Many of the surviving infants suffer serious morbidity such as respiratory distress syndrome, broncho-pulmonary dysplasia, intraventricular haemorrhage, retrolental fibroplasia and developmental problems.[34] The additional NHS costs to care for a preterm baby born before 33 weeks and 28 weeks are £61,509 and £94,190 respectively.[35] £939 million in extra costs for care of preterm babies per year in the NHS are linked to neo-natal care such as incubation, and hospital readmissions.[35] Delaying premature births by a week could potentially save £ 260 million a year.[35] Advances in perinatal healthcare have not reduced the rate of pre-term birth, but there are some effective interventions to reduce the risk of short and long term sequelae to the premature neonates.

d. Congenital Heart Disease In Newborns

Congenital heart disease (CHD) is the commonest group of congenital malformations and affects 7-8/1000 newborns.[36;37] It contributes to 3% of all infant mortality and 46% of deaths from congenital malformations, with most deaths occurring in the first year of life. [36] A significant proportion of these children require surgery in the first year. One of the major contributors to increased infant mortality and morbidity is clinical deterioration and collapse prior to diagnosis and treatment.[38-40] Early detection of congenital heart disease in the asymptomatic period immediately after birth will reduce clinical deterioration by instigation of appropriate, timely management. Survival rates for infants with CHD have increased dramatically in recent years and over 80% of children born with CHD will survive to the age of 16 years; this is due largely to improvements in surgical techniques. Although the commonest types of CHD do not usually develop serious problems in the neonatal period, there are a number of important cardiac defects which, if undiagnosed, can present with potentially life-threatening cardiovascular collapse in the first few days of life. Although individually less common, when taken together, these lesions contribute significantly to death in infancy. As death or poorer outcome following surgery is much more likely if cardiovascular collapse occurs prior to diagnosis, timely recognition of these cardiac defects prior to collapse is vital in order to improve outcome.

1.4 Aims of thesis

My thesis aims to conduct the Health Technology Assessment in maternal and perinatal medicine through the following four objectives:

A. To perform Delphi survey of experts where there is no robust evidence to inform practice and to plan further research

B. To review the methodological quality of existing reviews in maternal and fetal medicine

C. To perform systematic reviews and meta analyses of the effectiveness of various interventions that reduce maternal and perinatal mortality and morbidity

D. To conduct diagnostic reviews and meta analyses in maternal and perinatal medicine to assess the accuracy of tests in predicting maternal and fetal complications

The specific reaseach questions that I have attempted to answer in this thesis are given below, and summarised in a structured format in Table 1.1

- What tests in pre eclampsia are considered to be important by clinicians in predicting maternal and fetal complications in women with pre-eclampsia?

- What is the quality of systematic reviews in maternal medicine and is there a difference in quality between Cochrane reviews and non Cochrane reviews?

- What is the quality of systematic reviews in fetal medicine and is there a difference in quality between various areas in fetal medicine?

- Does the use of progesterones in women at risk of preterm labour reduce the risk of preterm births and neonatal mortality and morbidity?

- Does regular therapeutic monitoring of serum lamotrigine levels in pregnant women with epilepsy reduce the risk of seizures compared to management based on clinical features alone?

- How accurate are tests like proteinuria, uric acid, liver function tests, symptoms and blood pressure in women with pre eclampsia in predicting maternal and fetal complications?

- What is the accuracy of pulse oximetry as a screening tool in identifying congenital heart disease in newborns?

Table 1.1 Structured questions for each chapter of this thesis

Chapter Number	Population	Intervention or Test	Outcome(s)	Research Design
Objective A: Delphi Survey of practice where there is no robust evidence				
2, 3	Women with pre eclampsia	Tests including clinical history, examination and investigation	Maternal and fetal mortality and morbidity	Delphi survey
Objective B: To review the quality of systematic reviews in maternal and fetal medicine				
4	Maternal medicine reviews	Cochrane Vs Non Cochrane	Adherence to pre specified good quality items	Systematic review
5	Fetal medicine reviews	Quality across 4 areas: fetal aneuploidy, fetal therapy, fetal pathology and fetal growth	Adherence to pre specified good quality items	Systematic review
Objective C: To undertake systematic reviews and meta analyses of therapy studies				
6	Pregnant women at risk of pre term labour	Progeterone Vs Placebo	Delivery before 34 weeks, 36 weeks, perinatal mortality and other clinically relevant outcomes	Systematic review and meta analysis
7	Pregnant women with epilepsy on lamotrigine	Routine therapeutic monitoring Vs Management based on clinical features only	Seizures, any other relevant maternal and fetal outcome	Systematic review and meta analysis
Objective D: To undertake systematic reviews and meta analyses of test accuracy				
8-14	Women with pre eclampsia	-Proteinuria -Uric acid -Liver function tests -Symptoms -Blood pressure	Adverse maternal and fetal outcomes	Systematic review and meta analysis
15	Newborns	Pulse oximetry	Congenital heart disease	Systematic review and meta analysis

1.5 Health Technology Assessment methods in the thesis

1.5.1 Delphi survey

A valid Delphi process would consist of at least a three-iteration questionnaire survey, although decision about the number of rounds is largely pragmatic. The purpose of the initial iteration is to identify broad issues related to the various components of the issue at hand. A questionnaire consisting of open-ended questions is circulated to a panel of experts and opinion leaders. The responses to the open-ended questions are analysed qualitatively by sorting, categorising and searching for common themes. These responses are edited and then used to construct the second questionnaire.

The second and subsequent rounds are more specific with the questionnaire seeking the rating or ranking of various items in terms of their significance and analysed quantitatively. As the researcher feeds back results from the previous rounds there tends to be convergence to a consensus of opinion[41].

1.5.2 Systematic review of reviews

A good systematic review should: develop a focussed question, undertake a detailed search to identify all the relevant published and unpublished literature, independently selected the studies from specific inclusion and exclusion criteria as per the protocol, critically appraise the quality of included studies, extract relevant data and conduct appropriate meta analysis to formulate recommendations.

The checklist for the review of reviews in maternal and fetal medicine consisted of items divided into three domains concerning the review question, the literature search and the review methods.

These items evaluated the likelihood of errors and bias in the review process. A 'good' quality item was one where there was a clear description in the report of compliance with the items, whereas a 'bad' quality item either did not comply with or did not report sufficient details to assess the item.[42] Some of the items related to explicitness of reporting that results in scientific transparency in a review. There are various instruments reported in literature to evaluate the quality of systematic reviews. Although some may have face and content validity, they have not demonstrated satisfactory reproducibility or construct validity to be applied in practrice.[43]

1.5.3 Systematic review of effectiveness

Systematic reviews of effectiveness were carried out using review methodology based on a prospective protocol in line with the recommendations of the NHS Centre for Reviews and Dissemination and the Cochrane Collaboration.[44-49] The output from the reviews are based on existing guidelines and comply with QUOROM (QUality Of Reporting Of Meta-analyses) statement.[50] The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement was published recently after completion of the reviews included in the thesis.[51] The reviews are compliant with most of the PRISMA checklist components.

Study identification and selection: The structured questions were focussed and well defined in this thesis detailing population, interventions and comparison and study designs. A database of published and unpublished literature were assembled from searches in major electronic databases including Medline and Cochrane using a comprehensive search strategy, as well as hand searching. Language restrictions were not applied. The citation were scrutinised by two reviewers. Copies of full manuscripts of all citations that were likely to meet the selection criteria were obtained. Two reviewers then independently selected the studies, which met the predefined criteria. These criteria

were pilot tested using a sample of papers. Disagreements were resolved by consensus and/or arbitration involving a third reviewer.

Study quality assessment and data extraction: The quality of the selected primary randomised controlled trials (RCT's) and observational studies were assessed based on accepted contemporary standard.[52-54] To assess the quality, we considered first of all risk of bias (internal validity), i.e. the extent to which design, methods, execution and analysis did not control for bias in assessment of effectiveness.[46] Furthermore, we explored the (in-) consistency of results (heterogeneity), (in-) directness of the evidence (to the question under consideration, including surrogate parameters), (im-) precision of the results and publication bias. Individual studies were described by study type, intervention, numbers taking part, population denominator (eg pregnant women or fetuses) and study quality. In addition to using study quality as possible explanations for differences in results (heterogeneity), the extent to which primary research met methodological standards is important per se for assessing the strength of any conclusions that were reached. Study findings and data were extracted in duplicate using pre-designed and piloted data extraction forms.

Data synthesis: Separate analyses were performed on randomised and non-randomised data using Stata software. Any heterogeneity of results between studies was statistically and graphically assessed. The causes of the heterogeneity were explored and meta-analysis was performed if appropriate. To explore causes of heterogeneity subgroup analyses were planned a priori to see whether variations in clinical factors e.g. populations, interventions, outcomes or study quality affected the estimation of effects. Conclusions regarding the typical estimate of an effect size of the intervention were interpreted cautiously if there was significant heterogeneity.

1.5.4 Systematic review of test accuracy

Systematic reviews of test accuracy were conducted using established systematic review methodology in line with the recommendations of the NHS Centre for Reviews and Dissemination and the Cochrane Collaboration including those of Cochrane Methods Working Group on Screening and Diagnostic tests.[55;56]

Study identification and selection: This was performed as outlined in Section 1.3.3.

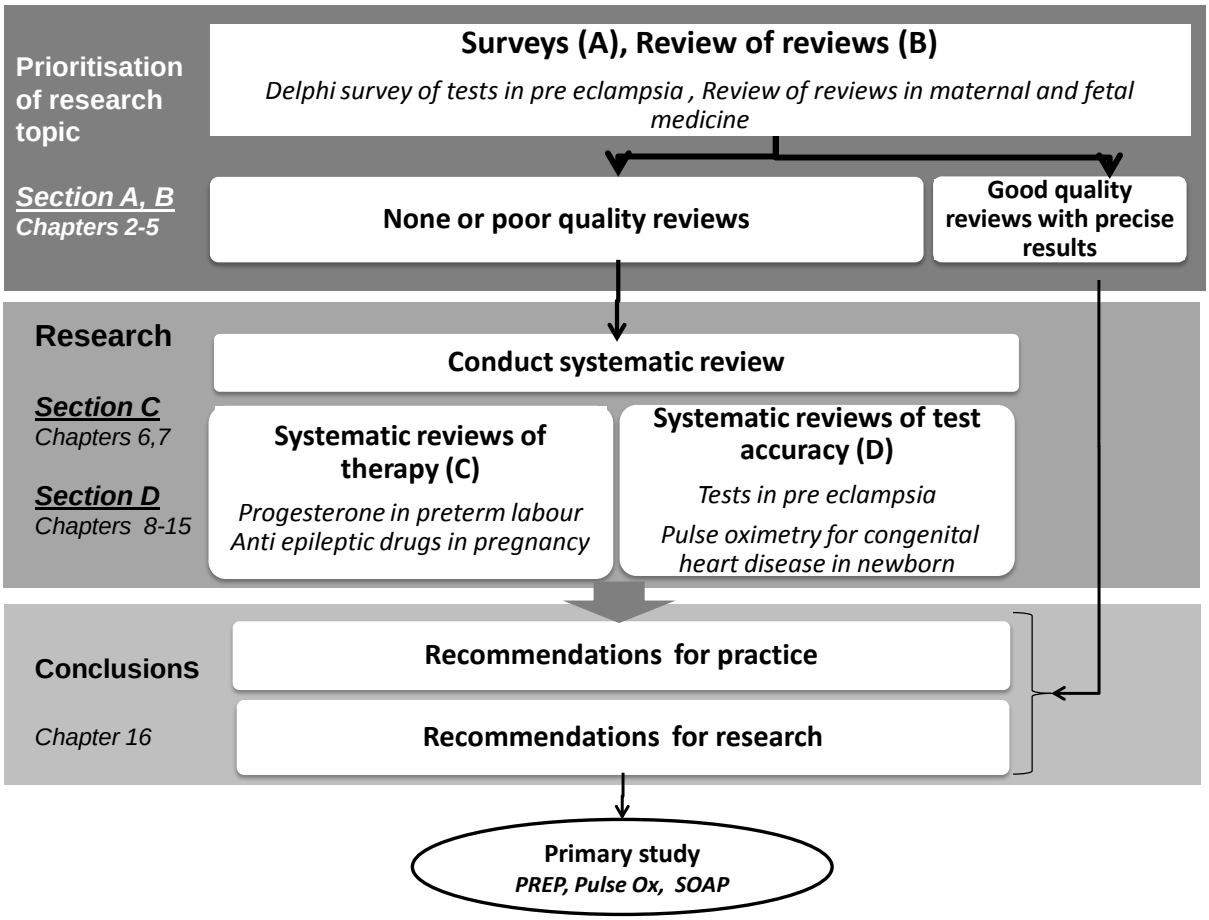
Study quality assessment and data extraction: Methodological quality of the selected primary studies were assessed based on elements of study design, conduct and analysis included in the validated assessment tool, QUADAS (Quality of Diagnostic Accuracy Studies), adapted to the topic area as necessary.[57] Data extraction was performed by two reviewers using pre-designed, piloted data extraction forms.

Data synthesis: Sensitivity, specificity and likelihood ratios for individual studies were derived. Presence of a threshold effect were examined by plotting sensitivity against 1- specificity in a receiver operating-characteristic analysis (ROC analysis) and by calculating Spearman correlation coefficients.[58] A bivariate random effects meta-regression model was used to fit a summary ROC (sROC) curve. Briefly, the bivariate model preserves the two-dimensional nature of diagnostic data in a single model. This model incorporates the correlation that may exist between sensitivity and specificity within studies due to possible differences in threshold between studies.[59] AUC (Area Under the Curve) values between 0.70 and 0.79 were deemed as having moderate discriminative properties, and those with AUC values of $\geq$ 0.80 as having good discriminative properties.

Heterogeneity of results between studies were investigated qualitatively by examining the distribution of sensitivities and specificities in (ROC) space and variability of accuracy estimates across studies using the forest plot.[58] Data was analysed using Metadisc and Stata softwares.

Fig 1.2 summarises the HTA in maternal and perinatal medicine conducted as part of this PhD thesis.

Fig 1.2. An overview of Health Technology Assessment of topics in maternal and perinatal medicine in the thesis



PREP – Prediction of Risks in Early onset Pre eclampsia
Pulse Ox –Pulse Oximetry as a screening tool for detecting congenital heart disease in newborn
SOAP – Study of Optimal Anti epileptic drug monitoring in Pregnancy

SECTION A

DELPHI SURVEY

In this section, I have undertaken a Delphi survey of experts to prioritise the list of tests in pre eclampsia that are considered to be predictive of adverse maternal and fetal outcomes

CHAPTER 2: THE DELPHI TECHNIQUE

2.1 Abstract

Background

The Delphi technique involves the collection and aggregation of expert opinion. It straddles the divide between qualitative and quantitative methodologies. The cardinal features of Delphi method are the use of a number of questionnaire rounds, feed-back of responses, the opportunity for participants to modify their responses and anonymity of responses.

Methods

A valid Delphi process would consist of at least a three-iteration questionnaire survey. The purpose of the initial iteration is to identify broad issues related to the various components of the issue at hand. The second and subsequent rounds are more specific with the questionnaire seeking the rating or ranking of various items in terms of their significance and analysed quantitatively. Most feedback is numerical or statistical with some form of aggregated group response. Statistical feed-back often uses medians, usually accompanied by minima and maxima, quartiles and/or the inter-quartile range.

Conclusion

The consensus-forging nature of the Delphi technique can be used to good effect in enabling evidence-based medical guidelines to become adopted by clinical groups. It is a useful tool for developing group consensus and can avoid many of the counterproductive pitfalls that can bedevil face-to-face meetings.

Citation of paper published from this work

Thangaratinam S, Redman CWE. The Delphi Technique. The Obstetrician and Gynaecologist. 2005; 7: 120-125

2.2 Background

The Delphi technique involves the collection and aggregation of expert opinion. It was initially used by the military to estimate the probable effects of massive atomic bombing but now has applications in economic and financial settings, civic planning and health care: very much a case of turning swords into ploughshares.

Its original purpose was to "obtain the most reliable consensus of opinion of a group of experts… by a series of intensive questionnaires interspersed with controlled opinion feed-back"[60], particularly in areas "where hard data was unavailable or too costly to obtain[61]". The cardinal features of Delphi method are the use of a number of questionnaire rounds, feed-back of responses, the opportunity for participants to modify their responses and anonymity of responses.

Delphis are about the harnessing and organising judgement, particularly in problems that are complex and require intuitive interpretation of evidence or informed guesswork. A Delphi can be used as an alternative to conventional meetings, avoiding problems arising from powerful personalities, group pressures and the effects of status. This is manifest more in the hierarchical structure of the health profession, where more junior practitioners may be reluctant to challenge the opinion of their seniors[62]. Its structure and sense of direction provides focus and avoids entropic and often counterproductive discussions and digressions that bedevil face-to-face group discussions.

2.3 Methods

2.3.1 Conduct of a Delphi survey

A valid Delphi process would consist of at least a three-iteration questionnaire survey, although decision about the number of rounds is largely pragmatic. The purpose of the initial iteration is to identify broad issues related to the various components of the issue at hand. A questionnaire consisting of open-ended questions is circulated to a panel of experts and opinion leaders. The responses to the open-ended questions are analysed qualitatively by sorting, categorising and searching for common themes. These responses are edited and then used to construct the second questionnaire. The second and subsequent rounds are more specific with the questionnaire seeking the rating or ranking of various items in terms of their significance and analysed quantitatively. As the researcher feeds back results from the previous rounds there tends to be convergence to a consensus of opinion[41]. A typical Delphi includes use of a number of questionnaire rounds, feed-back of responses, the opportunity for participants to modify their responses and anonymity of responses.

2.3.2 Methodological considerations

What's an expert?

Some would argue that an expert is "any individual with relevant knowledge and experience of a particular topic"[63]. This depends on the setting and objectives of the Delphi in question.

Size of Panel

There are no hard and fast rules. Linstone[64] suggests that "a suitable minimum panel size is seven" but panel sizes have ranged from 4 to 3000. It seems therefore that the decision about panel

size an empirical and pragmatic one taking into consideration factors such as time and expense[65]. Representation is assessed by the qualities of the expert panel than its numbers[66].

Selection of the panel

The Delphi technique straddles the divide between qualitative and quantitative methodologies; this is especially evident in the issue of how to select the panel. There is a danger of bias where experts are selected on the basis of acquaintance with researchers, which may be a difficult factor to address in intensely specialised areas[67]. Some express concern about bias resulting from poor selection methodologies whilst others dismiss these concerns. The implication is that random sampling may not always be appropriate particularly in areas of clinical intervention where it is more appropriate to select specialists in that area. It is sensible to describe what criteria were used.

Anonymity of panelists

Anonymity of individual responses is one of the key features said to characterise the Delphi[61]. It means that panelists will not know who made what response, although more extensive constructions of anonymity have been suggested, even to the point that the responses are anonymous to the researchers[68;69]. The advantage of anonymity is that it is a leveller of opinion, removing the effects of status, personalities and group pressures that can arise in meetings[69-71].

Questionnaire design and scoring methods

Panelists' views have been recorded using a variety of scoring methods. Linear numerical scales, such as described by Likert[72], are often used. Concern has been expressed about the validity of some of the scoring methods used and on the way the data have been aggregated. Delphi reports often give little information on the actual scoring and aggregation methods used and greater clarity in reports would be desirable.

Feed-back

Feed-back with an opportunity to revise earlier responses is an important Delphic feature but it is also a potential weakness. The researcher should be impartial and provide feed-back in a reliable and valid way highlighting the degree of dissent and divergence amongst participants' views[67]. Furthermore, feed-back response depends not only on the feed-back but also by the respondents' reaction to it.

Most feedback is numerical or statistical with some form of aggregated group response. Sometimes these data can be supplemented by non-quantitative information such as justifications or other comments. Statistical feed-back often uses medians, usually accompanied by minima and maxima, quartiles and/or the inter-quartile range. Participants should also be informed about the position of their scores in relation to the overall picture so that it gives them an opportunity to revise previous scores in view of the group response[66].

Number of rounds

A valid Delphi requires a minimum of two rounds (three if round one is open-ended). Feed-back to respondents and the opportunity to revise earlier responses are arguably defining features of Delphi. This requires a minimum of two rounds. Beyond that, the number of rounds is disputed. Walker and Selfe[73] make the sensible point that "repeated rounds may lead to fatigue by respondents and increased attrition". Most studies use only two or three rounds.

Consensus

The Delphi was originally developed as means for gaining consensus though this is not always the case. It has, nonetheless, been argued that the Delphi is "designed to force consensus"[74]. This might occur by the way the questionnaire data is presented or perhaps in the way it is analysed. Simple statistical summaries will conceal important variations in distribution, such as bimodal patterns that could demonstrate a lack of consensus[66]. Mullen[75] points out that the question of whether or not consensus should be sought depends: if the aim is to find the correct answer, as in a

positivist sense, outliers have to be considered as they might be right; when the aim is to obtain normative views, seeking consensus is appropriate.

2.4 Scientific Merit

One of the arguments against Delphi technique is that these studies mostly overlook reliability measurements and scientific validation of the findings[76]. However the role of Delphi comes into play to resolve a situation where no conclusive hard evidence is available, by drawing on, and sharing the knowledge and experience of experts. Therefore it should not be subject to the same validation criteria as hard science[77]. Alternate means have been suggested to express the validity and credibility of Delphi findings[66]. The findings of one study can be 'tested' or confirmed in another study with a different sample as a means of validation[78]. Inclusion of a clear decision trait that explains the appropriateness of the method selected to address a problem, choice of expert panel, data collection procedures, identification of justifiable consensus levels and means of dissemination and implementation are features that determine the credibility of the method[77].

2.5 Health Service Applications

Since 1969, there have been over 1400 publications using this technique in a health care setting, most of which have been published in the last 10 years. Its applications have included forecasting disease patterns and health funding requirements, addressing clinical problems, and education.

Forecasting

As a forecasting tool, researchers have used Delphi methodology to predict developments in a variety of health care areas, including child and maternal health. For example, Longhurst[79] used a

Delphi to predict how improvements in nutrition, family income and prenatal care would impact on birth weight and subsequent intellectual development.

Consensus in clinical problem-solving

Delphi can be used as a way of obtaining consensus about tackling clinical problems and, in this context, is useful as a clinical management tool. It has been particularly useful in the development of performance indicators, which is a notoriously controversial area[80]. This type of approach could be used to proactively determine performance indicators in a variety of clinical settings, including obstetric and gynaecological wards.

Clinical guidelines

The consensus-forging nature of the Delphi technique can be used to good effect in enabling evidence-based medical guidelines to become adopted by clinical groups. In essence this approach involves the development of evidence-based guidelines which were then modified and finally ratified by a Delphi process. This approach worked well in the multi-national context of European colposcopy whereby a set of evidence-based colposcopic clinical guidelines on treatment have been produced[81]. Discussion and exploration of differences were an important part of this process and this was served well by the iterative methodology inherent in the Delphi process. Guidelines developed in this way need a process of validation with some ensuing modification, if needed.

Education

In clinical education the Delphi technique has been used in a variety of ways which include forecasting and planning, and curriculum development.

2.6 Conclusion

As in any area of clinical practise, obstetrics and gynaecology generates an array of problems that are complex and not amenable to simple didactic analysis. In this context, the Delphi technique is a particularly useful tool for developing group consensus and can avoid many of the counterproductive pitfalls that can bedevil face-to-face meetings.

CHAPTER 3: PRIORITISATION OF TESTS FOR THE PREDICTION OF COMPLICATIONS OF PRE-ECLAMPSIA: A DELPHI SURVEY

3.1 Abstract

Background

Pre eclampsia is associated with several maternal and fetal complications. Numerous tests, including items of history, examination findings and investigations are used to predict such complications in women with pre-eclampsia. At present there are no robust systematic reviews, or large studies on accuracy of tests that could predict complications in women with pre eclampsia.

Method

To identify the tests which include items of history, examination and investigations, that are clinically relevant in predicting maternal and fetal complications in women with pre-eclampsia using a two generational Delphi method

Results

Blood pressure was rated as the best predictor of complications with mean score (SD) of 4.7 (± 0.47), followed by proteinuria 4.6 (± 0.5) and liver function tests (4.5, ± 0.52) (scale x to y anchored between 0 -5).

Conclusion

The list of tests that have been identified and prioritised will form the basis for future systematic reviewing of literature in this field.

Citation of paper published from this work

Thangaratinam S, Ismail K, Sharp S, Coomarasamy A, O'Mahony F, Khan KS, O'Brien S; TIPPS (Tests in Prediction of Preeclampsia's Severity) Review Group. Prioritisation of tests for the prediction of preeclampsia complications: a Delphi survey. Hypertens Pregnancy. 2007; 26: 131-8.

3.2 Background

Hypertensive disorders in pregnancy remain one of the largest causes of maternal and fetal mortality and morbidity.[82;83] The commonest among them, pre-eclampsia, is associated with several complications.[82] Clinical prediction of disease complications using a combination of patients' characteristics, symptoms, physical signs and tests, forms the basis of clinical care in this situation. Early prediction and identification of complications will be of benefit to patients by monitoring disease severity, use of antihypertensive therapy[84], administration of anticonvulsants[85], and steroids[86]. as well as allowing clinicians to avoid unnecessary interventions in low risk groups.[87;88] At present there are no systematic reviews or large studies on accuracy of tests that could predict complications in women with pre-eclampsia. There are a large number of tests in practice and research with considerable variation in their use. The need to identify clinically useful tests that predict maternal or fetal complications is the first step in determining the scope of the research in this broad field. We decided to use the Delphi method for the purpose of identifying and prioritising the relevant tests.

3.3 Method

The Delphi Technique

A two generational Delphi method was used to prioritise the clinically relevant tests that are considered helpful in predicting maternal and fetal complications of pre-eclampsia. The purpose of the first iteration was to narrow down the large number of tests that might aid in the prediction of complications of pre-eclampsia. The second iteration was conducted to prioritise the eventual list of relevant tests to clinical practice, determined by feedback from the initial round with convergence of opinion.

Selection of experts

The panel of experts was selected for their interest in the field of pre-eclampsia that included medical experts on the panel of APEC (Action on Pre-eclampsia) group and specialists with research interest in this area. They were selected for two reasons. Firstly as academics with special interest in this field, they have the knowledge and opinion of existing evidence. Secondly as practicing clinicians, they have the understanding of applicability and relevance of these tests to clinical practice. A total of twenty-five experts were included in the study, 24 from the United Kingdom and one from Australia.

First Iteration

We searched MEDLINE (1951-2004), EMBASE (1974-2004), Cochrane Library (2004:4) and MEDION (a database of diagnostic test reviews set up by Dutch and Belgian researchers) for relevant citations. We identified 33 tests that might aid in the prediction of maternal and fetal complications of pre-eclampsia. A structured list of these tests was sent along with a covering letter explaining the purpose of this survey. The questionnaire was sent by e-mail and anonymity was maintained between panelists (Appendix 31). Two reminders were sent to non responders by e-mail. In the first round, the experts were asked to rank the 'tests' for their importance to clinical practice in predicting possible maternal and fetal complications on a 0 to 5 scale (0-unnecessary; 1-not important; 2-slightly important; 3-moderately important; 4-very important; 5-essential). The mean score with standard deviation was calculated for each test.

Second Iteration

Tests that had a mean score 2.0 or more were included for rating in the second round. In this round, the experts were asked to reconsider their previous rating in view of the panel score (Appendix 32).

The new mean ratings were recalculated. Tests that scored 3.0 or more were considered to be clinically significant.

3.4 Results

First Iteration

Eighteen experts responded to the questionnaire in the first round and fifteen reported their results. Rating was not performed on the grounds of clinical inadequacy by one pure academician and personal uncertainty in the Delphi method of survey by two experts. Twenty five tests from a total of 33 had a mean score of 2.0 or more in this round. Blood pressure was rated as the best predictor with mean score (SD) of 4.8 (± 0.41), followed by ophthalmologic findings, liver function tests and proteinuria with mean scores (± SD) of 4.3 (± 1.1), 4.3 (± 1.3) and 4.3 (± 1.3) respectively. Weight gain (1.3 ± 1.1), oedema (1.3 ± 0.97), urinary calcium excretion (1.5 ± 1.3), microalbuminuria (1.8 ± 1.5), maternal serum alpha feto protein (1.2 ± 1.2), imaging techniques of brain (1.5 ± 1.2), serum human chorionic gonadotrophin (1 ± 0.92) and fibronectin (0.8 ± 1) that scored as poor predictors were excluded for rating in the second round.

Second Iteration

There was a 73% (11/15) response to the second round questionnaire. Eleven experts reconsidered their previous score in view of the panel results and four of them changed their previous ratings for a total of twenty four items. Seventeen tests that had a mean score of 3 or more were included in the final list (Table 3.1). Blood pressure and proteinuria were considered as the most important predictors of complications in pre-eclampsia with mean scores of 4.7 (± 0.47) and 4.6 (± 0.5) respectively followed by liver function tests (4.5, ± 0.52) and pre-eclampsia in the presence of pre-existing medical conditions like hypertension, renal disease and diabetes (4.4, ± 0.81). All four of

the above tests were considered to be clinically significant predictors by the entire group. Full blood count (4.3, ±0.9), renal function tests (4.1, ±0.94) and multiple pregnancy (3.7, ±0.79) were the other tests that were scored as significant predictors by all the experts. Only 64% of the group considered uric acid to be a moderately or very important predictor of complications. Coagulation screen mean score of 3 (±1.6) was derived from the first iteration only as it was missed for inclusion in the second round list of tests. Race, parity, obesity, family history of pre-eclampsia, deep tendon reflexes were considered to be not important or only slightly important predictors of adverse outcomes in pre-eclampsia.

Table 3.1. List of tests that are considered to be clinically important in predicting maternal and fetal complications of pre-eclampsia identified after first and second iterations of the Delphi survey

No.	Tests	First Iteration			Second Iteration		
		Mean	Standard deviation	% ≥ 2	Mean	Standard deviation	% ≥ 3
1	Blood pressure	4.8	0.41	100	4.7	0.47	100
2	Proteinuria (24 hr collection, dipstick)	4.3	1.3	93	4.6	0.50	100
3	Liver function tests	4.3	1.3	93	4.5	0.52	100
4	Pre existing hypertension, renal disease, diabetes	4.1	1.1	93	4.4	0.81	100
5	Full blood count	4.1	1.3	93	4.3	0.90	100
6	History of lupus, thrombophilia, other auto immune diseases	3.9	1.5	93	4.3	1.0	91
7	Symptoms-headache, epigastric pain , nausea, visual disturbance	4.1	1.2	93	4.2	0.87	91
8	Papilloedema, Retinal changes	4.3	1.1	100	4.1	1.1	82
9	Renal function tests	4.1	1.2	93	4.1	0.94	100
10	Ultrasound including Doppler	3.7	1.6	87	4.0	1.2	82
11	Previous history of severe pre-eclampsia / Eclampsia	3.9	1.2	87	3.9	0.94	91
12	Oliguria	3.9	1.2	100	3.9	0.94	91
13	Clonus	3.5	1.1	100	3.9	0.83	91
14	Multiple pregnancy	3.4	1.3	93	3.7	0.79	100
15	Symphysio fundal height	3	1.3	87	3.2	0.75	82
16	Coagulation screen	3	1.6	80	3*	1.6*	-
17	Serum uric acid	2.8	1.8	67	3.1	1.7	64
18	Hypoalbuminaemia	2.7	1.5	73			
19	Maternal age	2.7	1.7	60			
20	Family history of pre-eclampsia	2.7	1.5	67			
21	Exaggerated tendon reflexes	2.5	0.99	87			
22	Parity	2.5	1.6	67			
23	Race	2.3	1.2	80			
24	Obesity	2.3	1.5	67			
25	Thrombophilia screen	2.1	1.4	67			

* Score calculated from first iteration only

3.5 Discussion

One of the questions remaining after establishing effectiveness of magnesium sulphate[85], steroids[5] and anti-hypertensives[3] in reducing maternal and fetal mortality and morbidity in women with pre-eclampsia, is to identify those who will benefit most from these interventions. There are no guidelines, systematic reviews or large studies that provide evidence on the accuracy of various tests to predict complications of pre-eclampsia. Subsequently, we have embarked on the task of identifying and prioritising a list of such tests using the Delphi method. We plan to review the prioritised tests systematically in the near future.

The Delphi consisted of an iterative methodology that allowed the participants to maintain anonymity while preventing domination by particular individuals who might otherwise be overly influential in a group decision.[69-71] Communication via e mail was a cost effective, time saving exercise and had helped to overcome geographical boundaries. The feedback after successive rounds provided an opportunity to the respondents to reconsider their original opinion.[66] Some clinical and biochemical tests like deep tendon reflexes, clonus and serum uric acid are often given importance in clinical practice, but have scored poorly in this survey. A subsequent systematic review conducted by us has identified uric acid as a poor predictor of adverse maternal and fetal outcomes in pre-eclampsia (Chapter 10), thus substantiating the results of this survey.

The scientific merit and validity of such an exercise as the Delphi method that we used is often questioned.[76] However this method is important in situations where no conclusive hard evidence is available, by attempting to provide answers by relying on and sharing the knowledge and experience of experts in the field.[77] We acknowledge that there is the possibility that a panel with different composition might identify a different set of results.

3.6 Conclusion

This exercise has identified the tests that can be prioritised from the numerous proposed tests, for the purpose of conducting systematic reviews of diagnostic accuracy of the tests that predict complications of pre-eclampsia. This will help to generate practice guidelines and specific recommendations for future research.

SECTION B

REVIEW OF REVIEWS

In this section, I have evaluated the methodological quality of all systematic reviews in maternal and fetal medicine

CHAPTER 4: A REVIEW OF SYSTEMATIC REVIEWS IN MATERNAL MEDICINE

4.1 Abstract

Introduction

In maternal medicine, research evidence is scattered making it difficult to access information for clinical decision making. Systematic reviews of good methodological quality are essential to provide valid inferences and to produce usable evidence summaries to guide management. This review assesses the methodological features of existing systematic reviews in maternal medicine, comparing Cochrane and non-Cochrane reviews in maternal medicine.

Methods

Medline, Embase, Database of Reviews of Effectiveness (DARE) and Cochrane Database of Systematic Reviews (CDSR) were searched for relevant reviews published between 2001 and 2006. We selected those reviews in which a minimum of two databases were searched and the primary outcome was related to the maternal condition. The selected reviews were assessed for information on framing of question, literature search and methods of review.

Results

Out of 2846 citations, 68 reviews were selected. Among these, 39 (57%) were Cochrane reviews. Most of the reviews (50/68, 74%) evaluated therapeutic interventions. Overall, 54/68 (79%) addressed a focussed question. Although 64/68 (94%) reviews had a detailed search description, only 17/68 (25%) searched without language restriction. 32/68 (47%) attempted to include unpublished data and 11/68 (16%) assessed for the risk of missing studies quantitatively. The reviews had deficiencies in the assessment of validity of studies and exploration for heterogeneity. When compared to Cochrane reviews, other reviews were significantly inferior in specifying

questions (OR 20.3, 95% CI 1.1–381.3, p = 0.04), framing focussed questions (OR 30.9, 95% CI 3.7-256.2, p = 0.001), use of unpublished data (OR 5.6, 95% CI 1.9–16.4, p = 0.002), assessment for heterogeneity (OR 38.1, 95%CI 2.1, 688.2, p = 0.01) and use of meta-analyses (OR 3.7, 95% CI 1.3–10.8, p = 0.02).

Conclusion

This study identifies areas which have a strong influence on maternal morbidity and mortality but lack good quality systematic reviews. Overall quality of the existing systematic reviews was variable. Cochrane reviews were of better quality as compared to other reviews. There is a need for good quality systematic reviews to inform practice in maternal medicine.

Citation of published paper of this work

Sheikh L, Johnston S, **Thangaratinam S**, Kilby MD, Khan KS. A review of the methodological features of systematic reviews in maternal medicine. BMC Med. 2007;5:10.

4.2 Introduction

Maternal medicine has emerged as an increasingly important area for the obstetricians dealing with high risk pregnancies. It involves care of women with medical complications of pregnancy which may be specific to or predate the pregnancy.[89] Approximately half of complex pregnancies are related to an abnormal fetal or obstetric factor, whereas medical diseases constitute the remainder of this high risk obstetric population. Scientific developments in internal or general medicine have led to newer diagnostic and therapeutic strategies to manage medical diseases. The physiological changes during pregnancy can affect not only the clinical presentation of a medical problem but may give rise to difficulties in diagnosing and managing these problems. In order to provide the best possible quality of care to women with complicated pregnancies obstetricians dealing with the high risk obstetric cases should have evidence based knowledge on the diagnostic, therapeutic and prognostic aspects of maternal medicine.

As maternal medicine covers the issues related to pregnancy as well as general medicine, research evidence is scattered in the literature making it difficult to access information for clinical decision making. Systematic reviews provide a way forward as individual pieces of research can be collected within literature reviews and if appropriate subjected to meta-analysis.[90] Good methodological quality is essential for these reviews to have valid inferences and to produce usable evidence summaries to guide the obstetric management.[91] This study examines the methodological features of recently published systematic reviews in maternal medicine and specifically compares Cochrane to non-Cochrane reviews.

4.3 Methods

To determine the quality of current systematic reviews in maternal medicine, we developed *a priori* protocol based on recommended methods.[50;92;93] A computerised search of publicly available databases was conducted. Ovid Medline (1996 to 2006), Embase (1996 to 2006), Database of Reviews of Effectiveness and Cochrane Database of Systematic Reviews were searched for relevant reviews published between 2001 and 2006. Key word combinations like Pregnan$, Matern$, Gestation$, Obstetric$, Complication$, Systematic review$ and Meta analys$ were used for the search strategy in addition to word variants, subject headings and free text. The $ sign is a truncator used to capture any word that begin with the letters in front of the $ sign in the search terms used. Additionally common and specific medical problems related to pregnancy were searched using key words describing names of the disease such as Pre eclampsia, Hypertension, Diabetes, Cholestasis, Anaemia, Thrombocytopaenia, Thrombophilia, and Thromboembolism. A hand search of reference lists was conducted of all relevant articles to identify any missing reviews. The searches were limited to reviews between 2001 and 2006 due to increasing developments in the field of maternal medicine in recent years. Inclusion criteria required a minimum of two publicly available databases searched for a medical condition specific to or predating pregnancy and maternal factor as the primary outcome. We searched without language restrictions. All the reviews with fetal or neonatal factor as the primary outcome were excluded.

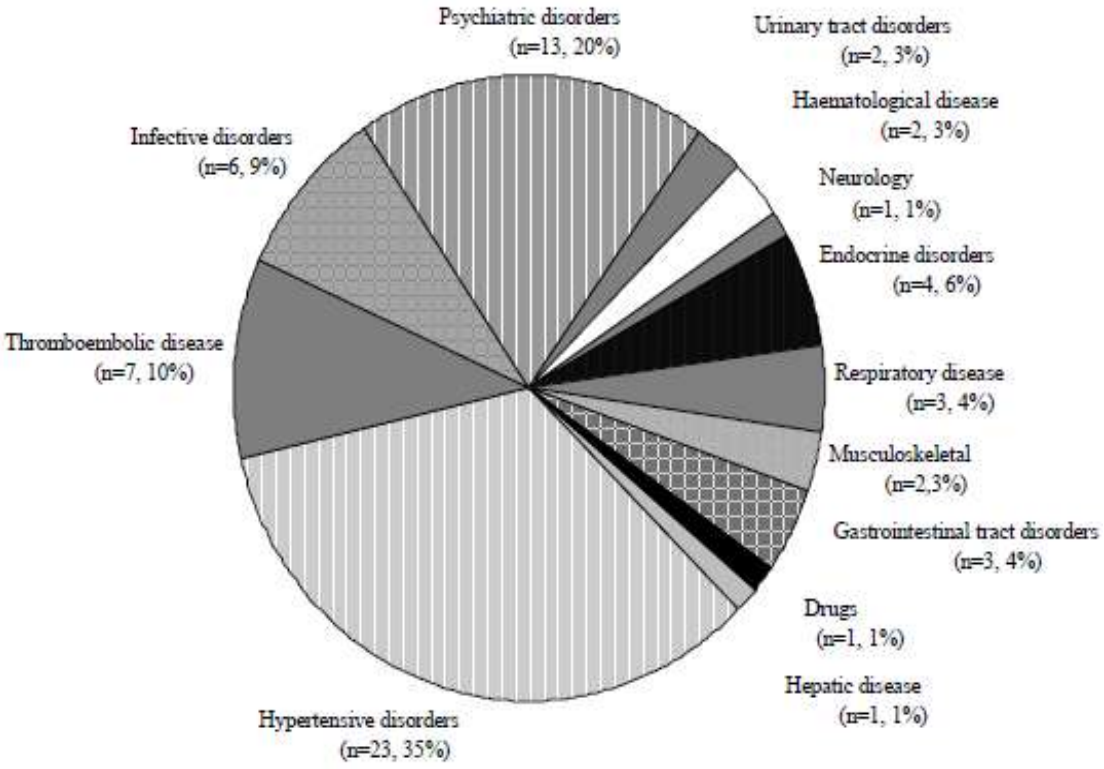
Two reviewers independently extracted and assessed the data according to a checklist formulated as part of our protocol (Appendix 30). The methodological quality of each review was assessed by focussing on framing of the question, literature search and review methods scrutinising methods of literature search and data synthesis. The items assessed internal validity and explicitness of reporting, both of which are important issues in quality of reviews. Differences between reviewers were resolved by discussion. We computed rates of compliance with the items in our checklist and

compared Cochrane and non-Cochrane reviews. Odds ratios (OR) and their 95% confidence intervals (CI) were computed. All statistical analysis was performed using Stata 8.0 statistical package.

4.4 Results

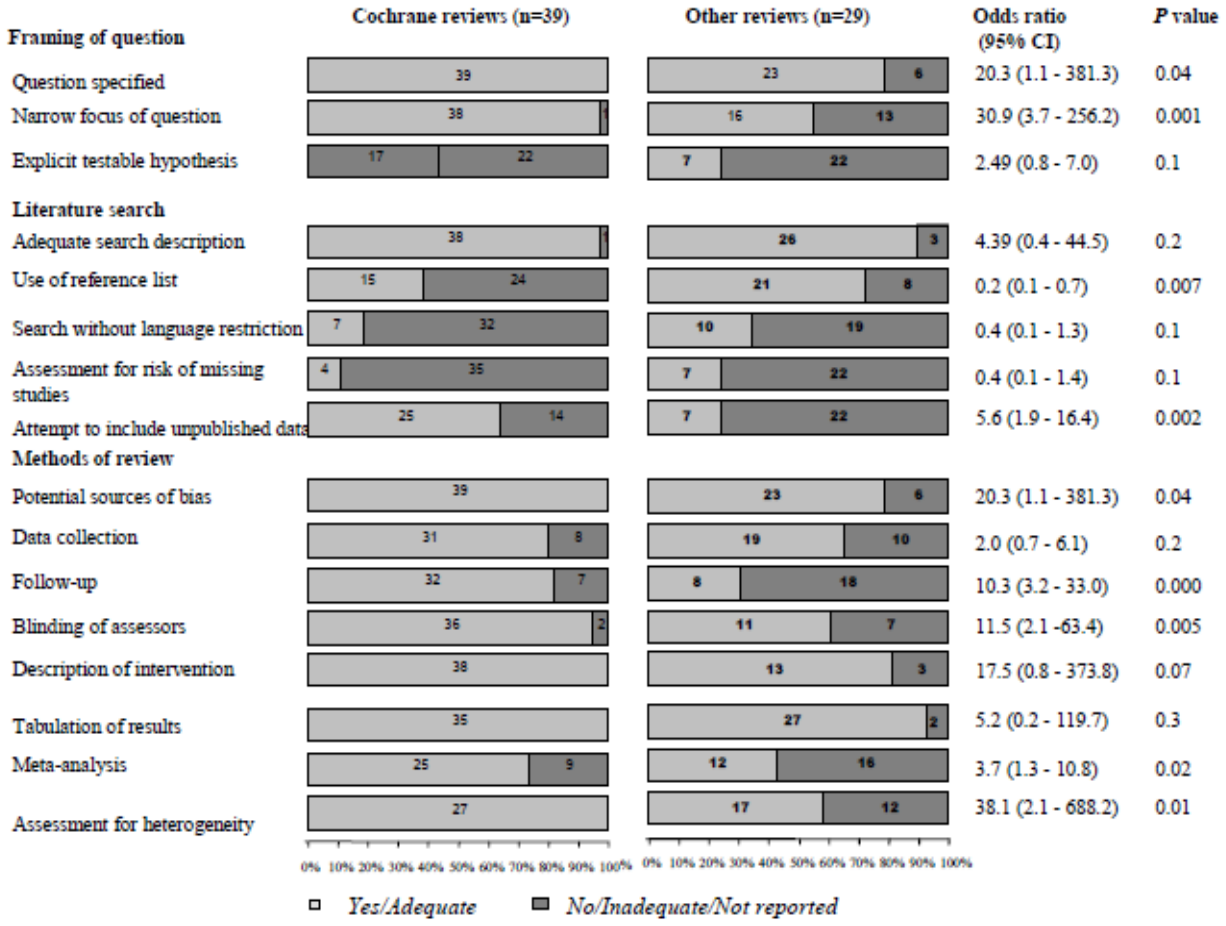
The initial literature search resulted in 2846 citations. The study selection process is shown in Appendix 1. Of these 68 reviews[94-161] fulfilled the inclusion criteria and were selected for detailed study. A total of 39 (57%) Cochrane reviews[94-132] and 29 (43%) non Cochrane reviews[133-161] were included. Most of the reviews assessed therapeutic interventions (50/68, 74%), and the rest were reviews on prognosis (12/68, 17%) and diagnosis (6/68, 9%). The range of clinical topics dealt with by the reviews is shown in Fig 4.1.

Fig 4.1. Review topics in maternal medicine



The overall quality of the existing systematic reviews was variable. The majority of the reviews (62/68, 91%) specified the question and 54/68 (79%) had a focussed question with clearly defined population and outcome measures. A large population of the reviews (64/68, 94%) had a detailed

Fig 4.2 Methodological quality of Cochrane and non Cochrane reviews included



search description including databases searched and key words used. Almost half of the reviews (32/68, 47%) attempted to include unpublished data. However only 11/68 (16%) assessed the risk of missing studies quantitatively and 17/68 (25%) searched without language restriction. Almost all the reviews had good tabulation of results and characteristics of included studies (65/68, 96%).

The quality of Cochrane and non Cochrane reviews is given in Fig 4.2. Cochrane reviews had specified the questions more often than non Cochrane reviews[133-137;139-141;150;151;153-157] (OR 20.3, 95% CI 1.1–381.3, p = 0.04) and were also framed narrowly focussed questions specifying the population, interventions and comparisons, outcome of the study and the study design (OR 30.9, 95% CI 3.7- 256.2, p = 0.001). Cochrane reviews attempted more often to include unpublished data in literature search (OR 5.6, 95% CI 1.9–16.4, p =0.002). Twelve out of 29 non-Cochrane reviews[134;136;139-141;150-152;154-157] performed a meta-analysis, but there was good awareness of where this technique was valuable and where it was not applicable. Meta analysis technique (OR 3.7, 95% CI 1.3–10.8, p = 0.02) and assessment for heterogeneity (OR 38.1, 95%CI 2.1, 688.2, p = 0.01) was found to be employed significantly more often by Cochrane reviews.

4.5 Discussion

This study showed that the Cochrane reviews were of consistently high methodological quality and had a greater level of assessment for quality of included studies. They always did a meta-analysis[95;96;99;105-111;113-126;130-132] where applicable. This is reassuring for clinicians who rely on them for decision-making. It is possible that the restriction on the length of published non Cochrane reviews by journals could have influenced their quality scores. However this issue has been addressed by increase in the web publishing of additional material in the electronic format by many journals in recent years.

This work has highlighted that literature searches in reviews are currently generally poor. A search that is not thorough risks giving biased inferences. We identified considerable room for improvement in certain methodological features of non Cochrane reviews. However all the selected reviews were similar in searches without language restriction and assessment for risk of missing

studies. Interestingly the use of reference list of the selected papers to identify any other eligible studies for inclusion in the review was found to be more frequent in non Cochrane reviews (OR 0.2, 95% CI 0.1–0.7, $p < 0.007$). This could be a result of the generic search strategy employed by Cochrane reviews with unclear mention of the use of reference lists in individual reviews. Cochrane reviews were found more likely to attempt to include unpublished data compared to non Cochrane reviews (OR 5.6, 95% CI 1.9–16.4, $p < 0.002$). This attempt to avoid publication bias is significant as the odds of publication are higher if the results are found to be significant compared to studies with non-significant results.[162]

This study identified areas of maternal medicine that lack good quality systematic reviews. The majority of the reviews were on hypertensive disorders[94;95;97;98;105-109;117-120;123;134;139;141;144;150;151;155;156] psychiatry[102;113;129;133;136-138;142;143;145;147;160;161], or thromboembolism.[112;128;148-152;154] Even among these commonly addressed areas, a very narrow spectrum of diseases was covered. For example reviews in psychiatry were solely focussed on depression during pregnancy and reviews in hypertension focussed mainly on pre eclampsia. Reviews for some very common medical problems during pregnancy were missing or of poor quality. We found very few reviews on diabetes mellitus[99;125;135;159] and chronic hypertension and none on thyroid disorders.

With advancement in neonatology and paediatric medicine, more and more women with congenital problems such as congenital heart disease and inherited metabolic diseases are reaching child bearing age and considering pregnancy. There is an urgent need to have some cumulative evidence on management of this high risk group in the best possible way.

This study has some potential limitations. With our strict criteria to include reviews conducted with two publicly available databases, it is possible that some of the good quality reviews in maternal medicine using single database are missed. Another limitation relates to maternal outcome as the main focus of our study. We excluded all those reviews in which association between maternal disease and perinatal outcome was assessed. Keeping in mind the primary goal of an obstetrician being directed towards achieving a healthy and safe outcome for both mother and fetus, good quality evidenced based information on medical problems during pregnancy can only be achieved by reviewing methodological features of all aspects of maternal medicine irrespective of the endpoint. Due to the absence of blinding of the reviewers to the source of the review it is difficult to completely rule out any resultant bias.

4.6 Conclusion

Evidence based healthcare continues to make important contributions to the well being of pregnant women. This study has identified areas in maternal medicine that lack good quality systematic reviews. Overall quality of the existing systematic reviews was variable, with Cochrane reviews better than other reviews. To achieve better understanding and provide high quality obstetric care for pregnant women with medical problems, it is important to ensure that systematic reviews in maternal medicine are conducted to cover a wider spectrum of diseases, and are reported at the highest possible quality. Deficiencies identified in the areas of prognostic / diagnostic review are covered in this thesis.

CHAPTER 5: A REVIEW OF SYSTEMATIC REVIEWS IN FETAL MEDICINE

5.1 Abstract

Introduction

Systematic reviews of fetal medicine can serve as a tool for translation of research findings from a few expert centres to a wider healthcare specialty. The extent to which reviews of fetal medicine research are systematic and unbiased is not known.

Methods

We searched, without language restrictions, Medline, Embase, DARE, Cochrane Library (from database inception to 2005), bibliographies of known reviews and contacted experts to identify potentially relevant citations of literature for reviews of fetal medicine studies. The selected reviews were assessed for information on framing of question, literature search and methods of review.

Results

The search yielded 659 citations of which 84 reviews met the inclusion criteria. Most of the reviews were in the field of fetal pathology (49/84, 59%). A majority of reviews (58/84, 69%) specified the question to be answered but only half (44/84, 52%) addressed a focussed question. Although 57/84 (68%) reviews had a detailed search description, only 32/84 (38%) searched without language restriction. 45/84 (54%) searched in multiple databases and 27/84 (32%) assessed for the risk of missing studies. There was no difference in quality between reviews of fetal pathology, screening

for aneuploidy, fetal growth and fetal therapy, except with respect to specifying the question ($p<0.03$), search without language restriction ($p<0.004$), assessment of risk of missing studies ($p<0.006$) and study quality assessment ($p<0.002$) where reviews of fetal growth performed better than other domains.

Conclusion

Our study reflects the paucity of good quality reviews in fetal medicine research. Existing reviews tend to be poor in reporting of methodological features. Particularly not enough attention is paid to assessment of validity of included studies and means to improving reliability of results through appropriate use of meta-analysis. There is a need for conducting further reviews and for rigour when reviewing fetal medicine research.

Citation of published paper of this work

Ellen M Knox, **Thangaratinam S**, Mark D Kilby, Khalid S Khan. A review of the methodological features of systematic reviews in fetal medicine. Eur J Obstet Gynecol Reprod Biol 2009. 146: 121-128

5.2 Introduction

Fetal medicine can broadly be described as the assessment, management and treatment of diseases or conditions affecting the fetus. Fetal medicine focuses on the "fetus as the patient" the same way as a newborn is managed by a neonatologist.[163] Once the fetus has been found to be at risk, interventions aimed at improving neonatal outcome can be employed. The management of many fetal conditions diagnosed prenatally has been transformed by the advances in the field of fetal imaging, genomics, minimally invasive techniques and in utero fetal therapy.[164] However, there is concern that current fetal medicine research is often restricted to single centres, that it is observational in nature and that individual results are imprecise. The specialist nature of this area has required experience to be centralised, however, this is a rapidly expanding subspecialty area. It is important that any new advances in fetal medicine are validated in research prior to being introduced as "usual practice". Practices in this field have become established without serious multicentre trials, although there are some exceptions.[165;166] Current policy making in this field relies on the evidence that is constrained by paucity of systematic reviews collating findings of existing research.

Erroneously, some think that reviews should be limited to collating randomised evidence. The high risk nature of interventions, especially in the domain of in utero therapy, makes it difficult to conduct randomised controlled trials (RCTs) in fetal medicine, resulting in very few published RCTs. Current practice is, thus, largely based on evidence from observational studies often carried out in single centres with imprecise estimates i.e wide confidence intervals due to small sample size. The deficiencies due to imprecision can be overcome by collating studies in high quality systematic reviews. There has been increasing application of this approach in summarising observational research to better understand the value of health technologies and to translate findings

of preliminary research for further research or for wider application.[167;168] However, the extent and the quality of systematic reviews of fetal medicine studies are unknown. We therefore determined what evidence existed for current practice and the foundations for that evidence by undertaking a systematic review of all systematic reviews relevant to fetal medicine and examining their methodology.

5.3 Methods

To determine the quality of current systematic reviews in fetal medicine, we developed *a priori* protocol based on recommended methods.[50;93]

We searched from database inception to 2005, MEDLINE, EMBASE, DARE and the Cochrane library using the terms fetus, fetal diseases, therapy and applying a sensitive search filter for systematic reviews. In addition, reference lists were hand searched for additional reviews. There were no language restrictions. The electronic searches were examined and the full manuscripts of all the potentially relevant citations were obtained. Fetal maternal medicine specialists in the United Kingdom were also asked for knowledge of any additional papers in the literature or in press. Inclusion criteria required a minimum of one publicly available database searched for studies specific to feal medicine. Fetal medicine was defined as the assessment management or treatment of diseases and conditions affecting the fetus. For example, a paper examining the relationship between uterine artery Doppler and subsequent preclampsia was excluded but if the outcome measure was stillbirth it was included. We subgrouped reviews into those relating to fetal pathology, fetal screening for aneuploidy, fetal growth and fetal therapy.

We extracted and assessed the data according to a checklist formulated as part of our protocol. The methodological quality of each review was assessed by focussing on framing of the question,

literature search and review methods scrutinising methods of literature search and data synthesis. The items assessed internal validity and explicitness of reporting, both of which are important issues in quality of reviews. These included study quality assessment, tabulation of findings, assessment for heterogeneity, and assessment of risk of missing studies quantitatively or graphically with funnel plots and use of meta-analysis where appropriate. Differences between reviewers were resolved by discussion. All reviews were classified as being therapeutic, prognostic, diagnostic or etiological in nature and we compared the quality between the four reviews in the above domains.

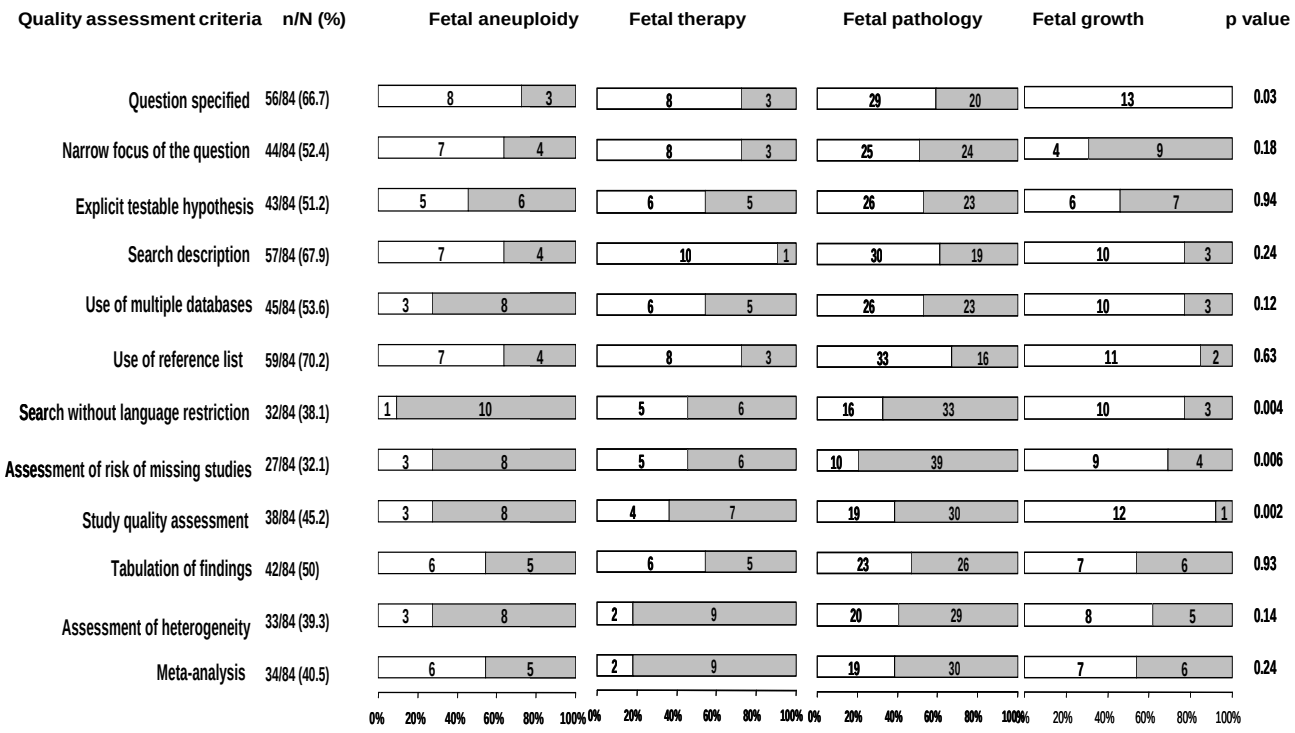
5.4 Results

The initial literature search resulted in 659 citations. Of these 121 reviews fulfilled the inclusion criteria and were selected for detailed study (Appendix 3). A further 12 papers were obtained from reference lists. Forty nine reviews were rejected because there was no systematic literature search of at least one database (n= 6) or the reviews were found to be pertaining to maternal rather than fetal medicine (n= 43). The details of the 84 included reviews are shown in Appendix 14.

The results of methodological quality of the included reviews are provided in Fig 5.1. Although the majority of reviews (58/84, 69%) specified the question to be answered, they had a narrow focus with clearly defined population and outcome measures in 52% (44/84). Most of the reviews (57/84, 68%) had a detailed search description including databases searched and key words used with 54% (45/84) using multiple databases to search for relevant studies. Only 38% (32/84) searched without language restriction. Assessment of heterogeneity was performed in 39% (33/84) of the reviews. Less than half the reviews (45%, 38/84) performed study quality assessment and only 32% (27/84)

performed assessment for risk of missing studies quantitatively or by funnel plots. Meta analysis was performed in 40% of reviews (34/84).

Fig 5.1. Quality of existing systematic reviews in various domains of fetal medicine



Most of the systematic reviews were in the field of fetal pathology (49/84, 59%) followed by fetal growth (13/84, 21%), fetal therapy (11/84, 10%) and fetal aneuploidy (11/84, 10%). Reviews of fetal growth were generally of the best quality, although heterogeneity was assessed in only 61% (8/13) of studies (Fig 5.1). Fetal growth reviews performed significantly better than reviews in other areas in question specification ($p<0.03$), search without language restriction ($p<0.004$), assessment of risk of missing studies ($p<0.006$) and study quality assessment ($p<0.002$). There was no difference in other quality items (Fig 5.1).

Of the 84 included reviews, only 15 were Cochrane reviews. Due to the smaller number of the Cochrane reviews, we refrained from attempting a comparison between Cochrane and non Cochrane reviews of fetal medicine unlike the maternal medicine reviews in Chapter 4.

5.5 Discussion

We found that even with a lenient definition for systematic reviews, reviews of fetal medicine studies were relatively infrequent considering the large amount of research that goes on in this field (Appendix 2). Reviews that addressed the rapidly advancing field of fetal therapy were particularly few. Overall the reporting of methodological features amongst reviews was poor, although reviews in the fetal growth domain performed better than those in other domains.

From our study, a number of lessons have emerged for reviewers of fetal medicine research. Firstly, when interrogating databases for reviews of fetal medicine research, searches could be restricted if the majority of the findings are kept confidential by the centres that initiated the work. In this situation, systematic reviews are likely to be flawed, particularly if clear evidence of publication bias can be demonstrated. The proportion of the work that is published in a form that is available to the public (rather than just being available to experts and the regulatory authorities) is unknown. However, assessments for risk of missing studies scarcely featured in the reviews we assessed. Special efforts (contact with experts, regulatory bodies, etc) will be needed to retrieve unpublished data. This is one of most important challenges for reviewers of fetal medicine studies.

Secondly, validity or quality of the studies included in a review is a key issue in avoiding biased influences. Despite its importance this issue was often not assessed in the reviews we studied

thereby risking erroneous conclusions. As many fetal medicine studies are observational in nature, reviewers would have to develop quality checklists carefully adapting existing tools for validity assessment. Finally, one key objective of such reviews is to improve precision of results to generate narrower confidence intervals around point estimates. In our study, the proportion of reviews that included meta-analysis or statistical pooling was small, but the actual number of times this approach was feasible or appropriate remains unknown. Disturbingly, we found that data synthesis among the reviews included in our study usually ignored methods to assess heterogeneity so that the suitability of combining results in meta-analysis could not be evaluated. Another related issue is that of use of appropriate methods for pooling results of small sized observational studies. Standard statistical approaches typically used in reviews of larger to medium sized studies may produce biased summaries when applied to pooling of studies with paucity of data.[167]

5.6 Conclusion

This study reflects the poor state of current reviews in fetal medicine research. It suggests the need for focusing attention on conducting good quality reviews and meta-analyses to generate valid inferences. It highlights the fact that systematic reviews should be an essential prerequisite to guidelines on fetal medicine practice and further research in this field.

SECTION C

SYSTEMATIC REVIEWS OF EFFECTIVENESS

In this section, I have systematically reviewed the therapeutic studies and summarised the evidence of effectiveness by meta analyses, in the areas of: a) preterm labour by evaluating the use of progesterone in preventing pre term delivery and b) epilepsy in pregnancy by comparing the effects of regular monitoring of serum lamotrigine compared to management based on clinical features only in reducing seizures

CHAPTER 6: PROGESTERONE FOR THE PREVENTION OF PRETERM BIRTH: A SYSTEMATIC REVIEW OF EFFECTIVENESS

6.1 Abstract

Background

Adequate concentration of progesterone in the myometrium reduces the risk of uterine activity. Progestagens can be used as agents to prevent preterm delivery.

Methods

Systematic review of literature evaluating the effectiveness of progesterone in reducing preterm births and neonatal mortality and morbidity with conventional and cumulative meta analysis. The effectiveness of progesterone across women at various risks of preterm birth was evaluated by L'Abbe plots.

Results

The systematic review of literature identified nine randomised trials that evaluated the effects of progestational agents in the prevention of preterm delivery. These studies were of variable quality. Meta-analyses showed reductions in delivery rates before 37 weeks (OR 0.42, 95% CI 0.31 to 0.57) and 34 weeks (OR 0.51, 95% CI 0.34 to 0.77) as well as in respiratory distress syndrome (OR 0.55, 95% CI 0.31 to 0.96) with progestational agents. A cumulative meta-analysis showed that the treatment benefit for the outcome of delivery before 37 weeks exceeded conventional level of statistical significance in 1975 ($p<0.01$); by 1985, the p-value was <0.001, and by 2003, it was

<0.0001. Another cumulative meta-analysis in which the studies were added to the pooled analysis by decreasing quality score showed significant benefit was shown even when the analysis was limited to just the highest quality trials (OR 0.47, 95% CI 0.33, 0.66, p<0.0001). An exploration of the applicability of the effects across various baseline risks using an L'abbe plot found that the benefit was consistent across a range of risks.

Conclusion

Women at high risk of preterm birth should be recommended progestational agent therapy.

Citation of paper arising from this work

Coomarasamy A, Thangaratinam S, Gee H, Khan KS. Progesterone for the prevention of preterm birth: a critical evaluation of evidence. Eur J Obstet Gynecol Reprod Biol. 2006; 129: 111-8.

6.2 Background

Basic science evidence suggests that adequate concentration of progesterone in the myometrium counteracts the stimulatory activity of prostaglandins, lowers the concentration of oxytocin receptors, and inhibits the formation of gap junctions, raising the possibility of use of progestagens as agents to prevent preterm delivery.[169] Over many decades, several randomised trials have shown a role for the use of progestational agents in this context, although this has not resulted in their use in clinical practice. The reasons for the lack of use could be related to a perceived concern about the quality of the trials assessing these agents, as well as ignorance of the totality of existing evidence. Systematic reviews can help with both assessment of quality and presentation of the totality of evidence, although this is conditional to a large extent on the robustness with which the reviews are carried out.

A recent meta-analysis of randomised trials of progestational agents found it to be effective in reducing the risk of preterm delivery below 37 weeks.[170] However, it did not report on the quality of the included studies, nor explore the effect of the quality on the inferences. Moreover, the study failed to report on outcomes such as delivery rates before 34 weeks, which is a clinically more relevant endpoint than the 37 weeks threshold. This is because delivery before 34 weeks' gestation accounts for three-quarters of neonatal mortality and one-half of long term neurological impairment in children.[171] Additionally, before clinicians could recommend, and women accept, progestational agent therapy, the applicability of the evidence and the safety of the drug need to be established.

A systematic review with conventional as well as cumulative meta-analyses was therefore carried out, firstly to explore the size and significance of the effects as trials accumulated over time, and secondly to evaluate the impact of quality of trials on effects. Furthermore, the applicability of the

evidence to women at various baseline risks is assessed, and the evidence for safety of progestational agents is reviewed.

6.3 Methods

We searched MEDLINE (1966-2004), EMBASE (1980-2004), Cochrane Library (2004:3), and SCISEARCH (1974-2004) for relevant citations. A combination of Medical Subject Headings (MeSH) and textwords were used to generate two subsets of citations, one indexing progesterone ('progesterone', 'progestational hormones', 'progestational agents' and 'progest$') and the other indexing preterm birth ('preterm', 'premature', 'early labo(u)r' and 'pret$'). These subsets were combined using 'AND' to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Articles frequently cited were used in the Science Citation Index to identify additional citations.

Studies were selected if the target population was women with risk factors for preterm birth, the therapeutic intervention was progesterone or a progesterone metabolite (synthetic progestagens were excluded), and the studies were of randomised design. Studies in which the population was exclusively multiple pregnancies were excluded.

The selected studies were assessed for methodological quality using the components of study design that are related to internal validity.[172] Information on the adequacy of randomisation, concealment, blinding, description of withdrawals, and follow-up rates was sought. Odds ratios from individual studies were pooled using fixed and random effects models.[173;174] Heterogeneity of

treatment effects was evaluated graphically using forest plot and statistically using Chi-square test. Exploration of the causes of heterogeneity was planned using variation in features of the population, intervention, outcome and study quality. To assess for publication bias, a funnel-plot analysis was performed, using Egger's test to evaluate for asymmetry.[175]

In addition to conventional meta-analysis, cumulative meta-analysis was performed in which the meta-analysis is updated whenever a new relevant trial becomes available for inclusion in the review.[176] Such analysis allows the retrospective identification of the point in time when a treatment effect reached conventional levels of statistical significance.[177] In another cumulative meta-analysis, analysis was started with the highest quality studies, and lesser quality studies were added progressively, to explore the effect of study quality on the results.

In some trials of progesterone, the baseline risks in the control arms may be high, raising the issue of whether the evidence of effectiveness applies to populations in which the baseline risks may be substantially lower. Although there are several issues to be considered when assessing applicability and, ultimately, assessment of applicability is a clinical judgement, the concern over baseline risks were explored by evaluating the size of effects across a range of baseline risks using L'Abbe plot. The L'Abbe plot graphs the event rate in the control group (i.e., the baseline risk) against the event rate in the treatment group, thus allowing a visual assessment of homogeneity of effects across a range of baseline risks.[178]

The systematic review of randomised trials of progestational agents may not show any evidence of harm. Moreover, as trials generally involve patients studied for a short period, they are not likely to

detect delayed adverse events.[179] We, therefore, conducted a review for safety of non-synthetic progestational agents using the following words and their word variants in MEDLINE (1966 – 2004) and EMBASE (1988 – 2004) bibliographic databases: ('progesterone' OR 'progestational hormones' OR 'progestational agents' OR 'progest$') AND ('adverse effects' OR 'complications' OR 'side effects' OR 'harm') AND "pregnancy".

6.4 Results

6.4.1 Systematic review of effectiveness of progestational agents

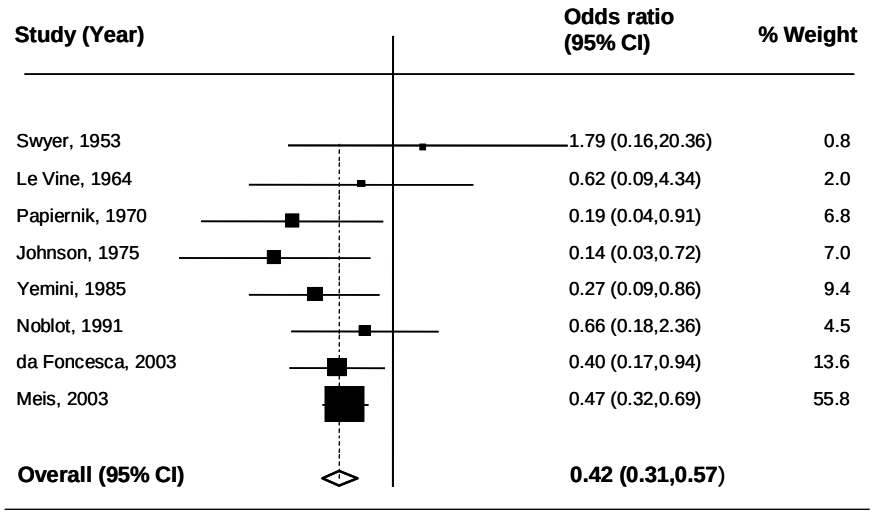
We identified 1430 relevant citations from the search in databases. Full copies of seventy studies were retrieved for detailed evaluation. Nine studies with 1048 patients were identified for inclusion in the review after examination of the full manuscripts of studies that satisfied the selection criteria. The effect of 17 hydroxy progesterone caproate was assessed in five studies,[180-184] vaginal progesterone suppositories in two studies,[185;186] oral progesterone in one study[187] and intramuscular progesterone pellets in one study.[188] The quality of the studies is presented in Appendix 12, where each study is scored for quality using Moher's criteria.

Pooling of the results from the studies showed a significant benefit of progestational agents in reducing preterm delivery before 37 weeks (OR 0.42, 95% CI 0.31 to 0.57, Fig. 6.1 a). A significant benefit was also observed for the clinically more relevant outcome of delivery before 34 weeks (OR 0.51, 95% CI 0.34 to 0.77, Fig. 6.1 b). No heterogeneity was identified for both results (p values of 0.59 and 0.10 for deliveries before 37 weeks and 34weeks respectively).

There was a significant reduction in respiratory distress syndrome (RDS) with the use of progestagens (OR 0.55, 95% CI 0.31 to 0.96, Fig. 6.1 c). The results were again homogenous

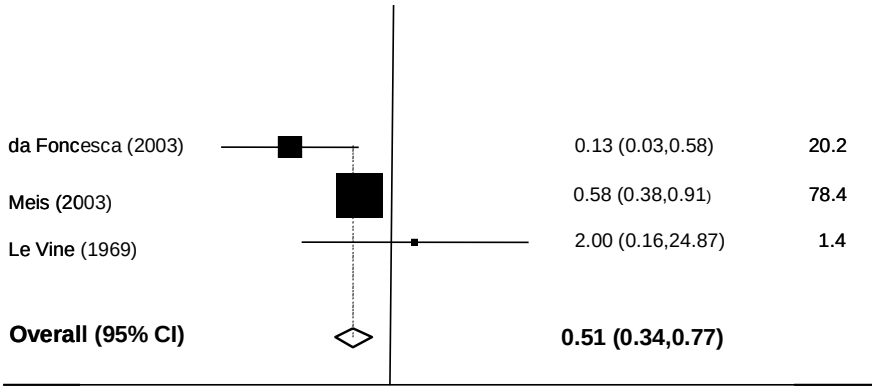
(p=0.425). Funnel plot analysis indicated that publication and related biases were unlikely (Egger's test, p=0.384).

Figure 6.1: Meta-analysis of randomised trials evaluating the effectiveness of progestational agents in the reduction of a) delivery before 37 weeks, b) delivery before 34 weeks, and c) respiratory distress syndrome



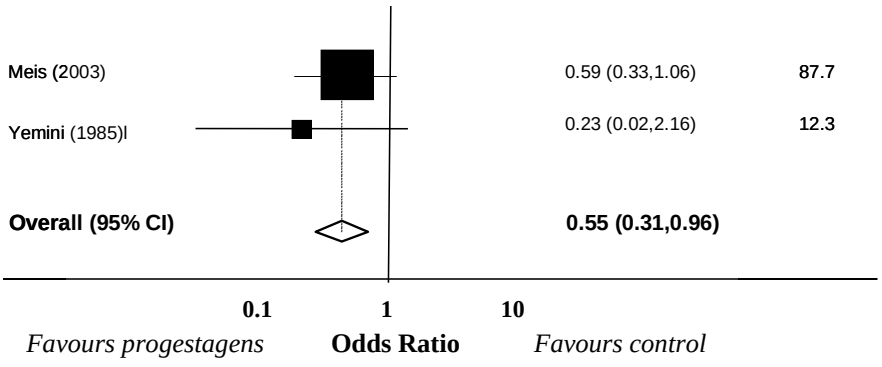
Heterogeneity chi squared p=0.585

Fig 6.1a: delivery before 37 weeks



Heterogeneity chi squared p=0.094

Fig 6.1b: delivery before 34 weeks



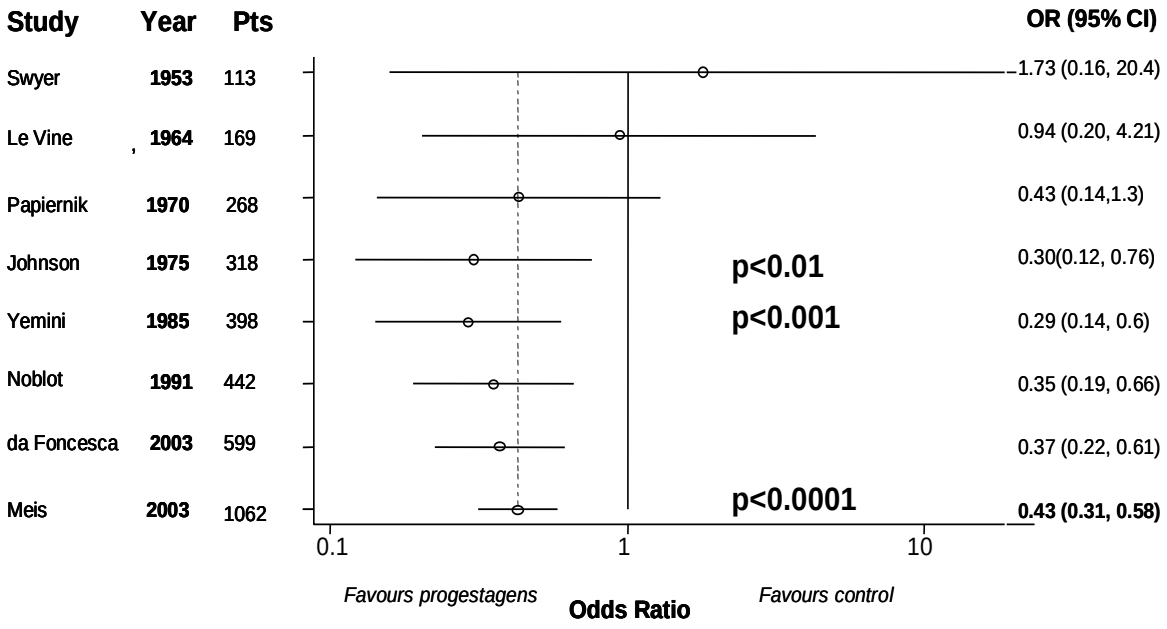
Heterogeneity chi squared p=0.425

Fig 6.1c: respiratory distress syndrome

6.4.2 Cumulative Meta-analysis by time

Cumulative meta-analysis by year of study showed that the beneficial effect of progestational agents in reducing pre term delivery before 37 weeks' gestation exceeded conventional level of statistical significance in 1975 ($p<0.01$); by 1985, the OR was 0.29(95 % CI 0.14, 0.6) with very high level of statistical significance ($p<0.001$); and by 2003, the statistical significance was impressively high at $p<0.0001$ (Fig 6.2). There has been a gradual narrowing of confidence intervals with increasing statistical certainty of benefit around a point estimate of about 60% reduction in the odds of pre term delivery with progestational agents.

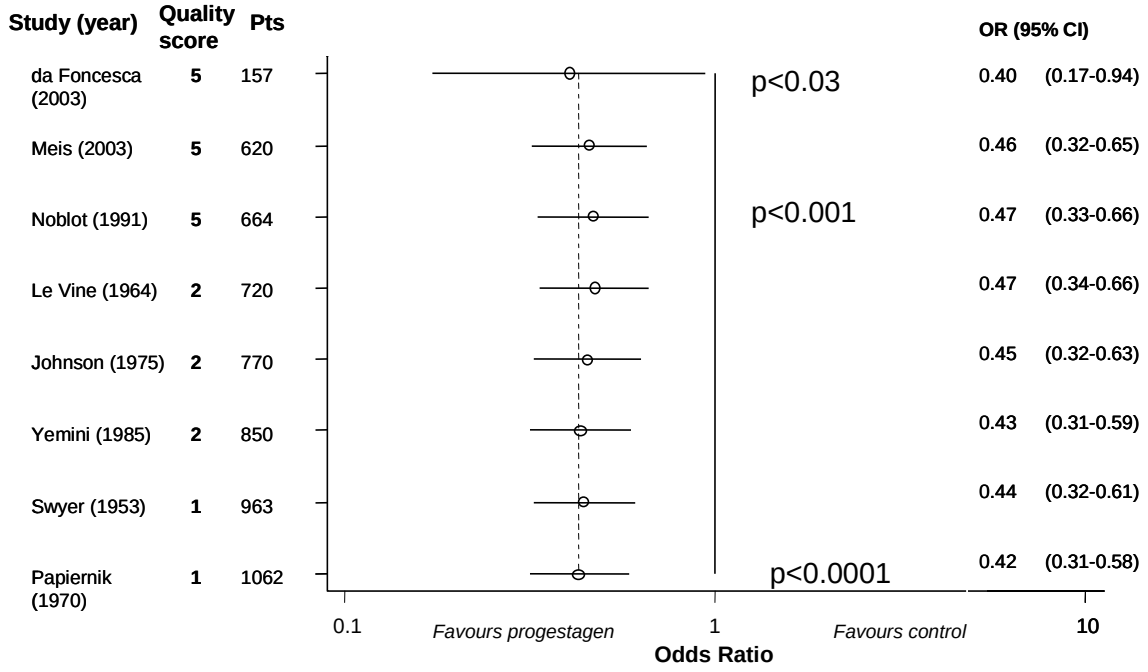
Fig 6. 2. Cumulative meta-analyses by year of study of randomised trials evaluating the effectiveness of progestagens in preventing delivery before 37 weeks



6.4.3 Cumulative Meta-analysis by study quality

Cumulative meta-analysis in which the studies were ranked by decreasing quality score showed that statistically significant benefit was shown even when we limited the analysis to the highest quality studies with the maximum quality score of 5 (OR 0.47, 95% CI 0.33, 0.66, p<0.001, Fig 6.3). Addition of the poorer quality trials simply improved the precision, but did not alter the inferences drawn from the highest quality studies alone.

Fig 6.3. Cumulative meta-analysis by quality score of randomised trials evaluating the effectiveness of progestagens in preventing delivery before 37 weeks

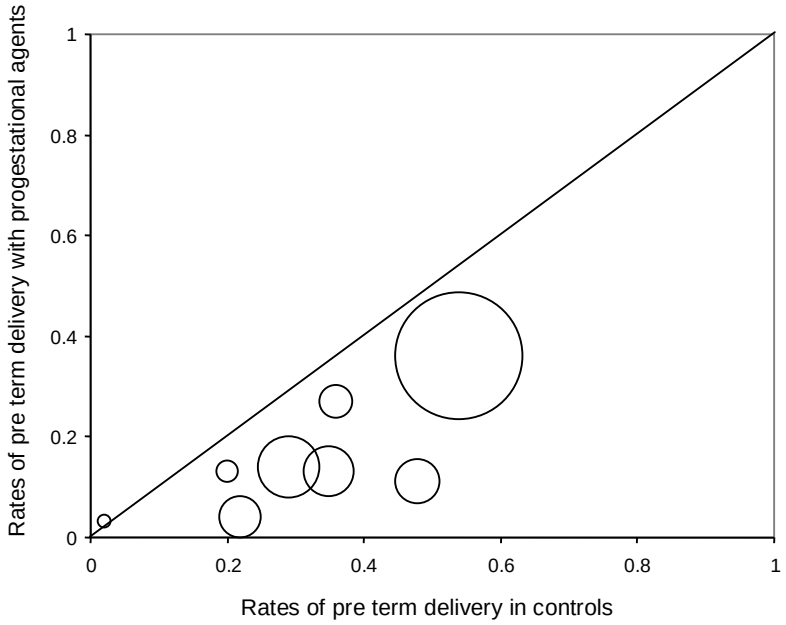


6.4.4 Variation in effectiveness across different baseline risks

The L'Abbe plot which graphed event rate in the treated group against the control group for the outcome of delivery before 37 weeks, is presented in Fig 6.4. This scatter plot shows that the magnitude of benefit from progestational agents does not change across a range of baseline risks (x-axis in Fig 4). This supports the applicability of the findings to a wide range of populations with

varying baseline risks. Naïve regression analyses based on the L'Abbe plots were not done as they could suffer from regression to mean bias.

Fig 6.4 L'Abbe plot of effect of progestational agents with varying baseline risk



6.4.5 Safety of progestational agents

Our systematic review did not show any evidence of harm from progestagen therapy. We identified a Cochrane review of RCTs and a meta analysis of observational studies evaluating the harm from progestagen treatment.[189;190] The Cochrane review evaluated progestagens for various indications such as prevention of miscarriages and stillbirth and identified 14 trials consisting of 1988 women, and found no evidence of harm to mother or baby, thus confirming our review findings. The systematic review of observational studies of first trimester sex hormone exposure identified 14 studies, consisting of 65,567 women. This included 7 cohort and 7 case control stuies. The sex hormone in several of these 14 studies was progestagens alone or with other steroids. No harm,

particularly any external genital malformation (OR 1.09; 95% CI 0.90, 1.32), was found in this review.

However, a recent case control study suggested an association between progestagens and genital abnormalities, especially hypospadias.[191] This study had a small number of cases, a weak case control design and included use of progestagens in early pregnancy, thus making the evidence unlikely to be relevant to the later use of progestagens in the prevention of preterm birth. The extensive review by Brent et al has firmly ruled out any association between the use of progestagens and nongenital malformations.[192]

6.5 Discussion

This review shows that progestational agents have a large treatment effect in reducing the risk of a number of clinically relevant outcomes, especially delivery rates before 34 weeks and respiratory distress syndrome. The results were homogenous, and significant regardless of the statistical approach used for meta-analysis. In addition, there was no evidence of publication and related biases from funnel plot analysis. The cumulative meta analysis of randomised trials shows that a significant benefit of progestagens in reducing preterm delivery was evident from 1975, and subsequent studies have increased our confidence to such a striking level that statistical uncertainty could not be cited as a reason for not using progestational agents. Reduced confidence in the quality of the older trials has been thought to be one of the reasons for not using progestagens. However, this could no longer be a reason as the findings from the highest quality recent randomised controlled trials concur with the older studies.

Studies whose populations were exclusively women with multiple pregnancies were not included. Earlier reviews showed that the consistent beneficial effect of progesterone was not observed in women with multiple pregnancies. It might be that there are important factors other than what could be influenced by progestational agents that contribute to preterm birth in multiple pregnancies, and our review evidence is limited to singletons - a theory that needs further research. The exclusion of multiple pregnancies in two of the recent, good quality, large randomised trials that showed significant benefit of progestagens lends support for this hypothesis.

In the existing review of progestational agents to prevent preterm birth, the authors have reported *average* Numbers Needed to Treat (NNT) calculated from the pooled meta-analyses results. Such analyses can be seriously misleading, as NNT are sensitive to changing baseline risks – the lower the risk, the higher the NNT, and the lower are our and women's expectations of benefit from treatment. Conversely, the higher the baseline risk, the lower the NNT, and the higher are our and women's expectations of benefit from therapy, and the more inclined we would be to recommend, and women to accept therapy. NNT will, therefore, need to be tailored according to baseline risks. We have, therefore, given a range of NNT appropriate for various baseline risk for the several outcomes in Appendix 16.

There is no clear consensus on the dosage, route, or the release formulation, as well as the period of treatment with progestational agents. However, the largest high quality study used intramuscular 17 hydroxy progesterone caproate at a dose of 250 mgs weekly started between 16 to 20 weeks and continued until 36 weeks or delivery – this study was also associated with large treatment effects. Two other studies also used intramuscular 17 hydroxy progesterone caproate at same dosage as above, and found large treatment effects. Another regime used in one of the recent and high quality

study that again showed large treatment effects was vaginal progesterone suppositories of 100mg every night. We recommend either of these regimens. There is substantial evidence for the safety of progestagens on the fetus and has not shown any adverse effect.

6.6 Conclusion

The very large treatment effects in clinically important outcomes of delivery before 34 weeks (50% reduction in odds) and respiratory distress syndrome (45% reduction in odds) cannot, and should not be ignored. Reluctance to use a very effective and safe therapy, which is based on level 1a evidence, is likely to cause untold amount of harm, similar to the harm caused by the delay in the introduction of streptokinase therapy after myocardial infarction, or steroids in preterm birth.

CHAPTER 7: A SYSTEMATIC REVIEW OF EFFECTIVENESS OF LAMOTRIGINE DOSAGE BASED ON SERUM LEVELS COMPARED TO CLINICAL FEATURES IN REDUCING SEIZURES IN PREGNANCY

7.1 Abstract

Background: Epilepsy is one of the significant causes of indirect maternal deaths in pregnancy. Both seizures during pregnancy and AED (Anti Epileptic Drug) exposure in utero influence the poor outcomes in children born to mothers with epilepsy. Lamotrigine (LTG) is the first choice for AED in women of child-bearing age. In pregnancy, serum levels of lamotrigine fall with resulting increase in seizures. There is clinical equipoise with clinicians either increasing the dose of LTG based on serum levels or based on clinical features alone. There is a need to systematically review the available evidence assessing the effectiveness of the 2 dosage regimens on maternal and fetal outcomes to inform clinical practice.

Methods: We searched MEDLINE (1966–2009) and EMBASE (1980–20098), for relevant citations on the effectiveness of different dose regimes of LTG in pregnancy. Study selection, quality assessment and data extraction were carried out by 2 independent reviewers. We calculated the relative risk (RR) and the rates of seizures for maternal and fetal outcomes.

Results: Five studies with a total of 101 pregnant women with epilepsy were included to evaluate the effectiveness of the different LTG regimes on seizure control in pregnancy. Two studies assessed the effectiveness of LTG dose management based on serum levels and two evaluated LTG dosage based on clinical features alone. One study compared the effectiveness of both regimens on seizure deterioration. The combined rate of seizure deterioration was 0.40 (95% CI 0.26 to 0.55) in

women with LTG dosage based on serum levels compared to 0.73 (95% CI 0.56 to 0.86) in those managed by clinical monitoring alone.

Conclusion: LTG dose management based on serum levels in pregnancy appears to be better in reducing seizures than dose management based on clinical features alone. The included studies are small, heterogeneous, non randomised and not controlled thereby limiting recommendations for clinical practice from the review.

7.2 Background

Epilepsy affects 0.5-1% of general population.[18] Approximately one third of people receiving AEDs are of reproductive age.[19;20] There is a 10-fold increase in mortality among pregnant women with epilepsy which greatly exceeds the two to three-fold mortality rate observed in all people with epilepsy.[21] In 2000-2002, 13 maternal deaths in the UK were attributed to epilepsy.[22] These were invariably a direct consequence of seizures. There is one in 250 pregnancies exposed to AEDs .[23;24] AED exposure in-utero is associated with congenital malformations.[25] Fetal risk is related to the number of AEDs, AED type and probably AED dose. Furthermore, there are concerns about the long-term neurological development of children exposed to AEDs in-utero. There is a general consensus that the risks of uncontrolled convulsive seizures in the mother outweigh the potential teratogenic risk of the medication, and most women with active epilepsy are advised to continue with medication during pregnancy.[18] The effects of seizures extend into daily living resulting in loss of driving licence, negative impact on employment and relationships and reduced Quality of Life (QoL).[26] The triennial Confidential Enquiries into Maternal Deaths in the UK reported concerns about epilepsy management during pregnancy.[22]

Seizure control is important during pregnancy. Uncontrolled epilepsy, with generalised tonic-clonic convulsions, carry risks of harm including miscarriage, fetal hypoxia and acidosis, and fetal loss.[27-29] The reasons for fetal loss are not entirely understood but are more likely to be related to maternal seizures than to fetal exposure to AEDs.[29;30] This is supported by the finding of fetal heart rate decelerations during maternal seizures.[31]

There is clear evidence that blood levels of various anti-epileptic drugs fall in women with epilepsy due to physiological changes in pregnancy altering AED pharmacokinetics and AED concentrations. There is decreased gastric tone and motility, increased plasma volume, increased renal clearance and albumin levels and protein binding.[193-196]Among the newer AEDs, levels of Lamotrigine (LTG) have been shown to fall significantly in pregnancy. A significant decrease in the ratio of Lamotrigine concentration-to-dose by 65% has been observed in second and third trimesters compared to pre-conception baseline levels[197]. This has been correlated with significant increase in seizure activity by up to 75% in pregnancy.[198]

In pregnancy, therapeutic drug monitoring could guide adjustment of AED dosage to achieve good seizure control while minimising fetal exposure. If possible, it is advisable to establish the total and free pre pregnancy AED concentrations at which the seizures are well controlled in the woman as a baseline. Regular monitoring of LTG levels has been advocated in each trimester and shortly after delivery, with adjustment of dosage to avoid seizure precipitation during pregnancy and to avoid of toxicity after birth. A fall in serum levels in pregnancy is diagnosed by comparing to the patient's pre pregnancy levels at which they had good seizure control. The risk of seizures associated with a fall in levels is discussed with the woman and the dose of AED is increased appropriately. Although reference ranges for levels of AEDs including LTG exist, the therapeutic range, i.e. the optimal serum LTG level for seizure control varies between individuals. The therapeutic range may lie outside the reference range in some individuals with increase in risk of toxicity when the therapeutic range lies above the reference range for the individual.[199] Regular and frequent serum monitoring reduces the above risks. Most often in clinical practice, the pre pregnancy levels are not available. The earliest tested level in pregnancy i.e. the booking is then considered to be the baseline level. There is uncertainty about the degree of fall in levels at which an increase in dose of LTG is essential. Monitoring of serum AED levels including LTG in each trimester and after

delivery has been recommended by the American Academy of Neurology based on consensus as a good practice.[200] In the UK however, the SIGN (Scottish Intercollegiate Guidelines Network) guideline does not recommend regular AED monitoring in pregnancy due to paucity of evidence.[201]

Existing practice on the dosage of lamotrigine in pregnancy is based on the preference of individual clinicians. The management of women with epilepsy on LTG is aimed at achieving seizure control on the lowest possible dose and number of AEDs. Current practice in most units is based on the clinical features, with increase in dose of LTG if there is an impending risk of seizures or actual aggravation of seizures. Routine LTG serum level monitoring is not done except in the following states: suspicion of non compliance, risk of toxicity or uncontrolled seizures. Given the significant reduction in LTG levels in pregnancy some clinicians advocate routine dose escalation of LTG based on serum levels, even in the absence of seizures, to reduce the risk of their occurrence. There are no systematic reviews that have evaluated the effectiveness of the two alternative regimes and looked at maternal and fetal outcomes including neurodevelopmental outcomes and major congenital malformations in babies.

7.3 Method

We searched MEDLINE (1966–2009) and EMBASE (1980–2009) for relevant citations. A combination of Medical Subject Headings (MeSH) and text words were used to generate for subsets of citations, one indexing Lamotrigine (‘Lamotrigine’ and ‘Lamictal’) another indexing pregnancy (‘pregnancy’); the third indexing epilepsy (‘epilepsy’) and the final indexing dose response relationship (‘dose increase’, ‘increase dose’, ‘decrease dose’ and ‘dose decrease’). These subsets were combined using ‘AND’ to generate a subset of citations relevant to our research question. The reference lists of all known primary and review articles were examined to identify cited articles not

captured by electronic searches. Articles frequently cited were used in the Science Citation Index to identify additional citations.

Studies which evaluated the effectiveness of LTG dosage in pregnant women with epilepsy based on serum levels or clinical features alone were selected in a two-stage process. First, the electronic searches were scrutinised and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Secondly, final inclusion or exclusion decisions were made by 2 reviewers after examination of these manuscripts. Studies which met the predefined and explicit criteria regarding population, intervention, outcomes and study design were selected for inclusion in the review. When disagreements occurred, they were resolved by consensus. In cases of duplicate publication, the most recent and complete versions were selected. There were no language restrictions.

Studies were selected if the target population was pregnant epileptic women; the therapeutic intervention was LTG (or a combination of LTG and other antiepileptic drugs) and the studies mentioned dose escalation versus dose maintenance therapy. The outcomes studied were seizure frequency, the presence or absence of seizures, maternal quality of life and fetal risks.

All manuscripts meeting the selection criteria were assessed for their methodological quality. The selected studies were assessed for methodological quality using the components of study design that are related to internal validity. Quality was defined as the confidence that the study design, conduct and analysis minimised bias in the estimation of therapeutic effectiveness. Based on existing checklists, quality assessment involved scrutinising study design and relevant features of the population, intervention and outcomes of the study. A study was considered to be of good

quality if it used a prospective design, randomised patients, consecutive enrolment, blinding, adequate description of intervention, outcome and adequate follow up. We calculated the relative risk (RR) of seizures in both regimes and maternal and fetal outcomes. Data was obtained on the dose of LTG, and adverse maternal and fetal effects.

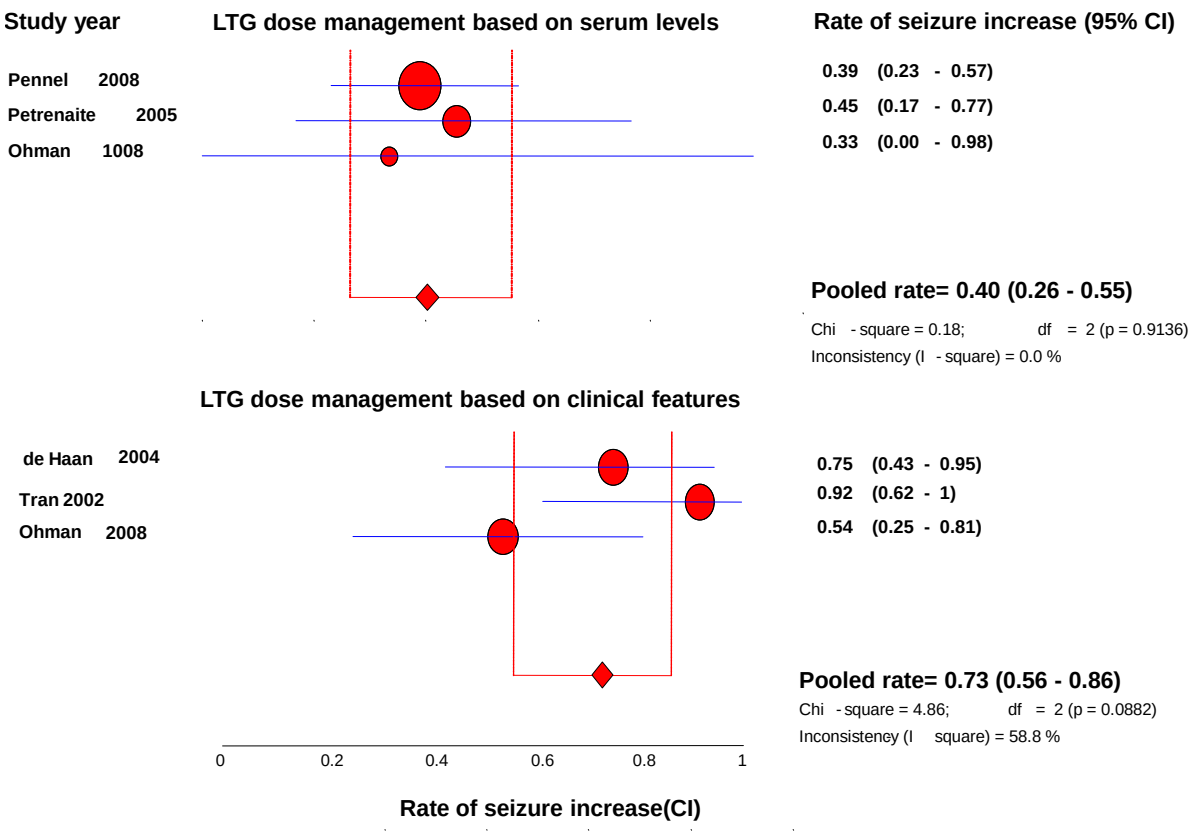
7.4 Results

Appendix 4 summarises the process of literature identification and selection. We identified 389 relevant electronic citations. After screening the titles and abstracts, 359 were rejected, and 33 were considered for detailed evaluation study selection. Finally 5 primary articles met the selection criteria for inclusion in the review with a total of 101 women (Appendix 18).[194;202-205] The included studies consisted of pregnant women with epilepsy treated with on Lamotrigine alone or Lamotrigine in combination with other anti-epileptic drugs. The quality of the included studies is provided in Appendix 13.

Three studies evaluated the effectiveness of LTG dosage regime based on serum levels in reducing seizure frequency.[194;203;204] Three studies reported on the effectiveness of LTG dosage regime based on clinical features alone.[202;203;205] One study provided comparative data on seizure frequency in both the cohorts, LTG dosage based on serum levels and clinical features alone.[203] Patients involved in 2 studies were treated with other AED in addition to LTG. The therapeutic drug monitoring was reported as LTG plasma concentration (mmol/l)/LTG dose (mg) ratio, apparent clearance equal to the dose (mg/kg/d) / level (mg/l) or Ratio to Target Concentration (RTC total LTG / target LTG). The LTG RTC threshold for increasing seizure frequency was reported as 0.65, with a true positive rate (TPR) of 83.3% and a low false positive (FPR) of 4.2%. Increasing the RTC threshold to 0.78 gave a TPR of 100% and a FPR of 25%.

The rates of seizure increase in the groups that managed LTG dose based on serum levels were0.39 (95% CI 0.23 - 0.57),[194] 0.45 (95% CI 0.17 - 0.77)[204] and 0.33 (95% CI 0.00 - 0.98).[203] In the group that managed LTG dose on the basis of clinical features alone, the rates of seizure increase were 0.75 (95% CI 0.43 - 0.95),[202] 0.92 (95% CI 0.62 - 1.00)[205] and 0.54 (95% CI 0.25 - 0.81).[203] The combined rate of seizure deterioration was 0.40 (95% CI 0.26 to 0.55) in women with LTG dosage based on serum levels compared to 0.73 (95% CI 0.56 to 0.86) in those managed by clinical monitoring alone. (Fig 7.1)

Fig 7.1. Rates of increase in seizure in pregnant women with dose LTG management based on serum levels compared to management based on clinical features



There was one incidental pregnancy loss in the included studies.[198] Maternal toxicity was reported in 1 study after delivey.[206] No association was found between small for gestational age, fetal and neonatal death, neonatal intensive care unit admissions or low Apgar scores. There was one congenital malformation (renal hydronephrosis, resolved by 4 months), one newborn diagnosed with a heart murmur (resolved early) and two premature deliveries.[206]

7.5 Discussion

The data from existing studies suggest that LTG dosage based on serum levels escalation is associated with decreased seizure frequency and that dosage based on clinical features alone is associated with an increase in seizures.

This systematic review included a detailed search of the major medical databases studies on the basis of their quality and relevance to this subject to provide information on the dosage regime of LTG on maternal seizures and fetal outcome. It has systematically collated and evaluated the quality of existing evidence in this area. The limitations of this review arise from the characteristics of the included studies. The studies were small, not randomised, nor controlled, with heterogeneous results and there was imprecision with small numbers of women, making findings unreliable. There is insufficient evidence on other outcome measures like neurodevelopmental outcome in the offspring and maternal quality of life. The inclusion of other AEDs in addition to LTG means that seizure deterioration and subsequent control could be confounded by the fall in levels of other drugs, their interaction with LTG and their effectiveness in seizure control. Furthermore the studies are heterogeneous in the identification and classification of fall in serum levels of LTG that necessitate an increase in dosage of LTG. There is no consistent evidence on the dosage of LTG that needs to be increased to prevent a seizure when there is a fall in serum levels.

Management of LTG dosage in pregnancy can be guided by 'Individual Therapeutic Level'. This is the level at which there is good seizure control with minimum toxicity.[207] The individual therapeutic level can be identified from pre pregnancy levels of LTG at which there was good seizure control. The dose adjustment was based on pre pregnancy serum levels in the 3 studies. Information of the sampling time from the last dose intake is necessary to maximise the benefit of dose management based on serum levels. Heterogeneity and lack of information on the sampling time when evaluating a drug like LTG with relatively short half life can affect the results.

One of the major concerns in increasing the dose of LTG in pregnancy is its potential short term and long term adverse effect on the fetus. A variety of adverse effects have been reported on infants born to women with epilepsy either treated or untreated, including intrauterine growth retardation, major and minor malformations and postnatal developmental delay.[18] The overall major congenital malformation rate for all AED exposed cases was 4.2% (95% Confidence Interval: 3.6%-5.0%).[208] The average frequency of major congenital malformations in cohorts of women using AED monotherapy only ranges between 1.03% and 4.5%.[209-212] The risk is highest in the first trimester during organogenesis. For LTG (n=647) the mean daily dose was found to be significantly higher for those with a major congenital malformation than for those without a major congenital malformation (respectively, 352.4 mg and 250.6 mg; p=0.005).[212] The North American Antiepileptic Drug (NAAED) Pregnancy Registry of 684 women on LTG monotherapy did not find dose related adverse effects.[213] Data related to dose from the LTG Pregnancy Registry found no increase in major defects with daily doses up to 400 mg; data for doses of 400 mg or more were insufficient to confirm or refute a dose effect.[210] There were 176 exposures at doses of 400 mg or more included in a recent report by the LTG Pregnancy Registry Advisory Committee with data from 2287 pregnant patients on LTG monotherapy.[214]

This includes 39 exposures in the range of 601 – 1200 mg. The Committee considered the data reassuring, providing no evidence of a dose effect. The available data suggest that any dose effect that might exist on malformation is likely to be small. Long-term follow up of children exposed to LTG in utero has been limited, so that more subtle effects on the subsequent neurological and cognitive development of children have been poorly studied. Besides exposure to LTG, neurodevelopment may also be affected by variables such as seizure type and frequency or severity during pregnancy, maternal age and IQ, genetics, and socioeconomic status. [215;216]

Large randomised studies sufficiently powered to investigate the use of AEDs including LTG in pregnancy and the optimal dosage regimen to maximise seizure control and minimise short term and long term adverse effects to the mother and fetus are needed. Such a study will determine, among pregnant women with epilepsy on AEDs, whether AED dose adjustment based on serum AED levels (intervention) reduces the risk of seizure deterioration compared to management based on clinical features only (control). There are several ways in which loss of seizure control can be defined and analysed. There is no consensus on the best approach.[217] The standard approaches to analysis assume normal distribution, but the data are likely to be highly skewed. This is because a large proportion (50-60%) of patients will remain seizure free throughout pregnancy.[218]

An optimal study design is needed to ensure statistical efficiency, feasibility and validity. Early randomisation of women to either therapeutic drug monitoring or not, i.e. AED dose management with serum AED level monitoring or without in a study would be similar to that of a trial comparing two testing protocols.[219] In this situation, only women in the intervention group whose serum AED levels fall will be in a position to benefit from intervention that follows

testing. This will reduce the size of effect than can be discovered and will introduce statistical inefficiency with the need to recruit very large numbers, otherwise the study would be underpowered risking type II error.[219] An alternative design could have both clinicians and patients blind in all groups using placebos. However, this may pose problems with logistics and acceptability. Pregnant women enter the pregnancy on various AED types, doses, combinations and preparations (generic and branded). The requirements for dummy dosing with identical placebos in different shapes, sizes and colours with central provision of drug supplies for participating centres would present an enormous logistic challenge apart from being prohibitively expensive. Furthermore, clinicians may be reluctant to participate if they were blinded to the intervention group. Such a study would thus be unfeasible. The key issue is to design the study in such a way so as to achieve blinding. A trial design where eligible pregnant women with epilepsy will be consented early to enrol in a comprehensive cohort study of therapeutic drug monitoring of antiepileptic drugs (AEDs) throughout pregnancy will ensure that both women and clinicians will be initially blinded to the serum AED levels. Those women who have a fall in serum AED levels will be randomised to either management based on serum levels in the intervention group (Group A) or management based on clinical features only in the control group (Group B). Women with stable serum AED levels will form the non-randomised cohort (Group C) to be followed-up in a manner identical to the randomised cohort. The clinicians and women cannot be blinded in the intervention group (Group A). However, both clinicians and women in Groups B and C can be kept blinded to whether serum AED levels have fallen or not, thereby minimising the risk of performance and measurement bias in the control group.

Such a design with early consent and randomisation only when the serum levels fall, will ensure that the data on all the randomised patients will contribute to estimation of the effect, enhancing the statistical power to detect a difference. Follow-up of the non-randomised cohort will make it

possible to blind the control group. Additional information collected from the non-randomised group will provide useful data for decision-analytic modelling. In order to accrue the large number of pregnancies necessary for a reliable evaluation, the trial will need the participation of a number of centres managing pregnant women with epilepsy. To make this practicable, the trial procedures need to be kept simple, with the minimal extra workload placed on the participating clinicians and centres, beyond that required to test and treat the mothers.

7.6 Conclusion

Existing evidence collated in our review seem to favour LTG dosage in pregnancy based on serum levels. Concerns about the quality of the studies with substantial imprecision in the results make it difficult to make any firm recommendations. A large well conducted randomised study incorporating patient acceptability data and cost economic evaluation will help clinicians and pregnant women with epilepsy on AEDs like LTG make decisions on the preferred choice of dosage regimen.

SECTION D

SYSTEMATIC REVIEWS OF TEST ACCURACY

In this section, I have systematically reviewed the test accuracy studies and summarised the evidence of accuracy by meta analyses, in the field of: 1) maternal medicine by evaluating the accuracy of proteinuria, uric acid, liver function tests, symptoms and blood pressure in predicting adverse maternal and fetal outcomes in women with pre eclampsia and 2) perinatal medicine in newborn by assessing the accuracy of pulse oximetry as a screening test in the detection of congenital heart disease (CHD) in newborn

CHAPTER 8: TESTS FOR PREDICTING COMPLICATIONS OF PRE-ECLAMPSIA: A PROTOCOL FOR SYSTEMATIC REVIEWS

8.1 Abstract

Background

Pre-eclampsia is associated with several complications. Early prediction of complications and timely management is needed for clinical care of these patients to avert fetal and maternal mortality and morbidity. There is a need to identify best testing strategies in pre eclampsia to identify the women at increased risk of complications.

Method

An extensive search was performed in MEDLINE (1951–2004), EMBASE (1974–2004) including manual searches of bibliographies of primary and review articles. The detailed search revealed 19,500 citations. Two reviewers were proposed to independently select studies and extracted data on study characteristics, quality and accuracy. Accuracy data will be used to construct 2 × 2 tables. Data synthesis will involve assessment for heterogeneity and appropriately pooling of results to produce summary Receiver Operating Characteristics (ROC) curve and summary likelihood ratios. Bivariate analysis will be performed to assess sensitivity and specificity.

Results and Discussion

The protocol led to the development of reviews that generated information on the accuracy of tests in predicting complications in women with pre-eclampsia.

Citation of paper from this work

Thangaratinam S, Coomarasamy A, Sharp S, Ismail KMK, Khan KS for the TIPPS (Tests in Prediction of Pre-eclampsia's Severity) review group Tests for predicting complications of pre-eclampsia: A protocol for systematic reviews of the literature BMC Pregnancy Childbirth 2008. 8:38

8.2 Background

Hypertension is a common medical complication of pregnancy, affecting about 6–8% of all pregnancies.[220] Hypertensive disorders in pregnancy consist of a group of disorders that include pre-eclampsia, latent or chronic essential hypertension, a variety of renal diseases, and transient (gestational) hypertension. The definitions used to distinguish these disorders differ, leading to uncertainty about their prevalence, natural history and response to treatment. Pre eclampsia is associated with several complications[221] and remains one of the largest single cause of maternal and fetal mortality and morbidity.[222;223] They have been reported to account for 14% of direct maternal deaths and 18% of fetal or infant deaths.[222;223]

Once the diagnosis of pre-eclampsia is established, timely management is of the essence to avoid or minimise mortality and morbidity. Clinical prediction of disease complications using a combination of patients' characteristics, symptoms, physical signs and investigations all of which we consider tests, forms the basis of clinical care in these situations.[139] Therefore, there is a need for guidance regarding the best testing strategies with which to predict the development of complications in pre-eclampsia. As well as allowing clinicians to avoid unnecessary interventions in low risk groups, this would allow high-risk groups to benefit from monitoring of disease severity, use of antihypertensive therapy, administration of anticonvulsants, and antenatal corticosteroids.[140;224]

8.3 Methods

A systematic quantitative overview of studies of complications of pre-eclampsia was conducted to obtain summary estimates of accuracy of all available tests. The proposed methodology was in line with the guidance of the NHS Centre for Reviews and Dissemination[172] and that of the Cochrane Methods Working Group on Screening and Diagnostic tests.[55] The investigation was be carried out

in the following recommended steps: (i) Question formulation, (ii) Study selection and identification, (iii) Study quality assessment, (iv) Data extraction and (v) Data synthesis. Our strategy for each of these steps was be based on a prospective protocol, which is outlined below:

Table 8.1: Structured questions in the systematic review of tests predicting complications in women with pre eclampsia

Question Components	
Population	Pregnant women with pre eclampsia
Tests	
History	Parity; Race; Maternal age; Previous severe pre eclampsia/Eclampsia; Family history of pre eclampsia/eclampsia; Obesity; Weight gain; Pre existing hypertension, renal disease, diabetes, lupus, thrombophilia, other auto immune diseases; Multiple pregnancy; Symptoms-headache, epigastric pain, nausea, visual disturbance or combination of symptoms
Examination	Blood pressure; Peripheral oedema; Exaggerated tendon reflexes; Clonus; Papilloedema; Retinal changes; Oliguria; Symphysio fundal height; Oxygen saturation
Investigations	**Biochemical**: Serum uric acid, Urine dipstick (Bedside Urinalyses), Urine Protein: Creatinine Ratio (PCR), Urine Albumin Creatinine Ratio (ACR), 24 hour urine protein; Urinary calcium excretion; Hypoalbuminaemia; Microalbuminuria; Fibronectin, Renal and liver function tests; **Ultrasound**: Growth , liquor volume, doppler (uterine, umbilical artery, middle cerebral artery, venous) bio Physical Profile; **Haematological**: Anti thrombin III; Platelet count; Haemoglobin; Fibrinogen; Thrombophilia screen; Maternal serum Alpha feto protein (MSAFP); Serum Human Chorionic Gonadotropin (HCG); Computerised Tomography; Magnetic Resonance Imaging
Outcome	***Maternal*** Eclampsia; Pulmonary oedema; Cerebral Haemorrhage; Hepatic, renal, haematological complications; Cardiac arrest; Abruption; Thromboembolism; stroke; Psychiatric problems; Complications of labour and delivery; Maternal death; Need for hospitalisation; Day care unit visits; Use of intensive care; Ventilation and dialysis ***Fetal*** Intra uterine growth restriction; Prematurity; Abnormal pH at birth or antenatal; Abnormal Apgar; Hypoxic Ischemic Encephalopathy; Perinatal death; Long term effect:learning disabilities, Developmental and special needs after discharge; Need for neonatal intensive care admission; Mechanical ventilation and duration of hospital stay
Study design	**Systematic review of test accuracy studies**

8.3.1 Question Formulation

The tests to be considered by the review are specified in the form of structured questions in Table 8.1. A priority list had been generated based on importance to clinical practice using a modified Delphi survey.[17] An exhaustive list of the tests and outcomes in the prediction of pre eclampsia were sent to experts in the field. Each one of the issues were rated according to their importance to clinical practice and ranked accordingly. The reviews will focus on the prioritised tests obtained from the survey.

8.3.2 Study Identification and Selection

A thorough search protocol was developed by which literature was identified via the general bibliographic databases including MEDLINE and EMBASE and a specialist database MEDION. The latter is a database of diagnostic test reviews set up by Dutch and Belgian researchers. Reference lists of articles obtained by iterative search will be checked as an adjunct to other methods.[225] Language restrictions will not be applied. A comprehensive database of relevant articles will be constructed. The search will be updated every year to enable inclusion of current evidence in the reviews. A search term combination was constructed after exhaustive planning and piloting of possible search concepts capturing the relevant population, tests and outcomes. Our search terms and flow chart of strategy are shown in Appendices 5 and 20. An initial search in Medline yielded 11711 citations. The search strategy was adapted for searching in Embase to obtain a total of 19500 citations. From this citation set, studies will be selected for inclusion in the review in a two-stage process.

In the first stage the electronic searches will be scrutinised by two independent reviewers and full manuscripts of all citations that are likely to meet the predefined selection criteria will be obtained. All available reports, irrespective of language will be included to reduce bias.[226] Subsequent final

inclusion or exclusion decisions will be made on examination of these manuscripts. In cases of duplicate publication, the most recent and complete versions will be selected. Two reviewers will then independently select the studies, which meet predefined and explicit criteria regarding population, tests, outcomes and study design (Table 8.1). These criteria will be piloted using a sample of papers and agreement between reviewers will be measured. When disagreements occur, the two reviewers will meet and if necessary the issue will be resolved by consensus involving a third reviewer.

8.3.3 Study Quality Assessment

A review of papers meeting the eligibility criteria will be conducted by the same reviewers who judged eligibility, but this time rating the methodological quality of the primary research. Methodological quality is a reflection of the degree to which the study design, conduct and analysis has minimised bias in addressing the research question. This ensures a high level of internal validity (i.e. the degree to which the results of an observation are correct for the patients being studied). The potential sources of bias and variability arising from spectrum composition and other variations in test protocol or the use of reference standard in individual studies will be considered when interpreting the results.[227] In addition to using study quality as possible explanation for differences in results, the extent to which primary research met methodological standards is important per se for assessing the strength of any conclusions that are reached.[172] We will evaluate elements of study design which are likely to have a direct relationship to bias and variability in a test accuracy study.[172;226-232]

8.3.4 Data Extraction

The extraction of study findings will be conducted in duplicate using a pre-designed and piloted data extraction form to avoid any errors. Two authors will independently extract information from

each article in order to construct 2×2 tables of the diagnostic test result and outcomes. Any disagreement will be resolved by consensus. Given the extent of insufficient reporting in the medical literature, we propose to obtain missing information from investigators whenever possible. It is otherwise impossible to distinguish between what was done but not reported and what was not done. To avoid introducing bias, unpublished information will be obtained in writing, and will be coded in the same fashion as published information with equal regard for inter-coder agreement. In addition to using multiple coders to insure the reproducibility of the overview, sensitivity analyses around important or questionable judgements regarding the inclusion or exclusion of studies, the validity assessments and data extraction will be performed.

8.3.5 Data Synthesis

We will explore causes of variation in results from study to study (heterogeneity), synthesise results from individual studies (meta-analysis) if appropriate[172;230] and assess for the risk of publication bias. Heterogeneity of results between studies will be graphically assessed looking at the distribution of rates, sensitivities and specificities in the ROC (Receiver Operating Characteristics) curve and likelihood ratios using Forest plots. To explore causes of heterogeneity we will conduct a sensitivity analysis by subgroups to see whether variations in population characteristics, tests, outcomes and study quality affect the estimate accuracy. Conclusions regarding the typical estimate accuracy will be interpreted cautiously if there is significant heterogeneity. Individual factors explaining heterogeneity will also be analysed using meta-regression to determine their unique contribution allowing for other factors. We will conduct meta-analyses to generate summary estimates of likelihood ratios (LRs), diagnostic odds ratios (ratio of LRs) and area under receiver operating characteristic (ROC) curves as appropriate. [230;233;234] To visualise data we will plot for each model combinations of sensitivity and specificity in receiver operating characteristic (ROC) plots.[233] In a ROC plot the upper left corner is the ideal position in an ROC curve because it reflects

the highest sensitivity and the lowest false positive rate. A bivariate random effects meta-regression model will be used to fit a summary ROC (sROC) curve. Briefly, the bivariate model preserves the two-dimensional nature of diagnostic data in a single model. This model incorporates the correlation that may exist between sensitivity and specificity within studies due to possible differences in threshold between studies.[59] AUC values between 0.70 and 0.79 are deemed as having moderate discriminative properties, and those with AUC values of ≥ 0.80 as having good discriminative properties.

The risk of publication bias is expected to be high in reviews of test accuracy.[235] Analysis for assessing the risk of publication bias will be carried out by producing funnel plots of accuracy estimates against corresponding variances. In the absence of publication bias it is to be expected that the point estimates will fill a funnel shape in the plot. Large gaps in the funnel indicate a group of possible 'missing' publications. These omissions are due to small studies showing limited accuracy and are unlikely to be missing at random. This phenomenon will also be statistically evaluated using Egger's test.

8.4 Discussion

In the same way as systematic reviews of effectiveness of treatments in obstetrics have been pursued over the last decade, research on test accuracy also needs systematic reviewing.[236;237] One of the questions remaining after establishing effectiveness evidence for magnesium sulphate, steroids and anti hypertensives is to identify those who will benefit most from these interventions.[238;239] Relying on the inclusion and exclusion criteria of the trials alone is not sufficient for determining who should and shouldn't get these treatments. Women at high risk of complications of pre-eclampsia are likely to benefit most whilst in low risk women, therapy may

cause more harm than good. Therefore, what is required is the prediction of risk of complications (such as eclampsia) of pre-eclampsia.

8.5 Conclusion

This project will collate and synthesise the available evidence regarding the value of the tests for predicting complications of pre-eclampsia. The systematic overviews will assess the quality of the available evidence and provide estimates of rate (or risk) of complications of pre-eclampsia given various patient characteristics and other findings. It will identify a set of tests that have maximal predictive value to aid in therapeutic decision-making. This will help to formulate practice recommendations and specific recommendations for future research.

CHAPTER 9: PROTEINURIA AS A PREDICTOR OF COMPLICATIONS IN PRE-ECLAMPSIA

9.1 Abstract

Background

Proteinuria is one of the essential criteria for the clinical diagnosis of pre-eclampsia. Increasing levels of proteinuria is considered to be associated with adverse maternal and fetal outcomes. We aim to determine the accuracy with which the amount of proteinuria predicts maternal and fetal complications in women with pre-eclampsia by systematic quantitative review of test accuracy studies.

Methods

We conducted electronic searches in MEDLINE (1951 to 2007), EMBASE (1980 to 2007), the Cochrane Library (2007) and the MEDION database to identify relevant articles and hand-search of selected specialist journals and reference lists of articles. There were no language restrictions for any of these searches. Two reviewers independently selected those articles in which the accuracy of proteinuria estimate was evaluated to predict maternal and fetal complications of pre-eclampsia. Data were extracted on study characteristics, quality and accuracy to construct 2×2 tables with maternal and fetal complications as reference standards.

Results

Sixteen primary articles with a total of 6749 women met the selection criteria with levels of proteinuria estimated by urine dipstick, 24-hour urine proteinuria or urine protein:creatinine ratio as a predictor of complications of pre-eclampsia. All 10 studies predicting maternal outcomes showed that proteinuria is a poor predictor of maternal complications in women with pre-eclampsia. Seventeen studies used laboratory analysis and eight studies bedside analysis to assess the accuracy of proteinuria in predicting fetal and neonatal complications. Summary likelihood ratios of positive and negative tests for the threshold level of 5g / 24h were 2.0 (95% CI 1.5, 2.7) and 0.53 (95% CI 0.27, 1) for stillbirths, 1.5 (95% CI 0.94, 2.4) and 0.73 (95% CI 0.39, 1.4) for neonatal deaths and 1.5 (95% 1, 2) and 0.78 (95% 0.64, 0.95) for Neonatal Intensive Care Unit admission. The area under the curve (AUC) for adverse maternal and fetal outcomes are 0.63 (95% CI 0.22, 0.91) and 0.59 (95% CI 0.36, 0.79) respectively.

Conclusion

Measure of proteinuria is a poor predictor of either maternal or fetal complications in women with pre-eclampsia.

Citation of paper from this work

Thangaratinam S, Coomarasamy A, O'Mahony F, Sharp S, Zamora J, Khan KS, Ismail KM. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med 2009 Mar 24; 7:10

9.2 Background

Proteinuria is one of the essential criteria for the clinical definition of pre-eclampsia. It is part of the fundamental investigations performed by healthcare professionals in primary and secondary care to monitor disease severity and predict complications in women with pre-eclampsia. Urinalysis by visual reagent strip tests is widely performed in antenatal clinics and in the community by various health professionals. Total protein estimation in a 24-hour urine sample is also frequently used to assess the severity of pre-eclampsia in patients admitted to the hospital. More recently, spot urine protein:creatinine ratio has been used to provide an accurate quantification of 24-hour proteinuria.[240] Estimation of the accuracy of the predictive value of proteinuria by any of the above methods in predicting maternal and fetal complications will aid in clinical management by identifying the highest risk women who may need aggressive management, and the lower risk women in whom unnecessary interventions may be avoided.

Proteinuria occurs due to renal glomerular endotheliosis, a manifestation of widespread endothelial damage in pre-eclampsia.[241] The association between proteinuria and adverse fetal outcomes was first highlighted by Page and Christianson.[242] Since then, increased excretion of protein in women with pre-eclampsia has been generally associated with adverse maternal and fetal outcomes.[243;244] However, the primary diagnostic studies that evaluate the association between increase in the levels of proteinuria and maternal and neonatal outcomes have not generally been conducted with sufficiently large sample size to provide precise accuracy estimates. Moreover, they vary widely in their definition of pre-eclampsia, maternal and fetal outcomes, the method used for measurement and optimal cut-off levels of proteinuria. There are no systematic reviews exploring the accuracy of proteinuria to predict complications of pre-eclampsia. We therefore conducted a comprehensive systematic review to obtain precise estimates of likelihood ratios of adverse maternal and fetal complications for various cut-off levels of proteinuria in women with pre-eclampsia.

9.3 Methods

The review was carried out with a prospective protocol using widely recommended methods described in Chapter 8, Section 8.3.

9.4 Results

9.4.1 Literature identification and study quality

Appendix 6 summarises the process of literature identification and selection. There were 16 primary articles that met the selection criteria including a total of 6749 women.[240;245-260] Eight articles reported estimation of proteinuria by laboratory method only[246;247;249;252;254;255;259;260], five by bedside dipstick urinalysis only[248;250;251;256;258], two by either of the above methods[253;257] and one by spot urine protein: creatinine ratio.[240]

The salient features (population subgroups, test characteristics and reference standards) of each individual study are provided in Appendix 21. The definition of pre-eclampsia differed widely between the studies. The test threshold in individual studies for laboratory estimation varied from 0.3g/24h to 10g/24h, or was reported as an increase in proteinuria by 2g/24h between two measurements. The cut-off levels for bedside urinalysis using visual reagents ranged from 1+ to 4+ of proteinuria. One study evaluated the accuracy of spot urine protein: creatinine ratio for threshold levels of 500mg/ mmol and 900mg/ mmol in the prediction of maternal and fetal complications.[240] The methodological quality of the included studies is given in Appendix 14.

9.4.2 Proteinuria to predict maternal outcomes

Table 9.1 summarises the accuracy estimates of various threshold levels of proteinuria in predicting adverse maternal outcomes.

Three primary studies evaluated the accuracy of proteinuria in predicting eclampsia in 5 2x2 tables for cut off levels of 5g/24h, 10g/24h and an increase by 2g in 24 hours.[249;252;255] The LR of positive test ranged from 1.7 (95% CI 0.94, 3.1) to 2.7 (95% CI 1.1, 6.2) respectively. The negative LR ranged from 0.54 (95% CI 0.06, 5.2) to 0.62 (95% CI 0.28, 1.4). The highest specificity 0.81 (95% CI 0.75, 0.86) was observed for cut off of 10g / 24 h and the highest sensitivity 67% was observed for cut offs of 5g / 24 h and an increase of 2g in 24 h.

Three primary studies estimated the accuracy of proteinuria in predicting placental abruption using a cut-off of increase in level more than 2g/24h.[246;249;255] The sensitivity of the 2 x 2 tables ranged between 0.29 (95% CI 0.19, 0.41) and 0.60 (95% CI 0.15, 0.95). The specificity varied from 0.59 to 0.77. Three of the 4 tables had specificity less than 70% and none had sensitivity above 60%.

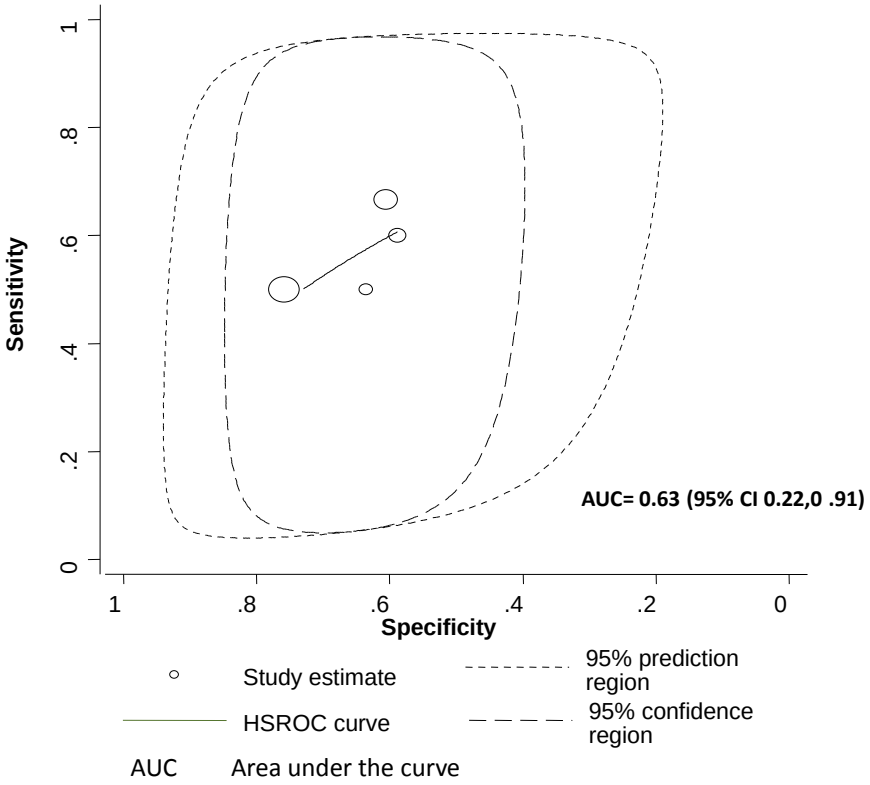
HELLP syndrome prediction was evaluated in three primary studies.[249;252;255] The sensitivity was less than 50% in all the studies with specificity more than 60% in all the studies. The LR of positive test ranged from 0.9 to 1.2. The negative LR varied from 0.96 to 1.1.

Table 9.1. Accuracy of proteinuria in the prediction of adverse maternal outcomes in women with pre eclampsia

Study Year	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Eclampsia					
Newman 2002	>5g	0.67(0.22,0.96)	0.60(0.54,0.67)	1.7(0.94,3.1)	0.55(0.18,1.7)
Hall 2002	>5g	0.50(0.07,0.93)	0.76(0.71,0.80)	2.1(0.76,5.6)	0.66(0.25,1.8)
Newman 2002	>10g	0.50(0.12,0.88)	0.81(0.75,0.86)	2.7(1.14,6.2)	0.62(0.28,1.4)
Schiff 1996	inc>2g	0.50(0.00,1.0)	0.67(0.51,0.75)	1.4 (0.19,10.0)	0.79(0.11,5.6)
Hall 2002	inc>2g	0.67(0.01,1.0)	0.62(0.50,0.73)	1.7(0.54,5.6)	0.54(0.06,5.2)
Abruption					
Buchbinder 2002	>5g	0.60(0.15,0.95)	0.59(0.49,0.69)	1.46(0.69,3.1)	0.69(0.23,2.0)
Hall 2002	>5g	0.29(0.19,0.41)	0.77(0.71,0.82)	1.25(0.81,1.9)	0.93(0.79,2.0)
Schiff 1996	inc>2g	0.40(0.05,0.85)	0.64(0.51,0.76)	1.11(0.36,3.4)	0.94(0.45,2.0)
Hall 2002	inc>2g	0.30(0.07,0.65)	0.59(0.45,0.72)	0.74(0.27,2.0)	1.2(0.75,1.9)
HELLP					
Newman 2002	>5g	0.47(0.302,0.65)	0.61(0.54,0.69)	1.22(0.82,1.81)	0.86(0.62,1.2)
Hall 2002	>5g	0.22(0.06,0.45)	0.76(0.70,0.80)	0.91(0.37,2.2)	1.03(0.80,1.3)
Newman 2002	>10g	0.22(0.10,0.39)	0.81(0.74,0.87)	1.17(0.59,2.3)	0.96(0.80,1.2)
Schiff 1996	inc>2g	0.33(0.10,0.65)	0.63(0.49,0.76)	0.9 (0.38,2.2)	1.06(0.68,1.7)
Hall 2002	inc>2g	0.33(0.00,1.0)	0.60(0.48,0.72)	0.84(0.09,8.2)	1.11(0.35,3.5)

The area under the curve (AUC) for adverse maternal outcomes is 0.63 (95% CI 0.22, 0.91) (Fig 9.1).

Fig 9.1. Area under the curve for predicting adverse maternal outcome by proteinuria in pre eclampsia



9.4.3 Proteinuria to predict fetal outcomes

Fetal, neonatal and perinatal mortality

Thirteen studies reported prediction of fetal, neonatal and perinatal mortality using both laboratory and bedside testing for proteinuria.[240;246;247;252;254-256;260;261] The largest study, involving 3260 patients that estimated the prediction of stillbirths in pre-eclampsia was conducted by Taylor et al using urine dipstick method.[262] The highest specificity (0.91, 95% CI 0.87, 0.94) was observed for cut off levels of PCR 500 mg/mmol for perinatal mortality. The highest sensitivity (1, 95% CI 0.29, 1) was reported for stillbirths for levels of 5g/24h proteinuria. (Table 9.2)

Table 9.2. Accuracy of proteinuria in the prediction of adverse fetal outcomes in women with pre eclampsia

Study Year	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Small for gestational age					
Lao 1988	1+	0.68(0.43,0.87)	0.52(0.40,0.64)	1.4(0.95,2.1)	0.61(0.30,1.24)
Odegaard 2000	2+	0.84(0.68,0.94)	0.40(0.30,0.42)	1.3(1.1,1.5)	0.45(0.21,1.0)
Brown 1996	2+	0.75(0.67,0.81)	0.18(0.15,0.21)	0.9(0.83,1.0)	1.39(1.01,1.91)
Odegaard 2000	3+	0.46(0.30,0.63)	0.76(0.70,0.81)	1.9(1.3,2.8)	0.72(0.53,0.97)
Furukawa 2006	3+	0.50(0.33,0.67)	0.61(0.45,0.76)	1.3(0.8,2.1)	0.82(0.55,1.23)
Waugh 2005	0.5g/24hBCA	0.47(0.30,0.65)	0.73(0.65,0.79)	1.7(1.11,2.7)	0.73(0.52,1.01)
Waugh 2005	0.3g/24hBCA	0.68(0.50,0.83)	0.30(0.23,0.38)	0.96(0.75,1.24)	1.09(0.63,1.86)
Buchbinder 2002	5g/24h	0.63(0.25,0.92)	0.60(0.49,0.69)	1.55(0.86,2.79)	0.63(0.25,1.56)
Neonatal death					
Newman 2002	5g/24h	0.56(0.21,0.86)	0.61(0.53,0.67)	1.4(0.77,2.59)	0.74(0.35,1.54)
Buchbinder 2002	5g/24h	1.0(0.03,1.0)	0.59(0.49,0.68)	1.80(0.79,4.1)	0.43(0.04,4.75)
Fleigner 1975	5g/24h	0.50(0.01,0.99)	0.59(0.48,0.69)	1.21(0.30,4.95)	0.85(0.21,3.44)
Hall 2002	5g/24h	0.10(0.00,0.45)	0.75(0.70,0.80)	0.40(0.06,2.61)	1.20(0.97,1.49)
Newman 2002	10g/24h	0.33(0.08,0.70)	0.81(0.75,0.86)	1.75(0.67,4.62)	0.82(0.52,1.31)
Hall 2002	inc>2g	0.00(0.00,0.71)	0.59(0.47,0.70)	0.31(0.02,4.14)	1.48(0.98,2.25)
Perinatal mortality					
Fleigner 1975	5g/24h	0.64(0.35,0.87)	0.62(0.51,0.73)	1.71(1.06,2.75)	0.57(0.28,1.18)
Brown 1996	2+	0.40(0.12,0.74)	0.19(0.16,0.22)	0.49(0.23,1.05)	3.18(1.88,5.37)
Paladini 1970	1g/l	0.54(0.43,0.65)	0.44(0.38,0.50)	0.96(0.77,1.21)	1.05(0.80,1.37)
Paladini 1970	2g/l	0.36(0.25,0.47)	0.64(0.59,0.70)	1.01(0.72,1.40)	1.0(0.83,1.20)
Chan 2004	PCR 500mg/ mmol	0.50(0.01,0.99)	0.91(0.87,0.94)	5.32(1.28,22.15)	0.55(0.14,2.21)
Intra uterine death					
Buchbinder 2002	5g/24h	1.0(0.29,1.0)	0.60(0.50,0.70)	2.16(1.40,3.35)	0.21(0.02,2.82)
Fleigner 1975	5g/24h	0.67(0.35,0.90)	0.62(0.51,0.72)	1.76(1.09,2.85)	0.54(0.24,1.22)
Hall 2002	5g/24h	0.50(0.01,0.99)	0.76(0.71,0.80)	2.06(0.51,8.35)	0.66(0.17,2.64)
Taylor 1954	1+	0.65(0.59,0.71)	0.51(0.49,0.52)	1.31(1.19,1.45)	0.69(0.59,0.82)
Taylor 1954	3+	0.36(0.30,0.42)	0.84(0.83,0.86)	2.26(1.89,2.72)	0.77(0.70,0.84)
Neonatal intensive care unit admission					
Newman 2002	5g/24h	0.44(0.36,0.52)	0.73(0.57,0.85)	1.60(0.96,2.67)	0.78(0.62,0.97)
Buchbinder 2002	5g/24h	0.52(0.33,0.70)	0.62(0.50,0.73)	1.35(0.87,2.11)	0.78(0.52,1.17)
Hall 2002	5g/24h	0.24(0.17,0.32)	0.52(0.42,0.62)	0.50(0.35,0.71)	1.47(1.19,1.80)
Newman 2002	10g	0.26(0.19,0.34)	0.95(0.87,1.0)	5.59(1.79,17.45)	0.77(0.69,0.87)
Hall 2002	inc>2g	0.50(0.26,0.74)	0.64(0.50,0.77)	1.40(0.78,2.50)	0.78(0.47,1.28)
Lao 1988	1+	0.70(0.35,0.93)	0.49(0.38,0.61)	1.38(0.87,2.19)	0.61(0.23,1.61)

Neonatal deaths were evaluated in five studies for cut-off levels of 5g/24h (*n*=3),[246;247;252] 10g/24h (*n*=1)[252] and increase by 2g in 24h (*n*=1).[261] The specificity was more than 60% in 3 of the 5 studies and the sensitivity was more than 60% in 1 study.

The threshold levels of proteinuria to predict perinatal deaths were 1g/l, 2g/l and 500 mg/ mmol. The positive LR was 5.3 (95% CI 1.3, 22.1) and the negative LR was 0.55 (95% CI 0.14, 2.2) for cut-off levels of 500mg/ mmol.[240]

Small for gestational age

Small for gestational age is the commonest outcome reported in 8 2x2 tables. Three primary studies assessed the accuracy of bedside urinalysis for cut-offs of 1+, 2+ and 3+ of proteinuria in urine dipstick.[248;250;253] The likelihood ratio of laboratory estimates of proteinuria levels of 0.3g/24h and 0.5g/24h were 0.96 (95% CI 0.75, 1.2) and 1.7 (95% CI 1.1, 2.7) for positive test and 1.09 (95% 0.63, 1.9) and 0.73 (95% CI 0.52, 1) for negative test respectively, using the benzethonium chloride assay (BCA).[259] The sensitivity was higher for levels of proteinuria less than 3+ or 0.5 g/24h compared low cut off levels. The specificity was high with increasing levels of proteinuria for predicting small for gestational age fetus.

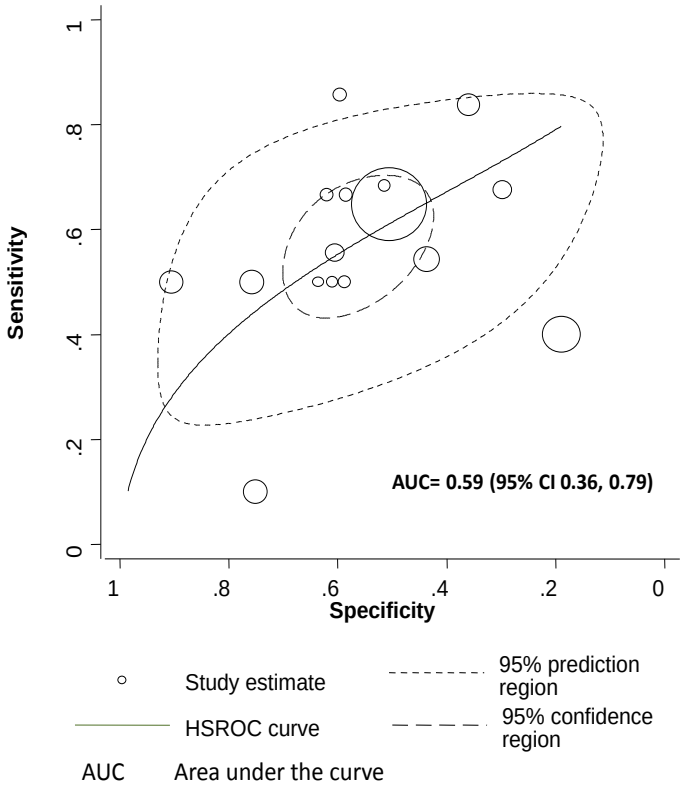
Neonatal Intensive Care Unit (NICU) admission

NICU admission was assessed as an outcome in 6 2x2 tables.[246;250;252;261] The highest specificity (0.95, 95% CI 0.87,1.0) and positive likelihood ratio (5.59, 95% CI 1.79,17.45) were observed for

levels of 10g/24h proteinuria. Urine dipstick of 1+ had the highest sensitivity (0.70, 95% CI 0.35, 0.93) in predicting NICU admission.

The area under the curve (AUC) for adverse fetal outcomes is 0.59 (95% CI 0.36, 0.79) (Fig 9.2).

Fig 9.2. Area under the curve for predicting adverse fetal outcome by proteinuria in pre eclampsia



9.5 Discussion

Proteinuria has usually been associated with increase in maternal and fetal mortality and morbidity.[244] Our review has shown that the magnitude of proteinuria in women with pre-eclampsia is a poor predictor of the major maternal and fetal complications.

For prediction of adverse fetal outcomes, the only statistically significant results were observed for positive test result with LR+ ranging from 1.3 to 2.3 for cut-off levels of 5g/24h, 1+ and 3+ proteinuria in the prediction of stillbirths.[246;247;256;261] Furthermore, we need to take into account that three of these five test accuracy studies were conducted more than 30 years ago.[247;256] The test was found to be a poor predictor of neonatal and perinatal deaths with no significant LRs for positive or negative test. The test performed poorly as evidenced by the increase in adverse events noticed in the test negative group compared with the test positive group, as noticed in some studies.[254;259;261] The overall low value of abnormal test and high value of normal test implies that the test is of 'very little' clinical value.

The validity of our review findings depends on the methodology of the systematic review and the quality of the individual studies included.[232] An extensive literature search was performed in relevant databases without any language restrictions to minimize the possibility of missing any studies. Methodological deficiencies such as verification bias and differential use of reference standards did not apply to the studies in the review, ensuring inclusion of studies of acceptable quality.

The methodological problems facing reviews of this nature are daunting. A significant limitation of this review is the heterogeneity noticed between individual studies with regards to population, definition of pre-eclampsia, method of performing the test, test thresholds, frequency of testing, interval between the test and outcome, and reference standards. The lack of information regarding the temporal relation between test findings and outcomes observed and possibility of confounding by other risk factors contributing to maternal and fetal complications may influence the observed predictive value of proteinuria for maternal and fetal complications. The wide confidence intervals

observed for the various outcomes are a reflection of the statistical uncertainty around the results due to the small sample size in many studies. Meta-analysis of studies using individual patient data may conquer many of the difficulties identified.

9.6 Conclusion

This systematic review has shown that estimation of levels of proteinuria in women is not a clinically useful test to predict fetal or maternal complications. The results of this review calls into question the commonly used practice of making clinical decisions in women with pre-eclampsia based on the severity of proteinuria. It has highlighted the need for large, well-designed prospective studies on this important question with the hope to expand future research.

CHAPTER 10: SERUM URIC ACID AS A PREDICTOR OF COMPLICATIONS IN PRE ECLAMPSIA

10.1 Abstract

Background

Uric acid is considered to be a clinical indicator of severity of disease in pre eclampsia. Through the systematic review we aim to determine the accuracy with which serum uric acid predicts maternal and fetal complications in women with pre eclampsia.

Methods

We conducted electronic searches in MEDLINE (1951-2004), EMBASE (1980-2004), the Cochrane Library (2004:4) and the MEDION database to identify relevant articles. A hand-search of selected specialist journals and reference lists of articles obtained was then carried out. There were no language restrictions for any of these searches. Two reviewers independently selected those articles in which the accuracy of serum uric acid was evaluated to predict maternal and fetal complications of pre eclampsia. Data were extracted on study characteristics, quality and accuracy to construct 2 x 2 tables with maternal and fetal complications as reference standard.

Results

There were 18 primary articles that met the selection criteria, including a total of 3675 women. The sensitivity of uric acid was higher than specificity in 9/15 (60%) and 13 /20 (65%) 2x2 tables predicting adverse maternal and fetal outcomes respectively. The area under the curve for adverse maternal and fetal outcomes were 0.75 (95% CI 0.46, 0.92) and 0.69 (0.39, 0.86) respectively.

Conclusion

Serum uric acid is a moderate predictor of adverse outcomes in pre eclampsia with better performance for maternal than fetal outcomes.

Citation of paper from this work

Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS; Tests in Prediction of Pre-eclampsia Severity review group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG. 2006;113:369-78.

10.2 Background

Hyperuricemia is one of the characteristic findings in pre-eclampsia. In clinical practice, uric acid determination is considered to be a part of the workup in patients with pre-eclampsia to monitor disease severity and aid management of the patients. The association between raised serum uric acid and pre-eclamptic pregnancy was first reported in 1917.[263] Reduced uric acid clearance secondary to reduced glomerular filtration rate, increased reabsorption and decreased secretion may be the reasons for elevated serum uric acid levels in women with pre-eclampsia.[264;265] The pathophysiologic mechanisms of pre-eclampsia comprising of increased trophoblastic tissue shedding, endothelial dysfunction, reduced blood flow in the feto-maternal unit have also been hypothesized as the underlying cause of hyperuricemia in this condition.[266]

Several studies have reported a positive correlation between elevated maternal serum uric acid levels and adverse maternal and fetal outcomes.[267-270] However, these primary diagnostic studies have not generally been conducted with large enough sample size to provide precise accuracy estimates and they vary widely in their definition of pre-eclampsia, maternal and fetal outcomes, and optimal cut off levels of uric acid in predicting maternal and fetal complications. There are no systematic reviews exploring the accuracy of uric acid to predict *complications* of pre-eclampsia. We therefore conducted a comprehensive systematic review to obtain precise estimates of maternal serum uric acid levels to predict maternal and fetal complications in women with pre-eclampsia.

10.3 Methods

The review was carried out with a prospective protocol using widely recommended methods as described in Chapter 8, section 8.3.

10.4 Results

10.4.1 Literature identification and study quality

Appendix 7 flow chart summarises the process of literature identification and selection.

There were 18 primary articles that met the selection criteria including a total of 3675 women.[245;251;265;267;268;271-283] Each study's salient features according to the population subgroups, test characteristics and reference standards are provided in Appendix 22. The definition of pre-eclampsia differed widely between the studies (2x2 tables). The most common cut off of uric acid was 6mg/dl (350 µmol/ l). The commonest maternal and fetal outcomes assessed were severity of hypertension and small for gestational age respectively. The methodological quality of the included studies is given in Appendix 14.

10.4.2 Uric acid to predict maternal outcomes

Eclampsia was evaluated as an outcome in three studies using a cut off level of 6mg/dl.[265;267;283] The sensitivity ranged between 0.36 (95% CI 0.17, 0.59) and 0.92 (95% CI 0.64, 1.0) and specificity from 0.54 (95% CI 0.44, 0.65) to 0.95 (95% CI 0.83, 1.0).

Six studies estimated the accuracy of uric acid levels more than or equal to 6mg/dl in predicting severe hypertension. The sensitivity and specificity were more than 70% in 5/8 and 4/8 studies respectively. Caesarean section was studied as an outcome using 3 cut offs, 6mg/dl, 5mg/dl and 8.5 mg/dl. The sensitivity and specificity were more than 60% in 3 of the four studies. The positive LR varied from 1.33 (95% CI 0.58, 3.04) to 2.64 (95% CI 1.44, 4.83) and the negative LR from 0.19 (95% CI 0.03, 1.25) to 0.97 (95% CI 0.88, 1.06).

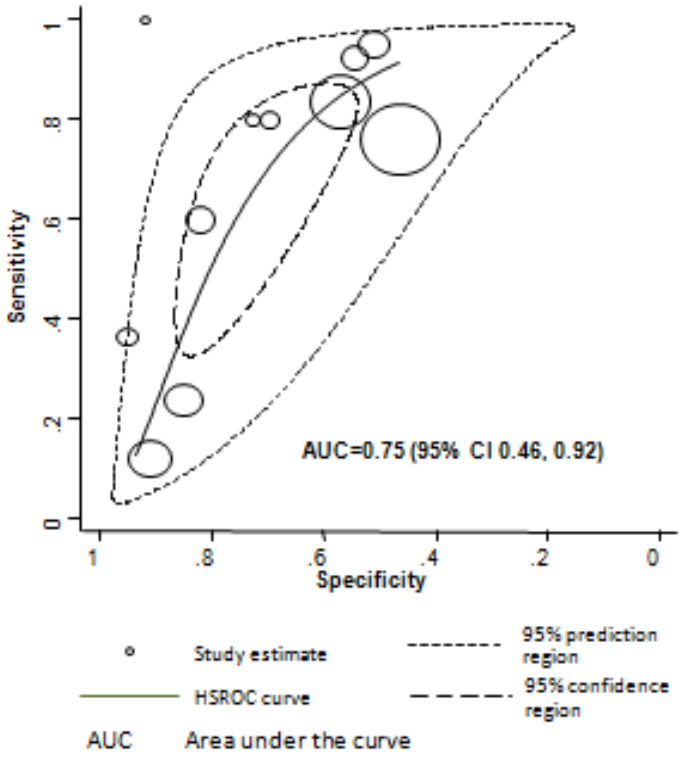
Two studies evaluated the prediction of HELLP syndrome using 7.6 mg/dl and 9mg/dl threshold levels. The LRs for predicting HELLP syndrome with a threshold of 7.6 mg/dl were 1.6 (95% CI 0.84, 2.9) and 0.90 (95% CI 0.76, 1.1) and with a threshold of 9mg/dl were 1.9 (95% CI 0.85, 4.2) and 0.92 (95% CI 0.81, 1.0).

Table 10.1 Accuracy of uric acid in the prediction of adverse maternal outcomes in women with pre eclampsia

Study Year	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Eclampsia					
Fadel 1969	6mg/dl	0.36(0.17,0.59)	0.95(0.83,1.0)	7.27(1.69,31.30)	0.67(0.49,0.93)
Yassaee 2003	6mg/dl	0.92(0.64,1.0)	0.54(0.44,0.65)	2.03(1.54,2.67)	0.14(0.02,0.94)
Lancet 1956	6mg/dl	0.84(0.70,0.93)	0.57(0.52,0.62)	1.94(1.65,2.29)	0.29(0.15,0.54)
Caesarean Section					
Liedholm 1984	6mg/dl	0.89(0.52,0.10)	0.59(0.33,0.82)	2.16(1.17,3.99)	0.19(0.03,1.25)
Yassaee 2003	6mg/dl	0.70(0.56,0.81)	0.73(0.57,0.85)	2.55(1.53,4.25)	0.42(0.27,0.64)
Odendaal 1996	8.7mg/dl	0.12(0.07,0.18)	0.91(0.82,0.96)	1.33(0.58,3.04)	0.97(0.88,1.06)
Dequiedt 1979	5mg/dl	0.80(0.44,0.98)	0.70(0.51,0.84)	2.64(1.44,4.83)	0.29(0.08,1.01)
Severe Hypertension					
Williams 2002	7.6mg/dl	0.25(0.16,0.38)	0.86(0.79,0.91)	1.79(0.99,3.24)	0.87(0.74,1.02)
Liedholm 1984	6mg/dl	0.80(0.52,0.96)	0.73(0.39,0.94)	2.93(1.08,7.96)	0.28(0.09,0.81)
Voto 1988	6 mg/dl	0.60(0.39,0.79)	0.82(0.73,0.89)	3.33(1.97,5.65)	0.49(0.30,0.80)
Lancet 1956	6mg/dl	0.69(0.60,0.77)	0.60(0.54,0.65)	1.70 (1.43,2.04)	0.52(0.39,0.69)
Connon 1968	6mg/dl	0.95(0.75,0.10)	0.51(0.41,0.61)	1.94(1.55,2.41)	0.10(0.01,0.67)
Brown 1996	6mg/dl	0.76(0.69,0.82)	0.46(0.43,0.50)	1.42 (1.27,1.58)	0.52(0.39,0.68)
Seitchik 1953	6mg/dl	1.00(0.16,1.0)	0.92(0.62,0.10)	7.22(1.48,35.34)	0.19(0.02,2.38)
Peralta Pedero 2004	3 mg/dl	0.78 (0.7,0.84)	0.32(0.21,0.45)	1.1(0.94,1.4)	0.7(0.44,1.1)
HELLP					
Williams 2002	7.6mg/dl	0.24(0.13,0.37)	0.85(0.78,0.90)	1.6 (0.84,2.90)	0.90(0.76,1.06)
Williams 2002	9 mg/dl	0.16(0.08,0.29)	0.91(0.85,0.96)	1.9(0.85,4.2)	0.92(0.81,1)

The AUC for predicting adverse maternal outcome was 0.75 (95% CI 0.46, 0.92). (Fig 10.1)

Fig 10.1 Area under the curve for predicting adverse maternal outcome by uric acid in pre eclampsia



10.4.3 Uric acid to predict fetal outcomes

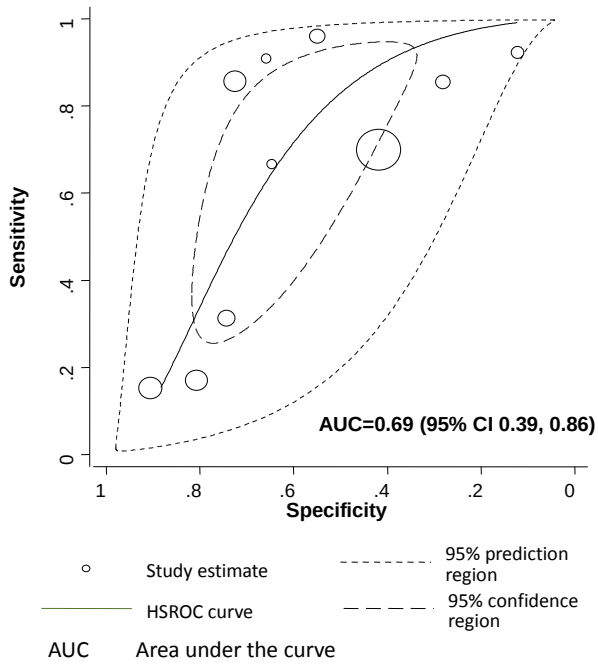
Seven studies evaluated the accuracy of uric acid to predict stillbirth or neonatal deaths for various threshold levels (Table 10.2). The positive LR was between 1.05 (95% CI 0.83, 1.33) and 3.12 (95% CI 2.14 ,4.56). The negative LR ranged from 0.07 (95% CI 0.01, 1.11) to 0.94 (95% CI 0.83, 1.05). The sensitivity was above 70% in 5 of the 7 studies and specificity more than 70% in 2/7 studies.

Table 10.2 Accuracy of uric acid in the prediction of adverse fetal outcomes in women with pre eclampsia

Study Year	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Still birth or neonatal death					
Varma 1982	5.5mg	0.86(0.42,1.00)	0.73(0.66,0.79)	3.12(2.14,4.56)	0.20(0.03,1.21)
Yassaee 2003	6mg	0.96(0.68,1.00)	0.55(0.44,0.65)	2.13(1.65,2.75)	0.07(0.01,1.11)
Odendaal 1996	8.7mg	0.15(0.07,0.27)	0.91(0.85,0.95)	1.62(0.76,3.47)	0.94(0.83,1.05)
Mathews 1980	6mg	0.67(0.22,0.96)	0.65(0.47,0.80)	1.89(0.91,3.90)	0.52(0.16,1.64)
Dequiedt 1979	5mg	0.91(0.41,1.00)	0.66(0.49,0.80)	2.66(1.59,4.44)	0.14(0.01,1.97)
Brown 1996	6mg	0.70(0.35,0.93)	0.42(0.38,0.45)	1.20(1.80,1.81)	0.72(0.28,1.86)
Sagen 1984	6mg	0.92(0.47,1.00)	0.12(0.05,0.23)	1.05(0.83,1.33)	0.64(0.04,9.84)
Small for gestational age					
Williams 2002	7.6mg/dl	0.17(0.08,0.31)	0.81(0.74,0.87)	0.89(0.44,1.80)	1.03(0.88,1.19)
Varma 1982	60 inc	0.52(0.37,0.67)	0.77(0.70,0.84)	2.30(1.54,3.43)	0.62(0.45,0.85)
Voto 1988	6mg/dl	0.31(0.11,0.59)	0.74(0.65,0.82)	1.22(0.55,2.70)	0.93(0.65,1.31)
D'Anna 2000	6mg/dl	0.86(0.74,0.93)	0.28(0.14,0.47)	1.19(0.94,1.51)	0.52(0.23,1.17)
Yassaee 2003	6mg/dl	0.70(0.56,0.81)	0.73(0.57,0.85)	2.55(1.53,4.25)	0.42(0.27,0.64)
Odendaal 1996	8.7mg/dl	0.09(0.04,0.15)	0.87(0.79,0.92)	0.65(0.31,1.39)	1.05(0.96,1.15)
Dequiedt 1979	5mg/dl	0.75(0.35,0.97)	0.66(0.48,0.81)	2.19(1.19,4.02)	0.38(0.11,1.29)
Sagen 1984	6mg/dl	1.0(0.90,1.0)	0.21(0.10,0.37)	1.26(1.06,1.50)	0.07(0.00,1.10)
Brown 1996	6mg/dl	0.71(0.63,0.78)	0.45(0.41,0.49)	1.29(1.14,1.45)	0.65(0.50,0.84)
Intra uterine death					
Varma 1982	5. 5mg/dl	1.0(0.16,1.00)	0.71(0.64,0.77)	2.88(1.66,5.00)	0.23(0.02,2.95)
Yassaee 2003	6mg/dl	1.00(0.74,1.00)	0.55(0.44,0.65)	2.13(1.66,2.74)	0.07(0.01,1.07)
Odendaal 1996	8.7mg/dl	0.17(0.04,0.41)	0.90(0.85,0.93)	1.60(0.53,4.83)	0.93(0.75,1.15)
Dequiedt 1979	5mg/dl	1.00(0.48,1.00)	0.66(0.49,0.80)	2.65(1.62,4.34)	0.13(0.01,1.83)

Uric acid showed moderate sensitivity and specificity (>70%) in 60% (5/8) of the studies. Four studies evaluated the accuracy of uric acid to predict intra uterine death, with high sensitivity (>90%) in 75% of the studies. The high specificity was observed in 25% of the studies. The AUC for adverse fetal outcome was 0.69 (95% CI 0.39, 0.86) as seen in Fig 10.2.

Fig 10.2 Area under the curve for predicting adverse fetal outcome by uric acid in pre eclampsia



10.5 Discussion

This review presents the best available evidence so far in addressing the question of significance of uric acid levels as a predictor of maternal and fetal complications in pre-eclampsia. Although uric acid as a marker may be of value in detecting pre-eclampsia,[284] it has been identified as a poor predictor of any complications of pre-eclampsia. The provision of likelihood ratios stratified by the severity of pre-eclampsia and test thresholds will enable clinicians to understand the poor clinical value of this test in predicting complications in women with pre-eclampsia.

The validity of our review findings depends on the methodology of the systematic review and the quality of the individual studies included.[55;232] An extensive literature search was performed in relevant databases without any language restrictions to minimise the possibility of missing any studies. Methodological deficiencies like verification bias, differential use of reference standards and case control design did not apply to the studies in the review ensuring inclusion of acceptable quality studies. A significant limitation of this review is the heterogeneity noticed between individual studies with regards to population, definition of pre-eclampsia, test thresholds, frequency of testing, interval between the test and outcome, and reference standards. This led us to analyse data within subgroups defined by severity of pre-eclampsia and threshold levels, resulting in the inclusion of a small number of studies in the subgroup meta-analyses.

Caution is needed in interpreting quantitative estimation of uric acid levels in relation to outcome. Apart from the variations in the methods for estimating uric acid levels, levels of uric acid could be raised due to the use of anti-hypertensives.[275] The outcomes could also be influenced by the different therapeutic interventions such as use of antenatal steroids in reducing respiratory distress syndrome[285] and anti-hypertensives[286] that might help to reduce fetal and maternal complications. Moreover, it is not possible to be certain of the finding where only a small number of studies exist in a subgroup, due to imprecision.

Our review has consistently observed poor performance of uric acid in predicting various maternal and fetal outcomes, across various studies, settings and population. The consistency of such poor performance of uric acid in predicting complications in those with pre-eclampsia cannot be ignored. The predictive value of a positive test was particularly poor for some fetal outcomes like stillbirths and neonatal deaths. The confidence intervals of the pooled LRs for a positive result extended to 1

or less than 1, suggesting the possibility of finding the same or more number of complications in those with normal urate levels compared to raised levels. The same anomaly was seen for a negative test result in predicting stillbirths and neonatal deaths (Table 10.2).

10.6 Conclusion

Given our results, uric acid does not seem to be a significant predictor of individual adverse maternal or fetal outcomes. The predictive capability is slightly better for composite adverse maternal outcome than fetal outcomes.

CHAPTER 11: LIVER FUNCTION TEST AS A PREDICTOR OF COMPLICATIONS IN PRE ECLAMPSIA

11.1 Abstract

Background

Liver function tests are considered to be markers of severity of pre eclampsia. This review aims to determine the accuracy with which liver function tests (LFTs) predict maternal and fetal complications in women with pre-eclampsia.

Methods

We performed systematic quantitative review of test accuracy studies. We conducted electronic searches without language restrictions in Medline (1951-2008), Embase (1980-2008), the Cochrane Library (2008) and MEDION databases and hand-searched specialist journals and reference lists of known relevant articles. Two reviewers independently selected articles and extracted data on study characteristics, quality and accuracy to construct 2 X 2 tables with maternal and fetal complications as separate reference standards. A bivariate model estimated area under summary Receiver Operating Characteristic curve (AUC), sensitivity and specificity.

Results

There were 13 primary articles selected including a total of 2813 women in 49 2 x 2 tables, 30 assessing maternal adverse outcomes and 19 assessing adverse fetal outcomes. LFTs assessed included AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), LDH (Lactate dehydrogenase), GGT (Gamma glutamyltransferase) and bilirubin. Studies usually did not provide

results of each analyte separately. The commonest maternal outcome assessed was eclampsia and the commonest fetal outcome evaluated was neonatal death. For predicting adverse maternal outcome, the Area Under the Curve (AUC) was 0.79 (95% CI 0.51, 0.93). For predicting adverse fetal outcomes the AUC was 0.65 (95% CI 0.26, 0.9). Sensitivity of the test was poor for both maternal and fetal outcomes with higher specificity.

Conclusion

LFTs performed moderately in predicting adverse fetal and maternal outcomes in women with pre eclampsia. Increased liver enzymes increase the probability of maternal and fetal complications, but normal liver enzymes do by no means rule out disease.

11.2 Background

Liver enzymes, aspartate aminotransferase (AST) or serum glutamic oxalocetic transaminase (SGOT) and alanine aminotransferase (ALT) or serum glutamic pyruvic transaminase (SGPT) are often raised in pre-eclampsia. The clinical manifestations of liver involvement are right upper quadrant or epigastric pain, elevated liver enzymes, and in severe cases, subcapsular hemorrhage or hepatic rupture. Hemolysis, Elevated Liver functions, and Low Platelets (HELLP) syndrome is diagnosed in 10 – 20 % of women with severe pre-eclampsia. Liver function tests (LFTs) are part of the routine workup to monitor disease severity to aid management of the patients.

Several studies have reported a positive correlation between elevated maternal serum liver enzyme levels and adverse maternal and fetal outcomes.[287-289] However, these studies have not generally been conducted with large enough sample size to provide precise accuracy estimates and they vary widely in their definition of pre-eclampsia and maternal and fetal outcomes. There are no systematic reviews exploring the accuracy of liver enzymes to predict complications of pre-eclampsia. We therefore conducted a comprehensive systematic review to obtain precise estimates of maternal serum liver enzyme levels to predict maternal and fetal complications in women with pre-eclampsia.

11.3 Methods

The review was carried out with a prospective protocol[290] using widely recommended methods as described in Chapter 8, Section 8.3.

11.4 Results

11.4.1 Literature identification and study quality

Appendix 8 flow chart summarises the process of literature identification and selection. There were 13 primary articles that met the selection criteria, consisting of 42 2 x 2 tables including a total of 2813 women.[251;287;289;291-300] Each study's salient features are provided in Appendix 23. Methodological quality of included studies (Appendix 14) showed that the index tests and reference standard (maternal and fetal outcomes) were adequately described in 3 (23 %) and 5 (38 %) out of 13 studies respectively. Five of the 13 studies were prospectively conducted and none of the studies were blinded for outcome measurement.[287;291;294-296]

11.4.2 Liver function tests to predict maternal outcomes

Thirteen primary studies evaluated accuracy of liver function tests (LFT) to predict adverse maternal outcomes in 30 2x2 tables.[251;275;287;289;291-297;299;300] Eclampsia was the commonest reported adverse outcome. The accuracy of LFT to predict adverse maternal outcome ranged from 0.04 (95% CI 0, 0.34) to 0.95 (95% CI 0.63, 1) for sensitivity and from 0.17 (95% CI 0.14, 0.20) to 0.97 (95% CI 0.93, 0.99) for specificity respectively. The highest sensitivity of 0.95 (95% CI 0.63, 1) was noted for raised levels of either LDH (600 U/l) or AST (70 U/l) or ALT (70 U/l) to predict DIC.[293] The highest specificity of 0.97 (95% CI 0.93, 0.99) was observed for increased levels of AST or ALT for prediction of eclampsia.[291] The best predicted likelihood ratio of a positive test was 9.11 (95% CI 3.26, 25.45)[291] and best predicted likelihood ratio of a negative test was 0.12 (95% CI 0.01, 1.77)[295] for raised levels of ALT or AST (Table 11.1). The AUC for predicting any adverse maternal outcome was 0.79 (95% CI 0.51, 0.93) (Fig 11.1).

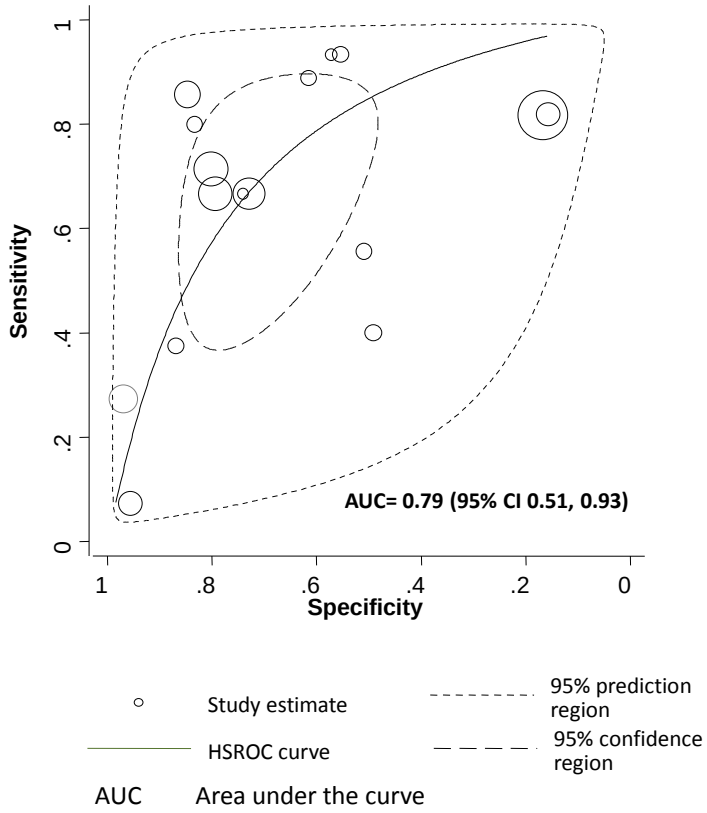
Table 11.1 Accuracy of liver function tests in the prediction of adverse maternal outcomes in women with pre eclampsia

Study Year	Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Eclampsia						
Borglin 1958	AST/ALT	Increased	0.67(0.02,1)	0.74(0.54,0.89)	2.6(0.70,9.4)	0.45(0.05,4.4)
Crisp 1959	AST	70	0.93(0.52,1)	0.55(0.41,0.69)	2.1(1.5,3)	0.12(0.01,1.8)
Romero 1988	AST	2SD	0.71(0.29,0.96)	0.80(0.75,0.85)	3.6(2.1,6.1)	0.36(0.11,1.2)
Aali 2004	AST/ALT	500/300	0.27(0.13,0.46)	0.97(0.93,0.99)	9.1(3.3,25.5)	0.75(0.61,0.93)
Audibert 1996*	LDH/AST/ALT	600/70/70	0.27(0.11,0.50)	0.73(0.66,0.78)	1(0.49,2.0)	1.0(0.77,1.31)
Abramovici 1999*	AST	70	0.13(0.05,0.26)	0.86(0.76,0.93)	0.94(0.37,2.4)	1(0.87,1.2)
Haddad 2000*	LDH/AST/ALT	600/70/70	0.56(0.21,0.86)	0.51(0.37,0.65)	1.1(0.59,2.2)	0.87(0.40,1.90)
Woldesellasie 2005	AST	43	0.82(0.48,0.98)	0.16(0.10,0.23)	0.97(0.73,1.3)	1.2(0.31,4.3)
Woldesellasie 2005	ALT	60	0.04(0,0.34)	0.97(0.92,0.99)	1.3(0.07,23.4)	0.99(0.87,1.1)
Woldesellasie 2005	LDH	180	0.70(0.35,0.93)	0.84(0.77,0.90)	4.5(2.5,8)	0.36(0.14,0.92)
Pulmonary oedema						
Romero 1988	AST	2SD	0.67(0.09,0.99)	0.79(0.74,0.84)	3.2(1.4,7.5)	0.42(0.08,2.1)
Audibert 1996*	LDH/AST/ALT	600/70/70	0.50(0.19,0.81)	0.73(0.67,0.79)	1.9(0.97,3.6)	0.68(0.37,1.3)
Haddad 2000*	LDH/AST/ALT	600/70/70	0.67(0.22,0.96)	0.52(0.38,0.65)	1.4(0.74,2.6)	0.64(0.2,2.1)
Adverse maternal outcome						
Martin Jr 1999*	AST	150	0.70(0.63,0.77)	0.48(0.43,0.53)	1.4(1.2,1.5)	0.62(0.48,0.8)
Martin Jr 1999*	LDH	1400	0.72(0.65,0.79)	0.49(0.44,0.54)	1.4(1.2,1.6)	0.57(0.44,0.74)
Martin Jr 1999*	ALT	100	0.66(0.59,0.73)	0.47(0.42,0.52)	1.2(1.1,1.4)	0.72(0.57,0.91)
Girling 1997	AST/ALT/Bil/GGT	30/32/14/	0.93 (0.52,1)	0.57(0.37,0.76)	2.2 (1.4,3.5)	0.12 (0.01,1.7)
Menzies 2007	ALT/AST	40/55	0.33(0.22,0.45)	0.80(0.77,0.84)	1.7(1.2,2.4)	0.83(0.71,0.99)
Menzies 2007	LDH	600	0.62(0.49,0.74)	0.60(0.56,0.64)	1.6(1.3,1.9)	0.63(0.46,0.86)
Abruption						
Odendaal 2000*	LDH	350	0.07(0.02,0.16)	0.96(0.88,0.99)	1.7(0.41,6.7)	0.97(0.89,1.1)
Audibert 1996*	LDH/AST/ALT	600/70/70	0.40(0.16,0.68)	0.73(0.67,0.79)	1.5(0.78,2.9)	0.82(0.54,1.2)
Haddad 2005*	LDH/AST/ALT	600/70/70	0.40(0.05,0.85)	0.49(0.36,0.63)	0.79(0.26,2.4)	1.2(0.57,2.6)
Maternal death						
Audibert 1996*	LDH/AST/ALT	600/70/70	0.67(0.02,1)	0.73(0.67,0.78)	2.5(0.78,7.8)	0.46(0.05,4.4)
Abramovici 1999*	AST	70	0.80(0.12,1)	0.83(0.71,0.92)	4.8(2.1.11.1)	0.24(0.02,2.8)
Yucesoy 2005	AST/ALT/LDH	Increased	0.86(0.23,1)	0.85(0.78,0.90)	5.6(3.19,9.7)	0.17(0.01,2.2)
Disseminated Intravascular Coagulation						
Audibert 1996*	LDH/AST/ALT	600/70/70	0.95(0.63,1)	0.76(0.70,0.81)	3.9(3.0,5.1)	0.06(0.00,0.94)
Haddad 2000*	LDH/AST/ALT	600/70/70	0.89(0.33,1)	0.62(0.47,0.75)	2.3(1.44,3.7)	0.18(0.01,2.5)
Intra Cranial						

Haemorrhage						
Audibert 1996*	LDH/AST/ALT	600/70/70	0.67(0.02,1)	0.73(0.67,0.78)	2.3(1.44,3.71)	0.46(0.05,4.4)
Acute renal failure						
Audibert 1996*	LDH/AST/ALT	600/70/70	0.80(0.12,1)	0.73(0.67,0.79)	3.0(1.56,5.75)	0.27(0.02,3.3)
Haddad 2000*	LDH/AST/ALT	600/70/70	.1 (0.03, 1)	0.51(0.38,0.64)	1.5(0.66,3.5)	0.49(0.04,5.5)

**severe pre eclampsia; ALT: Alanine transaminase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; GGT: Gamma glutamyltransferase; Bi:Bilirubin; SD: Standard Deviation*

Fig 11.1 Area under the curve for predicting adverse maternal outcomes by liver function tests in pre eclampsia



11.4.2 Liver function tests to predict fetal outcomes

Five primary studies evaluated accuracy of LFT to predict adverse fetal outcomes in 19 2x2 tables.[287;289;292;296;297] The commonest reported adverse fetal outcome was neonatal death in 3 studies.[287;289;292] The sensitivity and specificity of LFT to predict adverse fetal outcome ranged from 0.11 (95% CI 0, 0.67) to 0.82 (95% CI 0.60, 0.95) and from 0.51 (95% CI 0.59, 0.73) to 0.88

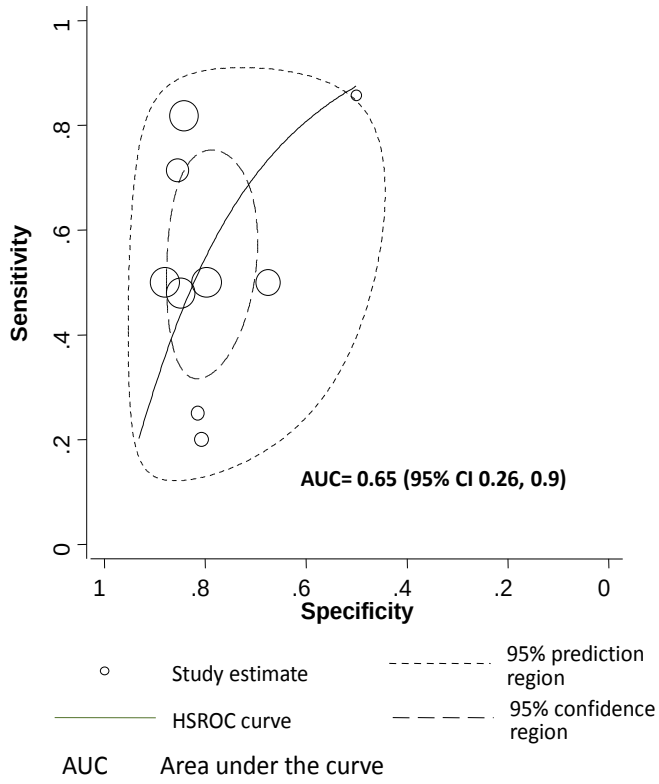
(95% CI 0.83, 0.92) respectively. The best likelihood ratios of positive and negative tests for adverse fetal outcome were 5.18 (95% CI 3.66, 7.31) and 0.22 (95% CI 0.09, 0.52) for levels of AST increased by 2 or more standard deviation (Table 11.2). The AUC for predicting any adverse fetal outcome was 0.65 (95% CI 0.26, 0.9) (Fig 11.2).

Table 11.2 Accuracy of liver function tests in the prediction of adverse fetal outcomes in women with pre eclampsia

Study Year	Test	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Intra uterine death						
Yucesoy 2005	AST/ALT/LDH	Inc	0.71(0.29,0.96)	0.86(0.79,0.91)	4.9(2.7,9)	0.33(0.1,1.1)
Haddad 2000*	LDH/AST/ALT	600/70/ 70	0.63(0.24,0.91)	0.52(0.38,0.65)	1.3(0.71,2.4)	0.72(0.29,1.8)
Neonatal death						
Romero 1988	AST	2SD	0.5(0.16,0.84)	0.80(0.75,0.84)	2.5(1.2,5.1)	0.63(0.31,1.3)
Abramovici 1999*	AST	70	0.5(0.19,0.81)	0.68(0.6,0.74)	1.5(0.8,3)	0.74(0.4,1.4)
Haddad 2000*	LDH/AST/ALT	600/70/ 70	0.38(0.09,0.76)	0.5(0.35,0.65)	0.75(0.29,1.9)	1.25(0.68,2.3)
Intra Uterine Growth Restriction						
Abramovici 1999*	AST	70	0.39(0.25,0.54)	0.68(0.6,0.74)	1.2(0.8,1.9)	0.9(0.7,1.1)
Romero 1988	AST	2SD	0.48(0.34,0.63)	0.85(0.8,0.89)	3.2(2,4.9)	0.61(0.47,0.8)
Respiratory Distress Syndrome						
Abramovici 1999*	AST	70	0.51(0.38,0.64)	0.74(0.66,0.81)	1.9(1.3,2.8)	0.67(0.51,0.88)
Romero 1988	AST	2SD	0.82(0.6,0.95)	0.84(0.79,0.89)	5.2(3.6,7.3)	0.22(0.09,0.53)
Haddad 2000*	LDH/AST/ALT	600/70/ 70	0.46(0.31,0.61)	0.40(0.12,0.74)	0.76(0.42,1.4)	1.4(0.6,3)
Intra ventricular haemorrhage						
Romero 1988	AST	2SD	0.6(0.15,0.9)	0.80(0.74,0.84)	3(1.4,6.3)	0.5(0.17,1.5)
Haddad 2000*	LDH/AST/ALT	600/70/ 70	0.33(0.01,0.91)	0.51(0.37,0.65)	0.68(0.13,3.5)	1.3(0.56,3)
Abramovici 1999*	AST	70	0.11(0,0.67)	0.66(0.59,0.73)	0.33(0.02,4.5)	1.3(0.96,1.9)
Necrotising Enterocolitis						
Abramovici 1999*	AST	70	0.2(0,0.88)	0.66(0.59,0.73)	0.59(0.05,7.1)	1.2(0.64,2.3)
Haddad 2000*	LDH/AST/ALT	600/70/ 70	0.5(0.07,0.93)	0.52(0.38,0.66)	1(0.38,2.9)	0.96(0.35,2.6)
Bronchopulmonary dysplasia						
Abramovici 1999*	AST	70	0.68(0.43,0.87)	0.70(0.63,0.77)	2.3(1.6,3.4)	0.45(0.23,0.88)
Mechanical ventilation						
Abramovici 1999*	AST	70	0.47(0.35,0.59)	0.74(0.66,0.82)	1.8(1.3,2.7)	0.71(0.56,0.9)
Preterm birth						
Romero 1988	AST	2SD	0.5(0.37,0.63)	0.88(0.83,0.92)	4.2(2.7,6.5)	0.57(0.44,0.73)
Adverse outcome						
Girling 1997	AST/ALT/Bi/GGT	30/32/14/ 41	0.86(0.23, 1)	0.5 (0.32,0.68)	1.7(0.99,3)	0.27(0.02,3.8)

**severe pre eclampsia; ALT: Alanine transaminase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; GGT: Gamma glutamyltransferase; Bi:Bilirubin; SD: Standard Deviation*

Fig 11.2 Area under the curve for predicting adverse fetal outcomes by liver function tests in pre eclampsia



11.5 Discussion

In women with preeclampsia, LFTs had at best moderate prediction of maternal and fetal complications. The test specificity, however, was better than sensitivity. This meant that with a positive test result one could be more confident about predicting poor outcome than one could about ruling out complications with a negative result.

Our review is the first to systematically collate and appraise the existing evidence on the predictive accuracy of LFTs in women with pre eclampsia. The validity of our findings depends on the

methodological quality of the systematic review and the quality of the included studies. We conducted an extensive search of literature with no language restrictions to minimise the risk of missing studies and used contemporary statistical methods. There were limitations in the included studies. Firstly, the definition of pre eclampsia differed between different studies. Secondly, very few studies provided details of the test methods and the gestation of testing. Information on gestational age may help in better interpretation of the predictive role of the test as women with early onset pre eclampsia with increased risk of maternal and fetal complications, where decision making often involves complex balancing of maternal benefits against fetal risks. Thirdly, no details were available on the temporality between the test results and the final maternal or fetal outcome. It is possible that the outcome could have been modified by time or any interventions like anti hypertensives, magnesium sulphate, corticosteroids (treatment paradox).[236] Fourthly, the definition of adverse outcome measures differed between the studies and was often not sufficiently described in detail. Contacting authors did not increase the number of included studies. Despite these provisos this is the best available summary of the available studies.

The role of a predictive test in clinical practice depends on the prevalence and severity of the outcome, the cost and acceptability of the test, and the interventions available to reduce or prevent the complications. Currently, pre-eclampsia accounts for about one-fifth of antenatal admissions, two-thirds of referrals to day assessment units and a quarter of obstetric admissions to intensive care units.[301] Although the rate of complications is relatively low in pre eclampsia, when present they are often associated with significant maternal and fetal mortality and morbidity. Clinicians need to identify the women at risk of severe complications who need effective interventions like magnesium sulphate, anti hypertensives and corticosteroids delivery to reduce or prevent risks of complications to mother or baby. LFTs are currently routinely performed in most obstetric units as part of the admission battery of tests in women with pre eclampsia. A Delphi survey of

international experts showed that LFTs are considered to be the third important predictor of maternal and fetal complications after blood pressure and proteinuria.[17]

Current national and international classifications of severity of pre eclampsia are hampered by the unknown disease aetiology. However, uteroplacental ischemia causing activation of the endothelium seems to play a major role. Endothelial dysfunction is considered to underlie many of the clinical symptoms of pre-eclampsia like hypertension, increased vascular permeability resulting in oedema and proteinuria, and expression of inflammatory parameters leading to coagulopathy.[302-304] These changes also cause ischemia of target organs, such as brain, liver, kidney and placenta. Fibrin deposition, periportal haemorrhage, ischemic lesions and microvesicular fat deposition are histological findings observed in the livers of preeclamptic women.[305] Our published reviews have shown the accuracy of uric acid and proteinuria in predicting maternal and fetal complications in women with pre eclampsia.[306;307] This paper adds further evidence to inform this subject.

For women with raised liver enzymes, the test sensitivity to predict adverse maternal outcome was relatively poor with point estimates more than 50% in only half the included studies. The test performed better with regards to specificity with point estimates more than 70% in 18 of the 30 2 x 2 tables. The test performance in predicting adverse fetal outcomes were similar with the specificity of the test was better than sensitivity.

11.6 Conclusion

Through this review we have highlighted the moderate ability of abnormal LFT in correctly identifying women at increased risk of maternal and fetal complications. However, given the

uncertainties in the data, making clinical recommendations or developing prediction rules for using LFTs is not possible without good quality large prospective studies. These studies should especially focus on the sub group of women with early onset pre eclampsia where monitoring has a critical role in prolonging gestation.

CHAPTER 12: SYMPTOMS AS A PREDICTOR OF COMPLICATIONS IN PRE ECLAMPSIA

12.1 Abstract

Background

Symptoms such as severe headache, visual disturbances, nausea and vomiting and epigastric pain are believed to be clinical markers of impending complications in pre-eclampsia. The objective of this review is to determine the accuracy of maternal symptoms in predicting complications in women with pre-eclampsia.

Methods

Systematic quantitative review of test accuracy studies was undertaken. We conducted electronic searches in Medline (1951-2009), Embase (1980-2009), the Cochrane Library (2009) and the MEDION database and hand-searches of selected specialist journals and reference lists of known articles to identify relevant papers without language restrictions. Two reviewers independently selected articles in which the accuracy of symptoms including headache, visual disturbances, nausea and vomiting and epigastric pain were correlated with development of maternal and fetal complications in pre-eclampsia. We extracted data on study characteristics, quality and accuracy. We constructed 2 x 2 tables for the prediction of a composite endpoint of maternal and fetal adverse outcomes. We summarised accuracy with a bivariate model estimating sensitivity, specificity and area under summary Receiver Operating Characteristic (AUC) curve.

Results

Six primary articles with 2573 women were included. The AUC for predicting complications with symptoms of headache, epigastric pain and visual disturbances were 0.58 (95% CI 0.24, 0.86), 0.70 (95% CI 0.3, 0.93) and 0.74 (95% CI 0.33, 0.94). The sensitivity and specificity of headache to predict adverse maternal outcomes were 0.54 (95% CI 0.27, 0.79) and 0.59 (95% CI 0.38, 0.76) respectively. The sensitivity of epigastric pain and visual disturbances are 0.34 (95% CI 0.22, 0.5) and 0.27 (95% CI 0.07, 0.65) with a specificity of 0.83 (95% CI 0.76, 0.89) and 0.81 (95% CI 0.71, 0.88) respectively. The sensitivity and specificity of nausea and vomiting to predict adverse outcomes were 0.24 (95% CI 0.21, 0.27) and 0.87 (95% CI 0.85, 0.89) respectively.

Conclusion

The presence of symptoms is useful for identifying women at risk of complications in primary and secondary care. This information should be employed judiciously to direct laboratory investigations.

Citation of paper arising from this work

Thangaratinam S, Gallos I, Meah N, Usman S, Ismail KMK, Khan KS. How accurate are maternal symptoms in predicting impending complications in women with pre-eclampsia? A systematic review. (Acta Obstet et Gynecol in press)

12.2 Background

Maternal symptoms of headache, vomiting, visual disturbances or epigastric pain in pregnancy may be the only pointers to underlying pre eclampsia that was not detected previously. An early warning system may employ maternal symptoms to raise an alert for diagnosis of pre eclampsia by measurement of blood pressure and proteinuria. In women known to have pre eclampsia, history of symptoms is obtained routinely in antenatal setting but the absence of quantitative information about their accuracy limits their use in decision making. A Health Commission's report identified that early warning symptoms for maternal complications in pre eclampsia were not recognised in 2 of 10 maternal deaths.[308] Failure to recognise symptoms as a marker of severity of pre-eclampsia is an established reason for medical negligence cases against health professionals.[309] The low awareness of the importance of symptoms in women with pre-eclampsia outside the antenatal setting may be due to absence of clear collated summaries of the evidence.

Symptoms such as severe headache, visual disturbances, epigastric pain, nausea and vomiting have a physiological basis. Headaches have been attributed to cerebral oedema or vasospasm of cerebral arteries.[310;311] Visual disturbances have been linked to impeding blood flow and ischemic injury secondary to vasospasm of retinal arteries.[312] Epigastric pain, nausea and vomiting are thought to reflect hepatic involvement and is postulated to result from obstructed blood flow in the hepatic sinusoids, mainly the periportal areas subsequent to vascular constriction caused by fibrin like deposits.[313]

Several studies have shown varying degrees of correlation between symptoms in pre eclamptic patients and presence of adverse maternal and fetal outcomes.[251;314;315] Current guidelines consider symptoms to be a surrogate marker of disease severity.[316-318] They may contribute to decisions

leading to delivery or admission to high dependency unit, when present alongside other abnormal tests. These guidance are not always evidence based. For example, the recommendations on the value of maternal symptoms in predicting complications are poorly referenced[318] or not referenced in the guidelines.[317] There are no systematic reviews on the accuracy of symptoms in predicting adverse outcomes in pre-eclampsia. We therefore conducted such a comprehensive systematic quantitative review evaluating the role of symptoms in women diagnosed to have pre eclampsia.

12.3 Methods

The review was carried out with a prospective protocol[290] using widely recommended methods as described in Chapter 8, Section 8.3.

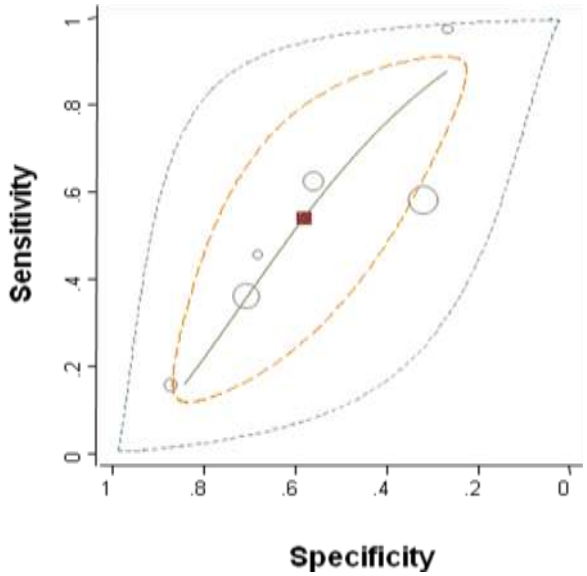
12.4 Results

12.4.1 Literature identification and study quality

The flow chart in Appendix 9 summarises the process of literature identification and selection. There were 6 primary articles that met the selection criteria,[288;315;319-322] consisting of 22 2 x 2 tables including a total of 2573 women. Each study's salient features are provided in Appendix 24. Methodological quality of included studies in Appendix 14 showed that the index tests was adequately described in 5 out of 6 studies (83 %) and reference standard adequately described in all the studies. Only two studies (30%) were prospectively conducted and none of the studies were blinded for outcome measurement.

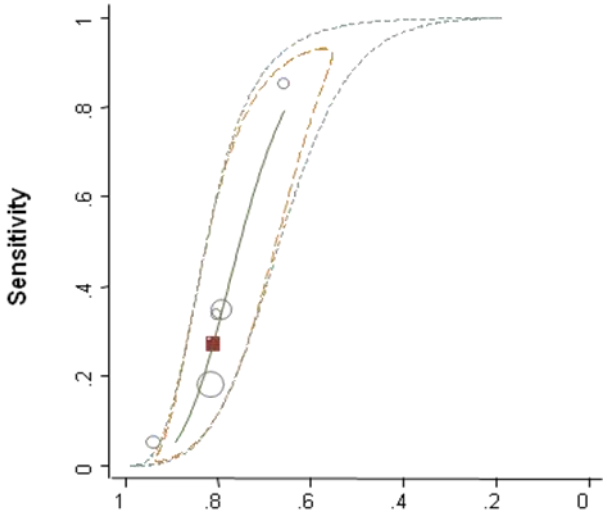
The symptoms assessed in the included studies were headache, epigastric pain, visual symptoms and vomiting. The adverse maternal outcomes reported were HELLP syndrome, eclampsia, severe pre-eclampsia, abruption and postpartum adverse outcome. None of the studies reported fetal outcome. The sensitivity and specificity of individual studies for various symptoms and outcomes are provided in Table 12.1. The summary sROC curve by bivariate model was fitted for headache, epigastric pain and visual disturbances that have more than 4 2x2 table data as shown in Fig 12.1.

Fig 12.1 Area Under the curve (AUC) for symptoms in predicting adverse maternal outcomes in women with pre eclampsia



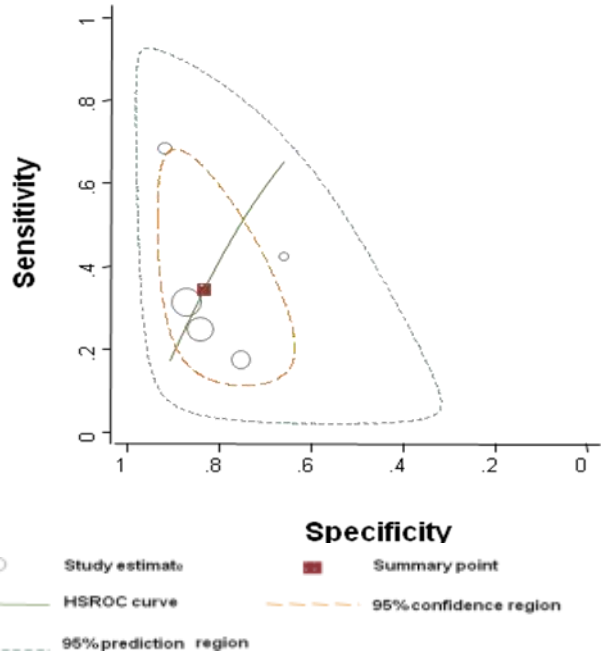
a. Headache

AUC = 0.58 (95% CI 0.24, 0.86)



b. Visual symptoms

AUC = 0.74 (95% CI 0.33, 0.94)



c. Epigastric pain

AUC = 0.70 (95% CI 0.30, 0.93)

12.4.2 Headache as a predictor of adverse maternal outcome

All 6 studies evaluated the accuracy of headaches in predicting adverse maternal outcomes.[288;315;319-322] The pooled sensitivity and specificity of headache as a test to predict adverse outcomes were 0.54 (95% CI 0.27, 0.79) and 0.59 (95% CI 0.38, 0.76) respectively. The summary positive and negative likelihood ratios were 1.3 (95% CI 0.96, 1.7) and 0.79 (95% CI 0.54, 1.2) respectively (Table 12.1). The highest sensitivity of 0.98 (95% CI 0.87, 1) was reported for the prediction of eclampsia. The test had the highest specificity for prediction of HELLP syndrome 0.87 (95% CI 0.82, 0.92). The AUC for any adverse maternal outcome was 0.58 (95% CI 0.24, 0.86) (Fig 12.2a).

Table 12.1. Sensitivity, Specificity and Likelihood ratios for predicting adverse maternal outcomes in women with pre-eclampsia using clinical symptoms

Study Year	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR - (95% CI)
Headache					
Witlin 1999	Abruption	0.61 (0.42 - 0.77)	0.53 (0.48 -0.58)	1.3 (0.97 - 1.7)	0.74 (0.48 - 1.1)
Ben Salem 2003	Eclampsia*	0.98 (0.87 - 1.00)	0.27(0.17 - 0.38)	1.3 (1.1 - 1.5)	0.09(0.01- 0.66)
Witlin 1999	Eclampsia*	0.63 (0.46 - 0.77)	0.56(0.51 - 0.61)	1.4 (1.1 - 1.9)	0.67 (0.44 - 1.0)
Black 2007	Severe pre-eclampsia*	0.46 (0.33 - 0.59)	0.68(0.52 - 0.82)	1.4 (0.85 - 2.5)	0.79 (0.58 - 1.1)
Harms 1991	HELLP*	0.16 (0.03 - 0.40)	0.87(0.82 - 0.92)	1.3 (0.41 - 3.8)	0.96 (0.79 - 1.2)
Martin 1999	HELLP*	0.58 (0.55 - 0.62)	0.32(0.26 - 0.39)	0.86 (0.76 - 0.96)	1.3 (1.0 - 1.6)
Menzies 1997	Adverse outcome*	0.36 (0.25 – 0.48)	0.71(0.67– 0.74)	1.2 (0.89 – 1.7)	0.90 (0.75 – 1.1)
Summary estimate	***Adverse outcome***	***0.54 (0.27 – 0.79)***	***0.59(0.38– 0.76)***	***1.3 (0.96 – 1.7)***	***0.79 (0.54 – 1.2)***
Visual symptoms					
Ben Salem 2003	Eclampsia*	0.85 (0.71 - 0.94)	0.66(0.54 - 0.76)	2.5 (1.8 - 3.5)	0.22 (0.1 - 0.47)
Witlin 1999	Eclampsia*	0.35 (0.21 - 0.52)	0.80(0.75 - 0.83)	1.7 (1.1 - 2.7)	0.82(0.65 - 1.0)
Witlin 1999	Abruption	0.27 (0.13 - 0.46)	0.78(0.74 - 0.82)	1.3 (0.7 - 2.3)	0.93 (0.75 - 1.2)
Black 2007	Severe pre-eclampsia*	0.34 (0.22 - 0.47)	0.80 (0.65 - 0.91)	1.7 (0.85 - 3.6)	0.82(0.65 - 1.0)
Harms 1991	HELLP*	0.05 (0.00 - 0.26)	0.94(0.89 - 0.97)	0.87 (0.12 - 6.4)	1.01 (0.90 - 1.1)
Menzies 1997	Adverse outcome*	0.18 (0.10 – 0.29)	0.82(0.79– 0.85)	0.99 (0.59 – 1.7)	1.0 (0.89 – 1.1)
Summary estimate	***Adverse outcome***	***0.27 (0.07 – 0.65)***	***0.81(0.71– 0.88)***	***1.4 (0.67 – 3.1)***	***0.89 (0.64 – 1.3)***
Nausea and vomiting					
Martin 1999	HELLP*	0.24 (0.21 - 0.27)	0.85(0.79- 0.90)	1.6 (1.1 - 2.3)	0.9 (0.84 - 0.96)
Harms 1991	HELLP*	0.47 (0.24 - 0.71)	0.92(0.87 - 0.96)	6.2 (3.1 - 12.3)	0.57(0.37- 0.88)
Witlin 1999	Eclampsia*	0.20 (0.09 - 0.36)	0.86(0.82 - 0.89)	1.4 (0.72 - 2.7)	0.93(0.80 - 1.1)
Summary estimate	***Adverse outcome***	***0.24 (0.21 – 0.27)***	***0.87(0.85– 0.89)***	***2.3 (1-5.4)***	***0.87 (0.74 – 1)***
Epigastric pain					
Martin 1999	HELLP*	0.31 (0.28 - 0.35)	0.87(0.81 - 0.91)	2.4 (1.7 - 3.6)	0.79 (0.73 - 0.85)
Witlin 1999	Eclampsia*	0.18 (0.07 - 0.33)	0.75(0.71 - 0.79)	0.71 (0.35 - 1.4)	1.1 (0.94 - 1.3)
Witlin 1999	Abruption	0.33 (0.18 - 0.52)	0.76(0.72 - 0.80)	1.4 (0.84 - 2.3)	0.87 (0.68 - 1.1)
Black 2007	Severe pre-eclampsia*	0.42 (0.30 - 0.56)	0.66(0.49 - 0.80)	1.2 (0.74 - 2.1)	0.88(0.64 - 1.2)
Harms 1991	HELLP*	0.68 (0.43 - 0.87)	0.92(0.87 - 0.95)	8.3 (4.7 - 14.7)	0.34(0.18-0.67)
Menzies 1997	Adverse outcome*	0.25 (0.16 -0.37)	0.84(0.81– 0.87)	1.6 (1 – 2.4)	0.89 (0.78 – 1.0)
Summary estimate	***Adverse outcome***	***0.34 (0.22 – 0.5)***	***0.83(0.76– 0.89)***	***2.1 (1 – 4.2)***	***0.79 (0.6 – 1)***

12.4.3 Visual disturbances as a predictor of adverse maternal outcome

Six studies reported the accuracy of visual disturbances to predict maternal complications.[288;315;319;320;322] The summary sensitivity and specificity were 0.27 (95% CI 0.07, 0.65) and 0.81 (95% CI 0.71, 0.88) respectively (Table 12.1). The pooled positive and negative likelihood ratios for adverse maternal outcome were 1.4 (95% CI 0.67, 3.1) and 0.89 (95% CI 0.64, 1.3) respectively. Visual disturbance had the highest sensitivity of 0.85 (95% CI 0.71, 0.94) in predicting eclampsia. The maximum specificity of 0.94 (95% CI 0.89, 0.97) was for HELLP syndrome. The AUC for any adverse maternal outcome was 0.75 (95% CI 0.3, 0.95) (Fig 12.2b).

12.4.4 Epigastric pain as a predictor of adverse maternal outcome

Epigastric pain was evaluated in 6 studies to assess prediction of eclampsia, HELLP syndrome, abruption, severe pre-eclampsia and adverse composite maternal outcome.[288;315;320-322] The summary sensitivity and specificity for adverse maternal outcome were 0.34 (95% CI 0.22, 0.5) and 0.83 (95% CI 0.76, 0.89) respectively. The pooled positive and negative likelihood ratios were 2.1 (95% CI 1, 4.2) and 0.79 (95% CI 0.6, 1) (Table 12.1). The maximum sensitivity and specificity of 0.68 (95% CI 0.43, 0.87) and 0.92 (95% CI 0.87, 0.95) respectively for HELLP syndrome was observed in the study by Harms et al. The AUC for any adverse maternal outcome was 0.70 (95% CI 0.3, 0.93) (Fig 12.2c).

12.4.5 Vomiting as a predictor of adverse maternal outcome

Vomiting was evaluated in 3 studies.[288;315;321] The highest sensitivity and specificity were 0.47 (95% CI 0.24, 0.71) and 0.92 (95% CI 0.87, 0.96) for HELLP syndrome. The summary sensitivity and specificity were 0.24 (95% CI 0.21, 0.27) and 0.87 (95% CI 0.85, 0.89) respectively (Table 12.1).

12.5 Discussion

Among women with pre-eclampsia, symptoms of visual disturbance and epigastric pain were moderately good predictors of maternal complications. Their predictive accuracy was better than headache as a test. The symptoms overall had high specificity than sensitivity. Thus, the presence of symptoms is clinically more useful for *ruling in* complications in comparison to their absence for *ruling out* complications.

The data from the largest study by Martin et al show that headache had poor specificity for predicting eclampsia in comparison to epigastric pain and vomiting for HELLP syndrome.[321] Patients with class 1 HELLP syndrome indicating a worsening of condition were 4 times more likely to have symptoms of epigastric pain or vomiting compared to class 3 HELLP. One of the largest population based surveys to date on eclampsia, BEST in UK, reported that 50% of women with eclampsia had headache preceding convulsions, visual disturbances in 19% and another 19% complained of epigastric pain.[314] Antepartum cases of eclampsia were slightly more likely to be preceded by prodromal symptoms than intrapartum or postpartum cases (RR 1.48 (95% CI 1.26, 1.73). This increase was also noticed for eclampsia occurring before term than term. However there is no comparative data to ascertain the incidence of symptoms in women without eclampsia.

The sensitivity and specificity of headache was low overall in the review except in the case control study by Ben Salem et al with 98% sensitivity for headache.[319] It is possible that with 60% of women with eclampsia having the first episode at home, recall bias may have influenced the reporting of symptoms prior to the episode.[319] The large prospective study by Menzies et al showed that although the specificity was over 80% for visual symptoms and epigastric pain the sensitivity

only ranged between 18 and 25%.[322] It reflects the overall pattern of the test performance with relatively higher specificity than sensitivity for adverse outcomes.

Our review has been the first to systematically collate and quantify the predictive value of symptoms through a prospective protocol.[290] We have employed an extensive search strategy to ensure that all relevant studies have been captured. The importance that clinicians attach to the symptoms has been determined through our Delphic survey of experts. We have used the composite maternal adverse outcome as reference standard that had been obtained by Delphic consensus and shown to be robust through piloting and validation.

The review is constrained by the heterogeneity in the definition of population, limitation in details of the tests and outcome and lack of data on the time elapsed between onset of symptoms and adverse events. Furthermore, the predictive accuracy may be affected by the presence of other risk factors and the effect of any interventions (treatment paradox). Clinical symptoms although routinely elicited in the management of any patient with pre-eclampsia are poorly reported in the literature. There is insufficient information on the gestational age of patients to assess the performance of the test according to gestation. Due to the paucity of the data we were restricted from undertaking further analysis by meta-regression to study the effects of other abnormal tests like blood pressure, proteinuria, liver function etc, the time interval between the symptoms and outcome and any interventions on the accuracy of symptoms.

12.6 Conclusion

Evidence from this review suggests that presence of symptoms is more useful in their ability to predict complications compared to their absence in confidently excluding adverse events.

However, the findings are limited due to a relatively small number of heterogeneous studies. This highlights the need for large prospective studies in this area to enable clinicians to confidently evaluate the added value of symptoms in the management of patients with pre-eclampsia.

CHAPTER 13: BLOOD PRESSURE AS A PREDICTOR OF COMPLICATIONS IN PRE ECLAMPSIA

13.1 Abstract

Background

Blood pressure is considered to be the most predictive of complications in women with pre eclampsia compared to the other tests.

Methods

We performed systematic quantitative review of test accuracy studies. We conducted an electronic search in MEDLINE (1951-2009), EMBASE (1980-2009), the Cochrane Library (2009) to identify relevant articles. A hand-search of selected specialist journals and reference lists of articles obtained was then carried out. There were no language restrictions for any of these searches. Studies were selected independently by two reviewers if blood pressure profile was evaluated to predict maternal and fetal complications of pre eclampsia. Data was extracted on study characteristics, quality and accuracy to construct 2 X 2 tables with maternal and fetal complications as reference standard.

Results

There were 8 primary articles in the review including a total of 2304 women. For the prediction of eclampsia, abruption, renal, neurological and liver impairment, mean arterial pressure (MAP) $\geq$ 140 mmHg or BP $\geq$ 170/110 had high specificity (more than 80%) and low sensitivity (<50%). The area under the curve (AUC) for any adverse maternal outcome was 0.68 (95% CI 0.29, 0.92). The

specificity for adverse fetal outcomes was more than 70% in 11/15 (73.3%) studies and sensitivity was more than 70% in 6/15 (40%) studies.

Conclusion

Blood pressure is a moderate predictor of adverse maternal and fetal outcomes, with severe hypertension more predictive of fetal complications than maternal complications.

13.2 Background

An increase in blood pressure (BP) is one of the essential criteria in the diagnosis of pre-eclampsia. It is the commonest test performed in primary and secondary care and is a frequent cause of referral and admission to obstetric units. There is currently no consensus on the levels of BP needing intervention in the form of delivery or anti-hypertensives. Although there are primary studies evaluating the predictive role of BP on maternal and fetal complications, there are no systematic reviews that collate the evidence on the significance of this important test. With the recent stress on outpatient management of women with mild pre-eclampsia, there is a need to identify the BP threshold above which there is increased likelihood of significant maternal and fetal complications that will enable us to identify the appropriate group of patients that need early intervention. It will also avoid unnecessary referral and treatment in the low risk group. We therefore conducted a comprehensive systematic review to obtain precise estimates of maternal levels of BP to predict maternal and fetal complications in women with pre-eclampsia.

13.3 Methods

The review was carried out with a prospective protocol[290] using widely recommended methods as described in Chapter 8, Section 8.3.

13.4 Results

13.4.1 Literature identification and study selection

The flow chart in Appendix 10 summarises the process of literature identification and selection. There were 8 primary articles that met the selection criteria including a total of 2304 women.[245;280;315;322-326] Each study's salient features according to the population subgroups, test

characteristics and reference standards are provided in Appendix 25. The definition of pre-eclampsia differed widely between the studies. The test thresholds were reported as systolic and diastolic BP readings or as Mean Arterial Pressure (MAP) in individual studies. Adverse maternal outcomes were reported in 20 2 x 2 tables (Table 13.1) and adverse fetal outcomes in 15 2 x 2 tables (Table 13.2). The methodological quality of the included studies is given in Appendix 14.

13.4.2 Blood pressure and maternal outcome

Four studies (2 x 2 tables) assessed the risk of eclampsia for threshold levels of MAP from 105 mmHg to 160 mm Hg. The positive likelihood ratio for MAP 105 to 160 mm Hg in the prediction of eclampsia ranged from 0.96 (95% CI 0.87, 1.0) to 2.3 (95% CI 0.8, 6.3) respectively. The negative likelihood ratio for the same outcome varied from 2.3 (95% CI 0.70, 7.9) to 0 .94 (95% CI 0.85, 1.0) for levels of MAP of 105 and 160 mm Hg respectively. The accuracy of BP in predicting abruption was reported in 4 studies. Two studies assessed the rate of caesarean section for various threshold levels of BP. The positive likelihood ratios for BP of 170/110 and 160/110 were 2.5 (95% CI 1.8, 3.5) and 2.6 (95% CI 1.8, 3.6) respectively. The negative likelihood ratios for the above cut offs were 0.28 (95% CI 0.16, 0.5) and 0.74 (95% CI 0.67, 0.82) respectively.

The sensitivity of BP in predicting any adverse maternal outcome was more than 70% in 6/20 (30%) studies and the specificity was more than 70% in 9/20 (45%) of the studies for various threshold levels of BP (Fig 13.1). For the prediction of eclampsia, abruption, renal, neurological and liver impairment, MAP $\geq$ 140 mmHg or BP $\geq$ 170/110 had high specificity (more than 80%) and low sensitivity (<50%). The area under the curve (AUC) for any adverse maternal outcome was 0.68 (95% CI 0.29, 0.92).

Table 13.1. Accuracy of blood pressure in the prediction of adverse maternal outcomes in women with pre eclampsia

Study Year	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Eclampsia					
Witlin 1999	MAP >105	0.93(0.80,0.98)	0.03(0.02,0.05)	0.96(0.87,1.05)	2.34(0.70,7.86)
Witlin 1999	MAP>120	0.78(0.62,0.89)	0.25(0.21,0.30)	1.04(0.87,1.24)	0.89(0.49,1.63)
Witlin 1999	MAP>140	0.28(0.15,0.44)	0.82(0.77,0.85)	1.49(0.86,2.56)	0.89(0.73,1.08)
Witlin 1999	MAP>160	0.10(0.03,0.24)	0.96(0.93,0.97)	2.25(0.80,6.33)	0.94(0.85,1.05)
Abruption					
Witlin 1999	MAP >105	0.88(0.72,0.97)	0.02(0.01,0.04)	0.90(0.79,1.02)	6.26(1.99,19.70)
Witlin 1999	MAP>120	0.67(0.48,0.82)	0.24(0.20,0.28)	0.87(0.68,1.12)	1.41(0.84,2.35)
Witlin 1999	MAP>140	0.18(0.07,0.36)	0.80(0.76,0.84)	0.92(0.43,1.94)	1.02(0.86,1.21)
Witlin 1999	MAP>160	0.06(0.01,0.20)	0.95(0.93,0.97)	1.25(0.31,5.12)	0.99(0.90,1.08)
Inpatient admission					
Peek 1995	170/110	0.60(0.48,0.71)	0.60(0.46,0.72)	1.49(1.04,2.12)	0.67(0.48,0.95)
Caesarean section (CS)					
Peek 1995	170/110	0.81(0.68,0.91)	0.68(0.57,0.78)	2.52(1.80,3.54)	0.28(0.16,0.50)
Xiong 1999	160/110	0.36(0.31,0.42)	0.86(0.81,0.90)	2.57(1.83,3.61)	0.74(0.67,0.82)
Elective CS					
Peek 1995	170/110	0.85(0.68,0.95)	0.60(0.50,0.69)	2.10(1.60,2.76)	0.25(0.11,0.58)
Emergency CS					
Peek 1995	170/110	0.75(0.51,0.91)	0.53(0.44,0.62)	1.60(1.16,2.19)	0.47(0.22,1.03)
Forceps					
Peek 1995	170/110	0.46(0.19,0.75)	0.48(0.39,0.58)	0.89(0.49,1.65)	1.11(0.65,1.90)
Renal impairment					
Brown 1996	170/110	0.45(0.32,0.58)	0.81(0.78,0.84)	2.40(1.74,3.28)	0.68(0.54,0.85)
Thrombocytopenia					
Brown 1996	170/110	0.44(0.33,0.55)	0.82(0.79,0.85)	2.42(1.81,3.22)	0.69(0.56,0.83)
Neurological complication					
Brown 1996	170/110	0.61(0.51,0.71)	0.88(0.82,0.88)	4.08(3.23,5.14)	0.46(0.36,0.58)
Liver disease					
Brown 1996	170/110	0.58(0.47,0.69)	0.83(0.80,0.86)	3.48(2.72,4.44)	0.50(0.39,0.65)
Adverse maternal outcome					
Menzies 2007	SBP>=160	0.67(0.55,0.77)	0.37(0.34,0.41)	1.06(0.89,1.26)	0.90(0.64,1.26)
Menzies 2007	DBP>=110	0.38(0.26,0.50)	0.68(0.64,0.71)	1.16(0.85,1.60)	0.92(0.77,1.11)

Fig 13.1 Receiver Operating Characteristic plane of Blood Pressure as a predictor of adverse maternal outcome in pre eclampsia

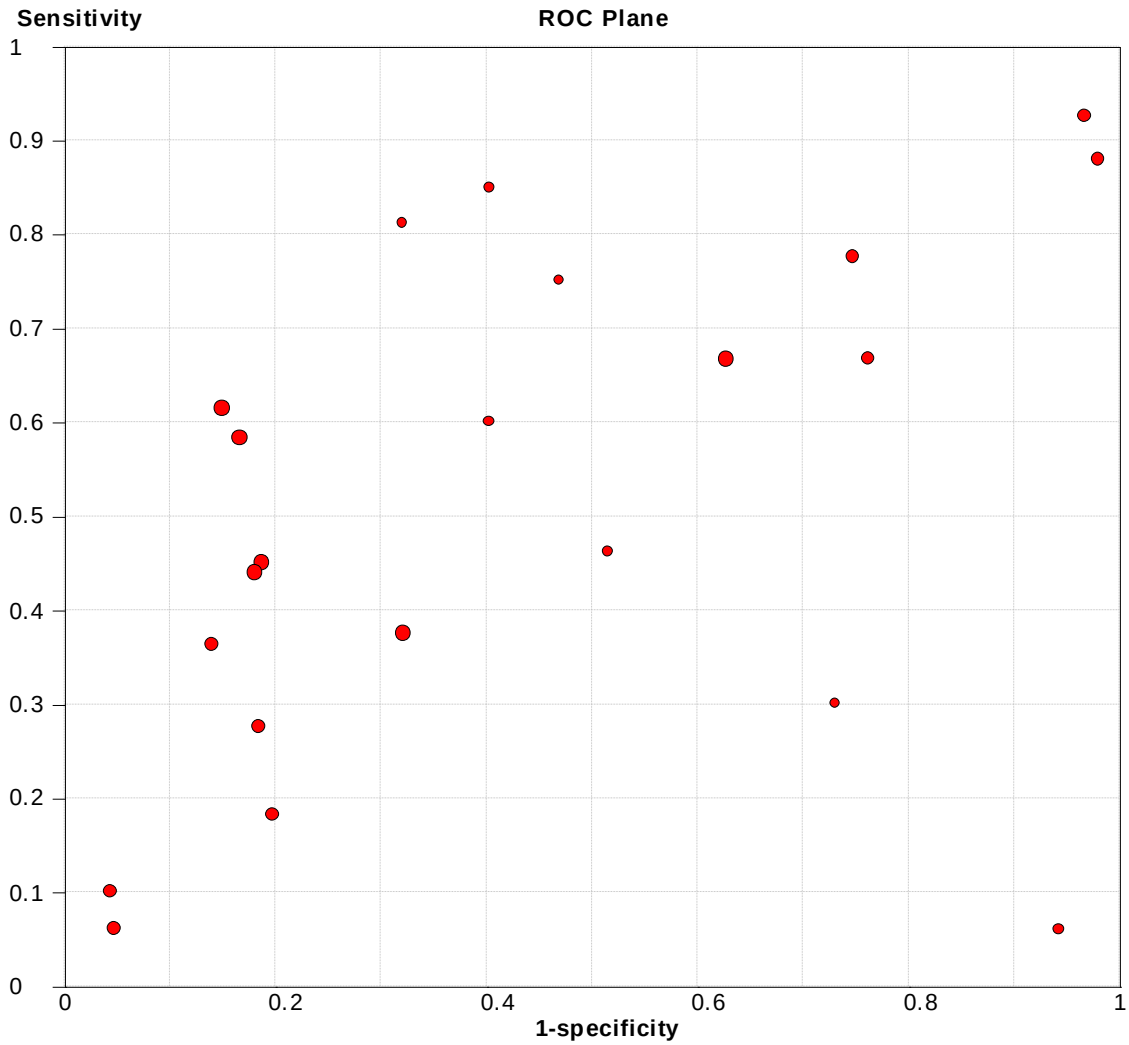
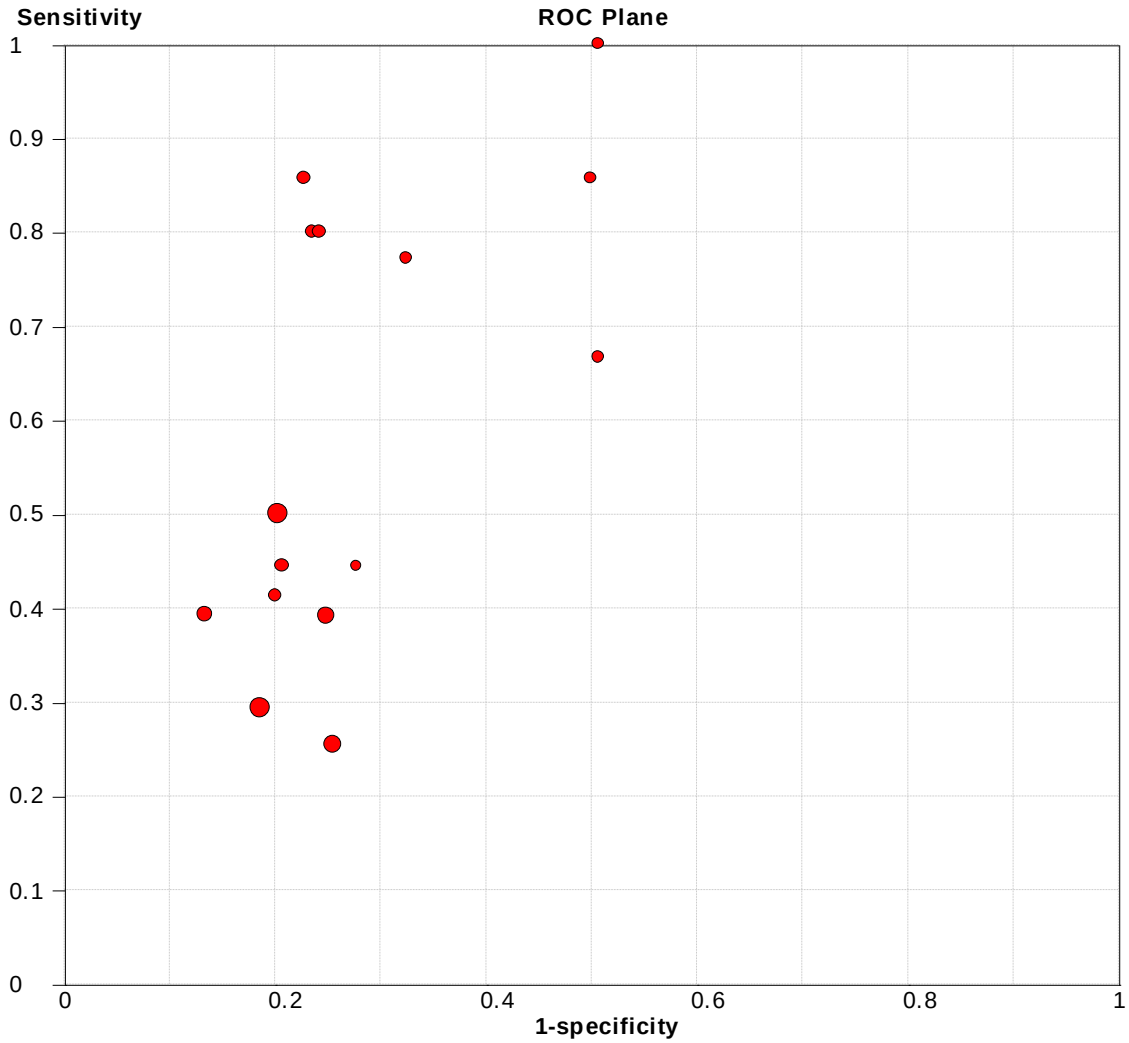


Fig 13.2 Receiver Operating Characteristic plane of Blood Pressure as a predictor of adverse fetal outcome in pre eclampsia



13.4.3 Blood pressure and fetal outcome

Six studies reported perinatal mortality, stillbirths and neonatal deaths for various threshold levels of BP. The sensitivity and specificity were more than 70% in 4/6 (66%) and 5/6 (83%) of the studies respectively. The LR+ ranged between 1.6 (95% CI 0.65, 3.9) and 3.8 (95% CI 2.5, 5.6) and the LR- between 0.19 (95% CI 0.03, 1.1) and 0.77 (95% CI 0.41, 1.4) respectively. 6 studies evaluated small for gestational age, fetal distress and preterm delivery. The specificity was more than 80% or more in all of them for threshold levels of BP 160/100 and 170/110. The sensitivity was less than 50% in the above studies (Table 13.2). Overall the specificity was more than 70% in 11/15 (73.3%) studies and sensitivity was more than 70% in 6/15 (40%) studies (Fig 13.2). The AUC for adverse fetal outcomes was 0.74 (SE 0.07).

Table 13.2. Accuracy of blood pressure in the prediction of adverse fetal outcomes in women with pre eclampsia

Study Year	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Small for gestational age					
Varma 1981	160/100	0.41(0.27,0.57)	0.80(0.73,0.86)	2.05(1.29,3.27)	0.74(0.57,0.95)
Brown 1996	170/110	0.29(0.22,0.37)	0.81(0.78,0.84)	1.57(1.17,2.09)	0.87(0.78,0.97)
Xiong 1999	160/110	0.25(0.15,0.38)	0.74(0.70,0.78)	0.99(0.63,1.58)	1.00(0.86,1.17)
Fetal distress					
Varma 1981	160/100	0.44(0.28,0.62)	0.79(0.72,0.85)	2.14(1.34,3.43)	0.70(0.52,0.95)
Neonatal death					
Varma 1981	160/100	0.80(0.28,1.00)	0.76(0.70,0.82)	3.40(2.05,5.62)	0.26(0.05,1.51)
Still Birth					
Varma 1981	160/100	0.80(0.12,1.00)	0.76(0.69,0.82)	3.30(1.69,6.43)	0.26(0.02,3.15)
Neonatal Intensive Care Unit admission					
Peek 1995	170/110	0.77(0.64,0.87)	0.68(0.56,0.78)	2.38(1.68,3.36)	0.34(0.20,0.56)
Perinatal mortality					
Varma 1981	160/100	0.86(0.42,1.00)	0.77(0.71,0.83)	3.76(2.52,5.60)	0.19(0.03,1.14)
Peek 1995	170/110	0.86(0.23,1.00)	0.50(0.41,0.59)	1.71(1.08,2.72)	0.29(0.02,3.74)
Brown 1996	170/110	0.50(0.19,0.81)	0.80(0.77,0.82)	2.46(1.30,4.63)	0.63(0.34,1.17)
Heilmann 1989	DBP>100	0.44(0.14,0.79)	0.72(0.55,0.86)	1.60(0.65,3.94)	0.77(0.41,1.43)
Necrotising enterocolitis					
Peek 1995	170/110	1.0(0.03,1.0)	0.49(0.41,0.58)	1.48(0.65,3.35)	0.51(0.05,5.63)
Intraventricular haemorrhage					
Peek 1995	170/110	0.67(0.09,1.00)	0.49(0.41,0.58)	1.31(0.58,2.98)	0.68(0.14,3.38)
Preterm delivery					
Xiong 1999	160/110	0.39(0.20,0.62)	0.75(0.71,0.79)	1.57(0.92,2.67)	0.81(0.58,1.13)
Dukler 2000	DBP>110	0.39(0.27,0.53)	0.87(0.82,0.90)	2.93(1.90,4.50)	0.70(0.57,0.88)

13.5 Discussion

Blood pressure was a better predictor of adverse fetal than maternal outcomes. Both sensitivity and specificity were lower for maternal complications than for fetal complications. A high BP reading

(160/100) is more likely to rule in adverse fetal outcomes, whereas a BP<160/100 is less likely to rule out a complication. The same phenomenon was observed for cut off levels of MAP>140 for eclampsia and abruption.

The review was performed by identifying the relevant studies using a detailed search srtaegy without any language restriction with robust methodology. The composite adverse maternal and fetal outcomes have been identified by Delphic survey of experts. As with reviews of other tests in pre eclampsia, the included studies differ in the definition of pre eclampsia, the threshold values and the method of reporting of test (systolic or diastolic BP or both, MAP) and definition of the reference standard. Furthermore, there is limited data on the use of any interventions like anti hypertensives, steroids and magnesium sulphate that may have an effect on the outcomes. There is a lack of data on other potential predictor variables like gestational age and other clinical and biochemical parameters that may influence the predictice accuracy of BP.

BP was prioritised as the most important test that can predict complications in women with pre eclampsia in the Delphi survey of experts.[17] The findings from the review suggest that it may not be the case. One explanation could be that BP is the most amenable of all abnormal tests to intervention. Effective anti hypertensives exist that control high BP of any severity. The finding of BP is only a moderate predictor of complications does not mean that they should not be taken into account. Women with severe hypertension with systolic BP>160 mm Hg and diastolic BP >110 mm Hg should be managed to reduce BP according to national or local guidelines.[327]

13.6 Conclusion

BP is a moderate predictor of adverse maternal and fetal outcomes, with severe hypertension more predictive of fetal complications than maternal complications. Existing studies are small and of too varied quality to make any robust recommendations from the review.

CHAPTER 14: ACCURACY OF PULSE OXIMETRY AS A SCREENING TOOL IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE IN NEWBORNS: A SYSTEMATIC REVIEW

14.1 Abstract

Background

Congenital heart disease is the commonest group of congenital malformations with most deaths in the first year of life. Early detection of congenital heart disease in the asymptomatic period immediately after birth will reduce clinical deterioration by instigation of appropriate, timely management. This review aims to evaluate the accuracy of pulse oximetry as a screening tool for congenital heart disease in asymptomatic newborns.

Methods

Systematic review of relevant studies identified through Medline, Embase, Cochrane Library, conference papers, and bibliographies of retrieved primary and review articles. Two reviewers independently extracted data on study characteristics, quality, and results to construct 2x 2 tables with congenital heart disease as the reference standard. We used a random-effects bivariate model to meta-analyse estimates of sensitivity and specificity. Logit pairs of sensitivity and specificity of each study were analysed in a single model, accounting for their correlation due to differences in threshold between studies.

Results

We extracted 8 studies with a total of 35,960 newborns. Pulse oximetry was performed on asymptomatic newborns in all studies, with three studies excluding newborns with an antenatal diagnosis of congenital heart disease. The studies measured either functional or fractional oxygen saturation by pulse oximetry with oxygen saturation below 95% considered as the cut off level in most studies. Based on 8 studies, the summary estimates of sensitivity and specificity were 63% (95% CI, 39% to 83%) and 99.8% (95% CI, 99% to 100%) respectively, yielding a false positive rate of 0.2% (95% CI, 0% to 1%).

Conclusion

Pulse oximetry has been shown to be a highly specific screening tool with very low false positive rates. Further large well conducted prospective studies are needed to assess its sensitivity with higher precision.

Citation of paper from this work

Thangaratinam S, Daniels J, Ewer AK, Zamora J, Khan KS. Accuracy of pulse oximetry in screening for congenital heart disease in asymptomatic newborns: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2007; 92: F176-80

14.2 Background

Congenital heart disease is the commonest group of congenital malformations and affects 7-8/1000 newborns.[36;37] It contributes to 3% of all infant mortality and 46% of deaths from congenital malformations, with most deaths occurring in the first year of life. [36] A significant proportion of these children require surgery in the first year.

One of the major contributors to increased infant mortality and morbidity is clinical deterioration and collapse prior to diagnosis and treatment.[38-40] Early detection of congenital heart disease in the asymptomatic period immediately after birth will reduce clinical deterioration by instigation of appropriate, timely management. Currently infants are screened to detect congenital heart disease by physical examination within 24 hours of birth and a further examination after 6-8 weeks.[328] However, this method of screening fails to detect up to 50% of congenital heart defects at birth.[329]

Pulse oximetry has been proposed as an alternative screening method for the detection of congenital heart defects. It is a simple, non invasive investigation which measures the percentage of haemoglobin in blood that is saturated with oxygen. It is proposed that the measurement of oxygen saturation identifies infants with mild cyanosis who do not have an audible murmur or other signs of cardiac abnormality and are not detected by routine clinical examination.[330] Several studies have reported the use of pulse oximetry as a screening tool for the detection of congenital heart disease.[331-338] Although very low false positive rates have been reported, individual studies have had only few cases with cardiac disease leading to imprecision in the estimation of true positive rates (sensitivity).

A recent Health Technology Assessment report reviewed the available evidence on the screening strategies for detection of congenital heart disease in newborns with the view to assist in policy making.[36] The review identified 4 studies in which pulse oximetry was used as a screening test for congenital heart disease in asymptomatic newborns. It did not pool the results statistically and suggested the need for further evaluation of pulse oximetry as a screening method. Since the publication of this report, further large primary studies have become available which may potentially alter the report's conclusion. We therefore conducted a systematic review to collate all results and to update information on accuracy of pulse oximetry to detect congenital heart disease in asymptomatic newborns.

14.3 Methods

The review was carried out with a prospective protocol using widely recommended methods.[55;230;236]

We searched MEDLINE (1996-2006), EMBASE (1996-2006), Cochrane Library (2006) and MEDION (a database of diagnostic test reviews set up by Dutch and Belgian researchers) for relevant citations using the search terms 'pulse NEAR oximetry', 'infant-newborn', 'neonate', 'newborn', 'infant', 'congenital heart disease'. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Language restrictions were not applied. A comprehensive database of potentially relevant citations was constructed.

Studies which evaluated the accuracy of pulse oximetry in asymptomatic newborns for the detection of congenital heart disease were selected in a two-stage process. First, the electronic

searches were scrutinised and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained by two independent reviewers (ST and JD). Secondly, final inclusion or exclusion decisions were made by the reviewers (ST and JD) after examination of these manuscripts. Studies which met the predefined and explicit criteria regarding population, tests, outcomes and study design were selected for the review. When disagreements occurred, they were resolved by consensus. In cases of duplicate publication, the most recent or complete versions were selected.

Information was extracted from each selected article on the study population including age, test characteristics together with frequency and method of testing, and methodological quality including verification of diagnosis of congenital heart disease by echocardiography. Accuracy data were used to construct 2 x 2 tables of pulse oximetry results (test positive if pulse oximetry values were below a threshold as defined in the primary study, and test negative if these were above the threshold) and presence or absence of congenital heart disease diagnosed by echocardiography (wherever employed). Where accuracy data were not extractable, we contacted the corresponding author by letter or email, to seek his or her assistance in data extraction.

All manuscripts meeting the selection criteria were assessed for their methodological quality. Quality was defined as the confidence that the study design, conduct and analysis minimised assessment bias in the estimation of test accuracy. Based on existing checklists,[55;58;232;236;339] quality assessment involved scrutinising study design and relevant features of the population, test and outcomes of the study. A study was considered to be of good quality if it used a prospective design, consecutive enrolment, full verification of the test result with reference standard, and had adequate test description.[58;232;236;339]

From individual studies, measures of accuracy like sensitivity and specificity were calculated with 95% confidence intervals (CI). The True Positive Rates (TPR) and False Positive Rates (FPR) for various test thresholds were plotted in the Receiver Operating Characteristics (ROC) space. We used a random-effects bivariate model to meta-analyse estimates of sensitivity and specificity. Rather than using a single outcome measure per study, like the diagnostic odds ratio in the summary Receiver Operating Characteristic (sROC) approach, the bivariate model preserves the two-dimensional nature of diagnostic data by directly analysing the logit transformed sensitivity log (sensitivity/(1-sensitivity)) and specificity log (specificity/(1-specificity)) of each study in a single model. This model estimates and incorporates the correlation that might exist between logit sensitivity and specificity within studies due to possible differences in threshold between studies.[59] A standard correction of adding 0.5 to all four cells of the 2x2 table was applied when either sensitivity or specificity was 100%. The model produces the following results: a random effect estimate of the mean sensitivity and specificity with corresponding 95% CI, the amount of between-study variation for sensitivity and specificity separately, and the strength and shape of the correlation between sensitivity and specificity. Using the parameters of the bivariate distribution we have calculated confidence ellipse around the summary estimates of sensitivity and specificity. All analyses were performed using MetaDisc statistical package[340] except to fit the bivariate model for which the Proc Mixed procedure in SAS version 8.2 for Windows (SAS Institute Inc, Cary, NC, USA) was used.

14.4 Results

14.4.1 Literature identification and study quality

Appendix 11 flow chart summarises the process of literature identification and selection. A total of

558 citations were identified by electronic searches. Detailed assessment of the papers led to inclusion of 8 primary articles that met the selection criteria including a total of 35960 newborns.[331-338] Salient features of each study according to the population subgroups, test characteristics and reference standards are provided in Appendix 26.

Pulse oximetry was performed on asymptomatic newborns in all studies, with three studies excluding newborns who were antenatally diagnosed to have congenital heart disease.[335;336;338] The studies measured either functional or fractional oxygen saturation by pulse oximetry with oxygen saturation below 95% considered as the cut off level in most studies. Functional saturation is the ratio of oxygenated haemoglobin to all haemoglobin capable of carrying oxygen, fractional saturation is the ratio of oxygenated haemoglobin to all haemoglobin (including those which do not carry oxygen). Fractional saturation is approximately 2% lower than functional saturation. There was variation in the age of first testing ranging from 2 hours to more than 24 hours. Four studies measured levels of oxygen saturation after 24 hours of birth or just before discharge.[332;335;336;338] The outcomes assessed were congenital heart disease or critical cardiovascular malformation in all studies. Six studies were prospective studies and two were case control studies. There was lack of blinding for the reference standard assessment in all the studies. There was differential verification of the pulse oximetry results for congenital heart disease by either echocardiography in neonates with low oxygen saturation or by clinical follow up in those with normal levels. The quality of the studies included in the review is provided in Appendix 15.

14.4.2 Accuracy of pulse oximetry as a screening tool for Congenital Heart Disease

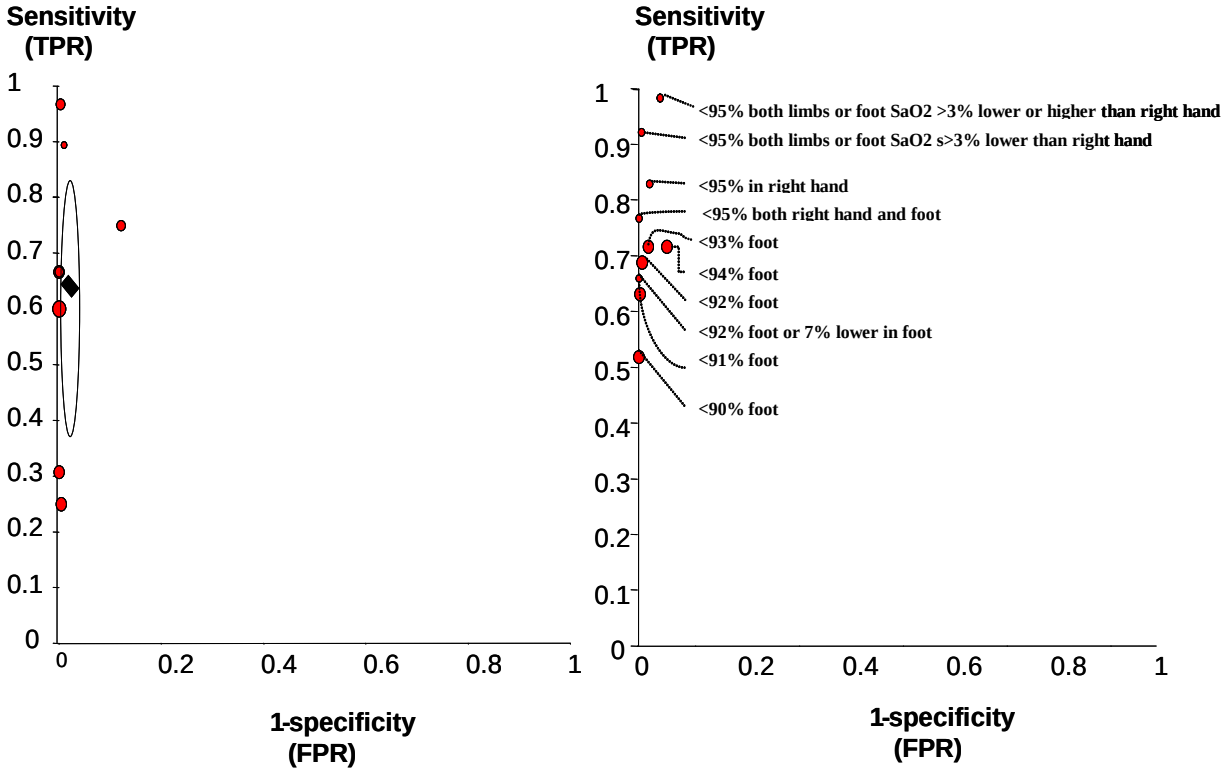
The sensitivity (True Positive Rate) of pulse oximetry for detection of CHD varied between 25% (95% CI, 13% to 41%)[341] and 98.5% (95% CI, 91.8% to 100%).[333] The test had high specificity in

seven studies [98% (95% CI, 98% to 99%) to 100% (95% CI 99.8% to 100%)] resulting in false positive rates between 0% and 2% (95% CI, 1% to 2%).[331-333;335-338] The case control study by Hoke et al[334] had relatively low specificity [88% (95% CI, 87 to 89)] and high false positive rate compared to other studies [12% (95% CI, 11% to 13%)] for threshold level of functional saturation less than 95% in the foot. The actual number of patients with false positive results was not certain in this study as not all newborns with abnormal screening tests underwent echocardiography or clinical examination. The highest sensitivity [98.5% (95% CI, 91.8% to100%)] was obtained using threshold levels of functional saturation <95% in both limbs or at least 3% difference in saturation between foot and right hand.[333] The highest specificity (100%) was obtained when the test was performed after 24 hours of birth or near discharge.[332;335;338] Only one study explored the added value of pulse oximetry above the accuracy achieved through clinical examination. The combination of pulse oximetry and clinical examination had a sensitivity of 76.9% (95% CI, 46.2% to 95%) and specificity of 99.9% (95% CI, 99.8% to 100%).[332]

Fig 14.1. True positive rates (TPR) and False positive rates (FPR) for various threshold levels of oxygen saturation ($SaO_{2)}$ measured by pulse oximetry for the detection of congenital heart disease in newborns

a. TPR and FPR of individual studies for the commonest threshold of SaO_2 <95% with summary estimates of sensitivity and specificity and confidence ellipse around the estimates

b. TPR and FPR for different threshold levels of SaO2



The bivariate summary estimates of sensitivity and specificity were 63% (95% CI, 39% to 83%) and 99.8% (95% CI, 99% to 100%) respectively, yielding a false positive rate of 0.2% (95% CI, 0% to 1%). The summary estimates of the individual studies are represented as a confidence ellipse in Fig 15.1a. The various other reported threshold levels of oxygen saturation and their accuracy measures are given in Fig 15.1b.

Table 14.1. The accuracy of pulse oximetry for diagnosing CHD in asymptomatic newborns

Test	*No. of patients*	*Sensitivity (TPR) % (95% CI)*	*Specificity % (95% CI)*	*False Positive Rate(FPR) % (95% CI)*
Most commonly used threshold				
saturation* ≤95% foot	11281	60 (14.7-94.7)	100 (100-100)	0
saturation* ≤95% foot or hand	2114	66.7(9.4-99.2)	99.9(99.7-100)	0.1(0-0.3)
saturation* ≤ 95% foot	3262	96.8(73.6-100)	99.7(99.5-99.9)	0.3(0.1-0.5)
saturation§ <95% foot	5626	25(12.7-41.2)	99.6(99.4-99.7)	0.4(0.3-0.6)
saturation* ≤ 95% foot	5292	66.7(9.4-99.2)	100(99.9-100)	0(0-0.1)
saturation§ <95% hand and foot	5211	30.8(9.1-61.4)	100(99.9-100)	0(0-0.1)
saturation* <95% foot	2733	75(57.8-87.9)	87.9(86.6-89.1)	12.1(10.9-13.4)
saturation* <95% foot	266	89.4(79.4-95.6)	99(96.4-99.9)	1(0.1-3.6)
Most accurate threshold				
saturation* <95% in both limbs or a differential of >3% between foot and right hand	266	98.5(91.8-100)		
Summary estimate	35785	63.4(38.7-82.5)	99.8(99-100)	0.2(0-1)

* functional oxygen saturation § fractional oxygen saturation
Summary using bivariate method of meta analysis

14.5 Discussion

Our review has identified pulse oximetry as a potentially useful screening test for congenital heart disease in asymptomatic newborns. It is a non-invasive, readily available, relatively cheap, well validated test performed currently by either nurses or doctors.[36] The high specificity reflecting the low false positive rate makes this test a suitable screening tool. The sensitivity of the test however is varied, with wide confidence intervals that may be attributed to the low prevalence of the condition. Previous individual studies have lacked the necessary large number of patients to confidently estimate the sensitivity of the test. Our review and the resulting meta-analysis have addressed this issue by providing a summary estimate of the accuracy measures by pooling the results of previously published studies.

The validity of our review findings depends on the methodology of the systematic review and the

quality of the individual studies included. An extensive literature search was performed in relevant databases without any language restrictions to minimise the possibility of missing any studies. The quality of most of the studies was compromised due to the differential verification by either echocardiography (in test positive cases) or clinical follow up (test negative) cases. However, this is perhaps unavoidable. Two were case control studies, a design that biases the results by overestimating the diagnostic odds ratio. Furthermore, the absence of blinding, absent or poor description of the test or reference standard could have affected the results of the review. The significant heterogeneity observed in the results could be a reflection of the type of saturation chosen for the cut off level (functional Vs fractional), method of testing and the inclusion or exclusion of newborns diagnosed to have congenital heart disease antenatally, thereby leading to spectrum variation. None of the studies evaluated acceptability of "babies" testing to parents and the psychosocial impact of false positive results or identification of non critical CHD.

We used bivariate analysis model for meta-analysis using a random effects approach to obtain summary estimates of both sensitivity and specificity. This model accounts for the heterogeneity between studies caused by different threshold settings. In addition, the model acknowledges the difference in precision by which sensitivity and specificity have been measured in each study. This means that studies with a larger number of patients with the target condition receive more weight in the calculation of the summary estimate of sensitivity, while studies with more patients without the target condition are more influential in the pooling of specificity. Finally the model accounts also for the residual heterogeneity due to clinical or methodological differences between studies. Unfortunately, we could not perform an explicit analysis of these potential sources of heterogeneity due to the limited number of studies included in our review.

14.6 Conclusion

Pulse oximetry has been shown to be a highly specific screening tool with very low false positive rates. Large well conducted robust studies are essential to confirm the value of pulse oximetry as a screening test, in isolation or in combination with clinical examination to obtain precise estimates of its sensitivity. Further evaluation is needed on the effect of screening on parents and its acceptability to parents and health care professionals, especially with the possibility of non significant lesions being detected during echocardiography and the costs and cost effectiveness of the screening program on healthcare services.

CHAPTER 15: CONCLUSION

15.1 Summary of findings

This chapter summarises the results of the individual chapters. The detailed results are provided separately within each of them. Below, is reproduced the table of structured questions from Chapter 1 (Table 15.1), with a final column of findings from the various chapters of this thesis:

Table 15.1: Structured questions of the chapters of this thesis with findings

Chapter Number	Population	Intervention or Test	Outcome(s)	Research Design	Results
Objective A: Delphi Survey of practice where there is no robust evidence					
2, 3	Women with pre eclampsia	Tests including clinical history, examination and investigation	Maternal and fetal mortality and morbidity	Delphi survey	Blood pressure and proteinuria were considered as the most important predictors with mean scores of 4.7 (± 0.47) and 4.6 (± 0.5) respectively followed by liver function tests (4.5, ± 0.52) and pre-existing medical conditions (4.4, ± 0.81). Full blood count (4.3, ±0.9), renal function tests (4.1, ±0.94) and multiple pregnancy (3.7, ±0.79) were the other tests that were scored as significant predictors by all the experts.
Objective B: To review the quality of systematic reviews in maternal and fetal medicine					
4	Maternal medicine reviews	Cochrane Vs Non Cochrane	Adherence to pre specified good quality items	Systematic review	Cochrane reviews had specified the question more than non Cochrane reviews (OR 20.3, 95% CI 1.1–381.3, p = 0.04). They also framed narrowly focussed questions (OR 30.9, 95% CI 3.7- 256.2, p = 0.001). Cochrane reviews attempted more often to include unpublished data in literature search (OR 5.6, 95% CI 1.9–16.4, p =0.002). Meta analysis technique (OR 3.7, 95% CI 1.3–10.8, p = 0.02) and assessment for heterogeneity (OR 38.1, 95%CI 2.1, 688.2, p = 0.01) was found to be employed significantly more often by Cochrane reviews.
5	Fetal medicine reviews	Quality across 4 areas: fetal aneuploidy, fetal therapy, fetal pathology and fetal growth	Adherence to pre specified good quality items	Systematic review	Fetal growth reviews performed significantly better than reviews in other areas in question specification ($p<0.03$), search without language restriction ($p<0.004$), assessment of risk of missing studies ($p<0.006$) and study quality assessment ($p<0.002$). There was no difference

					in other quality items.
Objective C: To undertake systematic reviews and meta analyses of therapy studies					
6	Pregnant women at risk of pre term labour	Progeterone Vs Placebo	Delivery before 34 weeks, 36 weeks, perinatal mortality and other clinically relevant outcomes	Systematic review and meta analysis	There were reductions in delivery rates before 37 weeks (OR 0.42, 95% CI 0.31 to 0.57) and 34 weeks (OR 0.51, 95% CI 0.34 to 0.77) as well as in respiratory distress syndrome (OR 0.55, 95% CI 0.31 to 0.96) with progestational agents.
7	Pregnant women with epilepsy on lamotrigine	Routine therapeutic monitoring Vs Management based on clinical features only	Seizures, any other relevant maternal and fetal outcome	Systematic review and meta analysis	The combined rate of seizure deterioration was 0.40 (95% CI 0.26 to 0.55) in women with lamotrigine dosage based on serum levels compared to 0.73 (95% CI 0.56 to 0.86) in those managed by clinical features alone.
Objective D: To undertake systematic reviews and meta analyses of test accuracy studies					
9	Women with pre eclampsia	Proteinuria	Adverse maternal and fetal outcomes	Systematic review and meta analysis	Sixteen primary articles with a total of 6749 women met the selection criteria. The area under the curve (AUC) for adverse maternal and fetal outcomes are 0.63 (95% CI 0.22, 0.91) and 0.59 (95% CI 0.36, 0.79) respectively.
10	Women with pre eclampsia	Uric acid	Adverse maternal and fetal outcomes	Systematic review and meta analysis	There were 18 primary articles that met the selection criteria, including a total of 3675 women. The area under the curve for adverse maternal and fetal outcomes were 0.75 (95% CI 0.46, 0.92) and 0.69 (0.39, 0.86) respectively.
11	Women with pre eclampsia	Liver function tests	Adverse maternal and fetal outcomes	Systematic review and meta analysis	There were 13 primary articles selected including a total of 2813 women. For predicting adverse maternal outcome, AUC was 0.79 (95% CI 0.51, 0.9). For predicting adverse fetal outcomes the AUC was 0.76 (95% CI 0.44, 0.93).
12	Women with pre eclampsia	Symptoms	Adverse maternal and fetal outcomes	Systematic review and meta analysis	Six primary articles with 2573 women were included. The AUC for predicting complications with symptoms of headache, epigastric pain and visual disturbances were 0.58 (95% CI 0.24, 0.86), 0.70 (95% CI 0.3, 0.93) and 0.74 (95% CI 0.33, 0.94). The sensitivity and specificity of headache to predict adverse maternal outcomes were 0.54 (95% CI 0.27, 0.79) and 0.59 (95% CI 0.38, 0.76) respectively. The sensitivity of epigastric pain and visual disturbances are 0.34 (95% CI 0.22, 0.5) and 0.27 (95% CI 0.07, 0.65) with a specificity of 0.83 (95% CI 0.76, 0.89) and 0.81 (95% CI 0.71, 0.88) respectively. The sensitivity and specificity of nausea and vomiting to predict adverse outcomes were 0.24 (95% CI 0.21, 0.27) and 0.87 (95% CI 0.85, 0.89) respectively.

13	Women with pre eclampsia	Blood pressure	Adverse maternal and fetal outcomes	Systematic review and meta analysis	Eight articles with 2304 women evaluated the accuracy of blood pressure in predicting adverse outcomes. The area under the curve (AUC) for any adverse maternal outcome was 0.68 (95% CI 0.29, 0.92).
14	Newborns	Pulse oximetry	Congenital heart disease (CHD)	Systematic review and meta analysis	8 studies with 35,960 newborns were included. The summary estimates of sensitivity and specificity for detecting CHD were 0.63 (95% CI 0.39, 83) and 0.998% (95% CI, 0.99, 100) respectively, yielding a false positive rate of 0.2% (95% CI, 0% to 1%).

Accuracy of tests in pre-eclampsia

Proteinuria has usually been associated with increase in maternal and fetal mortality and morbidity. Our review has shown that the magnitude of proteinuria in women with pre-eclampsia is a poor predictor of the major maternal and fetal complications. The review on uric acid presents the best available evidence so far in addressing the question of significance of uric acid levels as a predictor of maternal and fetal complications in pre-eclampsia. Although uric acid as a marker may be of value in detecting pre-eclampsia, it has been identified as a poor predictor of any complications of pre-eclampsia. The provision of likelihood ratios stratified by the severity of pre-eclampsia and test thresholds will enable clinicians to understand the poor clinical value of this test in predicting complications in women with pre-eclampsia. In women with preeclampsia, LFTs had at best moderate prediction of maternal and fetal complications. The test specificity, however, was better than sensitivity. This meant that with a positive test result one could be more confident about predicting poor outcome than one could about ruling out complications with a negative result. Among women with pre-eclampsia, symptoms of visual disturbance and epigastric pain were moderately good predictors of maternal complications. Their predictive accuracy was better than headache as a test. The symptoms overall had high specificity than sensitivity. Thus, the presence of symptoms is clinically more useful for *ruling in* complications in comparison to their absence for *ruling out* complications. Blood pressure was a better predictor of adverse fetal than maternal

outcomes. Both sensitivity and specificity were lower for maternal complications than for fetal complications. A high BP reading (160/100) is more likely to rule in adverse fetal outcomes, whereas a BP<160/100 is less likely to rule out a complication. The same phenomenon was observed for cut off levels of MAP>140 for eclampsia and abruption.

15.2 Strengths and limitations

The topic areas for the systematic reviews performed in the thesis were identified in a systematic, structured way through Delphi survey and review of existing reviews. The systematic reviews and the survey have been performed using robust methodology.[55;172] An extensive literature search was performed in relevant databases without any language restrictions to minimise the possibility of missing any studies. Study quality was evaluated rigorously in the reviews and data extraction was done using pre determined data extraction forms in duplicate. In the review of effectiveness of progesterone in reducing pre term birth, both conventional and cumulative meta-analyses was carried out, to explore the size and significance of the effects as trials accumulated over time, and to evaluate the impact of quality of trials on effects. Furthermore, the applicability of the evidence to women at various baseline risks was assessed, and the evidence for safety of progestational agents was reviewed. Methodological deficiencies like verification bias and differential use of reference standards did not apply to the studies in the diagnostic reviews ensuring inclusion of acceptable quality studies. Meta analysis was performed where appropriate, allowing for heterogeneity and bivariate approach was used in the diagnostic reviews to confirm the robustness of the results.

A significant limitation of the pre-eclampsia review was the heterogeneity noticed between individual studies with regards to population, definition of pre-eclampsia, test thresholds, frequency of testing, interval between the test and outcome, and reference standards. Furthermore there is inter and intra observer variation in the performance and interpretation of the test results. Lack of data on the results of other tests performed in these women meant that it was not possible to assess

the value of other tests on the performance of the test under review. They do not take into account the predictive role of more than one test result on the outcome. Furthermore, there was no separate quantification of risks especially in women with early onset pre eclampsia, given that gestational age was the most important determinant of perinatal outcome.[342] Clinicians are hesitant to advocate expectant management due to uncertainties about the scale of maternal risk. Given the small number of the individual adverse outcomes, the studies did not have suffient sample size for precise results. Due to the rarity of the outcome of perinatal deaths, the results were imprecise for the effectiveness of progesterone in women at risk of pre term labour. The therapeutic review on the effectiveness of AEDs in pregnant women with epilepsy had very small studies with variable quality with ensuing imprecise results.

15.3 Implications for clinical practice

- Blood pressure is believed to be the most important predictor of adverse outcomes in women with pre eclampsia according to Delphi survey of the experts. This will need to be a target for clinical management in pre eclampsia.

- Progesterone should be offered as a treatment option in women at risk of pre term labour given the very large treatment effects of progesterone in clinically important outcomes of delivery before 34 weeks (50% reduction in odds) and respiratory distress syndrome (45% reduction in odds) with evidence of safety.

- Estimation of levels of proteinuria in women is not a clinically useful test to predict fetal or maternal complications in women with pre eclampsia.

- Uric acid is not a significant predictor of individual adverse maternal or fetal outcomes in women with pre eclampsia.

- An abnormal liver function test in women with pre eclampsia has a moderate predictive value for identifying women at increased risk of maternal and fetal complications. An abnormal test result is more likely to 'rule in' a complication than a normal result 'ruling out' disease.

- In pre eclampsia, the presence of symptoms is more useful in their ability to predict complications compared to their absence in confidently excluding adverse events.

- An abnormal pulse oximetry reading in the newborn is very likely to identify congenital heart disease due to high specificity and very low false positive rate.

- The poor quality and small size of the studies evaluating the effective monitoring regimes (routine serum drug levels vs clinical features alone) in pregnant women with epilepsy on the anti epileptic drug lamotrigine means that there is very weak recommendation to follow either of the regimen.

15.4 Implications for research

- The quality of currently published systematic reviews in maternal and fetal medicine is variable. Future reviews should employ robust methods.

- The systematic review of tests in pre eclampsia identified the:
    - paucity of quality primary studies to evaluate the predictive accuracy of tests

- poor quality, such that studies varied in design and conduct, with lack of details about the tests and reference standards, the duration between tests and outcome
- the effect of other risk factors and interventions on prediction of complications
- lack of information to evaluate the accuracy of combination of tests; inadequate sample size to precisely estimate accuracy measures.

This has provided the evidence to justify a large prospective study in this area through a successful NIHR (National Institute for Health Research) grant to conduct a large multicentre prospective study, Prediction of Risks in Early onset Pre eclampsia (PREP) study. PREP will develop a prediction model in women admitted with early onset pre eclampsia for timely assessment of the risk of adverse maternal and fetal outcomes at 48 hours and at discharge and externally validate the model. The data collated give face validity of the choice of tests chosen for use in the prediction model.

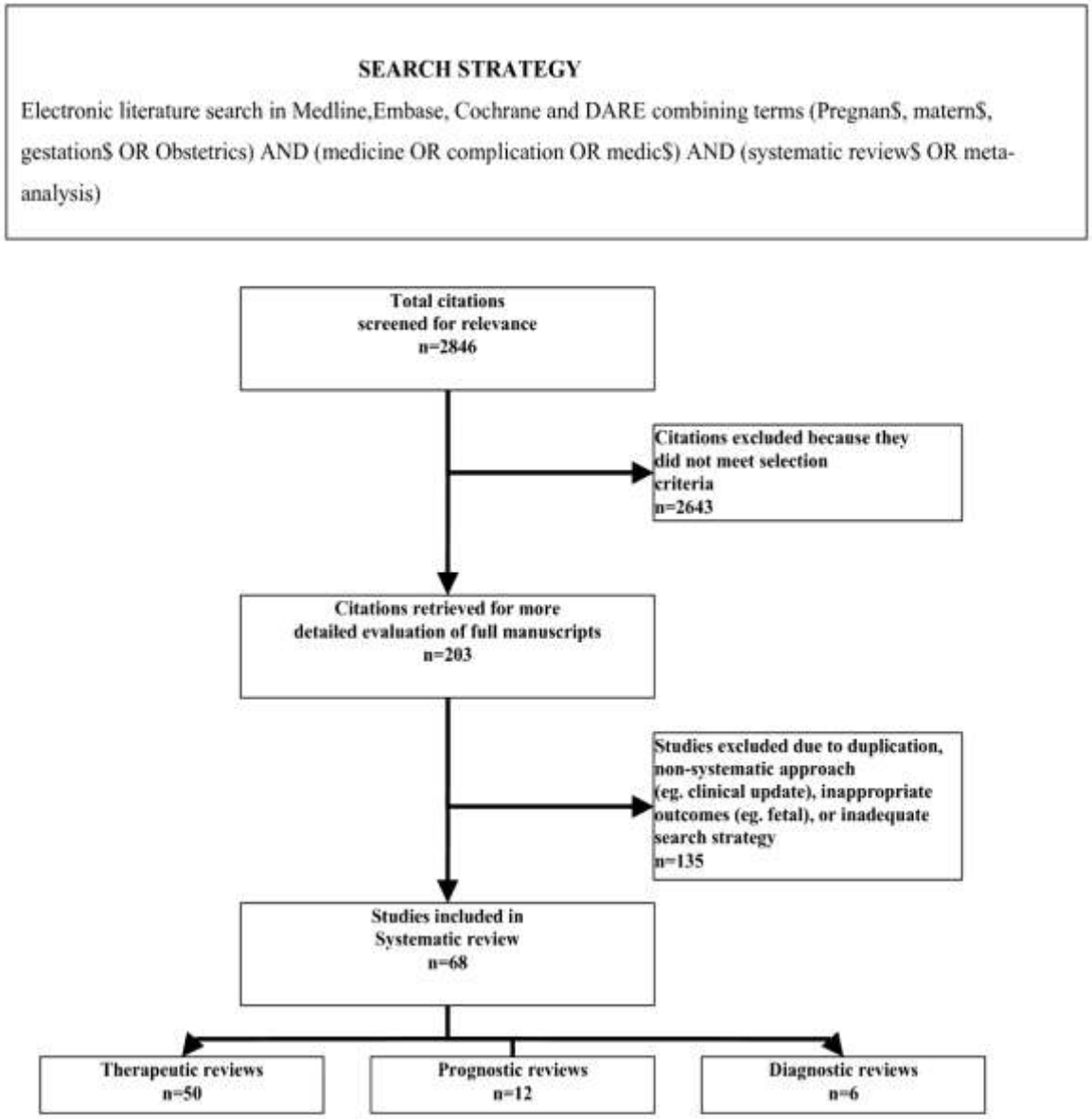
- The pulse oximetry test had high specificity but varied sensitivity in detecting congenital heart disease in newborn. The findings led to the successful NIHR proposal for the multicentre Pulse Ox study that will assess the accuracy of pulse oximetry as a screening tool for congenital heart disease in newborn babies and evaluate its cost-effectiveness.

- The evidence for the effective monitoring regimen in preventing seizures in pregnant women with epilepsy on the anti epileptic drug (AED) lamotrigine is of poor quality, indirect with imprecise results. The findings of this review had led to the start of a pilot study, SOAP (Study of Optimal Anti epileptic Drugs in Pregnancy) funded by the Research and Development (R & D) department of the Birmingham Women's Hospital. More recently, it has contributed to the successful HTA grant for a multicentre randomised controlled trial in this area, AntiEpileptic drug (AED) Management in PREgnancy: An

evaluation of effectiveness, cost effectiveness and acceptability of dose adjustment strategies (EMPiRE trial).

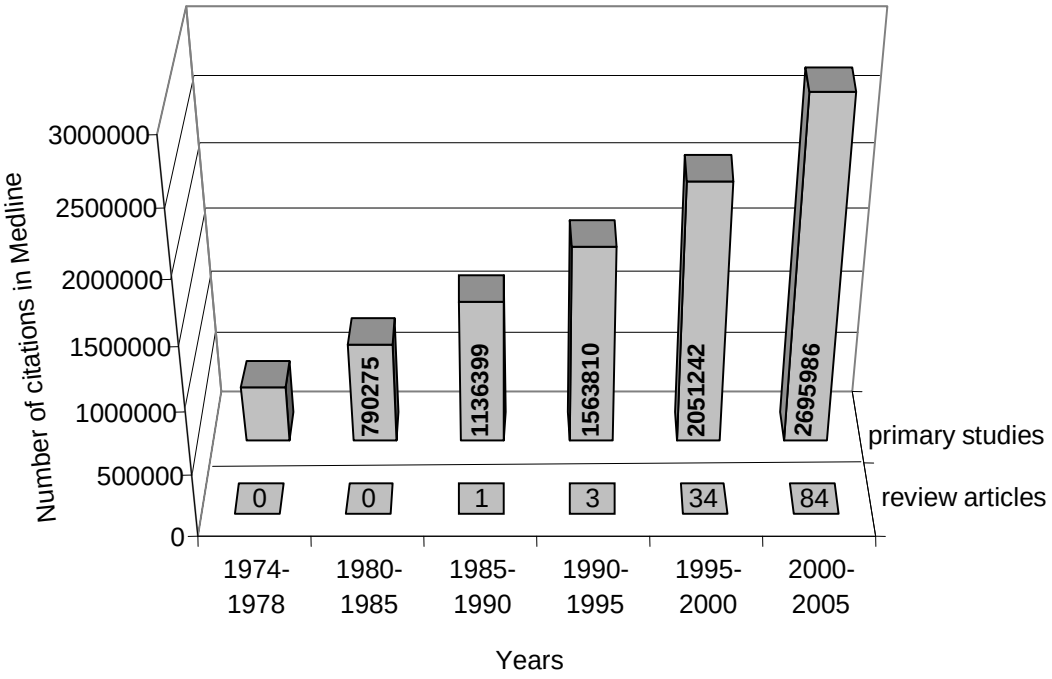
APPENDICES

Appendix 1. Flow chart of literature identification and study selection in the review of maternal medicine reviews

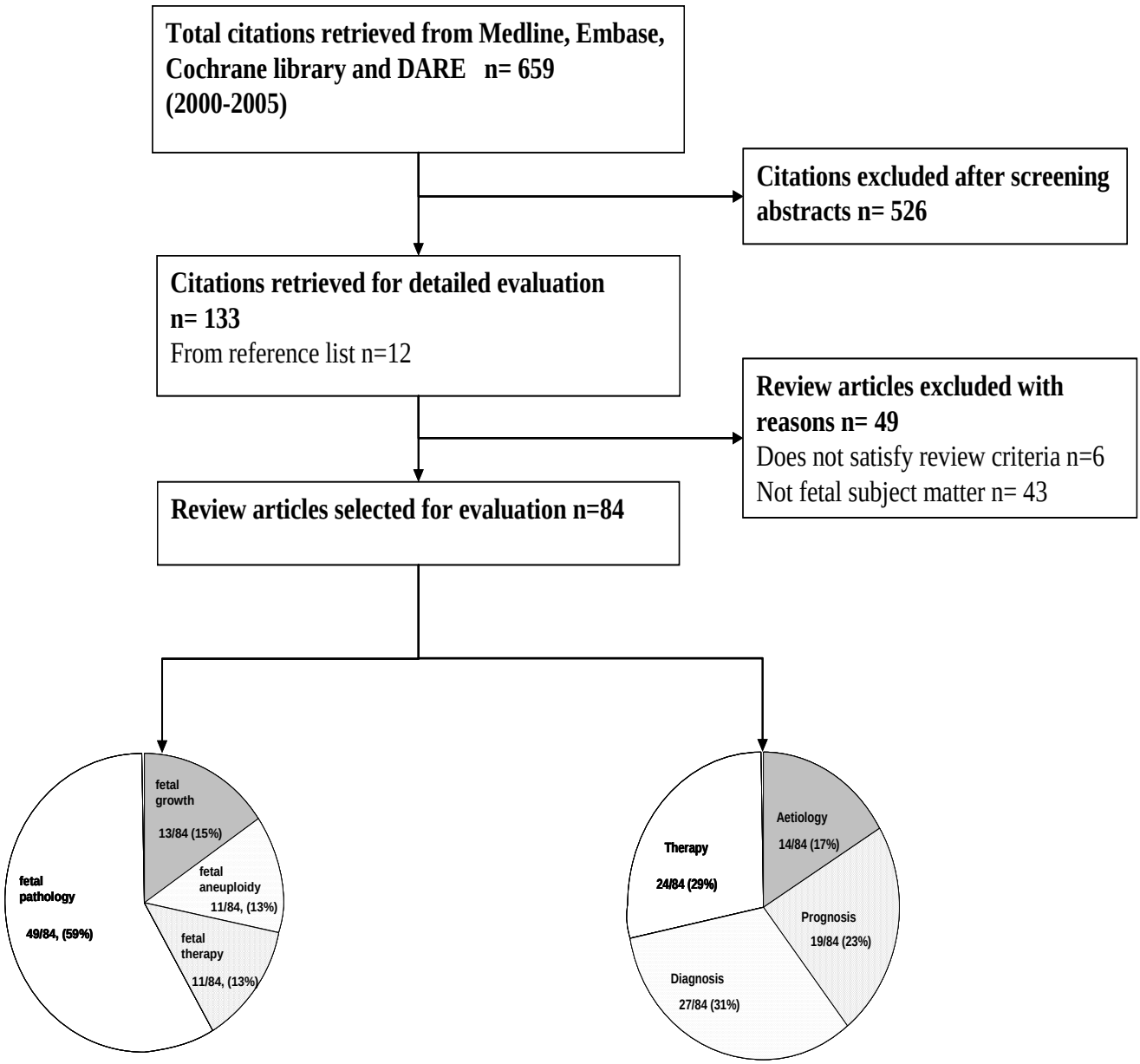


Appendix 2. Growth of primary research in fetal medicine and lack of corresponding development in their systematic reviews.

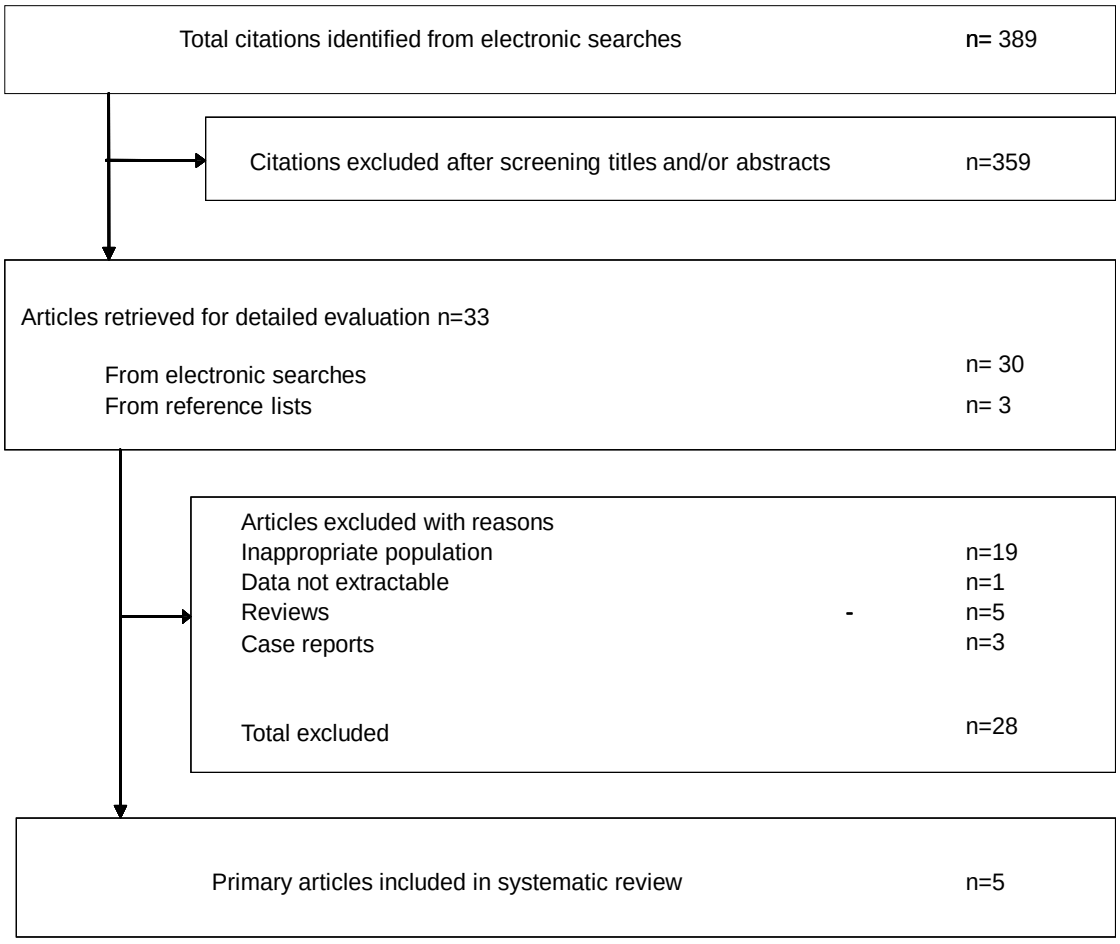
(Numbers within figure represent cumulative number of citations)



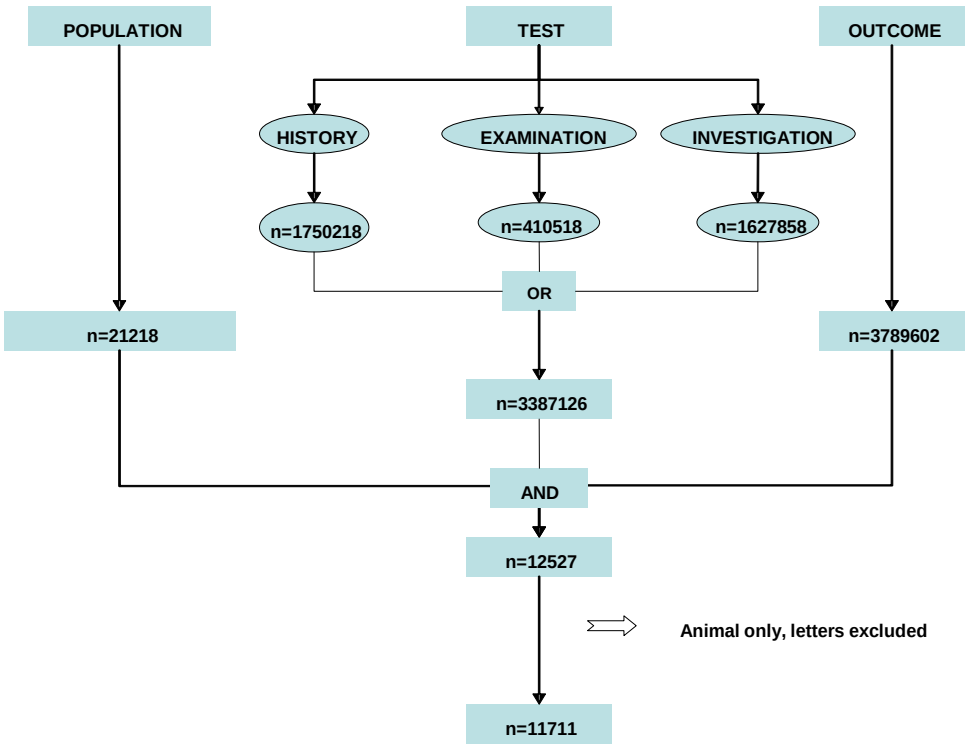
Appendix 3. Flow chart of literature identification and study selection in the review of fetal medicine reviews



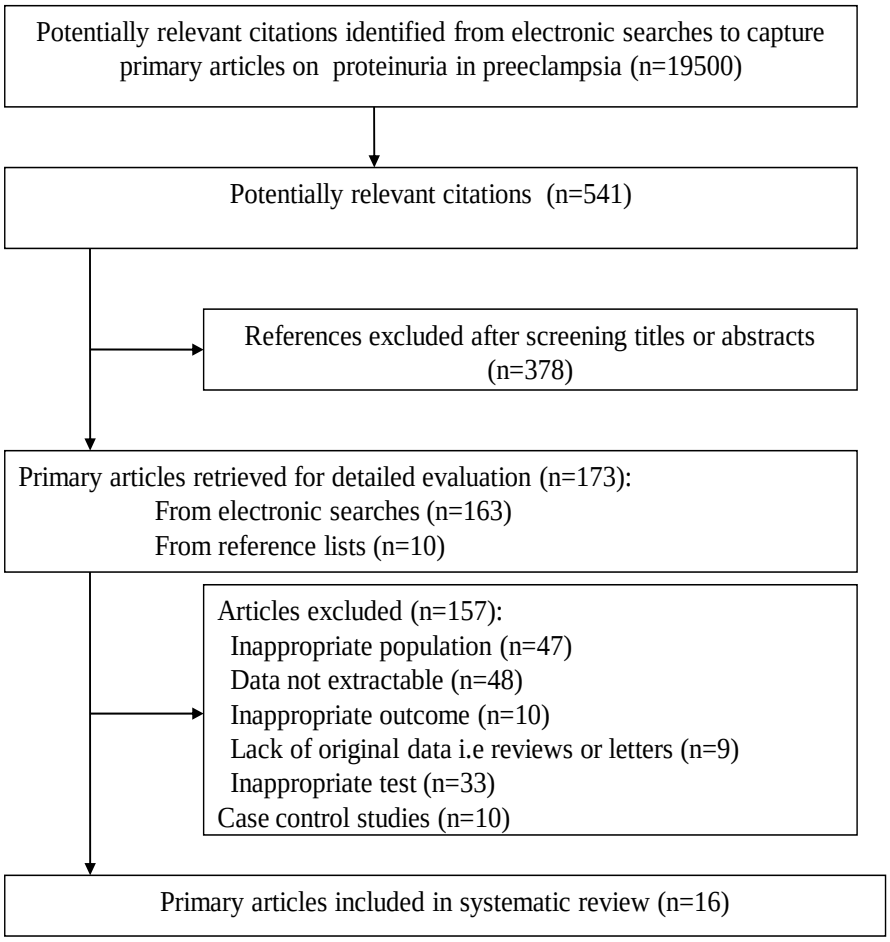
Appendix 4. Flow chart of literature identification and study selection review of effectiveness of lamotrigine dosage based on serum levels vs clinical features in the management of pregnant women with epilepsy



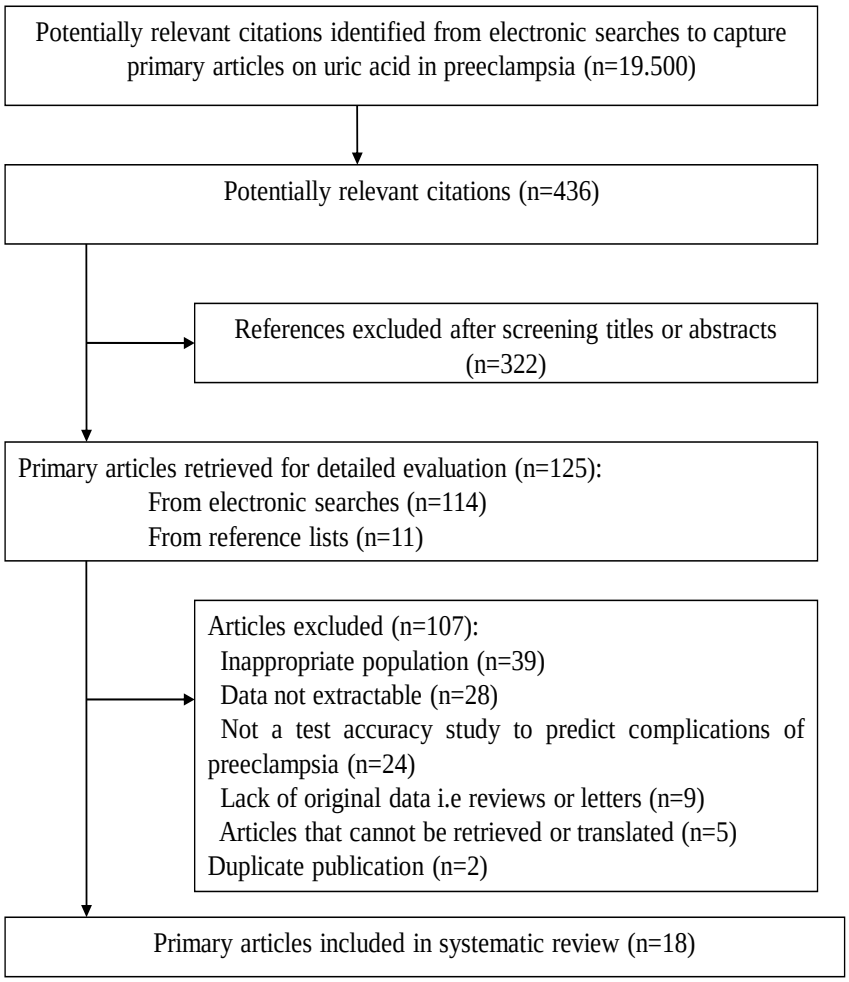
Appendix 5. Flow chart of literature identification in Medline and study selection process for systematic review of tests predicting complications in pre eclampsia



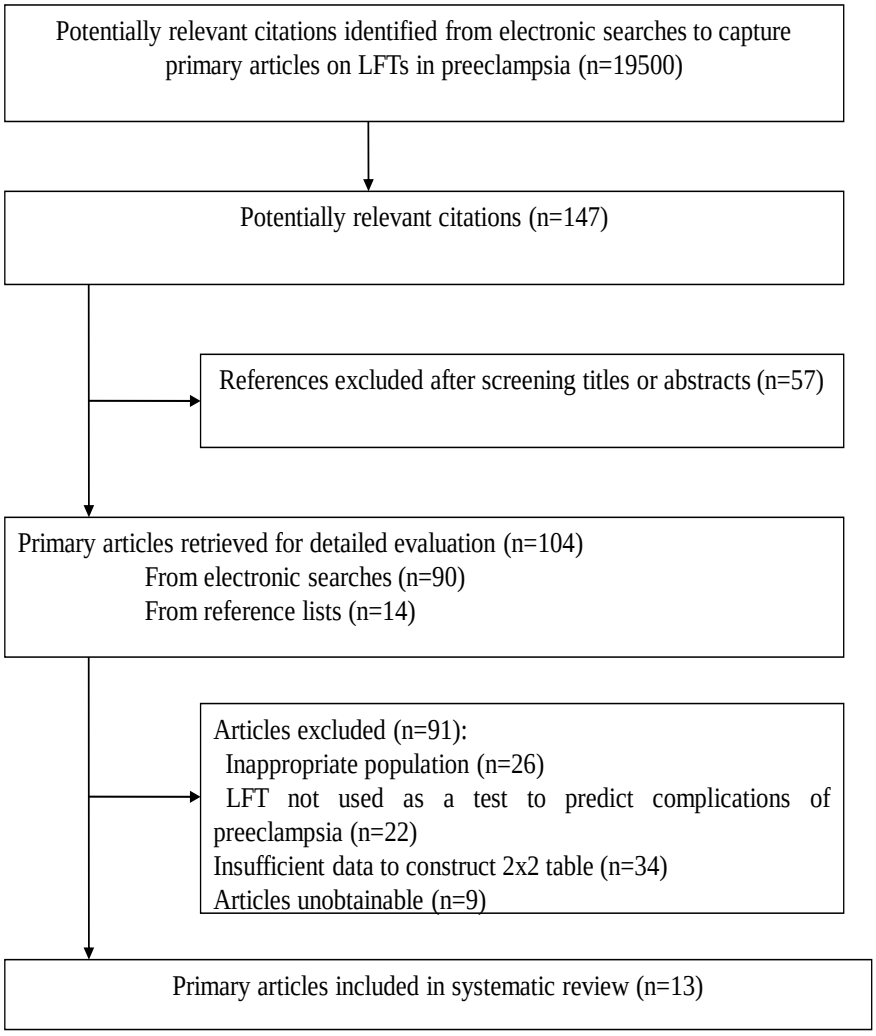
Appendix 6. Flow chart of literature identification and study selection for role of proteinuria in predicting maternal and fetal complications in preeclampsia



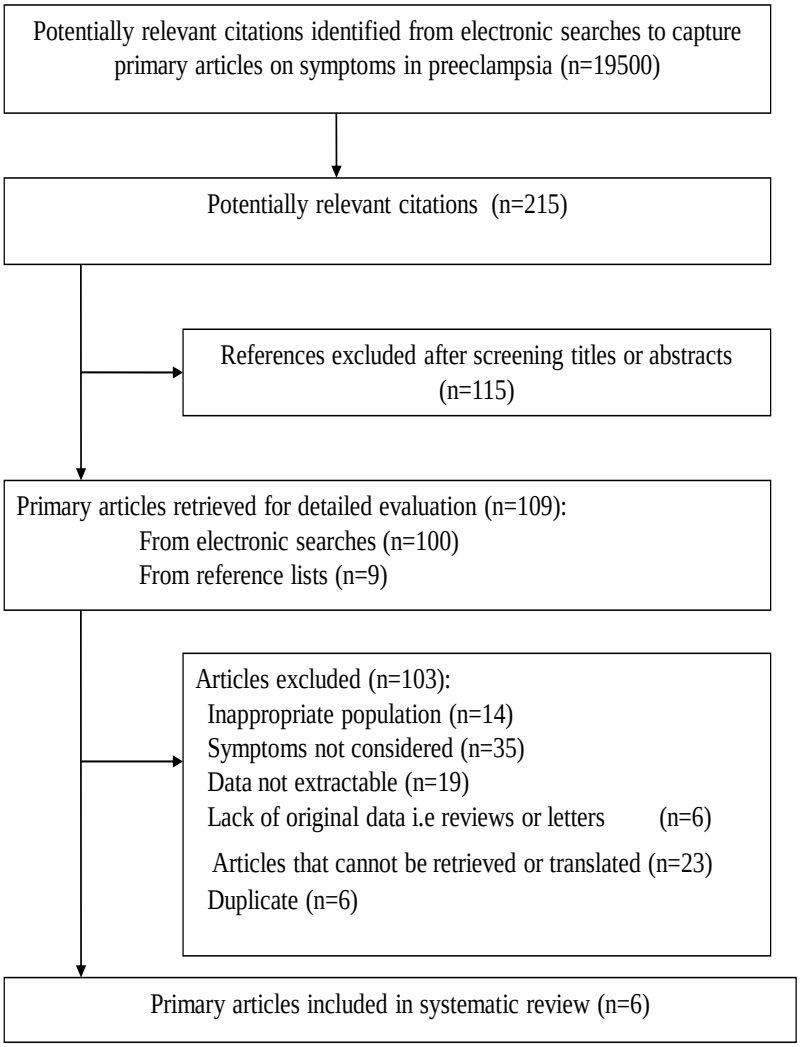
Appendix 7. Flow chart of literature identification and study selection process for role of uric acid in predicting maternal and fetal complications in preeclampsia



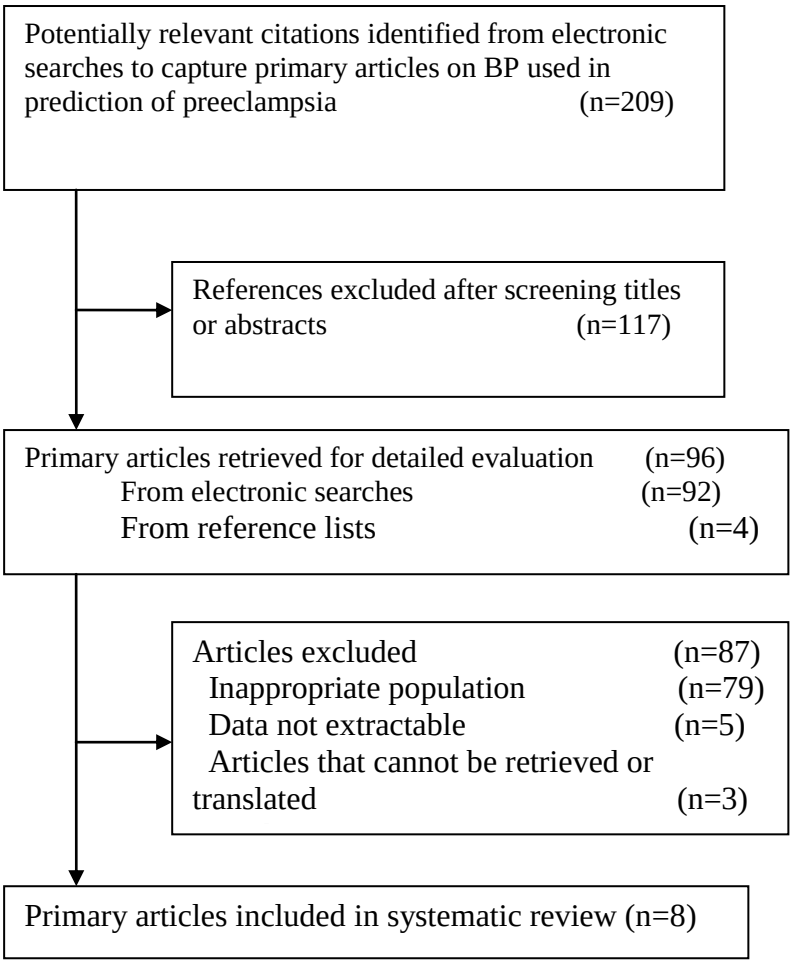
Appendix 8. Flow chart of literature identification and study selection process for role of liver function tests (LFT) in predicting maternal and fetal complications in preeclampsia



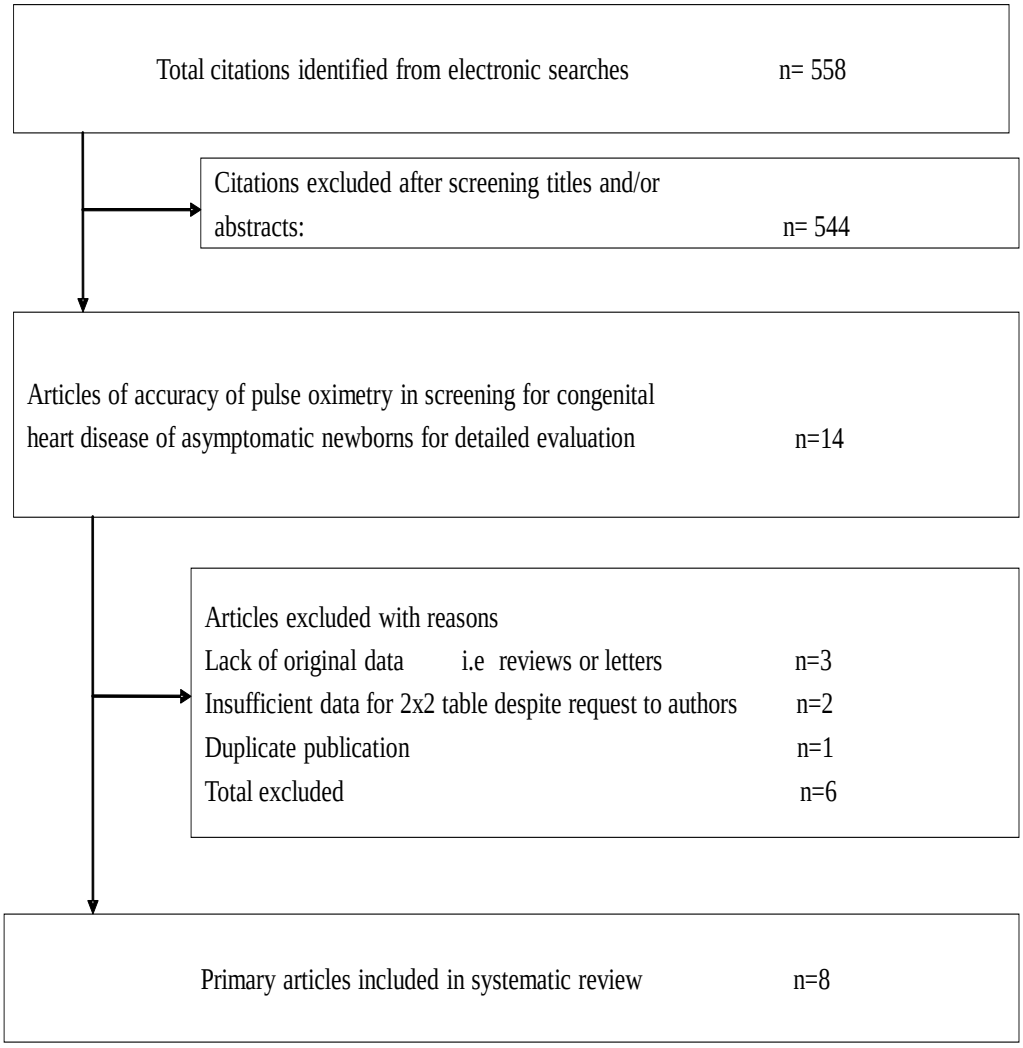
Appendix 9. Flow chart of literature identification and study selection process for role of symptoms in predicting maternal and fetal complications in preeclampsia



Appendix 10. Flow chart of literature identification and study selection process for role of blood pressure in predicting maternal and fetal complications in pre eclampsia



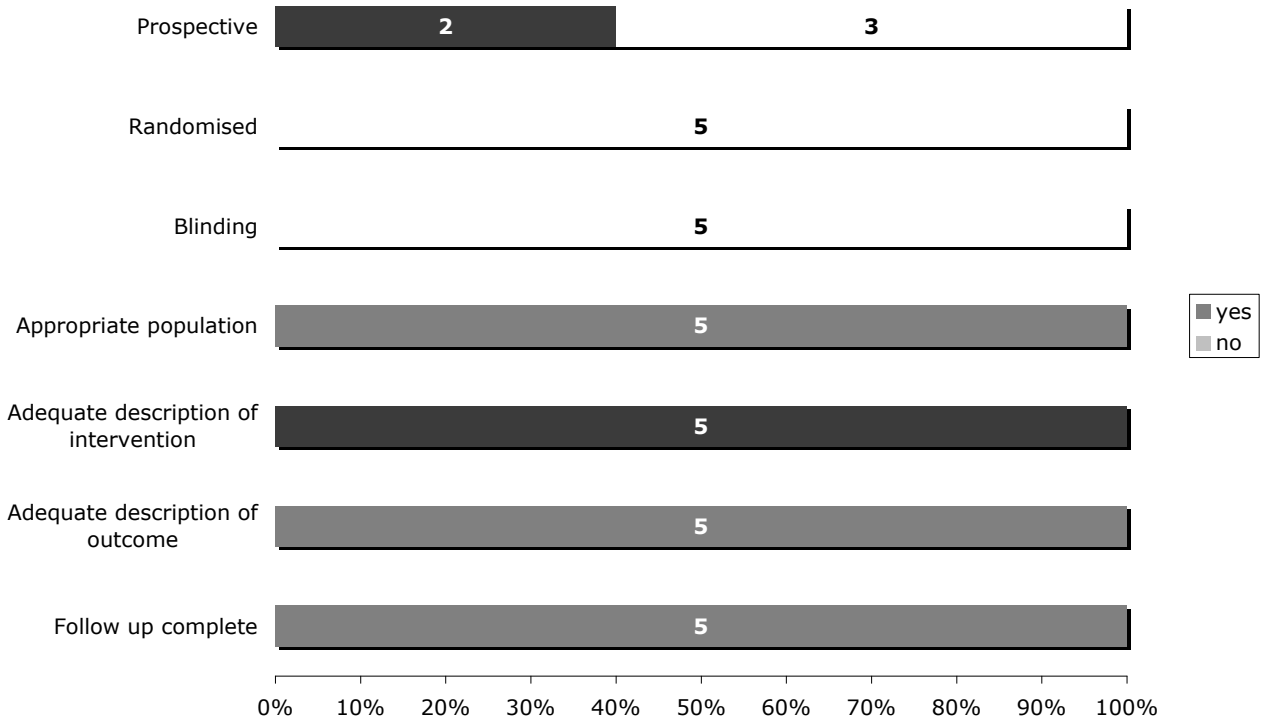
Appendix 11. Flow chart of literature identification and study selection process for systematic review of pulse oximetry as a screening test for congenital heart disease in newborn



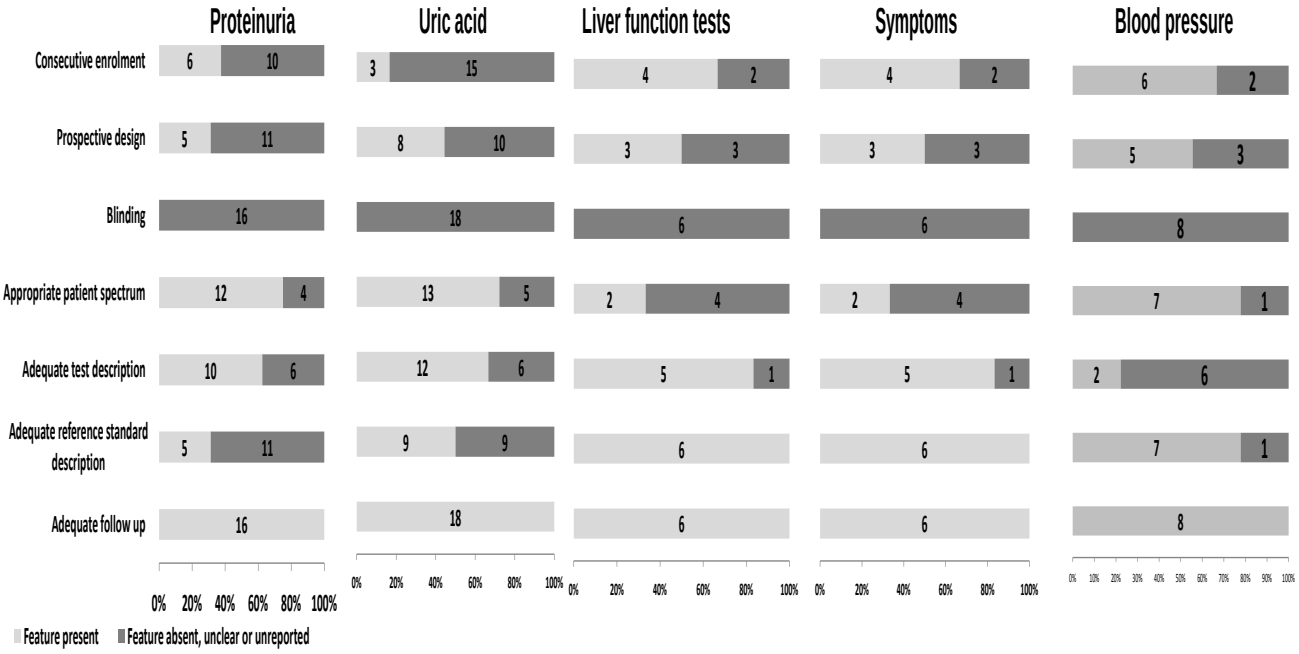
Appendix 12: Quality of trials included in the systematic review on the use of progestagens for the prevention of preterm birth

Study (Year)	Randomisation and Concealment	Blinding	Description of withdrawals	Follow up (%)	Quality score[343]
da Foncesca et al 2003	Adequate randomisation using random number table; Concealment adequate with consecutive sealed envelopes	Double blind	Yes	91	5
Meis et al 2003	Adequate randomisation by computer generated sequence; Adequate concealment	Double blind	Yes	99	5
Noblot et al 1991	Adequate randomisation using random number table; Adequate concealment	Double blind	Yes	100	5
Yemini et al 1985	Inadequate randomisation by last digit of registration number; Concealment inadequate	Double blind	Yes	99	2
Sondergaard 1985	'Randomised': details not given; Concealment unreported	Double blind	Yes	100	2
Johnson et al 1975	'Random double blind fashion': details not given; Concealment unreported	Double blind	Yes	86	2
Papiernik-Berkhauer 1970	'Randomised': details not given; Concealment unreported	Not known	Yes	100	1
Le Vine et al 1964	Inadequate randomisation by alternate placement in two groups; Concealment inadequate	Double blind	Yes	54	2
Swyer et al 1953	Inadequate randomisation by alternate assignment to each trial arms in one centre; "at random" in the other centre, but details not given; Concealment unreported	None	Yes	100	1

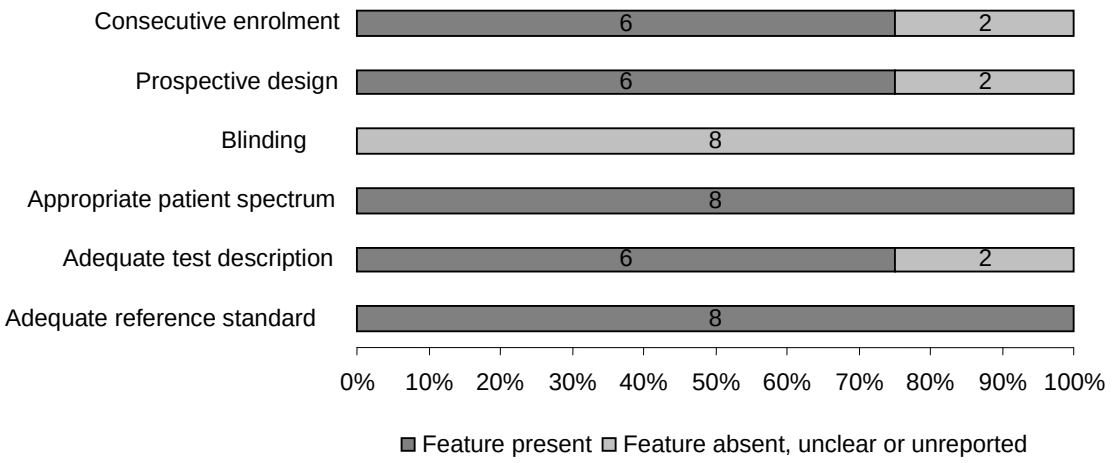
Appendix 13. Quality of studies included in the systematic review evaluating management of pregnant women on lamotrigine based on regular serum levels or clinical features alone



Appendix 14. Quality of included studies in the reviews of tests that predict complications in women with pre eclampsia



Appendix 15. Quality of included studies in the review of pulse oximetry as a screening test in the detection of congenital heart disease in newborn



Appendix 16. Details of included reviews in review of fetal medicine reviews

Author	Year	Topic (classifications)	No of Included studies	No of Infants	Summary of findings
Kramer[344]	1987	Determinants of growth in utero (growth, etiology)	895	Not reported	Pathophysiological factors reviewed. From this smoking cessation, calorie supplementation and malaria prophylaxis thought to be beneficial
Chang et al[345]	1992	Prediction of the SGA infant with ultrasound (growth, prognostic)	60	Not reported	In high risk subjects abdominal circumference below the tenth centile and estimated fetal weight below the tenth centile have the best association with SGA
Ukwu et al[346]	1992	HIV in pregnancy and perinatal infection (pathology, prognostic)	Not reported	Not reported	Majority of transmission occurs peripartum by a minor subset of HIV stains.
Giles et al[347]	1993	Use of Doppler ultrasound in high risk pregnancy (pathology, diagnostic)	6	4235	Significant reduction in perinatal mortality especially intrauterine deaths
Alfirevic et al[348]	1995	Doppler ultrasonography in high risk pregnancies (pathology, diagnostic)	12	7474	Associated with reduction in perinatal deaths
Forouzan[349]	1995	Absent end diastolic flow in the umbilical artery (pathology, prognostic)	Not reported	Not reported	Intense surveillance required and delivery at later gestations
Gross et al[350]	1995	Isolated choroid plexus cysts and trisomy 18 (aneuploidy, diagnostic)	13	748	Poor positive predictive value for isolated CPC and trisomy 18 does not support invasive testing on isolated finding

Crowther et al[351]	1996	Caesarean delivery for second twin not presenting cephalically (pathology, therapeutic)	1	120	No improvement in neonatal outcome, increased maternal febrile morbidity
Say et al[352]	1996	Calcium channel blockers for impaired fetal growth (growth, therapeutic)	1	100	Insufficient evidence to evaluate
Say et al[353]	1996	TENS for suspected placental insufficiency	0	0	Insufficient evidence to recommend practice
Say et al [354]	1996	Plasma volume expansion for suspected impaired fetal growth (growth, therapeutic)	0	0	Inadequate evidence exists to support practice
Schumacher et al[355]	1996	Fetal transfusion for red blood cell alloimmunization (therapy, therapeutic)	Not reported	Not reported	Transfusion is the best therapy remote from term, overall neonatal survival exceeds 80%
Sherer et al[356]	1996	Prenatal ultrasound assessment of ductus arteriosus (pathology, diagnostic)	Not reported	Not reported	Knowledge of pathophysiology and ultrasonography may aid management of complicated pregnancies
Sherer et al[357]	1996	Prenatal ultrasound assessment of ductus venosus (pathology, diagnostic)	Not reported	Not reported	Knowledge of pathophysiology and ultrasonography may aid management of complicated pregnancies
Smith et al[358]	1996	Triple screen versus double screen for trisomy 21 detection (aneuploidy, diagnostic)	8	143094	Triple test improves the detection of trisomy 21

Giacoia[359]	1997	Fetomaternal haemorrhage (pathology, prognostic)	Not stated	134	Alternative early detection methods needed, the role of in utero transfusion needs to be defined and long term follow up is needed
Goffinet et al[360]	1997	Use of Doppler ultrasound in high and low risk pregnancies (pathology, prognostic)	13	9162	One third reduction in perinatal death in high risk pregnancies
Gulmezoglu et al[361]	1997	Effectiveness of interventions to prevent or treat impaired fetal growth (growth, therapeutic)	126	Not reported	Most interventions have no effect on perinatal outcome. Antimalarial prophylaxis in primigravidae, smoking cessation and balanced protein/energy supplementation may be beneficial
Sherer et al[362]	1997	First trimester screening for fetal aneuploidy (aneuploidy, diagnostic)	Not recorded	Not recorded	First trimester nuchal translucency and maternal biochemistry are feasible screening methods
Sherer et al[363]	1997	Middle cerebral artery Doppler (pathology, diagnostic)	Not recorded	Not recorded	May assist diagnosis and management of complicated pregnancies
Conde-Agudelo et al[364]	1998	Triple test as screen for Down syndrome (aneuploidy, diagnostic)	20	194326	Effective screening method more effective in older than younger women
Giles et al[365]	1998	Doppler ultrasound in multiple pregnancy (pathology, diagnostic)	13 (1 RCT)	Not reported	appears to be useful in management of twins and in delineating those complicated by FGR and TTTS
Sherer et al [366]	1998	First trimester ultrasonography of multiple gestation (pathology, diagnostic)	Not reported	Not reported	Ultrasonography is useful in first trimester of multiple pregnancies.
Sherer et al[367]	1998	Antepartum fetal intracranial haemorrhage-predisposing factors and sonography (pathology, etiology)	Not reported	Not reported	Predisposing factors and sonographic findings reviewed

Sherer et al [368]	1998	Prenatal ultrasonographic diagnosis of fetal intracranial tumours (pathology, diagnostic)	Not reported	Not reported	Sonographic findings associated with different types of fetal tumours described
Thummala et al[369]	1998	Isolated single umbilical artery and risk of congenital malformations (pathology, prognostic)	37	643338	Isolated single umbilical artery has a small association with minor renal abnormalities
Yaegashi[370]	1998	Parvovirus B19 related hydrops fetalis following maternal infection (pathology, etiology)	9	1194	Timing correlates with hepatic period of haemopoetic activity
Brumback et al[371]	1999	Adverse effects of CVS (pathology, etiology)	31	1643655	CVS may be associated with an increased relative risk of limb defects between 2.4 and 8.7
Farrell et al[372]	1999	Intrapartum umbilical artery Doppler and adverse perinatal outcome (pathology, prognostic)	8	2700	Poor predictor of adverse perinatal outcomes
Pattinson et al[373]	1999	Cardiotocograph for antepartum fetal assessment (pathology, diagnostic)	4	1588	Not enough evidence exists to assess usefulness and limitations
Sherer et al[374]	1999	First trimester nuchal translucency screening for aneuploidy (aneuploidy, diagnostic)	Not reported	Not reported	Nuchal thickness >3mm between 10-4 weeks gestation may act as a screen for aneuploidy
Sherer et al[375]	1999	Ultrasound to diagnose conditions associated with potential umbilical cord compression (pathology, diagnostic)	Not reported	Not reported	Lack of prospective studies but suggests usefulness
Wallon et al[376]	1999	Treatment of congenital toxoplasmosis in pregnancy (therapy, therapeutic)	9	2077	Insufficient evidence that treatment reduces transmission

Yoder et al[377]	1999	Risk of trisomy 18 and 21 in second trimester fetus with isolated choroid plexus cyst (aneuploidy, diagnostic)	13	246545	Likelihood of trisomy 21 not increased. Trisomy 18 risk 13.6 times greater- suggest offering karyotype to maternal age >36 or serum screen >1:3000
Alfirevic et al[378]	1996	Biophysical profile for assessment in high risk pregnancies (pathology, diagnostic)	4	Not reported	Insufficient evidence to evaluate use
Chein et al[379]	2000	Uterine artery Doppler and prediction of pre eclampsia and intrauterine growth restriction (pathology, diagnostic)	27	Not reported	Insufficient evidence to recommend as a screening test
Hubinont et al[380]	2000	Treatment of twin to twin transfusion syndrome (TTTS) by amniodrainage and septostomy (therapeutic)	Not reported	Not reported	Severe TTTS amniodrainage and septostomy have similar survival to laser therapy
Skari et al[381]	2000	Mortality factors for congenital diaphragmatic hernia (pathology, prognostic)	51	2980	Prenatal diagnosis and associated abnormalities influence mortality rate
Van Dyke et al[382]	2000	Pharmacogenetics of congenital defects (pathology, etiology)	Not reported	Not reported	Gene polymorphisms for specific enzymes may be related to susceptibility to fetal anomaly
Von Dadelszen et al[383]	2000	Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension (growth, etiology)	45	3773	Treatment induced falls in maternal blood pressure may affect fetal growth
Vos et al[384]	2000	Accuracy of ultrasound detection of spina bifida in the second trimester (pathology, diagnostic)	13	123872	Overall sensitivity was 71%, specificity 100%
Whitecar et al[385]	2000	Songraphic methods to detect anaemia in red blood cell alloimmunisation (pathology, diagnostic)	Not reported	Not reported	Sonographic techniques may reduce the number of invasive procedures used to detect anaemia

Woo et al[386]	2000	Single fetal death in twins outcome and management (pathology, prognostic)	8	208	should be managed in tertiary centre and multidisciplinary approach required
Allen et al[387]	2001	Management of monoamniotic twins (pathology, prognostic)	49	113	Regular surveillance and appropriate steroids improves perinatal outcome
Crowther et al[388]	2001	Hospitalization and bed rest for multiple pregnancy (therapy, therapeutic)	6 (RCT)	1400	No sound evidence to support the policy of routine hospitalization
Divakaran et al[389]	2001	Noninvasive techniques to detect fetal anaemia secondary to red blood cell alloimmunisation (pathology, diagnostic)	8	362	Literature reporting non-invasive techniques methodologically poor
Murphy et al[390]	2001	Is abuse a risk factor for low birth weight (growth, etiology)	8	6895	Abuse may be part of a number of factors associated with low birth weight
Neal [391]	2001	Management of RhD isoimmunization (therapy, therapeutic)	Not reported	Not reported	All current strategies reviewed
Roberts et al [392]	2001	Interventions to treat twin to twin transfusion syndrome (therapy, therapeutic)	0	0	inadequate evidence to support any practice, needs RCT's
Say et al[393]	2001	Betamimetics for suspected impaired fetal growth (growth, therapeutic)	2	118	Insufficient evidence , larger well-designed studies needed
Segal et al[394]	2001	Fetal abdominal wall defects and mode of delivery (pathology, prognostic)	15	805	No benefit to caesarean delivery with abdominal wall defects
Smith-Bindman et al[395]	2001	Second trimester ultrasound to detect Down Syndrome (aneuploidy, diagnostic)	56	132295	Isolated soft markers have poor sensitivity
Spencer et al[396]	2001	Feto-maternal alloimmune thrombocytopenia (therapy, therapeutic)	219	433	Intravenous immunoglobulin appears to reduce the risk of fetal intracranial haemorrhage
Weissman et al[397]	2001	Umbilical cord sonography and implications for the risk of fetal chromosomal abnormalities (pathology, diagnostic)	Not recorded	Not recorded	Anatomical and Doppler abnormalities of the cord are associated with chromosomal aberrations

Westergaard et al[398]	2001	Umbilical artery Doppler in high risk pregnancies (pathology, diagnostic)	13	8465	Reduction in perinatal deaths and unnecessary interventions in pregnancies complicated by suspected intrauterine growth restriction and/or hypertensive disease of pregnancy
Demasio et al[399]	2002	Isolated choroids plexus cysts in low risk women less than 35 years old (aneuploidy, diagnostic)	8	106732	No evidence that isolated CPC increases trisomy 18 risk in this group
Gaytant et al[400]	2002	Congenital cytomegalovirus infection- Epidemiology and outcome (pathology, prognostic)	Not reported	Not reported	Preexisting maternal immunity reduces but does not prevent transmission and severity in the fetus
Patrick et al[401]	2002	Proinlammatory cytokines: link between chorioamnionitis and cerebral palsy (pathology, etiology)	Not reported	Not reported	Relationship exists between chorioamnionitis, cytokines and cerebral palsy but duration and severity of exposure required is unknown
Skupski et al[402]	2002	Intrapartum fetal stimulation tests (pathology, diagnostic)	11	1297	May be useful to rule out fetal acidaemia but caution advised
Skupski et al[403]	2002	Effect of treatment of Twin-twin transfusion syndrome on the decision to delivery interval (therapy, prognostic)	8	140	No difference in decision to delivery interval or survival for treatment versus expectant management. Small sample size
Su et al[404]	2002	Diagnosis and management of monoamniotic twins (pathology, therapeutic)	Not reported	Not reported	Optimal monitoring, timing and mode of delivery is controversial
Wu [405]	2002	Chorioamnionitis and cerebral palsy (pathology, etiology)	19	Not reported	Chorioamnionitis is a risk factor for cerebral palsy and cystic periventricular leucomalacia
Alfirevic et al[406]	2003	Amniocentesis and CVS association with adverse outcome (pathology, etiology)	14	Not stated	Second trimester amniocentesis safer than CVS. Earlier CVS safer than early amniocentesis.
Clark et al[407]	2003	Prenatal bladder drainage and fetal lower urinary tract obstruction (therapy,therapeutic)	23	342	Limited available evidence suggests drainage improves outcome in poor prognosis

Dodd et al[408]	2003	Elective delivery for twins from 37 weeks gestation (pathology, therapeutic)	1(RCT)	72	insufficient data to support the practice
Dodd et al [409]	2003	multifetal reduction for twins and higher order pregnancies (therapeutic)	11	Not reported	pregnancy reduction to twins improves outcome
Gutierrez-Alvarez[410]	2003	Use of anticonvulsant drugs in pregnancy and malformations in the newborn (pathology, etiology)	14	436399	Anticonvulsants increase risk of major malformations by 2-to3-fold
Hogle et al[411]	2003	Caesarean delivery for twins (pathology, therapeutic)	4	1932	no evidence to support planned CS, may reduce the risk of low apgar (particularly if 1st twin is breech)
Makrydimas et al[412]	2003	First trimester nuchal translucency and subsequent cardiac defects (pathology, prognostic)	8	58492	Nuchal translucency screening modestly efficient for detecting cardiac defects
Merialdi et al[413]	2003	Nutritional interventions for prevention or treatment of impaired fetal growth (growth, therapy)	65	Not reported	Balanced protein energy supplementation reduced the risk of SGA as did calcium supplementation
Neilson[414]	2003	Biochemical tests of placental function for assessment of high risk pregnancy (pathology, prognostic)	1	622	Insufficient evidence to recommend practice
Nordeng et al[415]	2003	Risk of anomalies with maternal antipsychotic medication (pathology, etiology)	Not reported	Not reported	Third trimester usage increases extrapyramidal side effects in the newborn. First generation drugs do not appear to be teratogenic
Ray et al[416]	2003	B12 deficiency and risk of neural tube defects (pathology, etiology)	17	Not reported	Moderate association between low maternal B12 and neural tube defects but better studies needed

Rowe[417]	2003	Social and ethnic inequalities in offer and uptake of prenatal screening (growth, etiology)	20	Not recorded	Ethnic inequalities exist in offer and uptake of screening
Say et al[418]	2003	Hormones for suspected impaired fetal growth (growth, therapeutic)	0	0	Insufficient evidence to recommend oestrogen for suspected impaired fetal growth
Say et al[419]	2003	Maternal nutrient supplementation for suspected impaired fetal growth (growth, therapeutic)	3	121	Not enough evidence to evaluate
Say et al[420]	2003	Maternal oxygen therapy for suspected impaired fetal growth (growth, therapeutic)	3	94	Insufficient evidence exists to support practice
Sotiriadis et al[421]	2003	Intracardiac echogenic foci and Down syndrome risk (aneuploidy,diagnostic)	11	51831	Intracardiac echogenic foci increase the down syndrome risk by 5 to 7-fold
Tan et al[422]	2003	minimally invasive treatment modalities for acardiac twins (therapy, therapeutic)	32	74	no difference in outcome b/w cord occlusion vs intrafetal ablation, ablation - simpler , safer, more effective
Helmerhorst et al[423]	2004	perinatal outcome of singletons and twins in assisted conception (pathology, prognostic)	25	10078	40% less PNM for twins, no difference in other outcome
Maymon et al[424]	2004	Pregnancy outcome of euploid fetuses with increased nuchal translucency (pathology, prognostic)	11	2128	70-90% of fetuses had normal outcomes

Olesen et al[425]	2004	Decreased fetal movements: assessment and management (pathology, prognostic)	Not reported	Not reported	insufficient evidence to guide management
Wilson et al[426]	2004	Congenital abdominal wall defects (pathology, prognosis)	Not reported	Not reported	Gastroschisis and omphalocoele are common abdominal wall defects with significant morbidity and mortality
Fox et al[427]	2005	Contemporary treatments for twin to twin transfusion syndrome. (therapy, therapeutic)	4 (1 RCT)	448	Laser photocoagulation seems to be more effective with reduced perinatal morbidity and mortality.

RCT=randomised controlled trial

Appendix 17. Examples of Numbers of women Needed to be Treated (NNTs) with progestational agents to prevent one case of various outcomes individualised according to baseline risks

Outcome	Historical risk factor	Baseline risk of the outcome (%)	Odds ratio (95% CI)	Number needed to be treated (95% CI)
Delivery before 37 weeks	Any previous preterm delivery	22[428]	0.42 (0.31 - 0.57)	9 (7 - 12)
	Previous preterm delivery between 23 and 27 weeks	27[428]		7 (6 - 10)
	Previous preterm delivery between 28 and 34 weeks	24[428]		8 (7 – 11)
	Previous preterm delivery between 35 and 36 weeks	21[428]		9 (7 – 13)
	Previous 2 preterm deliveries	40		5 (4 -7)
	Transvaginal scan cervical length*			
	<=15mm	64[429]		5 (4 – 7)
	<=25mm	50[429]		5 (4 – 7)
Delivery before 34 weeks	Any previous preterm delivery	5[428]	0.51 (0.34 – 0.77)	42 (31-90)
	Previous preterm delivery between 23 and 27 weeks	20[428]		12 (8 – 26)
	Previous preterm delivery between 28 and 34 weeks	14[428]		16 (11 – 35)
	Previous preterm delivery between 35 and 36 weeks	12[428]		17 (12 – 37)
	Transvaginal scan cervical length*			
	<=15mm	48[429]		6 (4 – 15)
	<=25mm	32[429]		8 (5 – 19)

Appendix 18. Clinical characteristics of studies evaluating the lamotrigine dose management based on serum levels or clinical features only

Author Year	Quality	Population			Intervention	Outcome
		Number of women	Inclusion Criteria	Exclusion criteria		
Petrenaite 2005	Retrospective cohort No blinding Appropriate population Adequate description of the intervention Adequate follow up	11	Pregnant women on LTG monotherapy	Not known	Management based on serum levels The percentage difference between LTG plasma concentration (mmol/l) /LTG dose (mg) ratio preconception and in each trimester and postpartum was calculated to increase the dose of LTG	Seizure deterioration from seizure diaries
Öhman 2008	Prospective Non randomised No blinding Appropriate population Adequate description of intervention Adequate follow up	15	Pregnant women with epilepsy on LTG monotherapy or polytherapy in combination with other AEDs (Levetiracetam, Clonazepam and topiramate).	Not specified	The LTG dose was not increased on LTG levels alone but increased if women had seizures. The baseline level was measured each trimester and one month after delivery. Reference group levels were taken from those on LTG monotherapy. The dose plasma concentration ratios were then calculated.	Dose/plasma concentrations for LTG and mean 2-N-GLUC/LTG ratios during different stages of pregnancy
Pennel 2008	Prospective cohort Non randomised No blinding Appropriate population Adequate description of intervention Adequate follow up	53 women on LTG monotherapy	Women who Pregnant women with epilepsy on LTG therapy for either epilepsy (juvenile myoclonic epilepsy, primary generalised epilepsy, unspecified, localisation-related epilepsy and epilepsy which was unclear whether focal or generalised) or psychiatric diagnoses.	Subjects with Uncontrolled thyroid disease, severe anaemia, ethanol or recreational drug abuse, renal or hepatic dysfunction, poor compliance, age < 17 year, active suicidal ideations, progressive cerebral	Management based on serum levels The Ratio to target concentration RTC was calculated (total LTG / target LTG).	LTG clearance, seizure frequency, maternal postpartum toxicity, fetal outcome

				disease, inability to keep a seizure calendar personally or by a caregiver and co-administration of medications known to influence the metabolism of LTG.		
De Haan et al 2004	Retrospective cohort (with 1 prospective subject.) Non randomised No blinding Appropriate population Adequate description of intervention Adequate follow up	9	Pregnant women on LTG monotherapy including 2 patients with juvenile absence epilepsy, 8 with symptomatic or cryptogenic localisation-related epilepsy and one with unilateral nodular periventricular heterotopia as aetiology of her epilepsy.	Not Known	Management based on clinical features 2 serum LTG levels were taken 1 hour apart. The level to dose ratioμg/ml×100/prescribed LTG dose (mg) was calculated. The mean level to dose ratio is given for each trimester (consecutive 10 week period).	Seizure type, seizure frequency and side effects. Seizure aggravation was reported as an increase of 100%
Tran 2002	Observational cohort Non randomised No blinding Appropriate population Adequate description of intervention Adequate follow up	12	Pregnant women on LTG and concomitant AED.		Management based on clinical features The apparent clearance AC was calculated and compared for pre conception, 1st, 2nd and 3rd trimesters and postpartum. AC is equal to the dose (mg/kg/d) / level (mg/l).	Increase in seizures.

Appendix 19. Rates of major congenital malformations in women exposed to lamotrigine (LTG) in pregnancy

Study/ Registry Year	Rate of major congenital malformation % (95% CI)		
	LTG monotherapy	LTG polytherapy with valproate	LTG polytherapy without valproate
Sabers A 2004	2 (0.1-10.7)	6.7 (0.8-22.1)	2.9 (1.1-8.2)
Lamotrigine Pregnancy Registry 2009	2.4 (1.7-3.4)	10.9 (6.5-17.3)	2.2 (1.1-4.3)
Tennis P. 2002	1.8 (0.5-5.5)		
Vajda FJ. 2003	7.7	10 (3.7-22.6)	4.3 (1.6-10.3)
North American Antiepileptic Drug Registry (NAAED) 2008	1.5 (1.0-2.4)		
UK Epilepsy and Pregnancy Registry 2006	3.2 (2.1-4.9)	9.5 (3.1-21.4)	2.5 (1.2-4.6)
Cunningham M. 2005		9.6 (5.7-15.7)	
Isojarvi JI. 2005	2.8 (1.8-4.4)	11.7 (6.6-19.5)	2.7 (1.0-6.6%)
Neurodevelopmental Effects of Antiepileptic Drug Study (NEAD). 2006	1.0		
Australian Pregnancy Register. 2007			
Reiff-Eldridge R. 2000	8.6 (-6.4-14.6)		
Meador K. 2008	6.5		
Vajda. 2006	2.9 (2.0-3.8)		
Swedish Medical Birth Registry 2004	0		
European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) 2008	4.4 6.0		

Appendix 20: Search term combinations for identification of studies predicting complications of pre eclampsia

Population	Test			Outcome	Final
	History	Examination	Investigation		Refinement
1. pre adj eclampsia 2. preeclampsia 3. hypertens$ 4. pregnan$ 5. pre-eclampsia#.DE. 6. hypertension#.DE. 7. pregnancy#.DE. 8. 3 or 6(hypertension) 9. 4 OR 7(pregnancy) 10. 8 and 9(pregnancy and hypertension)	12. history 13. parity 14. multiparity or nulliparity 15. matern$ near age 16. (previous or prior) near eclampsia 17. (previous or prior) near preeclampsia 18. (previous or prior) near pre adj eclampsia 19. multiple near pregnan$* 20. twin$ or triplet$ or quadruplet$ 21. symptom$ 22. headache 23. epigastric near pain 24. naus$ or vomit$ 25. race 26. diabet$ 27. stress 28. lupus 29. thrombophilia 30. medical-history-taking#.DE. 31. maternal-age#.DE. 32. pregnancy-multiple#.DE. 33. headache#.DE. 34. signs-and-symptoms-digestive#.DE. 35. vision-disorders#.DE. 36. weight gain#.DE. 37. population-groups#.DE. 38. diabetes-mellitus#.DE. 39. stress-psychological#.DE. 40. autoimmune-diseases#.DE. 41. thrombophilia#.DE.	43. blood adj pressure 44. oedema or edema 45. tendon$ near reflex$ 46. hyperreflexia 47. clonus 48. papilledema or papilloedema 49. retina$ near change$ 50. oliguria 51. symphys$ near fundal 52. symphys$ near height 53. cardiotocogra$ 54. oxygen near saturat$ 55. blood-pressure-determination#.DE. 56. edema#.DE. 57. reflex-abnormal#.DE. 58. retinal-diseases#.DE. 59.oliguria#.DE. 60. cardiotocography#.DE. 61.oximetry#.DE.	63. serum near uric adj acid 64. urin near analys$ 65. urin$ 66. maternal near (feto adj protein$ or fetoprotein$ or alphafetoprotein$) 67. urin$ near calcium 68. hypoalbuminemia or hypoalbuminaemia 69. microalbuminuria 70. fibronectin$ 71. proteinuria 72. renal adj function near test$ 73. liver adj function near test$ 74. liquor near volume 75. biophysical near profile 76. ultraso$ 77. antithrombin$ 78. platelet adj count 79. anti adj thrombin$ 80. fibrinogen 81. antiphospholipid$ 82. haemoglobin 83. uric-acid-QN.DE 84. alpha-fetoproteins#.DE 85. calcium-ur.DE 86. hypoalbuminemia#.DE. 87. fibronectins.DE. 88. proteinuria#.DE. 89. kidney-function-tests#.DE. 90. liver-function-tests#.DE. 91. ultrasonography#.DE. 92. haematologic-tests#.DE. 93. antithrombin-III.DE. 94. fibrinogen#.DE. 95. antibodies-antiphospholipid#.DE. 96. diagnostic-imaging#.DE.	99. complicat$ 100. (renal or kidney$) near (disease$ or complicat$) 101. (hepatic or liver$) near (disease$ or complicat$) 102. death or mortality 103. morbidity 104. eclampsia 105. (pulmonary or lung) near (complicat$ or disease$) 106. thromboembolism 107. pulmonary near(oedema or edema) 108. ventilat$ 109. stroke 110. uter$5 near haemorrhage 111. abruption 112. (heart or cardiac) near arrest$ 113. (psychiatric or mental) near (illness$ or complication$1 or disorder) 114. hospitali$ 115. hypox$ near isch$ 116. (development$ or learning) near (disorder$ or difficult$) 117. pregnancy-complications#.DE. 118. kidney-diseases#.DE. 119. renal-dialysis# 120. liver-diseases#.DE. 121. death# 122. eclampsia# 123. pulmonary-embolism.DE. 124. respiration-artificial# 125. cerebrovascular-disorders#.DE. 126. brain-edema.DE. 127. intracranial-hypertension#.DE. 128. uterine-haemorrhage.DE. 129. abruption-placentae#.DE. 130. heart-diseases# 131. mood-disorders#.DE. 132. hospitalization# 133. infant-newborn-diseases# 134. respiratory-distress-syndrome-newborn.DE. 135. mental-disorders-diagnosed-in-childhood#.DE.	137. 11 and 98 and 136 (Captures *Population* and *Test* and *Outcome*) 138. animal=yes 139. human=yes 140. 138 not 139 141. 137 not 140 142. PT= comment or PT= letter
11. 1 OR 2 OR 5 OR 10 (Captures *Population*)	**42. OR/12-41 (Captures history)**	**62. or/43-61 (Captures examination)**	**97. or/63-96 (Captures investigation)**	**136. or/99-135 (Captures *Outcome*)**	**143. 141 not 142 *Final citation set (animal only studies, comments and letters excluded)***
	98. 42 or 62 or 97 (Captures *Test*)				

Appendix 21. Study characteristics of the trials included in the systematic review of accuracy of proteinuria in predicting complications in women with pre-eclampsia

Study		Population				Test			Outcome
Study(Year) Language	**Quality**	**Number of patients**	**Inclusion criteria**	**Exclusion criteria**	**Any intervention**	**Gestation of testing**	**Frequency of testing**	**Cut off level**	
Newman (2002) English	Cross-sectional Not blind Consecutive Retrospective Test not described	209	Pre-eclampsia (ACOG definition) and chronic hypertension without proteinuria early in pregnancy	Multiple pregnancy, renal disease	Delivery if BP>=160/110, HELLP syndrome or fetal distress	Not Known	Within 48 hours of admission Freq??	>=5g/24h >=10g/24h	**Eclampsia** **Severe hypertension** **5'Apgar<7** **HELLP syndrome** **Neonatal death** **NICU admission** **Delivery<32w** **RDS** **IVH** **NEC**
Buchbinder (2002) English	Cross-sectional Not Blind Prospective Test not described Arbitrary	107	Singletons, previous H/O pre-eclampsia, BP≥140/90 on 2 occasions 4 hours apart or 1 DBP>=110 mm Hg, proteinuria>=300mg/ 24h or 2 dipstick >=2+ (100mg/dl) 4h apart with no evidence of UTI	Multiple pregnancy, DM, chronic HT, baseline proteinuria	Low dose aspirin	Not Known	Frequency not known	5g/24h	**Preterm delivery** (delivery <37 weeks) **Fetal death** **Neonatal death** **Abruptio placentae** (Antepartum haemorrhage+uterine tenderness+placental examination) **NICU admission** **IVH** **RDS** **Small for gestational age (Brenner table)**
RA Odegaard (2000)	Cross-sectional	307	Increase in DBP of 25mm Hg to at least	Multiple pregnancy,	Not available	Not Known	NA	2+ 3+ (500	**Small for gestational age** (2 SD below EFW or

English	Not blind Retrospective Enrolment not described Test described		90 mm Hg and proteinuria after 20w	Unknown GA				mg/24h)	>24%lower than expected BWt or 840g reduction in B Wt for term infant)
Schiff (1996) English	Cross-sectional Not blind Retrospective Enrolment not described Test not described	66	Severe pre-eclampsia (BP>140/90 and proteinuria >=300mg/24h and hyperuricemia ua >5mg/dl and one of following- SBP>=160 or DBP>=110, proteinuria >=5g/24h, AST >72 U/L) between 26 and 32 w	Chronic HT	Delivery if thrombocytopenia (<100,000/ml), uncontrolled HT or persistent symptoms	Between 26 and 32 weeks	Two tests 4 or more days apart after admission	Increase in 24h prot by >=2g	**HELLP** **CS for fetal distress** **Abruption** **Eclampsia** **Stillbirth** **5' Apgar <=6**
Von Dadelzen (2004) English	Cross-sectional Not blind Retrospective Consecutive enrolment Test described	594	Women admitted with at least 2 of the following Hypertension (Systolic BP >=140 and/or DBP>=90 MM Hg 2 readings 4 hours apart) after 20 weeks Proteinuria (>=0.3g/day or >=2+ dipstick) after 20 weeks HELLP syndrome Isolated eclamptic seizure without preceding hypertension or proteinuria	Women in spontaneous labour Maternal outcome achieved before fulfilling eligibility criteria	Not available	Not available	Last observation carried forward	1+, 2+, 3+ ,4+ 5+	**Adverse maternal outcome (death or complication involving hepatic or central nervous system or renal or respiratory or hematological systems)**

Hall (2002) English	Cross-sectional Not blind Prospective Test described Not consecutive enrolment	340	ISSHP definition of PE Singleton with early onset severe PE(>=24w, <34w) with heavy proteinuria (>=5g/24h)	N/A	Steroids 27-33w MgSO4 eclampsia or imminent sym IP Anti- HT to maintain BP at 160/110 mm Hg Del at 34w if major mat or fetal complications	24-34w	Twice weekly	Increase by 2g/24h in two samples	**Eclampsia** **Abruption** **HELLP** **CS** **Pulmonary oedema** **ITU admission** **Ascites** **Fetal death** **Low apgar** **NNIC admission**
Taylor(1954) English	Cross-sectional Not blind Retrospective Test not described Consecutive enrolment	3258	Toxemia with previous normal BP observations Toxemia > 28w previous observations not known	Vascular or renal disease	Not available	Not available	Not available	1+, 3+	**Intra uterine death**
Thurnau (1982) English	Cross-sectional Not blind Direction of data collection not available Not consecutive enrolment Test described	83	Pre eclampsia ACOG definition Patients>24w	Not available	Not available	Not available	Not available	1+, 2+, 3+, 5g	**Severe pre eclampsia (ACOG definition)**
Martin (1999) English	Cross-sectional Not blind Retrospective Not	568	Patients severe pre-eclampsia (ACOG definition)	Eclampsia	Not available	On admission	Not available	2+, 3+	**Significant maternal morbidity** Renal, hepatic and/or gastrointestinal

	consecutive enrolment Test described								
Paladini 1970 Italian	Cross-sectional Not blind Retrospective Not consecutive enrolment Test not described	379	Pre eclampsia defined as gestosis with systolic BP>140 and proteinuria>0.5g/l and oedema in 3rd trimester	Only 1 or 2 symptoms of gestosis	Not available	3rd trimester	Not available	1g/l 2g/l	**Perinatal death**
Fleigner 1975	Cross-sectional Not blind Prospective Enrolment not described Test not described	99	Patients with moderate or severe pre-eclampsia between 30 and 37 weeks	Multiple pregnancy Diabetes Stillbirth on admission Erythroblastosis	Anti-hypertensives Magnesium sulphate Anticonvulsants Parenteral sedation Diuretics	30-37 weeks	Not available	1-5g/l	**Stillbirth** **Neonatal death** **Perinatal death**
Lao 1988	Cross-sectional Not blind Prospective Consecutive enrolment Test described	87	Nulliparous patients with pre-eclampsia (ACOG definition of patients with BP >=140/90mm Hg)	Multiple pregnancy Diabetes Untreated urinary infection Renal disease Chronic hypertension Systemic Lupus Erythematosis (SLE)	Anti-hypertensives if DBP>=100 mm Hg on 2 or more occasions	Not available	4 times a day	1+	**Caesarean section** **Small for gestational age** **Neonatal Intensive Care Unit admission** **5' Apgar<4**
Weenik 1983	Cross-sectional	57	Pre-eclamptics with DBP>=100 mm Hg	Not available	Not available	Not available	Not available	0.5, 1,2,3,4,5 g/24h	**Perinatal death or Neonatal Intensive Care**

	Not blind Direction of data collection not available Enrolment not described Test described		or 20 mmHg above non pregnant levels						**Unit admission**
Chan 2005	Cross-sectional Not blind Retrospective Consecutive enrolment Test described	321	Pre-eclampsia (ISSHP definition) Hypertension (Systolic BP >=140 and/or DBP>=90 mm Hg) and Proteinuria (>=0.3g/24 hrs or a spot urine protein/creatinine ratio>=30 mg/mmol) after 20 weeks	Pre-eclampsia superimposed on pre-existing hypertension, unavailable spot urine results, booking BP>=140/90 mm Hg, postpartum diagnosis	Not available	Not Known	Not Known	Spot urine protein/ creatinine ratio 500 mg/mmol 900 mg/mmol	**Adverse maternal outcome** **Adverse fetal outcome** **Perinatal mortality**
Waugh 2005	Cross-sectional Not blind Prospective Consecutive enrolment Test described	195	Sustained diastolic BP>=90mmHg, or a systolic BP of >=140 mmHg on 2 occasions or a single diastolic BP of >110 mmHg or systolic BP>160 mm Hg in women over 20 wks gestation	Less than 20 weeks gestation	Not available	Not Known	Not Known	0.3g /24 h 0.5 g/24 h (Benzethonium chloride assay)	**Small for gestational age**
Furukawa 2006	Cross-sectional Not blind Retrospective Not Consecutive	79	Pre-eclampsia as defined by National High Blood Pressure Program	Multiple pregnancy, known renal disease, diabetes mellitus	Pregnancy terminated in persistent severe hypertension (BP>=160/110	At delivery	Not Known	3+	**Small for gestational age** **Non reassuring fetal heart rate** **Cord blood gas**

enrolment Test described		mm Hg), oliguria (<500 ml/day), low platelets (<100,000/cu mm), HELLP syndrome, pulmonary oedema, eclampsia, non reassuring fetal heart rate patterns, persistent biophysical scoring<=4, growth arrest of head circumference of more than 2 weeks in IUGR. IV hydrallazine in persistent severe hypertension. Magnesium sulphate for seizure prophylaxis

Appendix 22. Study characteristics of the trials included in the systematic review of accuracy of uric acid in predicting complications in women with pre-eclampsia

Study		**Population**					**Test**		**Outcome**	
Study (Year) Language	**Quality**	**Number of patients**	**Inclusion criteria**	**Exclusion criteria**	**Any intervention**	**Gestation of testing**	**Frequency of testing**	**Name of Test Cut off level**	**Maternal**	**Fetal**
Yassaee (2003)	Cohort Not blind Can't tell enrolment Can't tell direction of data collection Test not described	103	Severe pre-eclampsia	Not available	Not available	Not available	Not available	Uric acid 6mg/dl	**Eclampsia** **Maternal death** **Caesarean section**	**Intra uterine death** **Intra uterine growth restriction**
Williams (2002) English	Cross-sectional Not Blind Prospective Test described Can't tell enrolment	194	BP≥140/90 after 20weeks and proteinuria≥1+ or 300mg/24hr	Diabetes Chronic Hypertension Multiple pregnancy	Not known	Not Known	On admission Frequency not known	Uric acid 450micmol/l (7.6 mg/dl) 540micmol/l (9mg/dl)	**HELLP syndrome** (SGOT>40IU/L,LDH>600IU/L,haemolysis on blood film, platelets ≤150 x10^9/L) **Severe Hypertension** (Systolic BP≥160 and/or diastolic	**Small for gestational age** (Birth weight <10^{th} centile)

									BP≥110 on 2 occasions)	
D'Anna (2000) English	Cross-sectional Not blind Retrospective Can't tell enrolment Test described	94	National Working Group on HT in pregnancy criteria for PE	Chronic medical disease	Not available	Within 24 hrs before delivery	NA	Uric acid 339 micmol/l (5.7mg/dl)		**Intra uterine growth restriction**
Martin Jr(1998) English	Cross-sectional Not blind Retrospective Not consecutive enrolment Test not described	568	Severe pre-eclampsia	Eclampsia	Not available	On admission	Single	Uric acid 6.5mg/dl 7.8mg/dl	**Significant maternal morbidity** Renal, hepatic and/or gastrointestinal	
Brown (1996) English	Cross-sectional Not blind Prospective data collection Consecutive enrolment Test not described	825	Australasian Society for the study of Hypertension in Pregnancy		Anti-hypertensives Anti convulsants Delivery before 38 weeks for fetal compromise, inability to control BP, persistent neurological disturbances, increasing liver enzymes or decreasing platelets	Not available	Twice weekly	Uric acid 350micmol/l (6mg/dl)	**Severe Hypertension** Systolic BP>=170 mm Hg or Diastolic BP>=110 mmHg	**Small for gestational age** Birth weight <=10th centile corrected for sex **Perinatal mortality** Stillbirths and neonatal deaths per 1000 hypertensive pregnancies
Odendaal (1996) English	Cross-sectional Not blind	229	Severe pre eclampsia	Not available	Magnesium sulphate after admission	On admission until	Twice weekly Peak value	Uric acid 5.2mmol/l (8.7mg/dl)	**Caesarean section**	**Small for gestational age** (Tygerberg

	Prospective Can't tell enrolment Test described				Anti-hypertensives Delivery at 34 weeks or earlier if maternal or fetal distress	delivery	for analysis		**Preterm delivery**	hospital growth curves) **Intra uterine death** **Neonatal death** **Perinatal mortality** (within 7days)
Shah (1996) English	Cross-sectional Not blind Retrospective Consecutive enrolment Test description not adequate	271	Pre eclampsia (de novo development of hypertensive disorder in 2nd half of pregnancy). It includes proteinuric pre eclampsia >300mg/dl in 24h or≥1+ 6 hours apart AND non proteinuric pre eclampsia with increased BP in 2nd half of pregnancy and elevated uric acid or other systemic involvement markers.	Not available	No surfactant used in this period, Anti hypertensive if severe pre eclampsia	Not available	Not available	Uric acid 6mg/dl	**Caesarean section**	**Adverse perinatal outcome** that includes 1.perinatal death 2.perinatal morbidity of prematurity due to hypertensive disease, moderate or severe hyaline membrane disease, Patent ductus arteriosus, Intra ventricular haemorrhage 3. perinatal morbidity due to uteroplacental vasculopathy, Intra uterine growth restriction, abruption, fetal distress
Peralta Pedero (2004) Spanish	Cross-sectional Not blind to outcome	216	BP≥140/90 after 20 weeks and ≥1+ proteinuria	Liver and renal insufficiency, Diabetes	Not available	From admission to delivery	Multiple	Uric acid 3mg/dl	**Severe hypertension** BP≥160/110	

	Can't tell enrolment Test not described			mellitus						
Voto (1988) English	Cross-sectional Not blind Can't tell enrolment Test not described	125	BP≥140/90 in 3rd trimester Mild pre-eclampsia BP 140-159/90-99 Severe pre-eclampsia BP ≥160/100	Not available	Not available	Not available	Maximum concentration of uricemia	Uric acid 6mg/dl	**Severe Hypertension** BP≥160/100	**Intra uterine growth restriction**
Sagen (1984) English	Cross-sectional Not blind Prospective Test described Not consecutive enrolment	72(actual recruitment) 52 (analysable data)	Severe pre-eclampsia BP≥160/110 and proteinuria≥5g/24hr	Uncertain dates, diuretic treatment, twins, congenital anomalies, bloods taken after fetal death	All patients had protein rich food, bed rest, hydralazine derivatives	From admission to delivery	Twice weekly Interval between last test and delivery was 1-3 days	Uric acid Urate increment ≥50 micmol/l in last 3days prior to delivery, ≥350mmol/l (6mg/dl)		**Perinatal distress** (perinatal death, apgar,7 at 1' or 5', later development of neonatal asphyxia, Respiratory distress syndrome, hypoglycemia or fits) **Small for gestational age** (<10th centile)
Liedholm (1984) English	Cross-sectional Not blind Retrospective Test described Consecutive enrolment	26	BP≥140/90 after 20weeks, proteinuria≥=1+ on two or more occasions	Urate values not available, patients on treatment other than Beta blockers or hydralazine, Diabetes	Use of beta blockers or hydralazine	Not available	Not available	Uric acid 350micmol/l (6mg/dl)	**Caesarean section** **Use of any 1 anti-hypertensive, use of 2 anti-hpertensives** (hydralazine added on to Beta blocker)	

Varma (1982) English	Cross-sectional Not blind Prospective Not consecutive enrolment Test described	200	BP≥140/90 after 24weeks on two or more occasions 24 hours apart. Mild Pre eclampsia BP<160/100without albuminuria Severe Pre-eclampsia BP≥160/100,with albuminuria	Not available	Early delivery if serious maternal risk or impending fetal death. All patients delivered between 38 and 40weeks	On diagnosis of pre-eclampsia Last test performed 24-48 hours before delivery	Weekly	Uric acid ≥60micmol/l on ≥2 consecutive samples or max ≥330 micmol/l (5.5mg/dl)		**Intra uterine growth restriction** (Birth Weight <10th centile) **Fetal distress** in labour **Neonatal death** **Stillbirth**
Mathews (1980) English	Cross-sectional Not blind Prospective Not consecutive enrolment Test described	40	Diastolic BP≥90, >trace protein	Infection in High vaginal swab/Midstream urine, < two consecutive tests before delivery, protocol amendment	All patients had chlormethiazole qds orally 20patients were rested 20 patients were ambulatory	On admission	Daily for 4 days , at least maximum 7 days	Uric acid 0.24mmol/l (4mg/dl) before 34weeks 0.36 mmol/l (6mg/dl) after 34weeks		**Perinatal death**
Dequiedt (1979) French	Cross-sectional Not blind Prospective data collection Can't tell enrolment Test described	43	BP>=140/80 with proteinuria in 3rd trimester and blood pressure returned to normal post natally	Not available	Not available	Not available	Not available	Uric acid 300micmol/l (5 mg/dl)	**Caesarean section**	**Intra uterine growth restriction** **Still birth**
Fadel (1969) English	Cross-sectional Not blind Prospective Test described Can't tell enrolment	62	'Pre-eclamptic' patients BP>140/90 and/or proteinuria in latter half of pregnancy	Not available	Not available	Within 24 hours of admission	Not available	Uric acid 4mg/dl 6mg/dl	**Eclampsia**	
Connon	Cross-	124	BP≥140/90 with	Not available	Not available	Not	Not	Uric acid	**Severe pre-**	

(1968) English	sectional Not blind Retrospective data collection Not consecutive enrolment Test described		proteinuria			available	available	6mg/dl	**eclampsia**
Lancet (1956) English	Cross-sectional Not blind Can't tell enrolment Can't tell data collection Test not described	469	Not available	Not available	Not available	Not available	Daily in eclampsia	Uric acid 6mg/dl	**Severe pre-eclampsia** **Eclampsia**
Seitchik (1953) English	Cross-sectional Not blind Retrospective data collection Method of enrolment not known Test described	14	BP≥140/90 mm Hg	Not available	Not available	Third trimester	Not available	Uric acid 6mg/dl	**Severe pre-eclampsia**

Appendix 23. Study characteristics of the trials included in the systematic review of accuracy of liver function tests in predicting complications in women with pre-eclampsia

Study		Population					Test		Outcome	
Study (Year) Language	**Quality**	**Number of patients**	**Inclusion criteria**	**Exclusion criteria**	**Any intervention**	**Gestation of testing**	**Frequency of testing**	**Name of Test Cut off level**	**Maternal**	**Fetal**
Odendall (2000) English	Casecontrol Retrospective Not consecutive patient enrolment Blinded Follow up complete	340	Early severe pre-eclampsia		Nil	>28/40	Multiple	Liver function LDH 350	**Abruption** Diagnosis of abruption placenta: ≥ 15% of the maternal surface of the placenta is covered with blood clots	
Audibert (1996) English	Cohort study Retrospective Consecutive enrolment Blinding not known Follow up complete	327	Severe pre-eclampsia or HELLP syndrome as defined by ACOG	Laboratory abnormalities from other disorders	Magnesium sulphate to all women with severe pre-eclampsia, glucocorticoids <34/40	Not specified	Not known	Liver function LDH 600 AST 70 ALT 70	**Eclampsia Caesarean section Blood transfusion Disseminated intravascular coagulation Pleural effusion Wound Haematoma Acute renal failure Abruption Pulmonary**	

									oedema **Intracerebral haemorrhage** **Death**	
Abramovici, (1999) English	Cross sectional Retrospective Consecutive Blinding not known Follow up complete	269	Severe pre eclampsia as defined by ACOG	History of renal, liver or haematological abnormalities, multiple pregnancies	Nil	24/40-36/40	Not known	Liver function LDH 600 AST 70	**Caesarean section**	**Intrauterine growth retardation** **Neonatal death** **Respiratory distress syndrome** **Necrotising enterocolitis grade 2-3** **Bronchopulmonary dysplasia** **Mechanical ventilation** **Intraventricular haemorrhage** grade 3-4
Haddad, (2000) English	Case control Retrospective Can't tell enrolment Not blinded Follow up complete	64	Severe pre eclampsia	History of haematological or liver diseases. Gestation >28 weeks at admission	Intravenous magnesium sulphate routinely to all severe pre-eclamptics	< 28/40	Not known	Liver function LDH 600 AST 70	**Eclampsia** **Abruptio placentae** **Disseminated intravascular coagulation** **Ascites** **Pulmonary oedema** **Pleural effusion** **Acute renal failure** **Transfusion of blood products**	**Neonatal death** **Respiratory Distress Syndrome** **Intraventricular Haemorrhage**

									Caesarean section
Martin Jr (1999) English	Retrospective Cohort Consecutive enrolment No blinding Follow up complete	568	Severe Pre-eclampsia with or without HELLP syndrome	Eclampsia	Not specified	Not specified	Admission data	Liver function LDH 1000-1400 AST 50-150 ALT 30-100	**Combined maternal adverse outcome** Renal, hepatic and/or gastrointestinal
Aali (2004) English	Cross sectional Prospective Consecutive No blinding Follow up complete	200	Pre eclampsia according to ACOG		Magnesium sulphate to all patients to prevent or control convulsions,i.v. hydralazine given when diastolic BP>110 mmHg, Betamethasone given from 24-34 weeks gestation to accelerate lung maturity	No	Multiple	Liver function AST 500 ALT 300	**Eclampsia**
Crisp	Cohort	64	Not specified		Nil	No	Multiple	Liver	**Eclampsia**

(1959) English	Prospective Consecutive Follow up complete							function AST 70		
Borglin (1958) English	Cohort Prospective Not blinded Follow up complete	53	Symptoms of toxaemia or liver damage	Evidence of chronic nephropathy	Nil	Last trimester	Multiple, weekly	Liver function Raised AST and ALT	**Eclampsia**	
Romero (1988) English	Cohort Retrospective Consecutive enrolment Not blinded Follow up complete	355	Pregnancy induced hypertension	Mean Arterial Pressure<105 in 3rd trimester, chronic hypertension without superimposed PIH, multiple gestation, cholelithiasis and liver diseases causing raised SGOT	Nil	>26/40	Multiple	Liver function AST 2SD	**Pulmonary oedema**	**Preterm delivery** **Respiratory distress syndrome** **Intrauterine growth retardation** **Fetal distress** **Neonatal death** Apgar<7 @1 min Apgar<7 @5min
Yucesoy (2005) English	Cross sectional Retrospective Consecutive enrolment Not blinded Follow up complete	255	Hypertensive disorder in pregnancy		Magnesium sulphate infusion in severe pre-eclampsia to prevent convulsions, Nifedipine to control high blood pressure,	>20/40	Multiple	Liver function Increase in AST / ALT /LDH	**Placental abruption** **Acute renal failure** **Disseminated intravascular coagulation** **Pulmonary edema** **Adult**	

					2 doses of betamethasone for foetal lung maturity in 28-34 weeks gestation.				**respiratory distress syndrome Retinal detatchment Intracranial bleeding Maternal death**	
Woldeselassie (2005) English	Retrospective, Cross sectional, Consecutive enrolment, Not blinded Follow up complete	230	Pre-eclampsia	Only symptomatic with no confirmed diagnosis	Anti-hypertensives and magnesium sulphate	Not specified	Multiple	Liver function ALT 60 AST 43 LDH 181	**Eclampsia Severe pre-eclampsia (HELLP)**	
Girling (1997) English	Prospective Cross sectional Consecutive enrolment Not blinded Follow up complete		Pre eclampsia 2 consecutive measurements of diastolic BP >=90 mm Hg 4 or more hours apart or a single reading >=110 mmHg, with proteinuria >0.3g/24h or >=2+ on dipstick testing	Liver pathology, hypertensio, multiple pregnancy	Not specified	Not specified	Multiple	Liver function Gestation specific 95% reference range ALT 32 AST 30 Bilirubin 14 GGT 41	**Maternal complications** (medical complication due to pre eclampsia) **Caesarean section Induction of labour**	**Neonatal death Pre term delivery**
Menzies (2007) English	Cohort Prospective Consecutive enrolment No blinding Adequate population,	737	Pre eclampsia of any severity Inclusion criteria: BP ≥140/90mmHg (twice ≥ 4 hours apart, after 20	Women who have already achieved any component of the adverse maternal	Anti hypertensives, magnesium sulphate	After 20 weeks	Multiple	LDH 600 ALT/AST 40/55	**Adverse maternal outcome** (death or complication involving hepatic or	

	test and outcome description Follow up complete	weeks) and either proteinuria (≥2+by dipstick, ≥ 0.3g/24h or ≥ 30 mg/mmol by spot protein:creatinine ratio) or hyperuricemia HELLP syndrome Superimposed pre eclampsia, defined as pre existing hypertension with accelerated hypertension, new proteinuria or new hyperuricemia. Exclusion criteria: Women who have already achieved any component of the adverse maternal outcome	outcome		central nervous system or renal or respiratory or haematological systems)

Appendix 24. Study characteristics of the trials included in the systematic review of accuracy of symptoms in predicting complications in women with pre-eclampsia

Study		Population					Test		Outcome
Study (Year) Language	**Quality**	**Number of patients**	**Inclusion criteria**	**Exclusion criteria**	**Any intervention**	**Gestation of testing**	**Frequency of testing**	**Name of Test Cut off level**	**Maternal**
Harms et al (1991)	Cohort Retrospective Enrolment not described Not blind Test method not described Follow up complete	201	Preeclampsia defined as 2 BP (≥140/90mmHg) readings within 6 hours of each other	No paper	Not known	Not known	Not known	Symptoms Headaches, Visual Disturbances, Epigastric pain Nausea and vomiting	HELLP
Witlin (1999)	Cohort Prospective Consecutive enrolment No blinding Follow up complete Adequate population, test and outcome description	445	Severe preeclampsia and eclampsia according to ACOG	Women with indication for immediate delivery (nonreassuring fetal status, vaginal bleeding, eclampsia, uncontrolled severe hypertension, pulmonary edema, compromised renal function, persistent	Antihypertensive therapy if BP is >160/100 Magnesium sulphate and Corticosteroid to those who are for conservative management (<34 weeks) Delivery for HELLP syndrome or gestation >34 weeks	Not known	Not known	Symptoms nausea and vomiting, epigastric pain, headache, visual symptoms	Abruption placentae eclampsia

				severe headache or visual changes, platelet count <100,000/mm, or aspartate aminotransferase or alanine aminotransferase value more than twice the upper limit of normal, with epigastric pain or right upper-quadrant tenderness)					
Martin (1999)	Case-control Retrospective Consecutive No blinding Follow up not known Adequate population, test and outcome description	777	Severe preeclampsia and eclampsia with or without HELLP syndrome		Not known	Not known	Not known		cardiopulmonary hematologic and coagulation central nervous system and visual renal hepatic and gastrointestinal infection preeclampsia fluid-related
Ben Salem (2003)	Case-control Retrospective Matched No blinding Follow up not known Adequate population, test and outcome description	120	Preeclampsia and eclampsia according to WHO criteria	Women with other causes of convulsions, epilepsy, meningitis, cerebral haemorrhage and cerebral tumours	Not known	Not known	Not known	Symptoms headache, visual symptoms	Eclamptic convulsions
Black	Case-control	100	Mild and severe		Not known	Not known	Not known	Symptoms	Severity of

(2005)	Prospective Consecutive No blinding Follow up not known Adequate population, test and outcome description		preeclampsia					Vertigo, epigastric pain, headache, blurred vision, scotoma, inability to concentrate	preeclampsia
Menzies (2007)	Cohort Prospective Consecutive enrolment No blinding Adequate population, test and outcome description Follow up complete	737	Pre eclampsia of any severity Inclusion criteria: BP ≥140/90mmHg (twice ≥ 4 hours apart, after 20 weeks) and either proteinuria (≥2+by dipstick, ≥ 0.3g/24h or ≥ 30 mg/mmol by spot protein:creatinine ratio) or hyperuricemia HELLP syndrome Superimposed pre eclampsia, defined as pre existing hypertension with accelerated hypertension, new proteinuria or new hyperuricemia.	Women who have already achieved any component of the adverse maternal outcome	Anti hypertensives, magnesium sulphate	After 20 weeks	Multiple	Symptoms Frontal headache Visual disturbances Persistent right upper quadrant pain Severe nausea and vomiting	Adverse maternal outcome (death or complication involving hepatic or central nervous system or renal or respiratory or hematological systems

Appendix 25. Study characteristics of the trials included in the systematic review of accuracy of blood pressure in predicting complications in women with pre-eclampsia

Study			Population				Test		
Study (Year) Language	**Quality**	**Number of patients**	**Inclusion criteria**	**Exclusion criteria**	**Any intervention**	**Gestation of testing**	**Frequency of testing**	**Name of Test Cut off level**	**Outcome**
Dukler D (2001) English	Retrospective Cohort Not blinded Consecutive enrolment Prospective data collection Patient sample defined Test described	380	Pre-eclampsia [Systolic BP >140 & Diastolic BP >90 mm Hg and at least + of proteinuria on 2 occasions in the second trimester]	Lack of prenatal care Missing data	Induction of labour Caesarean section	Second trimester	Multiple	BP Mild hypertension= Diastolic BP between 90-110 Severe hypertension= Diastolic BP >110	**Maternal** **Spontaneous preterm labour and delivery** **Fetal**
Xiong Xu (1999) English	Retrospective Cohort Not Blind Consecutive enrolment Retrospective Patient sample defined Test described	428	Pre-eclampsia [Systolic BP >130 & Diastolic BP >90 mm Hg and proteinuria (at least 1+ and +2 in 2 dipstick samples or > 0.3g/ 24 hours urine collection of on 2 occasions 6 hours apart]	Chronic cardio-vascular disease, Chronic hypertension or history of hypertension, Chronic/ history of renal disease, Diabetes, Multiple gestation	Not stated	Third trimester	Mutiple	BP Mild preeclampsia = >130/90 and <160/110 mm Hg with Proteinuria +1 and +2 Severe hypertension= Diastolic BP ≥160/110 mm Hg and or Proteinuria of >2+ on dipstick or 5g	**Caesarean section** **Instrumental delivery** **Preterm delivery** **Low birth-weight baby** **Intrauterine growth restriction**

								in 24-hours urine.		
Witlin (1999) English	Prospective Cohort Consecutive enrollment Not blind Patient sample described	445	Severe Preeclampsia and eclampsia, as per ACOG definition:	Not stated	Antihypertensive therapy if BP is >160/100 Magnesium sulphate and Corticosteroid to those who are for conservative management (<34 weeks) Delivery for HELLP syndrome or gestation >34 weeks			BP Mean arterial pressure: ≤105 mm Hg >120 mm Hg >140 mm Hg >160 mm Hg	**Placental abruption Eclampsia**	
Brown (1996) English	Cohort Not blind Prospective data collection Arbitrary enrolment Test not described	825	Pre-eclampsia: Australian Society classification of Hypertension in Pregnancy [BP >140/90 mm Hg on repeated occasion and proteinuria ≥300 mg/24 hours]	Not stated	Laboratory tests. Treated if BP ≥160/90 mm Hg	Before delivery	Multiple	BP Mild hypertension= Diastolic BP between 90-110 Severe hypertension= Diastolic BP >110	**Renal impairment Liver dysfunction Thrombocytopenia Neurological abnormalities**	**Perinatal mortality Low birth-weight baby Intrauterine growth restriction**
Peek MJ (1995) English	Cohort Not blinded Consecutive enrolment Prospective data collection Patient sample defined Test described	137	Pre-eclampsia (mild and severe): BP ≥140/90 or rise of systolic BP ≥ 25 and /or diastolic BP ≥ 15 mm Hg on 2 occasions, 6 hours apart; plus proteinuria >300mg/day or ≥ 2+ with dipstick	Chronic hypertension, Diabetes, Multiple gestation	Antihypertensives for both mild and severe hypertension.	Third trimester	Multiple	BP Mild preeclampsia= >130/90 and <160/110 mm Hg with Proteinuria +1 and +2 Severe hypertension=	**Spontaneous labour Spontaneous vaginal delivery In-patient admission Forceps delivery Caesarean section**	**Perinatal mortality Admission to NICU Intraventricular haemorrhage Necrotising enterocolitis**

								Diastolic BP ≥160/110 mm Hg and or Proteinuria of >2+ on dipstick or 5g in 24-hours urine.		
Heilmann L (1989) English	Case-control Not blind Retrospective Enrolment: not stated Test not described	52	Pregnancy-induced Proteinuric (>1% in 24 hours) hypertension (BP >140/85)	Not stated	Biochemical and cardio-pulmonary monitoring	After 24th week	Not stated	BP Mean arterial pressure: ≤105 mm Hg >120 mm Hg >140 mm Hg >160 mm Hg		**Perinatal mortality Birth weight**
Varma (1981) English	Cohort Not blind Prospective data collection Arbitrary enrolment Prospective Test described	200	Pre-eclampsia	Not available		Third trimester	Multiple	BP Mild hypertension= Diastolic BP between 90-110 Severe hypertension= Diastolic BP >110		**Fetal distress Stillbirth Perinatal death Neonatal death**
Menzies (2007)	Cohort Prospective Consecutive enrolment No blinding Adequate population, test and outcome description Follow up complete	737	Pre eclampsia of any severity Inclusion criteria: BP ≥140/90mmHg (twice ≥ 4 hours apart, after 20 weeks) and either proteinuria (≥2+by dipstick, ≥ 0.3g/24h or ≥ 30 mg/mmol by spot protein:creatinine ratio) or hyperuricemia HELLP syndrome	Women who have already achieved any component of the adverse maternal outcome				Systolic BP ≥160 mmHg Diastolic BP ≥110 mm Hg	**Adverse maternal outcome (death or complication involving hepatic or central nervous system or renal or respiratory or hematological systems)**	

	Superimposed pre eclampsia, defined as pre existing hypertension with accelerated hypertension, new proteinuria or new hyperuricemia.	

Appendix 26. Study characteristics of the trials included in the systematic review of accuracy of pulse oximetry in detecting congenital heart disease in asymptomatic newborns

Study		Population					Test			Outcome
Study (Year)	**Quality**	**No. of newborns**	**No. of newborns with CHD**	**Inclusion criteria**	**Exclusion criteria**	**Age at testing**	**Method of testing**	**Frequency of testing**	**Cut off level**	
De-Wahl Granelli (2005)	Case control Retrospective Non consecutive enrolment Test described Not blind	266	66	Cases – Normal full term infants		12 hours (controls) Prior to surgery (cases)	Right hand and either foot	Multiple	Functional saturation <95% in right upper and lower limbs and readings in lower limb 3% higher or lower than right hand	Critical Congenital Heart Disease (CCHD) – duct dependant or cyanotic heart disease
Bakr (2005)	Cross sectional Prospective Consecutive Test described Not blind	5211	13	Asymptomatic newborns	Symptomatic newborns NICU admission	Before discharge	Right hand and foot	Multiple	Fractional saturation <95% in right hand or foot	Congenital Heart disease
Arlettaz (2005)	Cross sectional Prospective Consecutive Test described Not blind	3262	15	Healthy newborns ≥35w	GA<35w Symptomatic Respiratory disorder in newborns	6-12 hours	Foot	Multiple	Functional saturation in foot <95%	Congenital Heart disease of functional consequence
Rosati (2005)	Cross sectional	5292	3	Asymptomatic	Symptomatic prior	>24 hours	N/A	Single	Saturation ≤ 95% in foot	Critical Cardio Vascular

	Prospective Consecutive Test described Not blind			newborns	to screening Prenatal diagnosis of CHD					Malformation (CCVM)
Koppel (2003)	Cross sectional Prospective Consecutive Test not described Not blind	11281	5	Asympto matic newborns	Symptom atic newborns Prenatal diagnosis of CHD	>24 hours or at discharge	Foot	Single	Functional Saturation ≤ 95% in foot	Critical Cardio Vascular Malformation (CCVM)
Richmond (2002)	Cross sectional Prospective Consecutive Test not described Not blind	5626	40	Asympto matic newborns	Symptom atic newborns	≥2 hours to before discharge	Foot	Multiple	Fractional saturation <95% in foot	Congenital Heart disease
Reich (2002)	Cross sectional Prospective Consecutive Test described Not blind	2114	3	Asympto matic newborns	Fetal echocardi ogram, Symptom atic newborns NICU admission Birth weight <1500g, assisted ventilation , transfer to a tertiary neonatal unit Consent not	As close to discharge as possible	Foot or hand	Multiple	Functional saturation ≤ 95% in foot or hand	Cyanotic Congenital Heart disease

					provided					
Hoke (2002)	Case control Ambispective Arbitrary recruitment Test described Not blind	2908	36	Cases-Newborns with congenital heart disease Controls-Healthy newborns at least 34 weeks gestational age at birth	Less than 34 weeks	Less than 6 hours of life, at 24 hours of life and/or at discharge	Right arm and either leg	Multiple	-functional saturation <95% in foot -functional saturation <92% lower limb or 7% lower in foot than hand -functional saturation<94% foot -functional saturation<93% foot -functional saturation<92% foot -functional saturation<91% foot -functional saturation<90% foot	Critical Congenital Heart Disease (CCHD) – duct dependant or left heart obstructive disease

Appendix 27. Data extraction form for review of progesterone for women at risk of pre term labour

Name of Reviewer: ID: Author: Year

1) **Population:**
   - Women at risk of preterm labour yes ☐ no ☐

2) **Intervention:**
   - Progesterone yes ☐ no ☐

3) **Comparison with:**
   - Placebo yes ☐ no ☐

4) **Outcome**

   - ***Maternal outcomes:*** yes ☐ no ☐

   - ***Fetal outcomes:*** yes ☐ no ☐

5) **Include paper:** yes ☐ no ☐
(Only include study if answered yes to ***all*** of the above criteria)

---

6) **Design:**
   RCT ☐ Cohort study ☐
   Quasirandomisation ☐

7) **Type:**
   prospective ☐ retrospective ☐

8) **Blinding**
   yes ☐ no ☐

   a) If *yes*:
   single blind ☐ double blind ☐

9) **Concealment:**
   yes ☐ no ☐

10) **Intention to Treat (ITT) analysis?**
   yes ☐ no ☐

11) Follow up:

> 90% ☐ 80-90% ☐ <80% ☐

Inclusion criteria:

Exclusion criteria:

Use of other tocolytics Yes No

Type of progesterone Parenteral vaginal Other

Progesterone commenced 1^{st} tri 2^{nd} tri

Dose stopped at .....weeks

Dose of progesterone

Use of steroids Yes No

Mode of delivery

GA at delivery

Birth weight Normal / SGA / LGA

Congenital abnormalities Yes No

Maternal side effects .....

Delivery before 37 weeks	yes	no
Progesterone		
Placebo		

Delivery before 34 weeks	yes	no
Progesterone		
Placebo		

Neonatal death	yes	no
Progesterone		
Placebo		

Appendix 28. Data extraction form for review of optimal dosage regimen of lamotrigine in pregnant women with epilepsy

Name of Reviewer: ID: Author Year

1) **Population:**
   - Pregnant females with epilepsy: yes ☐ no ☐

2) **Intervention:**
   - Increasing lamotrigine dose: yes ☐ no ☐

3) **Comparison with:**
   - Maintaining pre pregnancy lamotrigine dose: yes ☐ no ☐

4) **Outcome**
   - ***Pharmacokinetics of lamotrigine:*** yes ☐ no ☐
   - ***Maternal outcomes:*** yes ☐ no ☐
     - if *yes* what are they looking at:
   - ***Fetal outcomes:*** yes ☐ no ☐
     - if *yes* what are they looking at:

5) **Include paper:** yes ☐ no ☐
(Only include study if answered yes to ***all*** of the above criteria)

6) **Design:**
   RCT ☐ Cohort study ☐ Case controlled study ☐
   Quasirandomisation ☐

7) **Type:**
   prospective ☐ retrospective ☐

8) **Blinding**
   yes ☐ no ☐

   a) If *yes*:
   single blind ☐ double blind ☐

9) **Concealment:**
   yes ☐ no ☐

10) **Intention to Treat (ITT) analysis?**
   yes ☐ no ☐

11) Follow up:

> 90% ☐ 80-90% ☐ <80% ☐

Use of other AED Yes No

Total no. of AED 1 2 3 4

Other AED drugs Sodium valproate Carbamazepine Other

LTG commenced Pre-preg 1st tri 2nd tri 3rd tri

LTG dose escalation No 1st tri 2nd tri 3rd tri

Total dose of LTG / day ….mg/day

Mode of delivery Normal vaginal/Caesarean section/instrumental

Postpartum haemorrhage Yes No

Birth Weight

Congenital abnormalities Yes No

Population.....Outcome…….

	yes	no
LTG dose escalation		
LTG dose maintenance		

Population.....Outcome…….

	yes	no
LTG dose escalation		
LTG dose maintenance		

Appendix 29. Data extraction form for the review of tests in pre eclampsia

Reviewer: **Paper No.:** **Language:** **1st Author:**

1. population – women with pre eclampsia yes / no

2. Test proteinuria/uric acid/liver function test/symptom/blood pressure yes / no

3. Reference standard

Maternal : 1)severe pre eclampsia 2)eclampsia
3)abruption 4)death 5) other…….

Fetal: 1)death 2)IUGR 3)Low pH 4)Low Apgar
5)prematurity 6)other

2x2 table construction possible yes / no

Select this diagnostic test study (1-3 inclusive) yes / no *if no reject & specify reason below*

……
……..

……
……..

Data Retrieval:

Population:

Study Design Cohort / Cross-sectional / Case control / Other……

Data Collection Prospective / Retrospective / Cannot tell / Other…….

Patient Enrolment Consecutive / Arbitrary / cannot tell / Other……..

Additional Description of Study Design

Blind comparison with reference standard	Yes	No	Can't tell
Defined sample of patients	Yes	No	Can't tell
Narrow population spectrum	Yes	No	Can't tell
Differential use of reference standard	Yes	No	Can't tell

Baseline prevalence of the disease: ..... (State figure if provided, otherwise circle below)

High Low Not mentioned

Please circle characteristic of sample population(s): [Assuming this is not a risk factor study]

Mild Moderate Severe Associated medical problem Can't tell

If sample classified, state the definition:

.....

Inclusion criteria stated Yes

No

Description:

.....

No. patients recruited

A original population n=……

B Pre-enrolment exclusions n=……
(reasons eg pop characteristics)……

C actually recruited (**A-B**) n=……

D post-enrolment exclusions n=……
(reasons eg missing data etc)……

E analysable data **(C-D)** n=……

Setting Community / hospital

Parity stated: Yes No/not sure

Previous H/O pre eclampsia/eclampsia Yes No/not sure

Symptoms (Headache, Nausea, vomiting, visual, epigastric pain) Yes No/ not sure

If symptomatic, what symptom:……..

Intervention:

More than one test performed on the patient: Yes
No

Type of intervention ('the test'): ……

How many measurement(s): Single Multiple

Gestation at which 'the test' was applied: .....weeks or
..... trimester

Method described**:** Yes No Other interventions

If there's cut off level, this must be stated for the test to be considered adequate: Yes No

Cut off level of the test: ……

Test positive cases n=……

Test negative cases n=……

<u>Reference standard (maternal or fetal outcome):</u>

State maternal outcome:
……..

State fetal outcome: ……..

Blinding of test result
yes / no

Completeness of Follow up (%) >90 / 81-90 / <81 (FU% = **E/C** x 100% **=…… %)**

Completeness of Follow up (%) Positive cases % Negative cases%
Regarding the outcome(s):

How was the result reported [ie the summary outcome measure(s)]: {please circle}

Receiver Operator Curve (summary) ROC Likelihood Ratio (LR)

Sensitivity SpecificityNegative predictive value
Positive predictive value

Others (please state): .....

Space for free comment by reviewer:

Outcome (maternal or fetal complications): (2x2 table)

If deriving 2x2 by severity of pre eclampsia, then use separate table for category(mild,mod,severe)

State the type of outcome for these tables (eg Low Apgar,Eclampsia)

Population.....Outcome…….

	Outcome present	Outcome absent	Total
Positive			
Negative			
Total			

Population.....Outcome…….

	Outcome present	Outcome absent	Total
Positive			
Negative			
Total			

Appendix 30. Data extraction form for the review of Pulse Oximetry in detecting Congenital Heart Disease in asymptomatic newborns

Reviewer: **Paper No.:** **Language:** **1st Author:**

Selection criteria (diagnostic test

1. **population – asymptomatic newborns** **yes / no**

2. **Intervention** **pulse oximetry** **Yes / no**

   clinical examination **Yes / no**

3. **Reference standard** **Echocardiograph**

2x2 table construction possible **yes / no**

Select this diagnostic test study (1-3 inclusive) yes / no *if no reject & specify reason below*

……
……..

……
……..

Data Retrieval:

Population:

Study Design Cohort / Cross-sectional / Case control / Other……

Data Collection Prospective / Retrospective / Can't tell / Other…….

Patient Enrolment Consecutive / Arbitrary / can't tell / Other……..

Additional Description of Study Design

Blind comparison with reference standard	Yes	No	Can't tell
Defined sample of patients	Yes	No	Can't tell
Narrow population spectrum	Yes	No	Can't tell
Differential use of reference standard	Yes	No	Can't tell

Baseline prevalence of the disease: ..... (State figure if provided, otherwise circle below)

High Low Not mentioned

Please circle characteristic of sample population(s): [Assuming this is not a risk factor study]

Low risk Moderate risk severe risk Associated medical problem Can't tell

If sample classified, state the definition:
.....

Inclusion criteria stated Yes No
Description:

.....

No. patients recruited

A original population n=……

B Pre-enrolment exclusions n=……
(reasons eg pop characteristics)……

C actually recruited (**A-B**) n=……

D post-enrolment exclusions n=……
(reasons eg missing data etc)……

E analysable data **(C-D)** n=……

Setting Community / hospital

Age stated: Yes No Can't tell
…….

Previous antenatal diagnosis Yes No Can't tell
……..

GA at birth Yes No Can't tell
……..

Birth weight Yes No Can't tell
…….

Clinical examination Yes No Can't tell
……..

Intervention:

More than one test performed on the patient: Yes
No

Type of intervention ('the test'): ……

How many measurement(s): Single Multiple

Age after birth at which 'the test' was applied:.....hrs or
..... days or ……..

Method described**:** Yes No

Limb: Upper Lower Other ……

Saturation: Functional Fractional
If there's cut off level, this must be stated for the test to be considered adequate: Yes No

Cut off level of the test: ……

Test positive cases n=……

Test negative cases n=……

Clinical examination

Age after birth at which clinical examination was done .....
hrs or .....
days or ……..

Method described**:** Yes No
If there's cut off level, this must be stated for the test to be considered adequate: Yes No

Cut off level of the test: ……

Test positive cases n=……

Test negative cases n=……

Combined Pulse oximetry and clinical examination

Test positive cases n=……

Test negative cases n=……

Reference standard (Echocardiography):

Blinding of test result
yes / no

Completeness of Follow up (%) >90 / 81-90 / <81 (FU% = **E/C** x 100% **=…… %)**

Completeness of Follow up (%) Positive cases % Negative cases%

Outcome

CHD: Any CHD cyanotic CHD

Regarding the outcome(s):

How was the result reported [ie the summary outcome measure(s)]: {please circle}

Receiver Operator Curve (summary) ROC Likelihood Ratio (LR)

Sensitivity Specificity Negative predictive value Positive predictive value

Others (please state): .....

Space for free comment by reviewer:

Outcome (CHD): (2x2 table)

Population.....Outcome…….

	Outcome present	Outcome absent	Total
Positive			
Negative			
Total			

Appendix 31. Data extraction form for review of maternal and fetal medicine reviews

Reviewer Paper ID Author

Area – Maternal medicine / fetal medicine

Specify topic .....

Framing of question:	Yes/Adequate	No/Inadquate/Not reported	Not applicable
Question specified			
Narrow focus of question			
Explicit testable hypothesis			
Literature search			
Adequate search description			
Use of reference list			
Search without language restriction			
Assessment for risk of missing studies			
Inclusion of unpublished data			
Methods of review:			
Quality assessment of included studies:			
Potential sources of bias (ie. randomisation)			
Data collection (prospective/retrospective)			
Follow-up			
Blinding of assessors			
Description of intervention			
Tabulation of results (incl. study characteristics)			
Meta-analysis			
Assessment for heterogeneity			
Cochrane / Non Cochrane			

Appendix 32. Questionnaire of the list of tests to predict maternal and fetal complications of pre-eclampsia – First iteration of Delphi survey

Please score using the following scale
0-unnecessary; 1-not important; 2-slightly important; 3-moderately important; 4-very important; 5-essential
Mark 'X' in the appropriate boxes

Tests to predict complications of pre-eclampsia	0	1	2	3	4	5
History						
Parity						
Race						
Maternal age						
Previous history of severe pre eclampsia/Eclampsia						
Family history of pre eclampsia						
Obesity						
Weight gain						
Pre existing hypertension, renal disease, diabetes						
History of lupus, thrombophilia, other auto immune diseases						
Multiple pregnancy						
Symptoms-headache, epigastric pain, nausea, visual disturbance						
Examination						
Blood pressure						
Peripheral oedema						
Exaggerated tendon reflexes						
Clonus						
Papilloedema, Retinal changes						
Oliguria						
Symphysio fundal height						
Investigations						
Serum uric acid						
Proteinuria (24 hr collection, dipstick)						
Renal function tests						
Liver function tests						
Urinary calcium excretion						
Hypoalbuminaemia						
Microalbuminuria						
Fibronectin						
Maternal serum Alpha feto protein(MSAFP)						
Serum Human Chorionic Gonadotrophin (HCG)						
Coagulation screen						
Full blood count						
Thrombophilia screen						
Ultrasound including doppler						
CT/ MRI of brain						

Appendix 33. Tests in the order of priority for prediction of pre eclampsia complications – Second iteration of Delphi survey

Please score using the following scale

0-unnecessary; 1-not important; 2-slightly important; 3-moderately important; 4-very important; 5-essential

Tests to predict complications of pre eclampsia	Mean scores	Your previous rating	Your new rating
Blood pressure	4.8		
Papilloedema, Retinal changes	4.3		
Liver function tests	4.3		
Proteinuria (24 hr collection, dipstick)	4.3		
Symptoms- headache, epigastric pain , nausea, visual disturbance	4.1		
Full blood count	4.1		
Pre existing hypertension, renal disease, diabetes	4.1		
Renal function tests	4.1		
Oliguria	3.9		
Ultrasound including Doppler	3.7		
History of lupus, thrombophilia, other auto immune diseases	3.9		

Appendix 34. Search strategy for optimal dosage regimen of lamotrigine in pregnant women with epilepsy

1. MEDLINE; lamotrigine.af;

2. MEDLINE; lamictal.af;

3. MEDLINE; 1 OR 2;

4. MEDLINE; exp PREGNANCY/;

5. MEDLINE; pregnancy.ti,ab;

6. MEDLINE; 4 OR 5;

7. MEDLINE; exp EPILEPSY/;

8. MEDLINE; epilepsy.ti,ab;

9. MEDLINE; 7 OR 8;

10. MEDLINE; 3 AND 6 AND 9;

11. MEDLINE; exp DOSE-RESPONSE RELATIONSHIP, DRUG/;

12. MEDLINE; "dose increase".ti,ab;

13. MEDLINE; "increased dose".ti,ab;

14. MEDLINE; "decreased dose".ti,ab;

15. MEDLINE; "dose decrease ".ti,ab;

16. MEDLINE; 11 OR 12 OR 13 OR 14 OR 15;

17. MEDLINE; 10 AND 16;

18. MEDLINE; exp "QUALITY OF LIFE"/;

19. MEDLINE; (quality AND of AND life).ti,ab;

20. MEDLINE; 18 OR 19;

21. MEDLINE; 10 AND 20;

Appendix 35. Search for pulse oximetry as a test to diagnose congenital heart disease in newborns

1 MEDLINE − 1996 to date oximetry

2 MEDLINE − 1996 to date pulse

3 MEDLINE −1996 to date 1 AND 2

4 MEDLINE −1996 to date pulse NEAR oximetry

5 MEDLINE −1996 to date 3 OR 4

6 MEDLINE −1996 to date infant−newborn#

7 MEDLINE −1996 to date neonat$2

8 MEDLINE −1996 to date newborn

9 MEDLINE −1996 to date 6 OR 7 OR 8

10 MEDLINE −1996 to date 5 AND 9

11 MEDLINE −1996 to date

YEAR=2006 OR YEAR=2005 OR

YEAR=2004 OR YEAR=2003 OR

YEAR=2002 unrestricted

12 MEDLINE −1996 to date 10 AND 11 unrestricted

Appendix 36. Contributions to the chapters of the thesis

Chapter 1. Introduction

Shakila Thangaratinam

Chapter 2. The Delphi Technique

Shakila Thangaratinam: Drafting revision of the manuscript, literature serach

Charles Redman: Critical revision of the manuscript

Khalid S Khan: Supervision of the project; and constructive feedback into the manuscript

Chapter 3. Prioritisation of tests for the prediction of complications in pre eclampsia: A Delphi survey

Shakila Thangaratinam: Development of the protocol and questionnaire, conduct of survey, analysis, drafting and revision of manuscript

Arri Coomarasamy: Development of the protocol and questionnaire, critical revision of manuscript

Steve Sharp: Literature search

Khaled MK Ismail: Critical revision of manuscript

Shaughn O'Brien: Critical revision of manuscript

Fidelma O'Mahony: Critical revision of manuscript

Khalid S Khan: Development of the protocol and questionnaire; supervision of the project; and critical revision of manuscript

Chapter 4. A review of systematic reviews in maternal medicine

Shakila Thangaratinam: Contribution mainly to the analysis; drafting and revision of manuscript. Protocol revision input provided.

Lumaan Sheikh: Literature search; data extraction; and drafting of manuscript

Shelley Johnston: Data extraction

Khalid S Khan: Development of protocol; and critical revision of manuscript

Mark D Kilby: Critical revision of manuscript

Chapter 5. A review of systematic reviews in fetal medicine

Shakila Thangaratinam: Contribution mainly to the analysis; drafting and revision of manuscript. Protocol revision input provided.

Ellen Knox: Development of protocol; literature search; data extraction; and drafting of manuscript

Khalid S Khan: Development of protocol; supervision of the project; and critical revision of manuscript

Mark D Kilby: Development of protocol; critical revision of manuscript

Chapter 6. Progesterone for the prevention of preterm birth: A systematic review of effectiveness

Shakila Thangaratinam: Development of protocol; data extraction; and drafting and revision of manuscript

Arri Coomarasamy: Development of protocol; literature search; data extraction; analysis and critical revision of manuscript

Khalid S Khan: Supervision of the project; and critical revision of manuscript

Harry Gee: Critical revision of manuscript

Chapter 7. A systematic review of effectiveness of lamotrigine dosage based on serum levels compared to clinical features

Shakila Thangaratinam: Development of protocol; literature search; data extraction; analysis and drafting and revision of manuscript

Dulcie Pirie: Data extraction

Victoria Houston, Ayesha Siddiqua: Literature search; and data extraction

Manjo Doug: Revision of manuscript

Khalid S Khan: Supervision of the project; and critical revision of manuscript

Doug McCorry, Alex Pirie, Manny Bagary, Kelly HardLyn Greenhill: Critical revision of manuscript

Chapter 8. Tests for predicting complications of pre eclampsia: A protocol for systematic reviews

Shakila Thangaratinam: Development of protocol; literature search; and drafting and revision of manuscript

Arri Coomarasamy: Development of the protocol; and critical revision of manuscript

Steve Sharp: Literature search

Khaled MK Ismail: Development of the protocol; and critical revision of manuscript

Shaughn O'Brien: Critical revision of manuscript

Fidelma O'Mahony: Critical revision of manuscript

Khalid S Khan: Development of protocol; supervision of the project; and critical revision of manuscript

Chapter 9. Proteinuria as a predictor of complications in pre eclampsia

Shakila Thangaratinam: Development of protocol; literature search; data extraction; analysis; drafting and revision of manuscript

Arri Coomarasamy: Development of the protocol; and critical revision of manuscript

Steve Sharp: Literature search

Javier Zamora: Analysis

Fidelma O'Mahony, Khaled MK Ismail: Data extraction; and critical revision of manuscript

Shaughn O'Brien: Critical revision of manuscript

Khalid S Khan: Development of protocol; supervision of the project; and critical revision of manuscript

Chapter 10. Serum uric acid as a predictor of complications in pre eclampsia

Shakila Thangaratinam: Development of protocol; literature search; data extraction; analysis; drafting and revision of manuscript

Arri Coomarasamy: Development of the protocol; analysis and critical revision of manuscript

Steve Sharp: Literature search

Khaled MK Ismail: Data extraction; and critical revision of manuscript

Khalid S Khan: Development of protocol; supervision of the project; and critical revision of manuscript

Chapter 11. Liver function tests as a predictor of complications in pre eclampsia

Shakila Thangaratinam: Development of protocol; literature search; data extraction; analysis; drafting and revision of manuscript

Corinne Koopmans: Data extraction

Shalini Iyengar: Data extraction

Javier Zamora: Statistical input

Khaled MK Ismail: Critical revision of manuscript

Ben WJ Mol: Critical revision of manuscript

*Khalid S Khan: S*upervision of the project; and critical revision of manuscript

Chapter 12. Symptoms as a predictor of complications in pre eclampsia

Shakila Thangaratinam: Development of protocol; literature search; data extraction; analysis; drafting and revision of manuscript

Ioannis Gallos: Data extraction

Neki Meah: Study selection

Sa'ada Usman: Study selection

Khaled MK Ismail: Critical revision of manuscript

Khalid S Khan: Supervision of the project; and critical revision of manuscript

Chapter 13. Blood pressure as a predictor of complications in pre eclampsia

Shakila Thangaratinam: Development of protocol; literature search; data extraction; analysis; drafting and revision of manuscript

Adrija Datta: Data extraction

Khaled MK Ismail: Critical revision of manuscript

Khalid S Khan: Supervision of the project; and critical revision of manuscript

Chapter 14. Accuracy of pulse oximetry as a screening tool in the diagnosis of congenital heart disease in newborns: a systematic review

Shakila Thangaratinam: Development of protocol; literature search; data extraction; analysis; drafting and revision of manuscript

Jane Daniels: Data extraction

Andy Ewer: Critical revision of manuscript

Javier Zamora: Statistical input

Khalid S Khan: Supervision of the project; and critical revision of manuscript

Chapter 15. Conclusion

Shakila Thangaratinam

Reference List

(1) http://www ncchta org/about/whatishta shtml 2010.

(2) Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. JAMA 1994; 272:1367-1371.

(3) Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy: executive summary. Aust N Z J Obstet Gynaecol 2000; 40:133-138.

(4) Report of the National High Blood Pressure Education Program. Working group report on high blood pressure in pregnancy. Am J Obstet Gynecol 2000; 183:S 1-S 22.

(5) Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003; 102:181-192.

(6) Davey DA, McGiilivray I. The classification and definition of the hypertensive disorders in pregnancy. Am J OG 1988; 158:892-898.

(7) Confidential Enquiry into Maternal and Child Health (2007). Saving mothers' lives: reviewing maternal deaths to make motherhood safer. The seventh report of the confidential enquiries into maternal deaths in the United Kingdom. London 2007.

(8) Murphy DJ, Stirrat GM. Mortality and morbidity associated with early-onset preeclampsia. Hypertens Preg 2000; 19:221-231.

(9) Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J OG 1993; 169:1000-1006.

(10) MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. Obstet Gynecol 2001; 97:533-538.

(11) von Dadelszen P, Menzies JM, Payne B, PIERS (Pre-eclampsia Integrated Estimate of RiSk) Study Group. Predicting Adverse Outcomes in Women with Severe Pre-eclampsia. Seminars in Perinatology 2009; 33:152-157.

(12) von Dadelszen P, Magee LA, Roberts J. Subclassification of pre eclampsia. Hypertension in Pregnancy 2003; 22:143-148.

(13) Shennan AH. Recent developments in Obstetrics. BMJ 2003; 327:604-608.

(14) RCOG Green-top guideline 10(A). The management of severe pre eclampsia / eclampsia. Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists 2006.

(15) von Dadelszen P, Magee LA, Marshall JC, Rotstein OD. The Maternal Syndrome of Preeclampsia: A forme fruste of the Systemic Inflammatory Response Syndrome. Sepsis 2000; 4:43-47.

(16) Churchill D, Duley L. Interventionist versus expectant care for severe pre-eclampsia before term. Cochrane Database of Systematic Reviews 2002;Issue 3. Art. No.: CD003106.

(17) Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, O' Mahony F, Khan KS et al. Prioritisation of Tests for the prediction of Pre-eclampsia Complications: A Delphi survey. Hypertension in Pregnancy 2007; 26: 131-138.

(18) Adab N, Chadwick DW. Management of women with epilepsy during pregnancy. The Obstetrician and Gynaecologist 2006; 8:20-25.

(19) Yerby MS. Pregnancy, teratogenesis, and epilepsy. Neurologic Clinics 1994; 12(4):749-771.

(20) Yerby MS, Devinsky O. Epilepsy and pregnancy. Advances in Neurology 1994; 64:45-63.

(21) Adab N, Tudur SC, Vinten J, Williamson P, Winterbottom J. Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database of Systematic Reviews 2004;(3).

(22) Confidential Enquiry into Maternal and Child Health.Why Mothers Die 2000-2002. The Sixth Report of the Confidential Enquiry into Maternal Deaths in the United Kingdom. RCOG 2004.

(23) Lindhout D, Omtzigt JG. Pregnancy and the risk of teratogenicity. Epilepsia 1992; 33 Suppl 4:S41-S48.

(24) Lindhout D. Pharmacogenetics and drug interactions: role in antiepileptic-drug-induced teratogenesis. Neurology 1992; 42(4 Suppl 5):43-47.

(25) Adab N. Birth defects and epilepsy medication. Expert Review of Neurotherapeutics 2006; 6(6):833-845.

(26) Hovinga CA, Asato MR, Manjunath R, et al. Association of non-adherence to antiepileptic drugs and seizures, quality of life, and productivity: Survey of patients with epilepsy and physicians. Epilepsy & Behavior 2008; 13:316-322.

(27) Schupf N, Ottman R. Likelihood of pregnancy in individuals with idiopathic/cryptogenic epilepsy: social and biologic influences. Epilepsia 1994; 35(4):750-756.

(28) Schupf N, Ottman R. Reproduction among individuals with idiopathic/cryptogenic epilepsy: risk factors for reduced fertility in marriage. Epilepsia 1996; 37(9):833-840.

(29) Schupf N, Ottman R. Reproduction among individuals with idiopathic/cryptogenic epilepsy: risk factors for spontaneous abortion. Epilepsia 1997; 38(7):824-829.

(30) Steegers-Theunissen RP, Renier WO, Borm GF, Thomas CM, Merkus HM, Op de Coul DA et al. Factors influencing the risk of abnormal pregnancy outcome in epileptic women: a multi-centre prospective study. Epilepsy Research 1994; 18(3):261-269.

(31) Teramo K, Hiilesmaa V, Bardy A, Saarikoski S. Fetal heart rate during a maternal grand mal epileptic seizure. Journal of Perinatal Medicine 1979; 7(1):3-6.

(32) Marson AG, Al Kharusi AM, Alwaidh M, et al on behalf of the SANAD study group. Study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007; 369:1000-1015.

(33) National Collaborating Centre for Primary Care. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. http://www nice org uk/nicemedia/pdf/CG020fullguideline pdf 2004.

(34) Chien PF, Khan KS, Ogsten S, Owen P. The diagnostic accuracy of cervico-vaginal fetal fibronectin in predicting preterm delivery: an overview. BJOG : an international journal of obstetrics and gynaecology 1997; 104:436-444.

(35) Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The Cost of Preterm Birth Throughout Childhood in England and Wales. Pediatrics 2009; 123:e312-e317.

(36) Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C. Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis. Health technology assessment (Winchester England) 2005; 9(44):1-168.

(37) Wren C, Richardson S, Donaldson P. Temporal variability in the birth prevalence of cardiovascular malformations. Heart 2000; 83:414-419.

(38) Kuehl KS, Loffredo CA, Ferenez C. Failure to diagnose congenital heart disease in infancy. Pediatrics 1999; 103: 743-747.

(39) Malkin JD, Garber S, Broder MS, Keeler E. Infant mortality and early postpartum discharge. Obstetrics and Gynecology 2000; 96: 183-188.

(40) Meberg A, Otterstad JE, Froland G, Hals J, Sorland SJ. Early clinical screening for congenital heart disease: the cases we miss. Cardiol Young 1999; 169-174.

(41) Jairath N, Weinstein J. The Delphi methodology: A useful administrative approach. Canadian Journal of Nursing Administration 1994; 7: 29-42.

(42) Mignini LM, Khan KS. Methodological quality of systematic reviews of animal studies: a survey of reviews of basic research. BMC Medical Research Methodology 2006; 6:10.

(43) Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007; 7:10.

(44) Cochrane Adverse Effects Sub-Group of the Cochrane Non-Randomised Study Methods Group. Including adverse effects in systematic reviews: interim recommendations.

(45) Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003; 7 (27):1-173.

(46) Khan KS, ter Riet G, Glanville J, Sowden AJ, Kleijnen J. Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for Carrying Out or Commissioning Reviews. CRD Report Number 4 (2nd edition). 2nd ed. York: NHS Centre for Reviews and Dissemination, University of York; 2001.

(47) Khan KS, Kunz R, Kleijnen J, Antes G. Systematic reviews to support evidence-based medicine: How to review and apply findings of systematic reviews. London: Royal Society of Medicine; 2003.

(48) Loke YK, Price D, Herxheimer A for the Cochrane Adverse Effects Methods Group. Systematic reviews of adverse effects: framework for a structured approach. BMC Res Method 2007; 7(32).

(49) Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis.

(50) Clarke M. The QUORUM statement. Lancet 2000; 355:756-757.

(51) Moher D, Liberati A, Tetzlaff J, Altman D, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339:b2535.

(52) Alderson P, Green S, Higgins JPT (eds). Cochrane Reviewers Handbook 4.2.2. http://www cochrane org/resources/handbook/hbook htm 2005.

(53) Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. Ann Intern Med 2001; 134:657-662.

(54) Downs S, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52:377-384.

(55) Cochrane Methods Working Group on Systematic Reviews of Screening and Diagnostic Tests: Recommended Methods. 6-6-1996.

(56) CRD's guidance for undertaking reviews in healthcare. Systematic reviews. Centre for reviews and dissemination 2009.

(57) Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology 2003; 3: 25.

(58) Irwig LM, Tosteton AN, Gatsonis CA, Lao J, Colditz G, Chalmers TC et al. Guidelines for meta-analyses evaluating diagnostic tests. Annals of Internal Medicine 1994; 120: 667-676.

(59) Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005; 58:982-990.

(60) Dalkey NC, Helmer O. An experimental application of the Delphi method to the use of experts. Management Science 1963; 9: 458-467.

(61) Helmer O, Linstone HA, Turroff M, editors. Delphi Method: Techniques and applications. xix-xx. 1975. Mass., Addison-Wesley Publishing Company.
Ref Type: Generic

(62) Patricia L WIlliams, Christine Webb. The Delphi technique: A methodological discussion. Journal of Advanced Nursing 19, 180-186. 1994.
Ref Type: Generic

(63) Cantrill JA, Sibbald B, Buetow S. The Delphi and nominal group techniques in health services research. International Journal of Pharmacy Practise 4[2], 67-74. 1996.
Ref Type: Generic

(64) Linstone HA. The Delphi technique. Handbook of Futures Research. 271-300. 1978. Westport, CT, Greenwood.
Ref Type: Generic

(65) Hassan F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. Journal of Advanced Nursing 32, 1008-1015. 2000.
Ref Type: Generic

(66) Catherine Powell. Myths and realities of the Delphi technique. Journal of Advanced Nursing 41[4], 376-382. 2003.
Ref Type: Generic

(67) Murphy MK, Black N, Lamping DL, McKee CM, Sanders CFB, Askham J. Consensus development methods and their use in clinical guideline development. Health Technology Assessment 2[3]. 1998.
Ref Type: Generic

(68) Robinson JBL. Delphi methodology for economic-impact assessment. Journal of Transportation Engineering 117[3], 335-349. 2004.
Ref Type: Generic

(69) Sumsion T. The Delphi technique: an adpative research tool. British Journal of Occupational Therapy 61[4], 153-156. 1991.
Ref Type: Generic

(70) Charlton JR, Patrick DL, Matthews G, West PA. Spending priorities in Kent: a Delphi study. J Epidemiol Community Health 35[4], 288-292. 1981.
Ref Type: Generic

(71) Rudy SF. A review of Delphi surveys conducted to establish research priorities by specialty nursing organizations from 1985 to 1995. ORL Head Neck Nurs 14[2], 16-24. 1996.
Ref Type: Generic

(72) Likert R. A technique for measurement of attitudes. Archives of Psychology , 140. 1932.
Ref Type: Generic

(73) Walker AM, Selfe J. The Delphi technique: a useful tool for the allied health researcher. British Journal of Therapy and Rehabilitation 3[12], 677-680. 1996.
Ref Type: Generic

(74) Parston G. Introduction. The future of Public Services - 2007. 1995. Office for Public Management.
Ref Type: Generic

(75) Mullen PM. Delphi: myths and reality. J Health Organ Manag 17[1], 37-52. 2003.
Ref Type: Generic

(76) Sackman H. Delphi Critique. 1975. Boston, Lexington Books.
Ref Type: Generic

(77) Fink A, Kosecoff J, Chassin M, Brook R. Consensus Methods: Characteristics and Guidelines for Use. 1991. Santa Monica, California, RAND.
Ref Type: Generic

(78) Duffield C. The Delphi technique: a comparison of results obtained using two expert panels. Int J Nurs Stud 30[3], 227-237. 1993.
Ref Type: Generic

(79) Longhurst R. An economic evaluation of human resources program with respect to pregnancy outcome and intellectual development. 1971. Cornell University.
Ref Type: Generic

(80) Beattie E, Mackway-Jones K. A Delphi study to identify performance indicators for emergency medicine. Emerg Med J 21[1], 47-50. 2004.
Ref Type: Generic

(81) Behrens K, Shafi M, Dollery E, Jordan JA, Redman CWE. European standards in treatment of CIN. 2004. Proceedings of the BSCCP Annual Scientific Meeting.
Ref Type: Generic

(82) HMSO. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1997-99. 2001.
Ref Type: Report

(83) Montan S SNSN. Hypertension in Pregnancy – foetal and infant outcome. Hypertension in pregnancy 1987; B6:337-348.

(84) Rey E, Le Lorier J, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. CMAJ 157, 1245-1254. 1997.
Ref Type: Generic

(85) The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2003; 359:1877.

(86) Crowley P. Prophylactic corticosteroids for preterm birth. In: The Cochrane Library [Issue 3]. 2001. Oxford: Update software.
Ref Type: Generic

(87) Duley L, Henderson-Smart DJ, Knight M, King JF. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. BMJ 2001; 322:329-333.

(88) .

(89) Department of Health: Specialised Services National Definition Set: 4 Specialised services for women's health. Department of health 2006.

(90) Sacks HS, Reitman D, Pagano D. Meta-analysis: an update. Mt Sinai J Med 1996; 63:216-224.

(91) Petticrew M. Systematic reviews from astronomy to zoology: myths and misconceptions. BMJ 2001; 322:98-101.

(92) Jadad AR, Cook DJ, Jones A. Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. JAMA 1998; 280:278-280.

(93) Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol 1991; 44:1271-1278.

(94) Abalos E, Duley L, Steyn DW, Henderson-Smart D. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2001;(2):CD002252.

(95) Churchill D, Duley L. Interventionist versus expectant care for severe pre-eclampsia before term. Cochrane Database of Systematic Reviews 2002;(3):CD003106.

(96) Adab N, Tudur SC, Vinten J, Williamson P, Winterbottom J. Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database of Systematic Reviews 2004;(3):CD004848.

(97) Atallah AN, Hofmeyr GJ, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database of Systematic Reviews 2002;(1):CD001059.

(98) Bergel E, Carroli G, Althabe F. Ambulatory versus conventional methods for monitoring blood pressure during pregnancy. Cochrane Database of Systematic Reviews 2002;(2):CD001231.

(99) Boulvain M, Stan C, Irion O. Elective delivery in diabetic pregnant women. Cochrane Database of Systematic Reviews 2001;(2):CD001997.

(100) Brocklehurst P. Antibiotics for gonorrhoea in pregnancy. Cochrane Database of Systematic Reviews 2002;(2):CD000098.

(101) Cuervo LG, Mahomed K. Treatment for iron deficiency anaemia in pregnancy. Cochrane Database of Systematic Reviews 2001;(2):CD003094.

(102) Dennis CL, Creedy D. Psychosocial and psychological interventions for preventing postpartum depression. Cochrane Database of Systematic Reviews 2004;(4):CD001134.

(103) Burrows RF, Clavisi O, Burrows E. Interventions for treating cholestasis in pregnancy. Cochrane Database of Systematic Reviews 2001;(4):CD000493.

(104) Dodd J, Dare MR, Middleton P. Treatment for women with postpartum iron deficiency anaemia. Cochrane Database of Systematic Reviews 2004;(4):CD004222.

(105) Duley L, Henderson-Smart DJ. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database of Systematic Reviews 2002;(4):CD001449.

(106) Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database of Systematic Reviews 2003;(4):CD000128.

(107) Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. Cochrane Database of Systematic Reviews 2003;(4):CD000127.

(108) Duley L, Gulmezoglu AM, Henderson-Smart DJ. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database of Systematic Reviews 2003;(2):CD000025.

(109) Duley L, Henderson-Smart D, Meher S. Altered dietary salt for preventing pre-eclampsia, and its complications. Cochrane Database of Systematic Reviews 2005;(4):CD005548.

(110) French L, Smaill F. Antibiotic regimens for endometritis after delivery. Cochrane Database of Systematic Reviews 2004;(4):CD001067.

(111) Garner P, Gulmezoglu A. Drugs for preventing malaria-related illness in pregnant women and death in the newborn. Cochrane Database of Systematic Reviews 2002;(4):CD000169.

(112) Gates S, Brocklehurst P, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database of Systematic Reviews 2002;(2):CD001689.

(113) Howard LM, Hoffbrand S, Henshaw C, Boath L, Bradley E. Antidepressant prevention of postnatal depression. Cochrane Database of Systematic Reviews 2005;(2):CD004363.

(114) Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database of Systematic Reviews 2002;(1):CD000145.

(115) Jewell D, Young G. Interventions for treating constipation in pregnancy. Cochrane Database of Systematic Reviews 2001;(2):CD001142.

(116) Kroner C, Turnbull D, Wilkinson C. Antenatal day care units versus hospital admission for women with complicated pregnancy. Cochrane Database of Systematic Reviews 2001;(4):CD001803.

(117) Magee L, Sadeghi S. Prevention and treatment of postpartum hypertension. Cochrane Database of Systematic Reviews 2005;(1):CD004351.

(118) Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2003;(3):CD002863.

(119) Matchaba P, Moodley J. Corticosteroids for HELLP syndrome in pregnancy. Cochrane Database of Systematic Reviews 2004;(1):CD002076.

(120) Meher S, Abalos E, Carroli G. Bed rest with or without hospitalisation for hypertension during pregnancy. Cochrane Database of Systematic Reviews 2005;(4):CD003514.

(121) Orton L, Garner P. Drugs for treating uncomplicated malaria in pregnant women. Cochrane Database of Systematic Reviews 2005;(3):CD004912.

(122) Quijano CE, Abalos E. Conservative management of symptomatic and/or complicated haemorrhoids in pregnancy and the puerperium. Cochrane Database of Systematic Reviews 2005;(3):CD004077.

(123) Rumbold A, Duley L, Crowther C, Haslam R. Antioxidants for preventing pre-eclampsia. Cochrane Database of Systematic Reviews 2005;(4):CD004227.

(124) Smaill F. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database of Systematic Reviews 2001;(2):CD000490.

(125) Tuffnell DJ, West J, Walkinshaw SA. Treatments for gestational diabetes and impaired glucose tolerance in pregnancy. Cochrane Database of Systematic Reviews 2003;(3):CD003395.

(126) Vazquez JC, Villar J. Treatments for symptomatic urinary tract infections during pregnancy. Cochrane Database of Systematic Reviews 2003;(4):CD002256.

(127) Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. Cochrane Database of Systematic Reviews 2001;(3):CD001143.

(128) Walker MC, Ferguson SE, Allen VM. Heparin for pregnant women with acquired or inherited thrombophilias. Cochrane Database of Systematic Reviews 2003;(2):CD003580.

(129) Webb RT, Howard L, Abel KM. Antipsychotic drugs for non-affective psychosis during pregnancy and postpartum. Cochrane Database of Systematic Reviews 2004;(2):CD004411.

(130) Young G, Jewell D. Interventions for preventing and treating pelvic and back pain in pregnancy. Cochrane Database of Systematic Reviews 2002;(1):CD001139.

(131) Young G, Jewell D. Topical treatment for vaginal candidiasis (thrush) in pregnancy. Cochrane Database of Systematic Reviews 2001;(4):CD000225.

(132) Young G, Jewell D. Interventions for leg cramps in pregnancy. Cochrane Database of Systematic Reviews 2002;(1):CD000121.

(133) Boath E, Bradley E, Henshaw C, Boath E. The prevention of postnatal depression: a narrative systematic review. Journal of Psychosomatic Obstetrics & Gynecology 2005; 26(3):185-192.

(134) Brien T, Ray JG, Chan WS. Maternal body mass index and the risk of pre eclampsia: a systematic overview. Epidemiology 2003; 14(3):368-374.

(135) Brody SC, Harris R, Lohr K. Screening for gestational diabetes: a summary of the evidence for the U.S. Preventive Services Task Force. Obstetrics & Gynecology 2003; 101(2):380-392.

(136) Beck CT. Predictors of postpartum depression: an update. Nursing Research 2001; 50(5):275-285.

(137) Austin MP, Priest SR. Clinical issues in perinatal mental health: new developments in the detection and treatment of perinatal mood and anxiety disorders. Acta Psychiatrica Scandinavica 2005; 112(2):97-104.

(138) Beck CT. Postpartum depression: a metasynthesis. Qualitative Health Research 2002; 12(4):453-472.

(139) Coomarasamy A, Papaioannou S, Gee H, Khan KS. Aspirin for the prevention of preeclampsia in women with abnormal uterine artery Doppler: a meta-analysis. Obstetrics & Gynecology 2001; 98(5 Pt 1):861-866.

(140) Coomarasamy A, Honest H, Papaioannou S, Gee H, Khan KS. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. Obstetrics & Gynecology 2003; 101(6):1319-1332.

(141) Conde-Agudelo A, Villar J, Lindhmeimer M. World health organization syustematic review of screening tests for pre eclampsia. Obstetrics & Gynecology 2004; 104:1367-1391.

(142) Dennis CL. Preventing postpartum depression part II: A critical review of nonbiological interventions. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie 2004; 49(8):526-538.

(143) Dennis CL. Preventing postpartum depression part I: a review of biological interventions. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie 2004; 49(7):467-475.

(144) Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005; 330(7491):565.

(145) Eberhard-Gran M, Eskild A, Tambs K, Opjordsmoen S, Samuelsen SO. Review of validation studies of the Edinburgh Postnatal Depression Scale. Acta Psychiatrica Scandinavica 2001; 104(4):243-249.

(146) Gluck JC, Gluck PA. Asthma controller therapy during pregnancy. American Journal of Obstetrics & Gynecology 2005; 192(2):369-380.

(147) Goodman JH. Postpartum depression beyond the early postpartum period. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing 2004; 33(4):410-420.

(148) Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 2005; 106(2):401-407.

(149) Kujovich JL. Thrombophilia and pregnancy complications. American Journal of Obstetrics and Gynecology 2004; 191:412-424.

(150) Kosmas IP, Tatsioni A, Ioannidis JP. Association of Leiden mutation in factor V gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. Journal of Hypertension 2003; 21(7):1221-1228.

(151) Kosmas IP, Tatsioni A, Ioannidis JP. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. Journal of Hypertension 2004; 22(9):1655-1662.

(152) Kovalevsky G, Clarisa R, Gracia R, Jesse AB, Mary DS, Kurt TB. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. Archives Internal Medicine 2004; 164:558-562.

(153) Kwon HL, Belanger K, Bracken MB. Effect of pregnancy and stage of pregnancy on asthma severity: a systematic review. American Journal of Obstetrics & Gynecology 2004; 190(5):1201-1210.

(154) Lassere M, Empson M. Treatment of antiphospholipid syndrome in pregnancy - a systematic review of randomized therapeutic trials. Thrombosis Research 2004; 114(5-6):419-426.

(155) Magee LA, Cham C, Waterman EJ, Ohlsson A, von DP. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ 2003; 327(7421):955-960.

(156) Magee LA, Bull SB, Koren G, Logan A. The generalizability of trial data; a comparison of beta-blockers in pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 2001; 94:205-210.

(157) Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax 2006; 61(2):169-176.

(158) Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. American Journal of Obstetrics & Gynecology 2004; 191(6):1885-1897.

(159) Scott DA, Loveman E, McIntyre L, Waugh N. Screening for gestational diabetes: a systematic review and economic evaluation. Health Technology Assessment 2002; 6(11):1-161.

(160) Austin MP, Lumley J. Antenatal screening for postnatal depression: a systematic review. Acta Psychiatrica Scandinavica 2003; 107(1):10-17.

(161) Austin MP. Targeted group antenatal prevention of postnatal depression: a review. Acta Psychiatrica Scandinavica 2003; 107(4):244-250.

(162) Egger M, Smith GD. Meta-analysis bias in location and selection of studies. BMJ 1998; 316:61-66.

(163) James D. Fetal medicine. BMJ 316, 1580-1583. 1998.
Ref Type: Generic

(164) Kumar S, O'Briene A. Recent developments in fetal medicine. BMJ 328, 1002-1006. 2004.
Ref Type: Generic

(165) Mari G, Deter RL, Carpenter RL, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anaemia due to maternal red cell alloimmunization. Collaborative group for Doppler assessment of blood flow velocities of anaemic fetuses. N Engl J Med 342, 9-14. 2000.
Ref Type: Generic

(166) Senal MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser sugery versus serial amnioreduction for severe twin twin transfusion syndrome. N Engl J Med 351, 136-144. 2004.
Ref Type: Generic

(167) Bradburn MJ, Deeks JJ, Berlin JA, Russell LA. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med . 2006.
Ref Type: Generic

(168) Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F et al. Evaluating non-randomised intervention studies. Health Technol Assess , 7(27). 2003.
Ref Type: Generic

(169) Garfield RE, Kannan MS, Daniel EE. Gap junction formation in myometrium:control by oestrogens, progesterone, and prostaglandins. Am J Physiol 238, C81-C89. 1980.
Ref Type: Generic

(170) Sanchez-Ramos S, Kaunitz AM, Delke I. Progestational Agents to Prevent Preterm Birth: A Meta-analysis of Randomized Controlled Trials. Obsterics and Gynecology 105[2], 273-279. 2005.
Ref Type: Generic

(171) Paneth NS. The problem of low birth weight. Future Child 5, 19-34. 1995.
Ref Type: Generic

(172) Khan KS, Ter Riet G, Glanville J, Sowden AJ, Kleijnen J. Undertaking Systematic Reviews of Research on Effectiveness. CRD's Guidance for Carrying Out or Commissioning Reviews. 4. 2001. Centre for Reviews and Dissemination (CRD), University of York. CRD Report.
Ref Type: Report

(173) Mantel N, Haenzel W. Statistical aspects of the analysis of data frm retrospective studies of disease. J Natl Cancer Inst 22, 719-748. 1959.
Ref Type: Generic

(174) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 7, 177-188. 1986.
Ref Type: Generic

(175) Egger M, Davey SG, Shneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629-634. 1997.
Ref Type: Generic

(176) Egger M, Smith GD. Meta-analysis: Potentials and promise. 315, 1371-1374. 1997.
Ref Type: Generic

(177) Antman EM, Lau J, Kupelnik B, Mosteller F, Chalmers TC. A Comparison of Results of Meta-analyses of Randomized Contron Trials and Recommendations of Clinical Experts. JAMA 268, 240-248. 1992.
Ref Type: Generic

(178) Ferrer RL. Graphical methods for detecting bias in meta-analysis. Fam Med 30[8], 579-583. 1998.
Ref Type: Generic

(179) Ernst E, Pittler MH. Assessment of therapeutic safety in systematic reviews: literature review. BMJ 323, 546. 2001.
Ref Type: Generic

(180) Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 alpha hydroxy progesterone caproate in the prevention of preterm labour. N Engl J Med 293[14], 675-680. 1975.
Ref Type: Generic

(181) Levine L. Habitual abortion. A controlled study of progeststional therapy. west J Surg Obstet Gynecol 72, 30-36. 1964.
Ref Type: Generic

(182) Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai M, Moawad AH et al. Prevention of recurrent preterm delivery by 17 alpha hydroxy progesterone caproate. N Engl J Med 348[24], 2379-2385. 2003.
Ref Type: Generic

(183) Papiernik-Berkauer E. Etude en double aveugle d'un medicament prevenant la survenu prematuree de l'accouchement chez des femmes " a risue eleve" d'accouchment premature. Edition Schering Serie IV[fische 3], 65-68. 1970.
Ref Type: Generic

(184) Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner BM, Kessler I et al. Prevention of premature labour by 17 alpha hydroxy progesterone caproate. Am J Obstet Gynecol 151[5], 574-577. 1985.
Ref Type: Generic

(185) da Foncesca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double blind study. Am J Obstet Gynecol 188[2], 419-424. 2003.
Ref Type: Generic

(186) Sondergard F, Otteson B, Detlefsen GU, Schierup L, Pedersen SC, Lebech PE. Traitement par la progesterone des menaces d'accouchment premature avex taux bas de progesterone plasmatique. Contrception-Fertilite-Sexualite 13, 1227-1231. 1985.
Ref Type: Generic

(187) Noblot G, Audra P, Dargent D, Faguer B, Mellier G. The use of micronized progesterone in the treatment of menace of preterm delivery. Eur J Obstet Gynecol Reprod Biol 40[3], 203-209. 1991.
Ref Type: Generic

(188) Swyer GI, Daley D. Progesterone implantation in habitual abortion. Br Med J 1[4819], 1073-1077. 1953.
Ref Type: Generic

(189) Oates-Whitehead RM, Haas DM, Carrier JAK. Progestogen for preventing miscarriage. The Cochrane database of systematic reviews [4], Art. No.: CD003511. DOI: 10.1002/14651858.CD003511. 2003.
Ref Type: Generic

(190) Raman-Wilms L, Lin-in Tseng A, Wighardt S, Einarson TR, Koren G. Fetal genital effects of first trimester sex hormone exposure: A meta-analysis. Obsterics and Gynecology 85[1], 141-149. 1995.
Ref Type: Generic

(191) Carmichael SZ, Shaw GM, Laurent C, et al. Maternal progestin intake and risk of hypospadias. Arch Pediatr Adolesc Med 159, 957-962. 2005.
Ref Type: Generic

(192) Brent RL. Nongenital malformations following exposure to progestational drugs: The last chapter of an erroneous allegation. Birth Defects Research (Part A): Clinical and Molecular Teratology 73, 906-918. 2005.
Ref Type: Generic

(193) Adab N. Therapeutic monitoring of antiepileptic drugs during pregnancy and in the postpartum period: is it useful? CNS Drugs 2006; 20(10):791-800.

(194) Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology 2008; 70:2130-2136.

(195) Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation. Neurology 2003; 61(6 Suppl 2):S35-S42.

(196) Pennell PB, Hovinga CA. Antiepileptic drug therapy in pregnancy I: gestation-induced effects on AED pharmacokinetics. International Review of Neurobiology 2008; 83:227-240.

(197) Petrenaite V, Sabers A, Hansen-Schwartz J. Individual changes in lamotrigine plasma concentrations during pregnancy. Epilepsy Research 2005; 65(3):185-188.

(198) De Haan G-J., Edelbroek P, Segers J, Engelsman M, Lindhout D, vile-Notschaele M et al. Gestation-induced changes in lamotrigine pharmacokinetics: A monotherapy study. Neurology 2004; 63(3):571-573.

(199) Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008; 49(7):1239-1276.

(200) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: Management issues for women with epilepsy (summary statement) Report of the Quality Standard Subcommittee of the American Academy of Neurology. Neurology 1998; 51(4):944-948.

(201) Scottish Intercollegiate Guidelines Network 70; Diagnosis and management of epilepsy in adults. A national clinical guideline. www sign ac uk/pdf/sign70 pdf 1993.

(202) de Haan GJ, Edelbroek P, Segers J, Engelsman M, Lindhout D, Devile-Notschaele M et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology 2004; 63(3):571-573.

(203) Ohman I, Beck O, Vitols S, Tomson T. Plasma concentrations of lamotrigine and its 2-N-glucuronide metabolite during pregnancy in women with epilepsy. Epilepsia 2008; 49(6):1075-1080.

(204) Petrenaite V, Sabers A, Hansen-Schwartz J. Individual changes in lamotrigine plasma concentrations during pregnancy. Epilepsy Research 2005; 65(3):185-188.

(205) Tran TA, Leppik IE, Blesi K, Sathanandan ST, Remmel R. Lamotrigine clearance during pregnancy. Neurology 2002; 59(2):251-255.

(206) Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology 2008; 70(22 Pt 2):2130-2136.

(207) Perucca E. Is there a role for therapeutic drug monitoring of new anticonvulsants? Clinical Pharmacokinetics 2000; 38(3):191-204.

(208) Tomson T, Battino D, French J, Harden C, Holmes L, Morrow J et al. Antiepileptic drug exposure and major congenital malformations: the role of pregnancy registries. Epilepsy & Behavior 2007; 11(3):277-282.

(209) anonymous. A North American Registry for Epilepsy and Pregnancy, a unique public/private partnership of health surveillance. Epilepsia 1998; 39(7):793-798.

(210) Cunnington M, Ferber S, Quartey G, International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. Epilepsia 2007; 48(6):1207-1210.

(211) Cunnington MC. The International Lamotrigine pregnancy registry update for the epilepsy foundation. Epilepsia 2004; 45(11).

(212) Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R et al. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. Journal of Neurology, Neurosurgery & Psychiatry 2006; 77(2):193-198.

(213) Holmes LB, Baldwin EJ, Smith CR, Habecker E, Glassman L, Wong SL et al. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008; 70(22 Pt 2):2152-2158.

(214) GlaxoSmithKline International. The Lamotrigine Pregnancy Registry. Interim Report 1 September 1992 through 31 March 2009. 1-7-2009.
Ref Type: Generic

(215) Meador KJ, Zupanc ML. Neurodevelopmental outcomes of children born to mothers with epilepsy. Cleveland Clinic Journal of Medicine 2004; 71 Suppl 2:S38-S41.

(216) Motamedi GK, Meador KJ. Antiepileptic drugs and neurodevelopment. Current Neurology & Neuroscience Reports 2006; 6(4):341-346.

(217) Baker GA, Camfield C, Camfield P, Cramer JA, Elger CE, Johnson AL et al. Commission on Outcome Measurement in Epilepsy, 1994-1997: Final Report. [Report]. Epilepsia 1998; 39(2):213-231.

(218) EURAP Study Group. Utilization of antiepileptic drugs during pregnancy: comparative patterns in 38 countries based on data from the EURAP registry. Epilepsia 2009; 50(10):2305-2309.

(219) Bossuyt P, Lijmer JG, Mol BW. Randomised comparisons of medical tests: sometimes invalid, not always efficient. The Lancet 2000; 356:1844-1847.

(220) World Health Organization. The hypertensive disorders of pregnancy: Report of a WHO Study Group. 1987.
Ref Type: Report

(221) Duvekot JJ, Peeters LLH. Maternal haemodynamic adaptation to pregnancy. Obstet Gynecol Surv 1994; 49:S1-S14.

(222) HMSO. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1997-99. 2001.
Ref Type: Report

(223) Montan S SNSN. Hypertension in Pregnancy – foetal and infant outcome. Hypertension in Pregnancy 1987; B6:337-348.

(224) Coomarasamy A, Gee H, Khan KS, Braunholtz D. Aspirin has clinically significant benefit in high risk groups - Summary NNT can mislead clinicians. eBMJ 2001.

(225) Alderson P, Green S, Higgins JPT. Cochrane Reviewer's Handbook 4.2.2. 2004.
Ref Type: Report

(226) Egger M, Z-ZT, Zellweger-Zahner T, et al. Language bias in randomised controlled trials published in English and German. Lancet 1997; 350:326-329.

(227) Whiting PJ, Rutjes AWS, Reitsma JB, Bossuyt PM, Afina S Glas, Kleijnen J. Sources of Variation and Bias in Studies of Diagnostic Accuracy
A Systematic Review. Annals of Internal Medicine 140[3], 189-202. 2004.
Ref Type: Generic

(228) Bossuyt PM, Reitsma JB, Bruns DE, Glasziou PP, Gatsonis CA, Irwig LM et al. Towards complete and accurate reporting of studies on diagnostic accuracy:The STARD initiative. Family Practice 21[1], 4-10. 2004.
Ref Type: Generic

(229) Chein PFW, Khan KS. Evaluation of a clinical test.II: Assessment of validity. Br J Obstet Gynecol 108[6], 568-572. 2001.
Ref Type: Generic

(230) Deeks JJ. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. BMJ 2001; 323:157-162.

(231) Jaeschke R, Guyatt GH, Sackett DL. Users' guide to the medical literature. II. How to use an article about a diagnostic test. A. Are the results of the study valid? JAMA 1994; 271:389-391.

(232) Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JHP et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999; 282:1061-1066.

(233) Honest, Khan KS. Reporting of measures of accuracy in systematic reviews in diagnostic literature. BMC health series research 2[4]. 2002.
Ref Type: Generic

(234) Jaeschke R, Guyatt GH, Sackett DL. Users' guide to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? JAMA 1994; 271:703-707.

(235) Song F, Khan KS, Dinnes J, Sutton A. Asymmetric Funnel Plots and the Problem of Publication Bias in Meta-analyses of Diagnostic Accuracy. Int J Epidemiol 2001.

(236) Khan KS, Dinnes J, Kleijnen J. Systematic reviews to evaluate diagnostic tests. J Obstet Gynecol Reprod Biol 2001; 95:6-11.

(237) Khan KS, Honest, Bachmann LM. A generic framework for making clinical decisions integrating diagnostic and therapeutic research evidence in preterm birth. Fetal and Maternal Medicine Review. Fetal and Maternal Medicine Review 2003; 13:239-249.

(238) Chein PFW, Khan KS, Arnott N. Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomised trials. Br J Obstet Gynecol 103[11], 1085-1091. 1996.
Ref Type: Generic

(239) The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2003; 359:1877.

(240) Chan P, Brown M, Simpson J, Davis G. Proteinuria in pre-eclampsia: how much matters? BJOG : an international journal of obstetrics and gynaecology 2005; 112(3):280-285.

(241) Pollak VE, Nettles JB. **The kidney in toxemia of pregnancy: a clinical and pathologic study based on renal biopsies**. Medicine (Baltimore) 1960; 39:469-526.

(242) Page EW, Christianson R. The impact of mean arterial pressure in the middle trimester on the impact of pregnancy. Am J Obstet Gynecol 1976; 125:740-746.

(243) American College of Obstetrics and Gynecology. Diagnosis and management of preeclampsia and eclampsia. Practice Bulletin No 33 2002.

(244) Ferrazzani S, Caruso A, De CS, Martino I, V, Mancuso S. Proteinuria and outcome of 444 pregnancies complicated by hypertension. American journal of obstetrics and gynecology 1990 Feb P: 366-71, ISSN: 0002-9378.:-71, ISSN.

(245) Brown MA, Buddle ML. Hypertension in pregnancy: Maternal and fetal outcomes according to laboratory and clinical features. Medical Journal of Australia 1996; 165(7):360-365.

(246) Buchbinder A, Sibai BM, Caritis S, MacPherson C, Hauth J, Lindheimer MD et al. Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. American Journal of Obstetrics and Gynecology 2002; 186(1):66-71.

(247) Fliegner J-RH. Placental function and renal tract studies in pre eclampsia with proteinuria and long term maternal consequences. American Journal of Obstetrics and Gynecology 1976; 126(2):211-217.

(248) Furukawa S, Sameshima H, Ikenoue T. Intrapartum late deceleration develops more frequently in pre-eclamptic women with severe proteinuria. J Obstet Gynaecol Res 32, 68-73. 2006.
Ref Type: Generic

(249) Hall DR, Odendaal HJ, Kirsten GF, Smith J, Grove D. Expectant management of early onset, severe pre-eclampsia: Perinatal outcome. British Journal of Obstetrics and Gynaecology 2000; 107(10):1258-1264.

(250) Lao TT, Chin R-KH, Lam YM. The significance of proteinuria in pre-eclampsia; proteinuria associated with low birth weight only in pre-eclampsia. European Journal of Obstetrics Gynecology and Reproductive Biology 1988; 29(2):121-127.

(251) Martin JN, Jr., May WL, Magann EF, Terrone DA, Rinehart BK, Blake- P-G et al. Early risk assessment of severe preeclampsia: Admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. American Journal of Obstetrics and Gynecology 1999; 180(6 I):1407-1414.

(252) Newman MG, Robichaux AG, Stedman CM, Jaekle RK, Todd FM, Dotson T et al. Perinatal outcomes in preeclampsia that is complicated by massive proteinuria. American Journal of Obstetrics and Gynecology 2003; 188(1):264-268.

(253) Odegaard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. Obstetrics and Gynecology 2000; 96,(6):950-955.

(254) Paladini A, Frollo G, Nappi G. (Clinical-statistical study on the hypertension-edema-nephrosis syndrome. II. Sequelae for the fetus, particular attention to perinatal mortality). Archivio di Ostetricia e Ginecologia 1970; 75,(4):297-306.

(255) Schiff E, Friedman SA, Kao L, Sibai BM. The importance of urinary protein excretion during conservative management of severe preeclampsia. American Journal of Obstetrics and Gynecology 1996; 175(5):1313-1316.

(256) Taylor HC Jr, Tillman AJ, Blanchard J. Fetal losses in hypertension and preeclampsia. I. An analysis of 4432 cases. Obstet Gynecol 3, 225-239. 1954.
Ref Type: Generic

(257) Thurnau GR, Dyer A, Depp-III OR, Martin AO. The development of a profile scoring system for early identification and severity assessment of pregnancy-induced hypertension. American Journal of Obstetrics and Gynecology 1983; 146(4):406-416.

(258) von Dadelszen P, Magee LA, Devarakonda RM, Hamilton T, Ainsworth LM, Yin R et al. The prediction of adverse maternal outcomes in preeclampsia. Journal of obstetrics and gynaecology Canada 2004; 26,(10):871-880.

(259) Waugh J, Bell SC, Kilby MD, Lambert P, Shennan A, Halligan A. Urine protein estimation in hypertensive pregnancy: which thresholds and laboratory assay best predict clinical outcome? Hypertens Pregnancy 24, 291-302. 2005.
Ref Type: Generic

(260) Weenink GH, Treffers PE, Vijn P. Plasma antithrombin III levels in pre-eclampsia. Clinical and Experimental Hypertension - Part B Hypertension in Pregnancy 1983; Vol(Iss/Pg. 2/1):145-162.

(261) Hall DR, Odendaal HJ, Steyn DW, Grove D. Urinary protein excretion and expectant management of early onset, severe pre-eclampsia. International journal of gynaecology and 2002; 77,(1):1-6.

(262) Taylor HC Jr, Tillman AJ, Blanchard J. Fetal losses in hypertension and in pre-eclampsia. II. Prognosis for the fetus according to the week of gestation. Obstet Gynecol 3[4], 371-384. 1954.
Ref Type: Generic

(263) Siemons JM, Bogert LJF. The uric acid content of maternal and fetal blood. J Bioch 32, 63-67. 1917.
Ref Type: Generic

(264) Chesley LC, Williams LO. Renal glomerular and tubular function in relation to the hyperuricemia of preeclampsia and eclampsia. American Journal of Obstetrics and Gynecology 50, 367-375. 1945.
Ref Type: Generic

(265) Fadel HE, Northrop G, Misenhimer HR. Hyperuricemia in pre-eclampsia. A reappraisal. American journal of obstetrics and gynecology 1976 Jul 1 P: 640-7, ISSN: 0002-9378.:-7, ISSN.

(266) Many A, Hubel CA, Roberts JM. Hyperuricemia and xanthine oxidase in preeclampsia, revisited. American journal of obstetrics and gynecology 1996 Jan 1996; P: 288-91, Refs: 60, ISSN: 0002-9378.:-91, Refs.

(267) Lancet M, Fisher IL. The value of blood uric acid levels in toxemia of pregnancy. Obstet Gynaecol Br Emp 63, 116-119. 1956.
Ref Type: Generic

(268) Liedholm H, Montan S, Aberg A. Risk grouping of 113 patients with hypertensive disorders during pregnancy, with respect to serum urate, proteinuria and time of onset of hypertension. Acta obstetricia et gynecologica Scandinavica Supplement 1984 P: 43-8, ISSN: 0300-8835.:-8, ISSN.

(269) McFarlane CN. An evaluation of the serum uric acid level in pregnancy. J Obstet Gynaecol Br Commonw 70, 63-68. 1963.
Ref Type: Generic

(270) Redman CW, Beilin LJ, Bonnar J, Wilkinson RH. Plasma-urate measurements in predicting fetal death in hypertensive pregnancy. Lancet 1976 Jun 26 P: 1370-3, ISSN: 0140-6736.:-3, ISSN.

(271) Connon AF, Wadsworth RJ. An evaluation of serum uric acid estimations in toxaemia of pregnancy. The Australian & New Zealand journal of obstetrics & gynaecology 1968 Nov P: 197-201, ISSN: 0004-8666.:-201, ISSN.

(272) D'Anna R, Baviera G, Scilipoti A, Leonardi I, Leo R. The clinical utility of serum uric acid measurements in pre-eclampsia and transient hypertension in pregnancy. Panminerva medica 2000 Jun 2000; P: 101-3, ISSN: 0031-0808.:-3, ISSN.

(273) Dequiedt P, Tacquet A, Puech F, Cotteel M, Potier A, Leroy JL et al. The prognostic value of raised uric acid in the blood in arterial hypertension in pregnancy. 58 cases. Journal de gynecologie 1979; VOL: 8 ,(2), P: 115-20, ISSN: 0368-2315.:2-20, ISSN.

(274) Mathews DD, Agarwal V, Shuttleworth TP. The effect of rest and ambulation on plasma urea and urate levels in pregnant women with proteinuric hypertension. British journal of obstetrics and gynaecology 1980 Dec P: 1095-8, ISSN: 0306-5456.:-8, ISSN.

(275) Odendaal HJ, Pienaar ME. Are high uric acid levels in patients with early pre-eclampsia an indication for delivery? South African medical journal 1997 Feb 1997; P: 213-8, ISSN: 0038-2469.:-8, ISSN.

(276) Peralta-Pedrero ML, Basavilvazo-Rodriguez MA, Avelar A, Sanchez AS, Guzman-Ibarra-Maria-de-los- Angeles, Martinez-Garcia-Maria-del-Carmen. (Clinical significance of the laboratory determinations in preeclamptic patients). Ginecologaia y obstetricia de Maexico 2004 Feb P: 57-62, ISSN: 0300-9041.:-62, ISSN.

(277) Sackman H. Delphi Critique. 1975. Boston, Lexington Books.
Ref Type: Generic

(278) SEITCHIK J. Observations on the renal tubular reabsorption of uric acid. I. Normal pregnancy and abnormal pregnancy with and without pre- eclampsia. American journal of obstetrics and gynecology 1953 May P: 981-5, ISSN: 0002-9378.:-5, ISSN.

(279) Shah DM, Reed G. Parameters associated with adverse perinatal outcome in hypertensive pregnancies. Journal of human hypertension 1996 Aug 1996; P: 511-5, ISSN: 0950-9240.:-5, ISSN.

(280) Varma TR. Serum uric acid levels as an index of fetal prognosis in pregnancies complicated by pre-existing hypertension and pre-eclampsia of pregnancy. International journal of gynaecology and 1982 Oct P: 401-8, ISSN: 0020-7292.:-8, ISSN.

(281) Voto LS, Illia R, rbon-Grosso HA, Imaz FU, Margulies M. Uric acid levels: a useful index of the severity of preeclampsia and perinatal prognosis. Journal of perinatal medicine 1988 P: 123-6, ISSN: 0300-5577.:-6, ISSN.

(282) Williams KP, Galerneau F. The role of serum uric acid as a prognostic indicator of the severity of maternal and fetal complications in hypertensive pregnancies. Journal of obstetrics and gynaecology Canada 2002 Aug P: 628-32, ISSN: 1701-2163.:-32, ISSN.

(283) Yassaee F. Hyperuricemia and perinatal outcomes in patients with severe preeclampsia. Iranian Journal of Medical Sciences 2003; Vol(Iss /Pg. 28/4):198-199.

(284) Chappell LC, Seed PT, Briley A, Kelly FJ, Beverley J, Charnock-Jones DS et al. A longitudinal study of biochemical variables in women at risk of preeclampsia. American journal of obstetrics and gynecology 2002 Jul 2002; P: 127-36, ISSN: 0002-9378.:-36, ISSN.

(285) Crowley P. Prophylactic corticosteroids for preterm birth. [Review] [50 refs]. Cochrane Database of Systematic Reviews (2):CD000065, 2000.

(286) Rey E, Le Lorier J, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. CMAJ 157, 1245-1254. 1997.
Ref Type: Generic

(287) Abroug F, Boujdaria R, Nouira S, Abroug S, Souissi M, Najjar MF et al. Hellp syndrome: Incidence and maternal-fetal outcome - A prospective study. Intensive Care Medicine 1992; 18(5):274-277.

(288) Harms E, Baehr M, Kloeck FK. (The HELPP syndrome--a severe complication of pre-eclampsia. A presentation of 19 cases from 1983 to 1990). Zeitschrift feur Geburtshilfe und Perinatologie 1991; 195,(4):187-192.

(289) Romero R, Vizoso J, Emamian M, Duffy T, Riely C, Halford T et al. Clinical significance of liver dysfunction in pregnancy-induced hypertension. American Journal of Perinatology 1988; 5(2):146-151.

(290) Thangaratinam S, Coomarasamy A, Sharp S, O'Mahony F, O'Brien S, Ismail KMK et al. Tests for predicting complications of pre-eclampsia: A protocol for systematic reviews. BMC Pregnancy and Childbirth 8, 38. 2008.
Ref Type: Generic

(291) Aali BS, Ghafoorian J, Mohamad AS. Severe preeclampsia and eclampsia in Kerman, Iran: complications and outcomes. Medical Science Monitor 2004; 10,(4):CR163-CR167.

(292) Abramovici D, Friedman SA, Mercer BM, Audibert F, Kao L, Sibai BM. Neonatal outcome in severe preeclampsia at 24 to 36 weeks' gestation: Does the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome matter? American Journal of Obstetrics and Gynecology 1999; 180(1 I):221-225.

(293) Audibert F, Friedman S, Frangieh A, Sibai B. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. American Journal of Obstetrics and Gynecology 175, 460-464. 1996.
Ref Type: Generic

(294) Borglin NE. Serum Transaminase activity in uncomplicated and complicated pregnnacy and in newborns. J Clin Endocrin Metab 18, 872-877. 1958.
Ref Type: Generic

(295) Crisp WE, miesfeld RL, Frajola WJ. Serum glutamic oxalacetic transaminase levels in the toxemias of pregnancy. Obstetrics and Gynecology 13, 487-497. 1959.
Ref Type: Generic

(296) Girling JC, Dow E, Smith JH. Liver function tests in pre eclampsia: Importance of comparing with a reference range derived for normal pregnancy. British Journal of Obstetrics and Gynaecology 104, 246-250. 1997.
Ref Type: Generic

(297) Haddad B, Barton JR, Livingston JC, Chahine R, Sibai BM. HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome versus severe preeclampsia: onset at < or =28.0 weeks' gestation. American Journal of Obstetrics and Gynecology 2000; 183,(6):1475-1479.

(298) Odendaal HJ, Hall DR, Grove D. Risk factors for and perinatal mortality of abruptio placentae in patients hospitalised for early onset severe pre-eclampsia - A case controlled study. Journal of Obstetrics and Gynaecology 2000; Vol(Iss/Pg. 20/4):358-364.

(299) Woldeselassie. Pre-eclampsia and its outcome (Maternal and Neonatal Morbidity and Mortality) in the two Referral Hospitals (Windhoek Central and Katutura), Namibia. A mini-thesis submitted in partial fulfillment of the requirements for the degree of Master of Public Health (MPH) . 2005. School of Public Health, University of the Western Cape.
Ref Type: Generic

(300) Yücesoy G, Ozkan S, Bodur H, Tan T, Caliskan E, Vural B et al. Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: a seven year experience of a tertiary care center. Arch Gynecol Obstet 273, 43-49. 2005.
Ref Type: Generic

(301) Duley L. Pre-eclampsia and the hypertensive disorders of pregnancy. British Medical Bulletin 2003; 67(161):176.

(302) Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. American Journal of Obstetrics and Gynecology 180, 499-506. 2009.
Ref Type: Generic

(303) Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet 357, 53-56. 2001.
Ref Type: Generic

(304) Sibai BM, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 365, 785-799. 2005.
Ref Type: Generic

(305) Minamaki H, Oka N, Sato T, Tamada T, Yasuda Y, Hirota N. Preeclampsia: a microvesicular fat disease of the liver? American Journal of Obstetrics and Gynecology 159, 1043-1047. 1988.
Ref Type: Generic

(306) Thangaratinam S, Ismail KS, Sharp S, Coomarasamy A, Khan KS, Tests in Prediction of Pre-eclampsia Severity review group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. British Journal of Obstetrics and

Gynaecology 113, 369-378. 2006.
Ref Type: Generic

(307) Thangaratinam S, Coomarasamy A, O'Mahony F, Sharp S, Zamora J, Khan K et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Medicine 2009; 7(1):10.

(308) 2006 Commission for Healthcare Audit and Inspection. Investigation into 10 maternal deaths at, or following delivery at, Northwick Park Hospital, North West London Hospitals NHS Trust, between April 2002 and April 2005. London 2006.

(309) Rossiter and another v Tilsley and another - [2001] All ER (D) 167 (Feb). All England Reporter 2001.

(310) Matsuda H, Sakaguchi K, Shibasaki T, Takahashi H, Kawakami Y, Furuya K et al. Cerebral edema on MRI in severe preeclamptic women developing eclampsia. J Perinat Med 2005; 33:199-205.

(311) Williams K, Bianco Lim K, Wilson S, et al. Can clinical symptomology predict maternal cerebral perfusion pressure in preeclampsia? Rev Chil Obstet Ginecol 2004; 69:361-367.

(312) Do DV, Rismondo V, Nguyen QD. Reversible cortical blindness in pre eclampsia. Am J Ophthalm 2002; 134:916-918.

(313) Arias F, Marcilla JR. Hepatic fibrinogen deposits in pre-eclampsia immunoflourescent evidence. New Engl J Med 1976; 295:578-582.

(314) Douglas KA, Redman CW. Eclampsia in the United Kingdom. BMJ 1994; 309:1395-1400.

(315) Witlin AG, Saade GR, Mattar F, Sibai BM. Risk factors for abruptio placentae and eclampsia: analysis of 445 consecutively managed women with severe preeclampsia and eclampsia. American journal of obstetrics and gynecology 1999 Jun 1999; P: 1322-9, ISSN: 0002-9378.:-9, ISSN.

(316) Joanne Said. Managing pre eclampsia. O&G magazine RANZCOG 2006; 8:43-44.

(317) Magee LA, Helewa M, Moutquin JM, von Dadelszen P, Hypertension Guideline Committee, Society of Obstetricians and Gynaecologists of Canada. Treatment of the hypertensive disorders of pregnancy. In: Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. J Obstet Gynaecol Can 2008; 30:S24-S36.

(318) Tufnell DJ, Shennan AH, Waugh JJS, Walker JJ. The management of severe pre-eclampsia/eclampsia. Royal College of Obstetricians and Gynaecologists (RCOG) Guideline No 10 (A) 2006.

(319) Ben Salem F, Ben Salem K, Grati L, Arfaoui C, Faleh R, Jmel A et al. Risk factors for eclampsia: A case-control study. Annales Francaises d'Anesthesie et de Reanimation 2003; 22(10):865-869.

(320) Black KD. Stress, Symptoms, Self monitoring confidence, Well being and Social support in the progression of Pre eclampsia / Gestational Hypertension. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing 2007; 36:419-429.

(321) Martin JN, Jr., Rinehart BK, May WL, Magann EF, Terrone DA, Blake- P-G et al. The spectrum of severe preeclampsia: Comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. American Journal of Obstetrics and Gynecology 1999; 180(6 I):1373-1384.

(322) Menzies JM, Magee LA, MacNab YC, Ansermino JM, et al. Current CHS and NHBPEP criteria for severe pre eclampsia do not uniformly predict adverse maternal or perinatal outcomes. Hypertension in Pregnancy 2007; 26:447-462.

(323) Dukler D, Porath A, Bashiri A, Erez O, Mazor M. Remote prognosis of primiparous women with preeclampsia. European Journal of Obstetrics Gynecology and Reproductive Biology 2001; 96(1):69-74.

(324) Heilmann L, Siekmann U. Hemodynamic and hemorheological profiles in women with proteinuric hypertension of pregnancy and in pregnant controls. Archives of gynecology and obstetrics 1989 P: 159-68, Refs: 59, ISSN: 0932-0067.:-68, Refs.

(325) Peek MJ, Horvath JS, Child AG, Henderson-Smart DJ, Peat B, Gillin A. Maternal and neonatal outcome of patients classified according to the Australasian Society for the Study of Hypertension in Pregnancy Consensus Statement. Medical Journal of Australia 1995; 162(4):186-189.

(326) Xiong X, Mayes D, Demianczuk N, Olson DM, Davidge ST, Newburn C et al. Impact of pregnancy-induced hypertension on fetal growth. American Journal of Obstetrics and Gynecology 1999; 180(1 I):207-213.

(327) RCOG Green-top guideline 10(A). The management of severe pre eclampsia / eclampsia. Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists 2006.

(328) Hall DMB, Elliman D. Health for all children [4th Ed]. Oxford 2003.

(329) Wren C, Richardson S, Donaldson P. Presentation of congenital heart disease in pregnancy: Implications for routine examination. Archives of disease in childhood 1999; 80:F49-F53.

(330) Salyer J. Neonatal and pediatric pulse oximetry. Respiratory care 2003; 48(4):386-396.

(331) Arlettaz R, Bauschatz A, M÷nkhoff M, Essers B, Bauersfeld U. The contribution of pulse oximetry to the early detection of congenital heart disease in newborns. European journal of pediatrics 2006; 165(2):94-98.

(332) Bakr AF, Habib HS. Combining pulse oximetry and clinical examination in screening for congenital heart disease. Pediatric cardiology 2005; 26(6):832-835.

(333) de W, Mellander M, Sunnegσrdh J, Sandberg K, Ostman S, I. Screening for duct-dependant congenital heart disease with pulse oximetry: a critical evaluation of strategies to maximize sensitivity. Acta paediatrica (Oslo Norway : 1992) 2005; 94(11):1590-1596.

(334) Hoke TR, Donohue PK, Bawa PK, Mitchell RD, Pathak A, Rowe PC et al. Oxygen saturation as a screening test for critical congenital heart disease: a preliminary study. Pediatric cardiology 2002; 23(4):403-409.

(335) Koppel R, I, Druschel C, Carter T, Goldberg B, Mehta P, Talwar R et al. Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns. Pediatrics 2003; 111(3):451-455.

(336) Reich J, Miller S, Brogdon B, Casatelli J, Gompf T, Huhta J et al. The use of pulse oximetry to detect congenital heart disease. The Journal of pediatrics 2003; 142(3):268-272.

(337) Richmond S, Reay G, Abu H. Routine pulse oximetry in the asymptomatic newborn. Archives of disease in childhood Fetal and neonatal edition 2002; 87(2):F83-F88.

(338) Rosati E, Chitano G, Dipaola L, De F, Latini G. Indications and limitations for a neonatal pulse oximetry screening of critical congenital heart disease. Journal of Perinatal Medicine 2005; 33(5):455-457.

(339) Rennie D. Improving reports of diagnostic tests: the STARD initiave. JAMA 289, 89-90. 2003.
Ref Type: Generic

(340) Zamora J, Abraira V, Muriel A, Khan KS, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Medical Research Methodology 2006; 6.

(341) Richmond S, Reay G, Abu H. Routine pulse oximetry in the asymptomatic newborn. Archives of disease in childhood Fetal and neonatal edition 2002; 87(2):F83-F88.

(342) von Dadelszen P, Magee LA, Lee SK, et al. Activated protein C in normal human pregnancy and pregnancies complicated by severe preeclampsia: A therapeutic opportunity? Crit Care Med 2002; 30:1883-1892.

(343) Moher D, Ba'Pham, Jones A, Cook DJ, Jadad AR, Moher M et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? The Lancet 352, 609-613. 1998.
Ref Type: Generic

(344) Kramer MS. Intrauterine growth and gestational duration determinants. Pediatrics 80(4):502-11, 1987.

(345) Chang TC, Robson SC, Boys RJ, Spencer JAD. Prediction of the small for gestational age infant: Which ultrasonic measurement is best? Obstetrics & Gynecology Vol 80(6)()(pp 1030-1038), 1992 1992;(6):1030-1038.

(346) Ukwu HN, Graham BS, Lambert JS, Wright PF. Perinatal transmission of human immunodeficiency virus-1 infection and maternal immunization strategies for prevention. Obstetrics & Gynecology Vol 80(3 I)()(pp 458-468), 1992 1992;(3 I):458-468.

(347) Giles W, Bisits A. Clinical use of Doppler ultrasound in pregnancy: Information from six randomised trials. Fetal Diagnosis & Therapy Vol 8(4)()(pp 247-255), 1993 1993;(4):247-255.

(348) Alfirevic Z, Neilson JP. Doppler ultrasonography in high-risk pregnancies: Systematic review with meta-analysis. American Journal of Obstetrics & Gynecology Vol 172(5)()(pp 1379-1387), 1995 1995;(5):1379-1387.

(349) Forouzan I. Absence of end-diastolic flow velocity in the umbilical artery: A review. Obstetrical & Gynecological Survey Vol 50(3)()(pp 219-227), 1995 1995;(3):219-227.

(350) Gross SJ, Shulman LP, Tolley EA, Emerson DS, Felker RE, Simpson JL et al. Isolated fetal choroid plexus cysts and trisomy 18: A review and meta-analysis. American Journal of Obstetrics & Gynecology Vol 172(1)()(pp 83-87), 1995 1995;(1):83-87.

(351) Crowther. Caesarean delivery for the second twin. The Cochrane database of systematic reviews. The Cochrane database of systematic reviews CD000047. 1996.
Ref Type: Generic

(352) Say L, Gulmezoglu AM, Hofmeyr JG. Calcium channel blockers for potential impaired fetal growth. The Cochrane database of systematic reviews . 1996.
Ref Type: Generic

(353) Say L, Gulmezoglu AM, Hofmeyr JG. Transcutaneous electrostimulation for suspected placental insufficiency (diagnosed by Doppler studies). Cochrane Database of Systematic Reviews [1], CD000079. 1996.
Ref Type: Generic

(354) Say L, Gulmezoglu AM, Hofmeyr JG. Plasma volume expansion for suspected impaired fetal growth. The Cochrane database of systematic reviews CD000167[4]. 1996.
Ref Type: Generic

(355) Schumacher B, Moise Jr KJ. Fetal transfusion for red blood cell alloimmunization in pregnancy. Obstetrics & Gynecology Vol 88(1)()(pp 137-150), 1996 1996;(1):137-150.

(356) Sherer DM, Fromberg RA, Divon MY. Prenatal ultrasonographic assessment of the ductus venosus: A review. Obstetrics & Gynecology Vol 88(4 I)()(pp 626-632), 1996 1996;(4 I):626-632.

(357) Sherer DM, Divon MY. Prenatal ultrasonographic assessment of the ductus arteriosus: A review. Obstetrics & Gynecology Vol 87(4)()(pp 630-637), 1996 1996;(4):630-637.

(358) Smith ER, Petersen J, Okorodudu AO, Bissell MG. Does the addition of unconjugated estriol in maternal serum screening improve the detection of trisomy 21? A meta-analysis. Clinical Laboratory Management Review Vol 10(2)()(pp 176-181), 1996 1996;(2):176-181.

(359) Giacoia GP. Severe fetomaternal hemorrhage: a review. [Review] [80 refs]. Obstetrical & Gynecological Survey 52(6):372-80, 1997.

(360) Goffinet F, Paris-Llado J, Nisand I, Breart G. Umbilical artery Doppler velocimetry in unselected and low risk pregnancies: A review of randomised controlled trials. British Journal of Obstetrics & Gynaecology Vol 104(4)()(pp 425-430), 1997 1997;(4):425-430.

(361) Gulmezoglu AM, Hofmeyr GJ. Hormones for suspected impaired fetal growth.[update in Cochrane Database Syst Rev. 2003;(1):CD000109; PMID: 12535384]. [Review] [0 refs]. Cochrane Database of Systematic Reviews (2):CD000109, 2000.

(362) Sherer DM, Bombard AT, Kellner LH, Divon MY. Noninvasive first-trimester screening for fetal aneuploidy. Obstetrical & Gynecological Survey Vol 52(2)()(pp 123-129), 1997 1997;(2):123-129.

(363) Sherer DM. Prenatal ultrasonographic assessment of the middle cerebral artery: a review. [Review] [70 refs]. Obstetrical & Gynecological Survey 52(7):444-55, 1997.

(364) Conde-Agudelo A, Kafury-Goeta AC. Triple-marker test as screening for down syndrome: A meta-analysis. Obstetrical & Gynecological Survey Vol 53(6)()(pp 369-376), 1998 1998;(6):369-376.

(365) Giles WB. Doppler ultrasound in multiple pregnancies. Baillieres Clinical Obstetrics & Gynaecology Vol 12(1)()(pp 77-89), 1998 1998;(1):77-89.

(366) Sherer DM. First trimester ultrasonography of multiple gestations: A review. Obstetrical & Gynecological Survey Vol 53(11)()(pp 715-726), 1998 1998;(11):715-726.

(367) Sherer DM, Anyaegbunam A, Onyeije C. Antepartum fetal intracranial hemorrhage, predisposing factors and prenatal sonography: A review. American Journal of Perinatology Vol 15(7)()(pp 431-441), 1998 1998;(7):431-441.

(368) Sherer DM, Onyeije CI. Prenatal ultrasonographic diagnosis of fetal intracranial tumors: A review. American Journal of Perinatology Vol 15(5)()(pp 319-328), 1998 1998;(5):319-328.

(369) Thummala MR, Raju TNK, Langenberg P. Isolated single umbilical artery anomaly and the risk for congenital malformations: A meta-analysis. Journal of Pediatric Surgery Vol 33(4)()(pp 580-585), 1998 1998;(4):580-585.

(370) Yaegashi N, Niinuma T, Chisaka H, Watanabe T, Uehara S, Okamura K et al. The incidence of, and factors leading to, parvovirus B19-related hydrops fetalis following maternal infection; report of 10 cases and meta-analysis. Journal of Infection 37(1):28-35, 1998.

(371) Brumback BA, Holmes LB, Ryan LM. Adverse effects of chorionic villus sampling: A meta-analysis. Statistics in Medicine Vol 18(16)()(pp 2163-2175), 1999 Date of Publication: 30 AUG 1999 1999;(16):2163-2175.

(372) Farrell T, Chien PF, Gordon A. Intrapartum umbilical artery Doppler velocimetry as a predictor of adverse perinatal outcome: a systematic review. [Review] [58 refs]. British Journal of Obstetrics & Gynaecology 106(8):783-92, 1999.

(373) Pattinson RC. A meta-analysis of the use of corticosteroids in pregnancies complicated by preterm premature rupture of membranes. South African Medical Journal 89(8):870-3, 1999.

(374) Sherer DM, Manning FA. First-trimester nuchal translucency screening for fetal aneuploidy. [Review] [85 refs]. American Journal of Perinatology 16(3):103-20, 1999.

(375) Sherer DM, Manning FA. Prenatal ultrasonographic diagnosis of conditions associated with potential umbilical cord compression. [Review] [105 refs]. American Journal of Perinatology 16(9):445-58, 1999.

(376) Wallon M, Liou C, Garner P, Peyron F. Congenital toxoplasmosis: Systematic review of evidence of efficacy of treatment in pregnancy. British Medical Journal Vol 318(7197)()(pp 1511-1514), 1999 1999;(7197):1511-1514.

(377) Yoder PR, Sabbagha RE, Gross SJ, Zelop CM. The second-trimester fetus with isolated choroid plexus cysts: A meta- analysis of risk of trisomies 18 and 21. Obstetrics & Gynecology Vol 93(5 SUPPL)()(pp 869-872), 1999 1999;(5 SUPPL.):869-872.

(378) Alfirevic. Biophysical profile for fetal assessment in high risk pregnancies. Cochrane Database of Systematic Reviews CD000038[2]. 2000.
Ref Type: Generic

(379) Chien PFW, Arnott N, Gordon A, Owen P, Khan KS. How useful is uterine artery Doppler flow velocimetry in the prediction of pre-eclampsia, intrauterine growth retardation and perinatal death? An overview. British Journal of Obstetrics & Gynaecology Vol 107(2)()(pp 196-208), 2000 2000;(2):196-208.

(380) Hubinont C, Bernard P, Pirot N, Biard J, Donnez J. Twin-to-twin transfusion syndrome: treatment by amniodrainage and septostomy. [Review] [50 refs]. European Journal of Obstetrics, Gynecology, & Reproductive Biology 92(1):141-4, 2000.

(381) Skari H, Bjornland K, Haugen G, Egeland T, Emblem R. Congenital diaphragmatic hernia: A meta-analysis of mortality factors. Journal of Pediatric Surgery Vol 35(8)()(pp 1187-1197), 2000 2000;(8):1187-1197.

(382) Van Dyke DC, Ellingrod VL, Berg MJ, Niebyl JR, Sherbondy AL, Trembath DG. Pharmacogenetic screening for susceptibility to fetal malformations in women. Annals of Pharmacotherapy Vol 34(5)()(pp 639-645), 2000 2000;(5):639-645.

(383) Von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis.[see comment]. Lancet 355(9198):87-92, 2000.

(384) Vos JMI, Offringa M, Bilardo CM, Lijmer JG, Barth PG. Sensitive and specific screening for the detection of spina bifida by echography in the second trimester: Systematic review and meta-analysis. [Dutch]. Nederlands Tijdschrift voor Geneeskunde Vol 144(36)()(pp 1736-1741), 2000 Date of Publication: 02 SEP 2000 2000;(36):1736-1741.

(385) Whitecar PW, Moise KJ, Jr. Sonographic methods to detect fetal anemia in red blood cell alloimmunization. [Review] [49 refs]. Obstetrical & Gynecological Survey 55(4):240-50, 2000.

(386) Woo HH, Sin SY, Tang LC. Single foetal death in twin pregnancies: review of the maternal and neonatal outcomes and management. Hong Kong medical journal 6, 293-300. 2000.
Ref Type: Generic

(387) Allen VM, Windrim R, Barrett J, Ohlsson A. Management of monoamniotic twin pregnancies: a case series and systematic review of the literature. [Review] [35 refs]. BJOG: an International Journal of Obstetrics & Gynaecology 108(9):931-6, 2001.

(388) Crowther. Hospitalisation and bed rest for multiple pregnancy. Cochrane Database of Systematic Reviews CD000110. 2001.
Ref Type: Generic

(389) Divakaran TG, Waugh J, Clark TJ, Khan KS, Whittle MJ, Kilby MD. Noninvasive techniques to detect fetal anemia due to red blood cell alloimmunization: a systematic review. [Review] [61 refs]. Obstetrics & Gynecology 98(3):509-17, 2001.

(390) Murphy CC, Schei B, Myhr TL, Du MJ. Abuse: A risk factor for low birth weight? A systematic review and meta-analysis. CMAJ: Canadian Medical Association Journal Vol 164(11)()(pp 1567-1572), 2001 2001;(11):1567-1572.

(391) Neal JL. RhD isoimmunization and current management modalities. [Review] [124 refs]. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing 30(6):589-606, 2001;-Dec.

(392) Roberts D, Neilson JP, Weindling AM. Interventions for the treatment of twin-twin transfusion syndrome. [Review] [39 refs]. Cochrane Database of Systematic Reviews (1):CD002073, 2001.

(393) Say L, Gulmezoglu AM, Hofmeyr JG. Betamimetics for suspected impaired fetal growth. The Cochrane database of systematic reviews CD000036[4]. 2001.
Ref Type: Generic

(394) Segal SY, Marder SJ, Parry S, Macones GA. Fetal abdominal walldefects and mode of delivery: a systematic review. Obstet Gynecol 98, 867-873. 2001.
Ref Type: Generic

(395) Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome: A meta-analysis. Journal of the American Medical Association Vol 285(8)()(pp 1044-1055), 2001 Date of Publication: 28 FEB 2001 2001;(8):1044-1055.

(396) Spencer JA, Burrows RF. Feto-maternal alloimmune thrombocytopenia: a literature review and statistical analysis. [Review] [164 refs]. Australian & New Zealand Journal of Obstetrics & Gynaecology 41(1):45-55, 2001.

(397) Weissman A, Drugan A. Sonographic findings of the umbilical cord: implications for the risk of fetal chromosomal anomalies. [Review] [45 refs]. Ultrasound in Obstetrics & Gynecology 17(6):536-41, 2001.

(398) Westergaard HB, Langhoff-Roos J, Lingman G, Marsal K, Kreiner S. A critical appraisal of the use of umbilical artery Doppler ultrasound in high-risk pregnancies: use of meta-analyses in evidence-based obstetrics.[see comment]. Ultrasound in Obstetrics & Gynecology 17(6):466-76, 2001.

(399) Demasio K, Canterino J, Ananth C, Fernandez C, Smulian J, Vintzileos A. Isolated choroid plexus cyst in low-risk women less than 35 years old. American Journal of Obstetrics & Gynecology Vol 187(5)()(pp 1246-1249), 2002 Date of Publication: 01 NOV 2002 2002;(5):1246-1249.

(400) Gaytant MA, Steegers EA, Semmekrot BA, Merkus HM, Galama JM. Congenital cytomegalovirus infection: review of the epidemiology and outcome. [Review] [108 refs]. Obstetrical & Gynecological Survey 57(4):245-56, 2002.

(401) Patrick LA, Smith GN. Proinflammatory cytokines: a link between chorioamnionitis and fetal brain injury. [Review] [38 refs]. Journal of Obstetrics & Gynaecology Canada: JOGC 24(9):705-9, 2002.

(402) Skupski DW, Rosenberg CR, Eglinton GS. Intrapartum fetal stimulation tests: A meta-analysis. Obstetrics & Gynecology Vol 99(1)()(pp 129-134), 2002 2002;(1):129-134.

(403) Skupski DW, Gurushanthaiah K, Chasen S. The effect of treatment of twin-twin transfusion syndrome on the diagnosis-to-delivery interval. [Review] [21 refs]. Twin Research 5(1):1-4, 2002.

(404) Su LL. Monoamniotic twins: diagnosis and management. [Review] [44 refs]. Acta Obstetricia et Gynecologica Scandinavica 81(11):995-1000, 2002.

(405) Wu YW. Systematic review of chorioamnionitis and cerebral palsy. Mental Retardation & Developmental Disabilities Research Reviews 8(1):25-9, 2002.

(406) Alfirevic Z, Sundberg K, Brigham S. Amniocentesis and chorionic villus sampling for prenatal diagnosis. The Cochrane database of systematic reviews CD003252[3]. 2003.
Ref Type: Generic

(407) Clark TJ, Martin WL, Divakaran TG, Whittle MJ, Kilby MD, Khan KS. Prenatal bladder drainage in the management of fetal lower urinary tract obstruction: a systematic review and meta-analysis. [Review] [36 refs]. Obstetrics & Gynecology 102(2):367-82, 2003.

(408) Dodd JM, Crowther CA. Elective delivery of women with a twin pregnancy from 37 weeks' gestation. The Cochrane database of systematic reviews CD003582. 2003.
Ref Type: Generic

(409) Dodd JM, Crowther CA. Reduction of the number of fetuses for women with triplet and higher order multiple pregnancies. [Review] [16 refs]. Cochrane Database of Systematic Reviews (2):CD003932, 2003.

(410) Gutierrez-Alvarez AM. Use of anticonvulsive drugs during pregnancy and the risk of malformations in the newborn: A meta-analysis. [Spanish]. Revista de Neurologia Vol 37(11)()(pp 1022-1028), 2003 Date of Publication: 01 DEC 2003 2003;(11):1022-1028.

(411) Hogle KL, Hutton EK, McBrien KA, Barrett JFR, Hannah ME. Cesarean delivery for twins: A systematic review and meta-analysis. American Journal of Obstetrics and Gynecology 188, 220-227. 2003.
Ref Type: Generic

(412) Makrydimas G, Sotiriadis A, Ioannidis JPA. Screening performance of first-trimester nuchal translucency for major cardiac defects: A meta-analysis. American Journal of Obstetrics & Gynecology Vol 189(5)()(pp 1330-1335), 2003 2003;(5):1330-1335.

(413) Merialdi M, Carroli G, Villar J, Abalos E, Gulmezoglu AM, Kulier R et al. Nutritional interventions during pregnancy for the prevention or treatment of impaired fetal growth: An overview of randomized controlled trials. Journal of Nutrition Vol 133(5 SUPPL 1)()(pp 1626S-1631S), 2003 Date of Publication: 01 MAY 2003 2003;(5 SUPPL. 1):1626S-1631S.

(414) Neilson JP, Cloherty LJ. Hormonal placental function tests for fetal assessment in high risk pregnancies.[update in Cochrane Database Syst Rev. 2003;(2):CD000108; PMID: 12804386]. [Review] [2 refs]. Cochrane Database of Systematic Reviews (2):CD000108, 2000.

(415) Nordeng H, Spigset O. Use of antipsychotics during pregnancy and lactation. [Norwegian]. Tidsskrift for Den Norske Laegeforening Vol 123(15)()(pp 2033-2035), 2003 Date of Publication: 14 AUG 2003 2003;(15):2033-2035.

(416) Ray JG, Blom HJ. Vitamin B12 insufficiency and the risk of fetal neural tube defects. Qjm: Monthly Journal of the Association of Physicians Vol 96(4)()(pp 289-295), 2003 Date of Publication: 01 APR 2003 2003;(4):289-295.

(417) Rowe RE, Garcia J, Davidson LL. Social and ethnic inequalities in the offer and uptake of prenatal screening and diagnosis in the UK: A systematic review. Public Health Vol 118(3)()(pp 177-189), 2004 2004;(3):177-189.

(418) Say L, Gulmezoglu AM, Hofmeyr JG. Hormones for suspected impaired fetal growth. The Cochrane database of systematic reviews CD000109. 2002.
Ref Type: Generic

(419) Say L, Gulmezoglu AM, Hofmeyr JG. Maternal nutrient supplementation for suspected impaired fetal growth. The Cochrane database of systematic reviews CD000148. 2003.
Ref Type: Generic

(420) Say L, Gulmezoglu AM, Hofmeyr JG. Maternal oxygen administration for suspected impaired fetal growth. The Cochrane database of systematic reviews CD000137. 2003.
Ref Type: Generic

(421) Sotiriadis A, Makrydimas G, Ioannidis JPA. Diagnostic performance of intracardiac echogenic foci for Down syndrome: A meta-analysis. Obstetrics & Gynecology Vol 101(5)()(pp 1009-1016), 2003 Date of Publication: 01 MAY 2003 2003;(5):1009-1016.

(422) Tan TY, Sepulveda W. Acardiac twin: a systematic review of minimally invasive treatment modalities. [Review] [56 refs]. Ultrasound in Obstetrics & Gynecology 22(4):409-19, 2003.

(423) Helmerhorst FM, Perquin DAM, Donker D, Keirse MJN. Perinatal outcome of singletons and twins after assisted conception: A systematic review of controlled studies. BMJ 328, 261-264. 2004.
Ref Type: Generic

(424) Maymon R, Herman A. The clinical evaluation and pregnancy outcome of euploid fetuses with increased nuchal translucency. Clinical Genetics Vol 66(5)()(pp 426-436), 2004 2004;(5):426-436.

(425) Olesen AG, Svare JA. Decreased fetal movements: Background, assessment, and clinical management. Acta Obstetricia et Gynecologica Scandinavica Vol 83(9)()(pp 818-826), 2004 2004;(9):818-826.

(426) Wilson RD, Johnson MP. Congenital abdominal wall defects: An update. Fetal Diagnosis & Therapy Vol 19(5)()(pp 385-398), 2004 2004;(5):385-398.

(427) Fox C, Kilby MD, Khan KS. Contemporary treatments for twin-twin transfusion syndrome. Obstet.Gynecol 105, 1469-1477. 2005.
Ref Type: Generic

(428) Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, et al. The preterm prediction study:Effect of gestational age and cause of preterm birth on subsequent obstetric outcome. Am J Obstet Gynecol 181[5], 1216-1221. 1999.
Ref Type: Generic

(429) Hassan SS, Romero R, Berry SM, Dang K, Blackwell SC, Treadwell MC et al. Patients with an ultrasonographic cervical length <= 15mm have nearly a 50% risk of early spontaneous preterm delivery. Am J Obstet Gynecol 182, 1458-1467. 2000.
Ref Type: Generic