ACCURACY OF TESTS FOR PREDICTING SPONTANEOUS PRETERM BIRTH: SYSTEMATIC REVIEWS OF DIAGNOSTIC RESEARCH

by

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Abstract

Spontaneous preterm birth complicates about 3% of pregnancies before 34 weeks' gestation and 7 – 12% before 37 weeks' gestation. It is an important issue to public health worldwide. The aim of this thesis was to identify test(s) which would predict spontaneous preterm birth in early pregnancy when women are asymptomatic and in later pregnancy when they present with symptoms of threatened preterm labour, using systematic reviews and meta-analysis. If women at risk can be identified whether early in pregnancy or when they present with threatened preterm labour, interventions can be deployed to prevent or delay birth and to improve subsequent neonatal mortality/morbidity. Initially 40,243 title and abstract citations were scrutinised, resulting in shortlist of 1,650 full articles in which 319 were included in the systematic reviews, encompassing 22 tests. The quality of studies and accuracy of tests measured with likelihood ratio (LR) was generally poor. There were only a handful of studies for most of the tests. Few tests reached LR+ point estimates >5. In asymptomatic antenatal women these were ultrasonographic cervical funnelling and length measurement, cervico-vaginal prolactin and cervico-vaginal fetal fibronectin screening for predicting spontaneous preterm birth before 34 weeks' gestation. In this group, tests with LR- point estimates approaching <0.2 were detection of uterine contraction (by mammary stimulating test) and amniotic fluid CRP measurement. In symptomatic women with threatened preterm labour tests with LR+ point estimate >5 were absence of fetal breathing movements, cervical length measurement, amniotic fluid IL6 and IL8, serum CRP and cervico-vaginal hcg for predicting birth within 2-7 days of testing. In this group tests with LR- point estimate <0.2 were measurement of cervico-vaginal hcg, cervical length measurement, absence of fetal breathing movement, amniotic fluid IL6 and IL8, and serum CRP for predicting birth within 2 - 7 days of testing. In conclusion, no exceptional, but many promising tests for predicting spontaneous preterm birth was identified to aid the development of evidence based practice.

Dedication

I dedicate this thesis to Catherine and my family for their encouragement and support.

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None declared

List of Abbreviations/Glossary

95% CI	95% confidence intervals
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effect
dOR	Diagnostic odds ratio (LR+/LR-)
ln dOR	Natural logarithm of diagnostic odds ratio
HTA	Health Technology Assessment
HSROC	hierarchical summary receiver operating characteristic
IPD	Individual patient data (meta-analysis)
LR	likelihood ratio (LR+, LR for positive test result; LR-, LR for negative test result)
MeSH	Medical Subject Heading
MoM	Multiple of median
NRR	National Research Register
PROM	Pre-labour rupture of membrane
PPROM	Premature pre-labour rupture of membrane
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomised controlled trial
RDS	Respiratory distress syndrome
RR	relative risk
ROC	receiver operating characteristics
SD	standard deviation
SE	standard error
SIGLE	Systems for Information in Grey Literature in Europe
sLR	Summary likelihood ratio: sLR+ summary of positive test result, sLR- of negative test result

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Chapter 1 Thesis summary

Background

A viable preterm birth is defined as any delivery of a pregnancy at less than 37 completed weeks (<259 days) and more than 23 completed weeks of gestation. It is a heterogeneous condition where up to 30 - 40% of all cases of preterm births are due to elective delivery for a maternal or a fetal complication. The remaining 60 – 70% of preterm births occurs spontaneously, which is the focus of this thesis. It complicates about 3% of pregnancies before 34 weeks' gestation and between 7 – 12% before 37 weeks' gestation. The former particularly has serious effects on mother, child and society, which makes preterm birth an important issue to public health worldwide. If women can be identified to be at high risk in early pregnancy, they can be targeted for more intensive antenatal surveillance and prophylactic interventions. When women present with symptoms of threatened preterm labour, if the likelihood of having spontaneous preterm birth can be determined, interventions can be deployed to prevent or delay birth and to improve subsequent neonatal mortality/morbidity.

Objective

The aim of this thesis was to identify test(s) which would accurately predict spontaneous preterm birth in asymptomatic antenatal women in early pregnancy and in women symptomatic with threatened preterm labour in later pregnancy by undertaking a series of systematic reviews of accuracy of tests.

Methods

Protocols were developed for performing the systematic reviews of test accuracy using standard review methods including: literature searches without language restrictions, study quality assessment and meta-analysis where appropriate. Two populations of interest were defined: asymptomatic antenatal women and women symptomatic with threatened preterm

labour. Literature was identified from several sources (up to September 2005 inclusive), including databases: PUBMED (MEDLINE), EMBASE (Ovid), DARE, CENTRAL, MEDION, contact with experts including the Cochrane Pregnancy and Childbirth Group and checking of reference lists of review articles and papers that were eligible for the systematic reviews included in this thesis. Included were cohorts or case control studies of any pregnant women where the index test was compared to the reference standard of spontaneous preterm birth and a 2x2 table could be calculated. Quality assessment was based on modified QUADAS criteria. Meta-analyses of likelihood ratios (LR's) using random effects model and of sensitivity and specificity using the bivariate models were performed. In general, the higher the LR+ >1 (i.e. the likelihood ratio for a positive test) the more accurate is the test in ruling in the condition while the lower the LR- <1 (i.e. the likelihood ratio for a negative test) the more accurate is the test in ruling out the condition.

Results

Initially 40,243 title and abstract citations were scrutinised, resulting in the short listing of 1,650 full articles for which 319 were included for the systematic reviews, encompassing 22 tests that were evaluated in this thesis. The quality of studies and accuracy of tests was generally poor. For asymptomatic women, only testing for asymptomatic bacteriuria, cervico-vaginal fibronectin, assessment for periodontitis and bacterial vaginosis, and serum β-hcg were evaluated in more than 10 studies while for symptomatic women, aside from fetal fibronectin, and amniotic fluid IL6 which has been evaluated in 31 and 10 studies respectively, the remainder had only been evaluated in a handful of studies. Some tests were able to achieve high predictive value when positive, but at the expense of compromised low predictive value when negative. Only a few tests reached LR+ point estimates >5. In asymptomatic antenatal women these were ultrasonographic cervical funnelling and length measurement, cervico-vaginal prolactin and cervico-vaginal fetal fibronectin screening for

predicting spontaneous preterm birth before 34 weeks' gestation. In this group, tests with LR- point estimates approaching <0.2 were detection of uterine contraction (by mammary stimulating test) and amniotic fluid CRP measurement. For predicting spontaneous preterm birth before 37 weeks' gestation, only cervico-vaginal fibronectin achieved and serial salivary estriol testing achieved LR+ >5.0, while only home uterine activity monitoring and amniotic fluid CRP measurement achieved LR- <0.2. In symptomatic women with threatened preterm labour tests with LR+ point estimate >5 were absence of fetal breathing movements, cervical length measurement, amniotic fluid IL6 and IL8, serum CRP and cervico-vaginal hcg (for predicting birth within 2-7 days of testing); and serum CRP, amniotic fluid IL6, and MMP-9, cervico-vaginal fetal fibronectin and cervico-vaginal hcg (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation). In this group tests with LR- point estimate <0.2 were measurement of cervico-vaginal hcg, cervical length measurement, absence of fetal breathing movement, amniotic fluid IL6 and IL8, and serum CRP (for predicting birth within 2 - 7 days of testing); and cervico-vaginal fetal fibronectin and amniotic fluid IL6 (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation).

Conclusions

There are a number of promising tests identified by this thesis. The prominence of the detection of absence of fetal breathing movement, cervical funnelling and cervical length measurement provide a stronger impetus for a universal provision for high quality ultrasound machine in labour wards for predicting spontaneous preterm birth among women with a viable pregnancy who present with threatened preterm labour to direct management (e.g. administration of tocolytics, corticosteroids and in-utero transfer). Nevertheless, provision for round the clock trained personnel to perform such a scan in the interim is a challenge. Additionally, the feasibility and acceptability to mothers and health providers of such tests including more invasive (but potentially more accurate amniotic fluid assessment of IL6 and

8) strategies needs to be explored. Rigorous evaluation is needed of tests with minimal cost or invasiveness whose initial assessments suggest that they may have high levels of accuracy. Similarly, there is a need for high quality, adequately powered randomized controlled trials to investigate whether interventions are indeed effective in reducing (in asymptomatic women) and/or delaying (in symptomatic women with threatened preterm labour) spontaneous preterm birth. In future, an economic model should be developed which considers not just spontaneous preterm birth, but other related outcomes, particularly those relevant to the infant like perinatal death and shorter and longer term outcomes amongst survivors. Such a modelling project should make provision for primary data collection on the safety of interventions and their associated costs.

Chapter 2 Introduction

Definition of preterm birth

Textbooks define preterm birth as any delivery of a viable pregnancy at less than 37 completed weeks of gestation (<259 days), the lower limit of viability ex-utero being generally accepted to be at 23 completed weeks. Births before 23 completed weeks of gestation are classified as either miscarriages or abortions.

Aetiology of preterm birth

Preterm birth is a heterogeneous condition where up to 30 - 40% of all cases of preterm birth are due to elective delivery for a maternal or a fetal complication where it is judged that the baby is better delivered in the mother's interest or that of its own e.g. hypertension, diabetes, intra-uterine growth restriction.[1] The remaining 60 – 70% of preterm birth are likely due to covert or sub-clinical infective/inflammatory processes, cervical dysfunction, idiopathic (unknown), multiple gestations and possible social, nutritional, and environmental interactions.[2] This thesis focuses on the latter group of so called 'spontaneous' preterm birth among singletons regardless of aetiology.

Consequences of preterm birth

Preterm births, particularly those before 34 weeks' gestation, account for three-quarters of neonatal mortality and one-half of long term neurological impairment in children.[3-5] Many of the surviving infants also suffer from other serious short and long-term morbidity,[4;6;7] such as respiratory distress syndrome, broncho-pulmonary dysplasia, intraventricular haemorrhage, retrolental fibroplasia and developmental problems. Even those premature infants that are classified as developmentally 'normal' or classified as having 'mild' developmental problem, in the longer term, have higher rate of multiple problems that do affect their life.[8] Although complications of prematurity are significantly reduced after 32-34 weeks' gestation, minor

morbidities, which often lengthen hospitalisation, remain for neonates born between 34 –37 weeks' gestation.[9-13]

Burden of disease due to preterm birth

Spontaneous preterm birth before 37 weeks' gestation occurs in 7-12% of pregnancies[14-16] and it occurs in about 4% of pregnancies before 34 weeks' gestation.[17] Thus far advances in perinatal healthcare have not reduced the rate of spontaneous preterm birth.[15] Extrapolation from live births data in England and Wales (2004) live births data,[18] shows that an estimated 76,000 and 26,000 spontaneous preterm births occur before 37 weeks' and 34 weeks' gestation respectively.

Economically, preterm birth has a major and significant direct and indirect cost. There is a direct cost in terms of clinical resources use, e.g. intensive and often prolonged neonatal care as in-patient followed by higher rate of re-hospitalisation following discharge,[19;20] and emotional, psychological, and financial burden to the parents who are usually the main carers. There is also an indirect cost to the society where scarce public resources are utilized for long term care of the handicapped premature child and the fact that one or both parents may have to give up full time employment to care for their premature child.

Therefore, accurate prediction of the risk of preterm birth among asymptomatic pregnant women and those symptomatic with threatened preterm labour may offer the opportunity to target care at those most likely to benefit.

Potential clinical applications of output from this thesis

Antenatal care in the UK is a complex care package, within which screening for women at risk of preterm birth is an integral component. Often this is linked to screening for conditions (e.g. pre-eclampsia) that might predispose to the need for elective preterm delivery. Currently there is no routine screening test for spontaneous preterm birth apart from obtaining history of previous pregnancies. Once women are identified to be at risk, they may be able to be either

recruited for further intervention(s) or measure(s) to prevent spontaneous preterm birth or be targeted for more intensive antenatal surveillance and prophylactic measures that are currently available, as primary, secondary or tertiary preventions.

Primary prevention is preventing the onset of spontaneous preterm labour in asymptomatic women e.g. administration of maternal progestational agents injection or ensuring and maintaining healthy maternal genito-urinary tract and periodontal status. Secondary prevention is steps that can be taken to attenuate, stop or reverse the progress of spontaneous preterm labour in its early stages, well before advanced cervical dilatation, e.g. by administration of tocolytic agents. Tertiary prevention is measures aimed at preventing neonatal complications associated with prematurity, e.g. maternal administration of antenatal corticosteroids to accelerate fetal lung maturity. This thesis focuses on primary and secondary prevention.

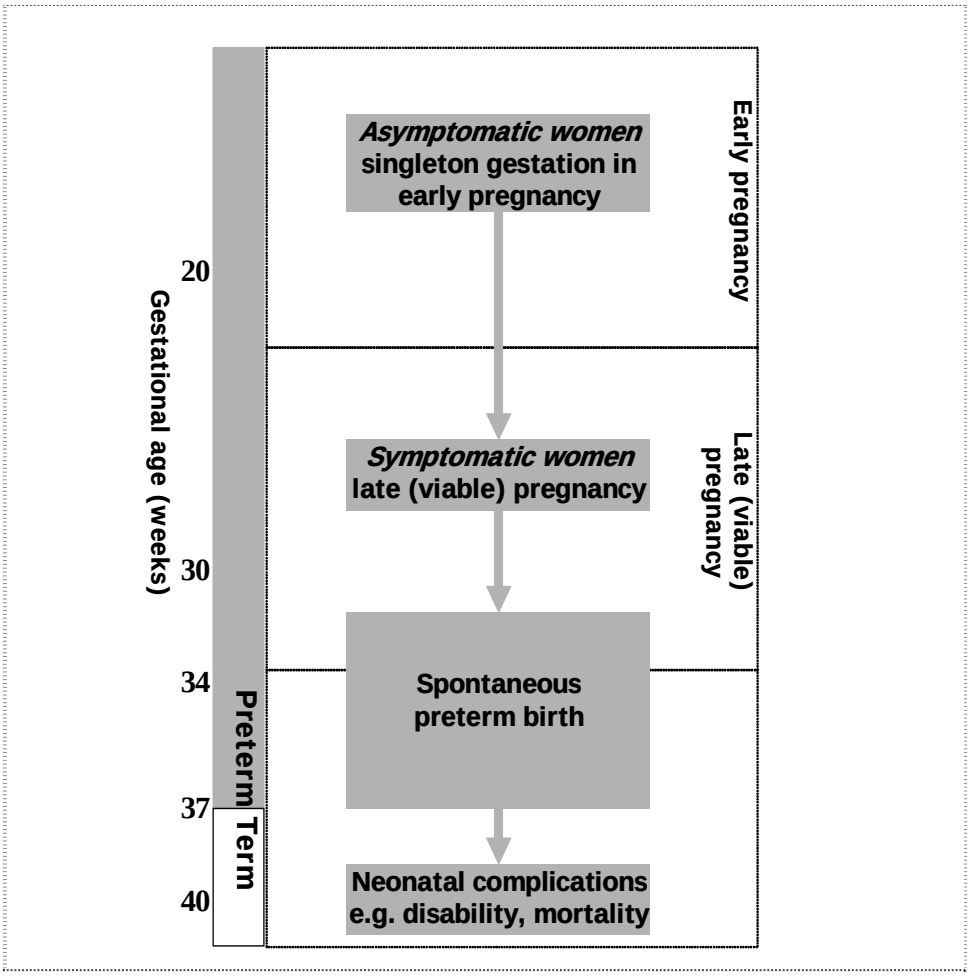
Delineation of the problem

Assessment of pregnant women's risk for preterm birth based on a combination of patients' characteristics, symptoms, physical signs and investigations, is important. This is because without an accurate assessment, clinicians are handicapped in the management of women at risk of preterm birth regarding institution of timely antenatal interventions. Wrong or delayed diagnosis can put mother and baby at risk of an adverse outcome whereas correct prediction of spontaneous preterm birth will provide an opportunity to institute effective interventions. This thesis will address these issues using systematic reviews to estimate the accuracy of tests for predicting spontaneous preterm birth.

There are two target populations of pregnant women that need to be tested for the risk of spontaneous preterm birth (Figure 1). The first is a population of antenatal asymptomatic women carrying a singleton gestation having routine care. In this important, and by far the largest epidemiological target of pregnant population, women are generally in a healthy state,

anticipating a normal course of pregnancy. They are usually regarded as 'low-risk' unless there are antecedent or current factor(s) and history that might increase the risk of preterm birth. If screening or testing could predict the risk of spontaneous preterm birth among these women, preventative measure(s) may be more appropriately targeted. For example if ultrasonographic measurement of cervical length in these women identifies shortened cervical length,[21] then cervical cerclage may be deployed to prevent progression to spontaneous preterm birth.[22] For these women, the key outcome measure would be prevention of spontaneous preterm birth before 34 and 37 weeks' gestation.

Figure 1 Target populations and outcomes in the course of pregnancy for diagnostic research on spontaneous preterm birth



The second population of interest is that of symptomatic women with singleton gestation who present with threatened preterm labour. For these women, there is a need to identify those who will go on to deliver prematurely as the key clinical decisions following testing relates to immediate management and outcome. For example, if cervico-vaginal fetal fibronectin testing could predict spontaneous preterm birth among these women before advanced cervical dilatation,[23] antenatal maternal intramuscular corticosteroid injection may be administered to accelerate fetal lung maturity to prevent respiratory distress syndrome.[24] In-utero transfer to a tertiary intensive neonatal care unit able to care for the premature neonate may also be considered.[25;26] Such a transfer, which may take some time to arrange (because of logistics, geography or lack of neonatal intensive care cots), would be inappropriate if birth were imminent, as this would risk delivery en-route. In such cases, knowledge of a higher likelihood of imminent birth may allow rational use of tocolytics agents, which aim to suppress or diminish contractions allowing time for antenatal corticosteroid administration to exert its beneficial effects.[27] Antenatal corticosteroids have maximal effectiveness in preventing neonatal complications of prematurity delivered within 2-7 days after administration.[24] Given the duration of time required for corticosteroids to exert beneficial effects and the potential for in-utero transfer and tocolytic administration, knowledge of impending birth within 48 hours to 7 days of testing would be a clinically meaningful outcome measure among women symptomatic of threatened preterm labour.

Aim

The aim of this thesis was to systematically review the evidence on tests that identify women with singleton pregnancy at risk of spontaneous preterm birth which would allow for the institution of measures to improve neonatal outcome.

Objectives

Considering the above background and aim, the research was undertaken to meet the following objectives:

1. To determine, among asymptomatic women with singleton gestation in early pregnancy (before 23 completed weeks of gestation) the accuracy of various tests (history, examination and investigations) for predicting the risk of spontaneous preterm birth and
2. To determine, among women with a viable singleton pregnancy (after 23 completed weeks of gestation), symptomatic of threatened preterm labour with intact amniotic membrane and before advance cervical dilatation (less than 2-3 cm dilatation) the accuracy of various tests (history, examination and investigations) for predicting the risk of imminent preterm birth.

From this work, the thesis aims to identify areas where evidence is strong enough to generate recommendations for clinical practice in addition to identifying key areas and research questions requiring further primary research.

Chapter 3 Methods

Protocol development

This thesis is based on systematic reviews, a scientific, replicable method of evidence synthesis explicitly describing the objectives, the search strategy for relevant literature, and the methods for processing information and deriving conclusions.[28] The process followed key steps involved in health technology assessment (HTA) of a diagnostic test.[29-31] Systematic reviews of accuracy of tests were carried out using contemporaneous methodology,[32-34] which is in line with the recommendations of the Centre for Reviews and Dissemination (CRD),[35] and the Cochrane Collaboration including those of Cochrane Methods Working Group on Screening and Diagnostic tests.[36] The research was based on a prospective protocol, which included reviews of existing test accuracy, updating those which were out-of-date; and performing reviews of topics not reviewed in the literature.

Research question

The following structured question was addressed:

Populations: Asymptomatic low-risk pregnant women with singleton gestation in early pregnancy and low-risk women symptomatic of threatened preterm labour with a viable singleton pregnancy. Singleton pregnancies were the focus because it represents an epidemiological significant pregnant population and because multiple gestations fall in a higher risk category that represents a different disease spectrum.

Tests: List of tests available for determining the risk of spontaneous preterm birth in asymptomatic pregnant women and those available for determining the risk of imminent birth in women symptomatic of threatened preterm labour (Appendix I).

Outcomes (reference standards): Spontaneous preterm birth <37 weeks' gestation and <34 weeks' gestation in asymptomatic pregnant women, and birth within 24, 48 hours and up to 7 - 10 days of testing or presentation in women symptomatic of threatened preterm labour.

Study designs: Test accuracy studies (observational: prospective or retrospective) of defined non-randomised populations in which the results of the test of interest were compared with the outcomes (reference standards) to generate 2x2 tables to compute indices of test accuracy.

Study identification and selection

Existing reviews were first identified, assessed for their quality and examined their currency. Through this process gaps were identified where reviews did not exist and where they needed updating. To fill these gaps, systematic reviews were performed where none was available or non-current existing reviews were updated where required. Therefore a formal search was undertaken to identify existing reviews of accuracy of tests for spontaneous preterm birth. The search strategy can be found in Appendix II. The Cochrane Library, the National Research Register (NRR), the Health Technology Assessment (HTA) database, the National Guideline Clearinghouse and a range of other guideline and effectiveness collections were searched for systematic reviews, guidelines and ongoing research using Medical Subject Headings (MeSH) terms and text words. A database of published and unpublished literature was assembled from update searches using an existing search strategy,[37] as well as hand searching, contacting manufacturers and consultation with experts in the area. No language restrictions were applied to electronic searches.

The following databases were searched for primary studies: MEDLINE, EMBASE, BIOSIS, MEDION, Pascal, Science Citation Index, and Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and HTA database. In addition, information on studies in progress, unpublished research or research reported in the grey literature was sought by searching a range of relevant databases including Inside Conferences, Systems for Information in Grey Literature (SIGLE), Dissertation Abstracts, Clinical Trials.gov and the NRR. Citations captured by the search were scrutinised for inclusion in the review in a two-

stage process using predefined and explicit criteria regarding populations, index tests, target conditions and study designs. First, a master database of the literature searches was constructed by amalgamation of all the citations from various database sources. 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.

The search revealed a number of test accuracy reviews at various levels of currency (Chapter 4: Identification of accuracy literature and Appendix I). Most of the identified reviews were updated, where experts surveyed for this thesis decided the priority on clinical grounds, and a few new rapid reviews were carried out to fill the identified gaps. To be included in updated systematic reviews, any recent systematic reviews or primary studies had to fulfil the individual criteria as stated in the original reviews, including the following criteria:

Population: Asymptomatic antenatal women and women symptomatic of threatened preterm labour with singleton gestation to allow interventions, which delay delivery and improve neonatal outcome for prematurely born infants.

Index Tests: Tests that purported to predict spontaneous preterm birth (Table 1).

Reference standards and other outcomes: Any outcomes as reported in the individual reviews. However, only data relating to the following outcome measures were used in the thesis: spontaneous preterm birth < 37 weeks gestation, <34 weeks gestation or within 2-7 days of testing, and resource use. If relevant outcomes were not reported in the original reviews this is noted.

Study designs: Systematic reviews of test accuracy studies were included; all reviews were of a standard quality accepted by DARE produced by the CRD, University of York (UK). For

primary studies, observational cohort studies were looked for and or, if unavailable, ‘case-control’ studies of test accuracy.

Table 1 List of tests that purported to predict spontaneous preterm birth

Type of tests or investigation	Predictive and diagnostic tests for preterm birth
History	Previous history of either spontaneous preterm birth*
Examination	Abdominal palpation+
	Cervical digital examination+
Biochemistry	Cervico-vaginal glycoproteins: Interleukins (IL-6, IL-8)+ β-hcg+ Fetal fibronectin*+ Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1)+
	Serum glycoprotein: α-fetoprotein, human chorionic gonadotrophin (as part of Down's screening)*
	Endocrine hormones: Salivary estriol+ Corticotrophin releasing hormone+
	Inflammatory markers (serum): C-reactive protein*+ Matrix metalloprotease (MMP)+ Interleukins*+
Microbiology	Detection of bacterial vaginosis*+ Periodontal screening* Midstream urine culture*+
Physiological	Uterine activity monitoring* Rheobase+ Mammary stimulation test+
Ultrasound scan	Absence of fetal breathing movements+
	Measurement of cervical length*+

*Test applied on asymptomatic women
+Test applied on symptomatic women

Study quality assessment and data extraction

For existing reviews, quality was assessed using existing guidance on conducting test accuracy reviews.[35;36;38] The methodological quality of the selected primary studies was assessed using predefined criteria based on elements of study design, conduct and analysis which are likely to have a direct relationship to bias in a test accuracy study (derived from 'QUADAS' (**Qu**ality **A**ssessment of **D**iagnostic **A**ccuracy **S**tudies) criteria (of which, these: clear description of population selection and enrolment criteria, complete verification of outcome using the same reference standard, sufficient test description for replication and blinding of assessors) were used).[39-42] In addition to using study quality as a possible explanation for differences (i.e. heterogeneity) 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. Data extraction pro-forma can be found in Appendix III. In the main text of the thesis, graphical summaries of the five most important quality items were provided for while others can be extracted from tables of study characteristics for the individual test (Appendix IV).

Any randomized trials of effectiveness of test-treatment combinations were assessed for validity separately to the diagnostic accuracy studies. Studies' findings were extracted in duplicate for 10% of randomly selected studies, while the remaining were done by the author, using pre-designed and piloted data extraction forms, which were developed and used in previously published reviews.[21;23;43-45] Previous reviews had assessed studies and extracted data in duplicate. For missing information attempt was made to obtain data from original investigators only if it was crucial to subsequent analysis. To avoid introducing bias, unpublished information was coded in the same fashion as published information. If there was a suspicion of double data counting (consequent from e.g. studies or publications from the same population for a particular test for different outcomes), clarification was sought from the

corresponding authors so that only information pertinent to the more significant outcomes e.g. birth before 34 weeks' gestation for asymptomatic women and within 7-10 days of testing were used in the situation.

Data synthesis

A brief narrative review of findings and quality was undertaken for each test considered. This was followed by exploration for the causes of variation in results from study to study (i.e. heterogeneity) and synthesis of results from individual studies (meta-analysis) if appropriate. Accuracy results were computed separately for different populations, tests and reference standards. Heterogeneity of results between studies was graphically assessed in forest plots of likelihood ratios (LR's) and distribution of sensitivity and specificity in summary receiver operating characteristics (ROC) space (for the latter only those reviews of 'more accurate tests' with the relevant clinical outcomes are shown in this thesis). The latter showed the trade-off between sensitivity and specificity across different studies with explicit or implicit variation in thresholds. A general guide for interpreting summary LR's is shown in Table 2.

Table 2 Guide to the likelihood ratio (LR) interpretation of a test's accuracy

Category of test accuracy usefulness	Likelihood ratio for a positive test result (LR+)	Likelihood ratio for a negative test result (LR-)	Interpretation
Very useful	>10	<0.1	Likely to generate large (and often) conclusive changes from pre-test to post-test probabilities
Useful	5 – 10	0.1 – 0.2	Likely to generate moderate shifts in pre-test to post-test probabilities
May be useful	2 – 5	0.2 – 0.5	Likely to generate small but sometimes important changes in pre-test to post-test probabilities
Not useful	1 – 2	0.5 - 1	May alter pre-test to post-test probabilities to a small (and rarely important) degree

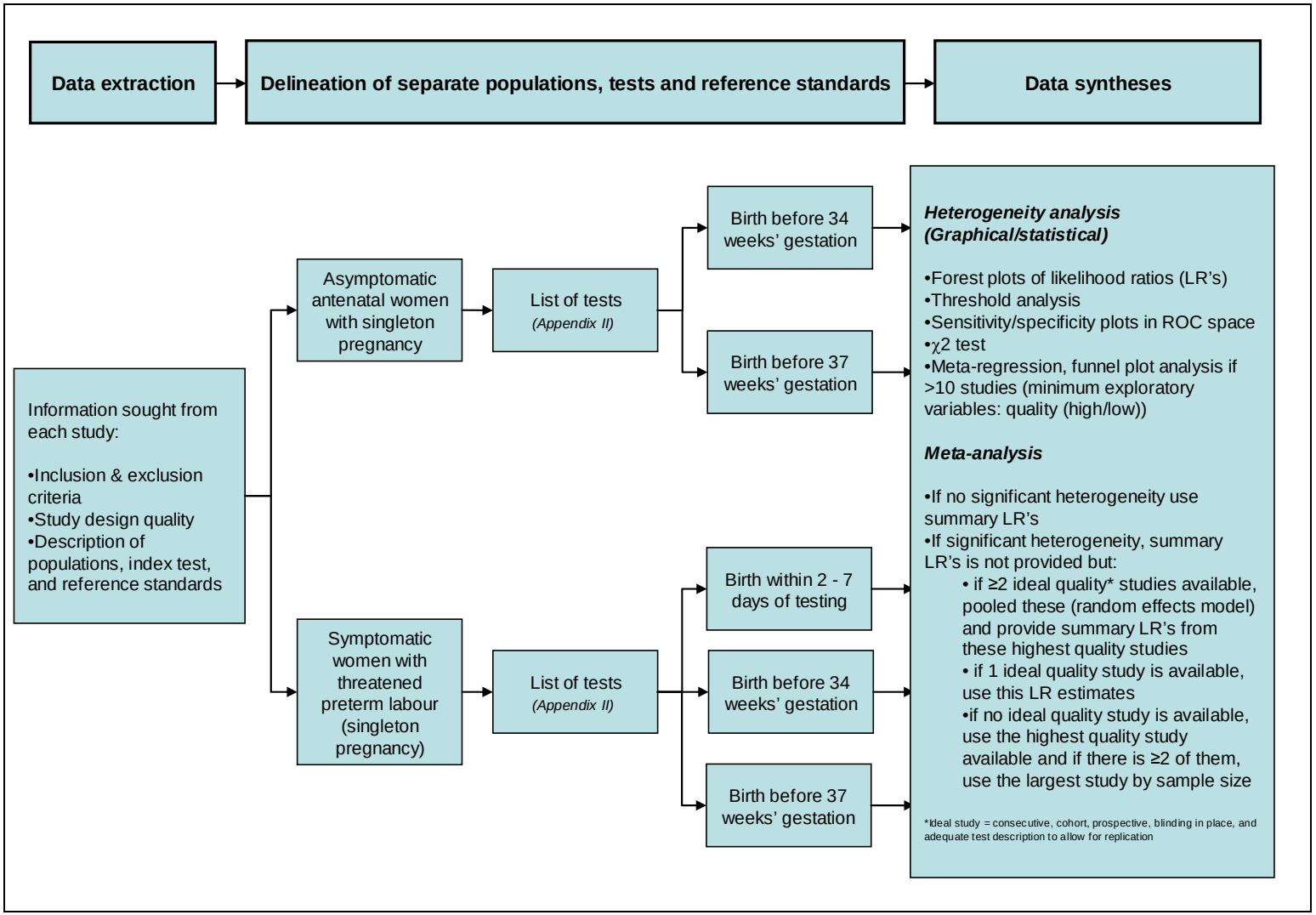
Derived from Jaeschke, Grimes and Fagan et al [46-48]
In any specific context however the value of LR below which positive result and above which negative result will be useless depends on how effective, safe and expensive the interventions that follow relative to costs and outcome of false negative cases.

Subgroup analyses were planned *a-priori* to explore causes of heterogeneity to check whether variations in populations, index test characteristics, target conditions and study quality affect the estimation of accuracy. Individual factors explaining heterogeneity were also analysed using meta-regression where there were more than 10 studies in a review to determine their unique contribution, allowing for other factor. Conclusions regarding the typical estimate of

accuracy were interpreted cautiously if there was significant heterogeneity.[49]

In addition to meta-analyses that generated summary estimates primarily of LR's, summary sensitivity and specificity using the bivariate model[50;51] and summary ROC curves using the hierarchical summary receiver operating characteristic (HSROC) model[50;52] were also generated where on balance, they would add to the interpretation of the results.[53] LR's are considered more clinically meaningful as measures of test accuracy[46-48] and would allow estimation of probabilities for use in a decision analytic modelling. These post test probabilities can be used to calculate the absolute effects of interventions according to test results.[54] Publication and related biases were assessed using funnel plots of diagnostic odds ratio (dOR) against corresponding variances amongst reviews with more than 10 studies.[35] Appendix V aids for the interpretation of summary ROC curves and funnel plots. Stata version 8.2 software was used in the statistical analyses. The procedural flow chart for systematic reviews of test accuracy is shown in Figure 2.

Figure 2 Flow chart of procedures for reviews of test accuracy studies

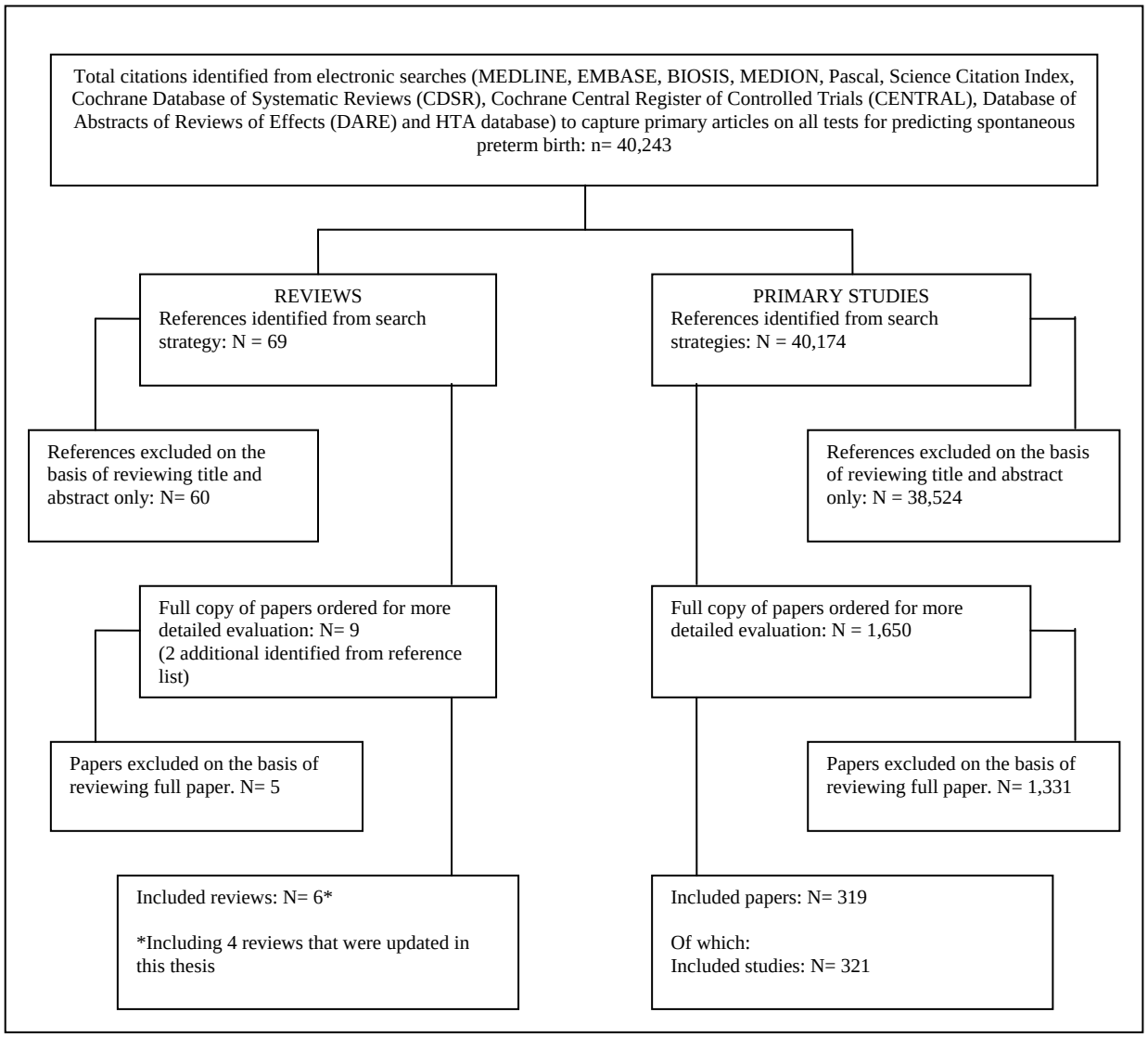


Chapter 4 Results

Literature selection

List of tests reviewed and their currency can be found on Appendix I. The reviews of tests' accuracy were divided into history, examination and investigations. 40,243 title and abstract electronic citations were obtained from the comprehensive literature searches from the various databases. These citations were scrutinised, with duplicates and those citations which do not meet the inclusion criteria excluded, resulted in the short listing of 1,650 citations for which the full article was requested. Upon further scrutiny of the full article, 319 were finally included for the systematic reviews, encompassing 22 tests that were evaluated in this thesis. The 22 tests aimed at the prediction of spontaneous preterm birth in asymptomatic women in early pregnancy and in women symptomatic with threatened preterm labour in the later part of their pregnancy. Figure 3 summarizes the process of the identification of literature reviews for test accuracy studies.

Figure 3 Identification of test accuracy literatures for systematic reviews in this thesis



Previous history of spontaneous preterm birth

Previous medical history of having spontaneous preterm birth is clinically used as a predictor for another spontaneous preterm birth. With the advent of dating scan, this history can be accurately assessed at antenatal booking consultation.

Study characteristics and quality

There were 10 studies evaluating the accuracy of previous history of spontaneous preterm birth among asymptomatic antenatal women in predicting spontaneous preterm birth in the subsequent pregnancy (n=55,885).[55-64] One study[65] was excluded on closer inspection because it used the same population as another included study.[61] Table 10 summarized the salient characteristics of the included studies. There were no studies on symptomatic women with threatened preterm labour. Most of the studies did not differentiate between previous single or more episodes of spontaneous preterm birth. Two studies evaluated the accuracy of two against one previous history of spontaneous preterm births histories,[58;64] while one study evaluated the accuracy of gestation at which the previous spontaneous preterm birth occurred in predicting spontaneous preterm birth in subsequent pregnancy.[62]

None of the study fulfilled the criteria of ideal quality study. None of the studies reported blinding and consecutive enrolment. The quality features were summarized in Figure 4. Aside from two studies,[59;61] the remaining studies reported birth before 37 weeks' gestation as their outcomes.

Accuracy of previous history of spontaneous preterm birth in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, previous history of spontaneous preterm birth had an LR+ 4.62 (95% CI 3.28 - 6.52) and LR- 0.68 (95% CI 0.56 - 0.82).[59] For predicting spontaneous preterm birth before 37 weeks' gestation, previous history of spontaneous preterm birth had a range of LR+ from 0.52 (95% CI 0.42 - 0.64)[58]

with one previous spontaneous preterm birth to 10.12 (95% CI 4.54 - 22.59)[58] with two previous spontaneous preterm births and a range of LR- from 0.45 (95% CI 0.33 - 0.61)[62] with previous history of spontaneous preterm birth before 26 weeks' gestation to LR- 1.38 (95% CI 1.27 - 1.49)[58] with one previous spontaneous preterm birth. The highest quality study has LR+ 2.26 (95% CI 1.86 - 2.74) and LR- 0.72 (95% CI 0.64 - 0.81) Goldenberg *et al*.[61] The accuracy estimates of previous history of spontaneous preterm birth in predicting subsequent spontaneous preterm birth is shown in Figure 5 while Figure 6 showed plot of sensitivities and specificities and their summary estimates for the accuracy of previous history of spontaneous preterm birth in asymptomatic woman in predicting spontaneous preterm birth. Individual accuracy data are summarized in Table 11. Figure 7 showed an asymmetric funnel plot indicating possible presence of publication or related biases for studies of the accuracy of previous history of spontaneous preterm birth in asymptomatic women.

Figure 4 Methodological quality of studies of previous history of spontaneous preterm birth in predicting subsequent spontaneous preterm birth included in the systematic review. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

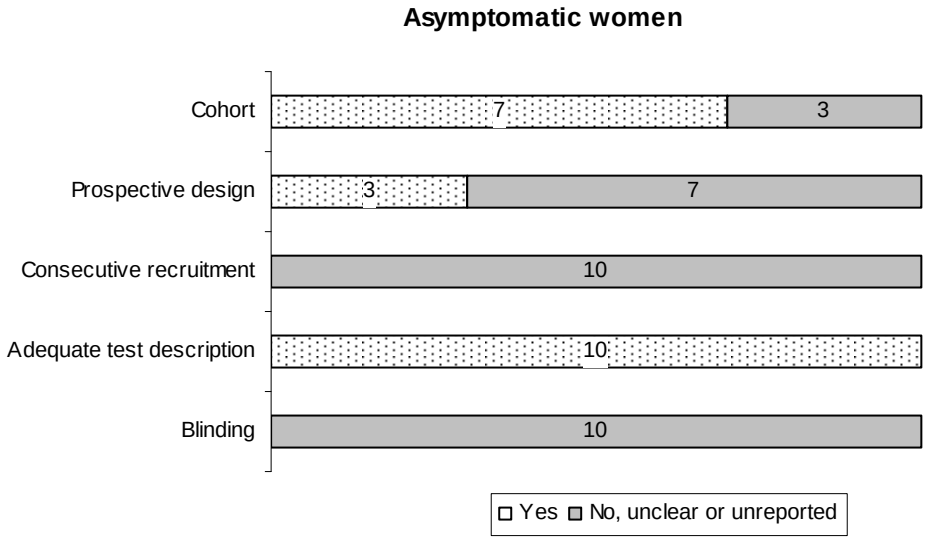
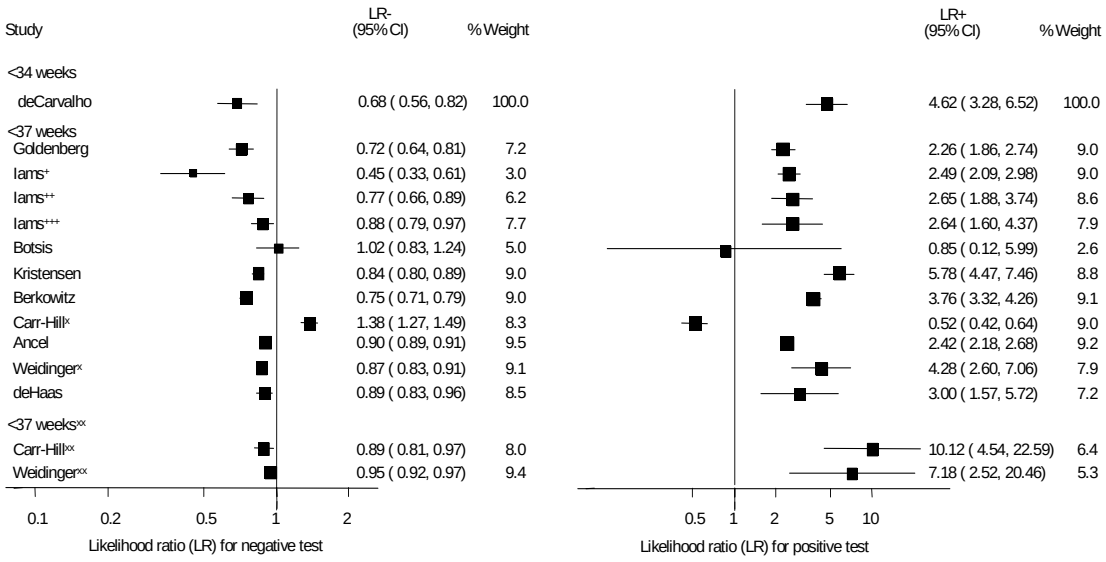


Figure 5 Forest plots of likelihood ratios (LR's) of the accuracy of previous history of spontaneous preterm birth in asymptomatic women for predicting spontaneous preterm birth stratified according to outcome gestation*



$\chi 2$ heterogeneity test p = 0.00012 for LR+ and p = 0.0017 for LR- of spontaneous preterm birth before 37 weeks' gestation
* Studies are listed in descending order of quality
+ Previous spontaneous preterm birth before 26 weeks' gestation
++ Previous spontaneous preterm birth before 31 weeks' gestation
+++ Previous spontaneous preterm birth before 36 weeks' gestation
x One previous spontaneous preterm birth
xx Two previous spontaneous preterm birth

Figure 6 Plot of sensitivity against specificity including summary values of the accuracy of previous history of spontaneous preterm birth in asymptomatic women for predicting spontaneous preterm birth before 37 weeks' gestation

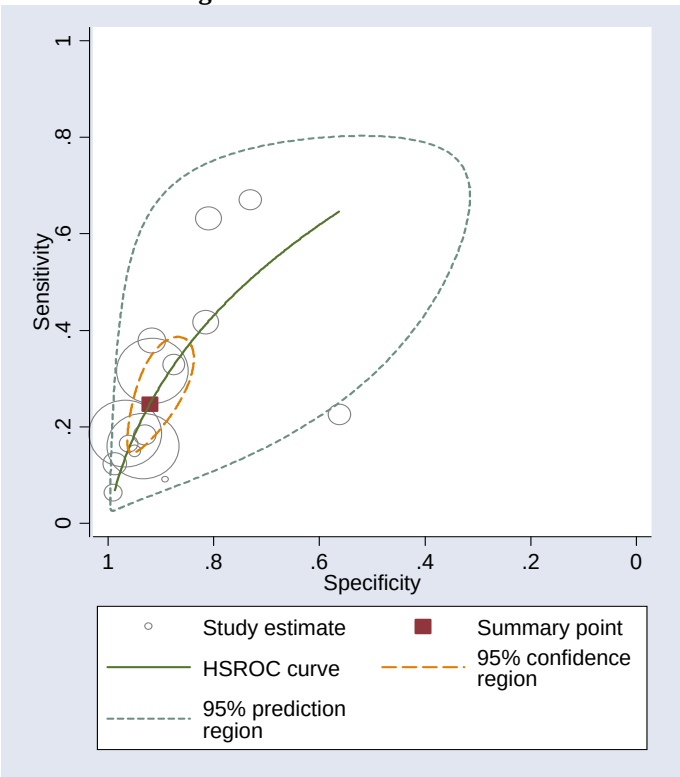
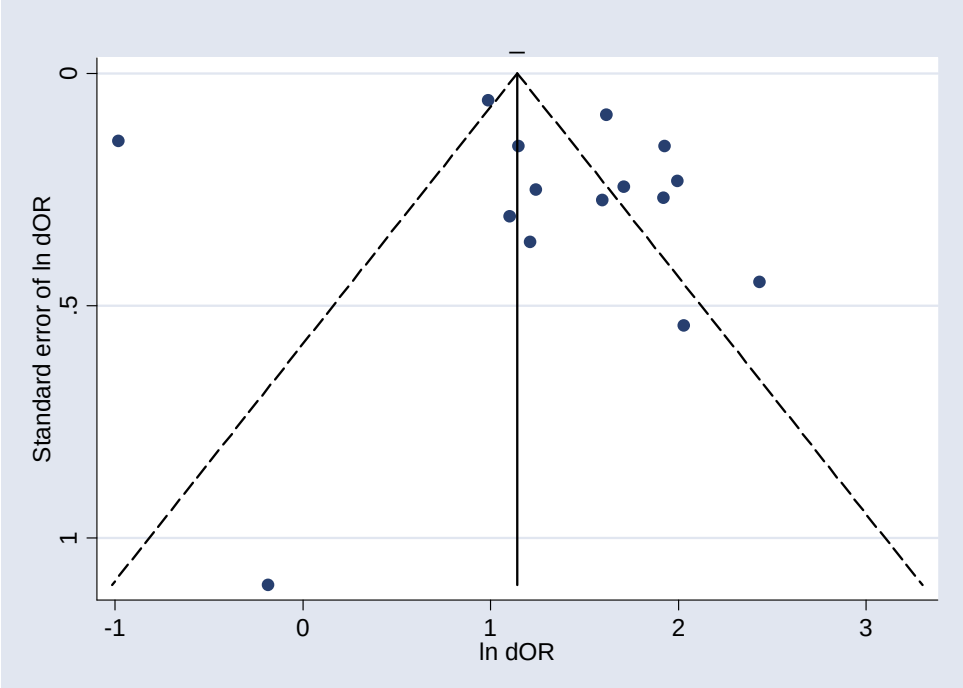


Figure 7 Funnel plot analysis of accuracy studies evaluating previous history of spontaneous preterm birth in asymptomatic women for predicting spontaneous preterm birth before 37 weeks' gestation



Digital examination

Physical examination is one of the cornerstones of medicine. Vaginal digital examination to assess the cervix is simple to do but its accuracy in the assessment of either asymptomatic antenatal women or symptomatic pregnant with threatened preterm labour to predict spontaneous preterm birth has not been evaluated in a systematic review.

Study characteristics and quality

There were 10 studies that evaluated the accuracy of cervical digital examination in predicting spontaneous preterm birth, 9 in asymptomatic antenatal women (n = 12,325)[66-74] and 1 study in symptomatic women symptomatic (n = 90) with threatened preterm labour.[75] There was a variation in testing gestation, frequency of testing and thresholds' selection among the included studies. Noticeably, for all of the studies, testing gestation commenced after 24 weeks' gestation, currently accepted lower limit of neonatal viability. Aside from three studies, which used birth before 34 and 35 weeks' gestation[69-71] as their outcome measurement, the other studies used 37 weeks' gestation. Individual study characteristics are summarized in Table 12.

One study fulfilled the criteria for ideal quality study;[70] otherwise the remaining studies lacked one or more criteria for ideal quality study with consecutive enrolment being the most commonly absent feature. Blinding was only reported by 4 studies in asymptomatic women. Methodological quality of the included study is summarized in Figure 8.

Accuracy of digital examination in asymptomatic women

There was a wide variation in the accuracy of digital examination in asymptomatic antenatal women in predicting spontaneous preterm birth (Figure 9). For predicting spontaneous preterm birth before 34 weeks' gestation, digital examination showed an LR+ 9.25 (95% CI 3.91 - 21.85) and LR- 0.46 (95% CI 0.19 - 1.08) in a mixed population of nulliparous and multiparous antenatal asymptomatic women and a threshold of >2cm cervical dilatation.[70] For

predicting spontaneous preterm birth before 37 weeks' gestation, LR+ ranged from 0.46 (95% CI 0.03 - 6.85) in multiparous women with a threshold of >2-3 cm cervical dilatation[73] to 9.17 (95% CI 0.52 - 160.08) in a mixed population of nulliparous and multiparous antenatal asymptomatic women with a centrally positioned cervix and >1.5 cm dilatation,[68] and LR- ranged from 0.42 (95% CI 0.26 - 0.68) in a nulliparous antenatal women with soft cervix[66] to 2.46 (95% CI 0.11 - 55.35) in a mixed population of nulliparous/multiparous antenatal asymptomatic women and a threshold of posterior cervix >1.5 cm dilatation.[68] The highest quality study from Parikh *et al* has LR+ 1.15 (0.86 - 1.53) and LR- 0.89 (0.68 - 1.16), which evaluated digital examination in a mixed population of nulliparous and multiparous women using the threshold of admitting a finger at cervical internal os.[72] Individual accuracy results are summarized in Table 13.

Accuracy of digital examination in symptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation digital examination in symptomatic women with threatened preterm labour had a range of LR+ from 2.01 (95% CI 1.26 - 3.22) to 2.38 (95% CI 1.46 - 3.87) and LR- from 0.47 (95% CI 0.29 - 0.79) to 0.54 (95% CI 0.34 - 0.88) corresponding to a choice of threshold >2 cm cervical dilation or >40% effacement (the latter threshold correspond to the less accurate results).[75] Individual accuracy results are summarized in Table 13.

Figure 8 Methodological quality of studies included in the systematic review of accuracy of digital examination in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

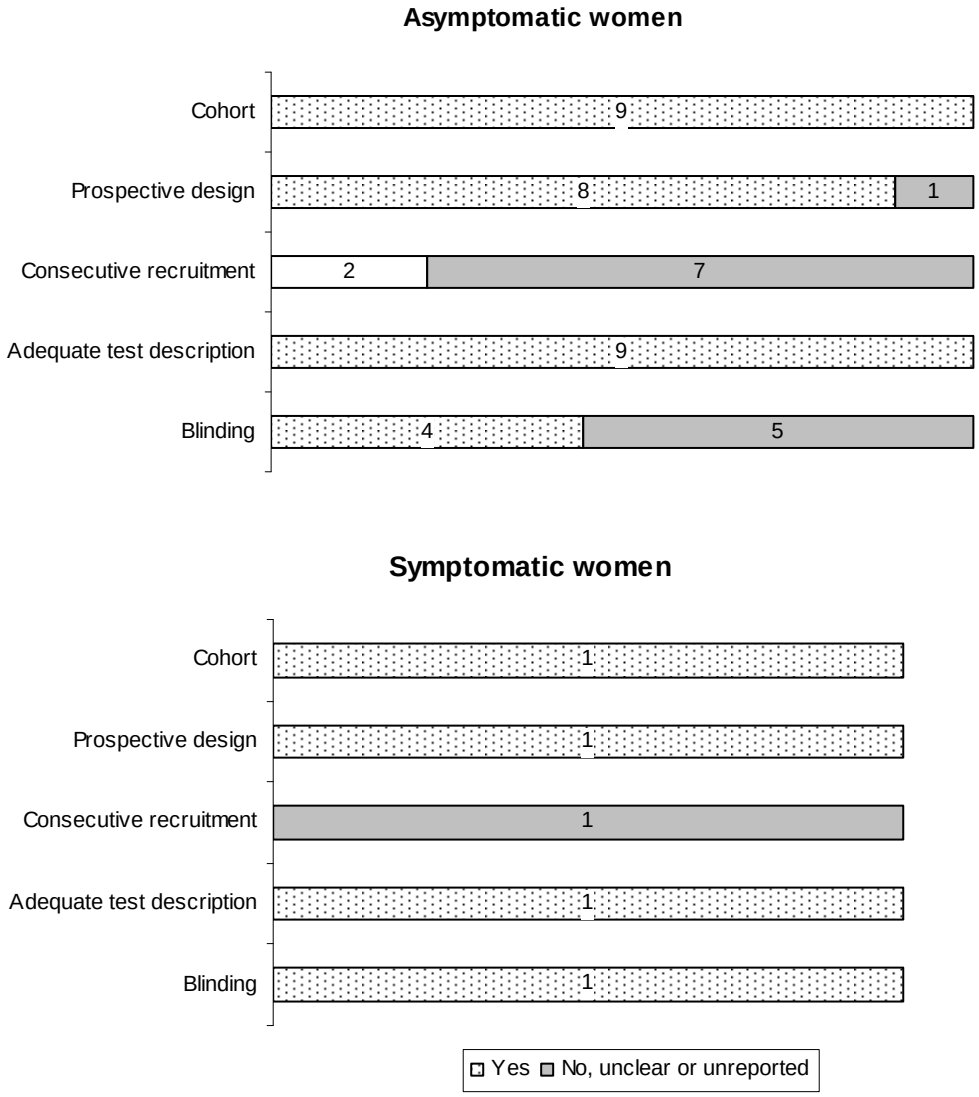
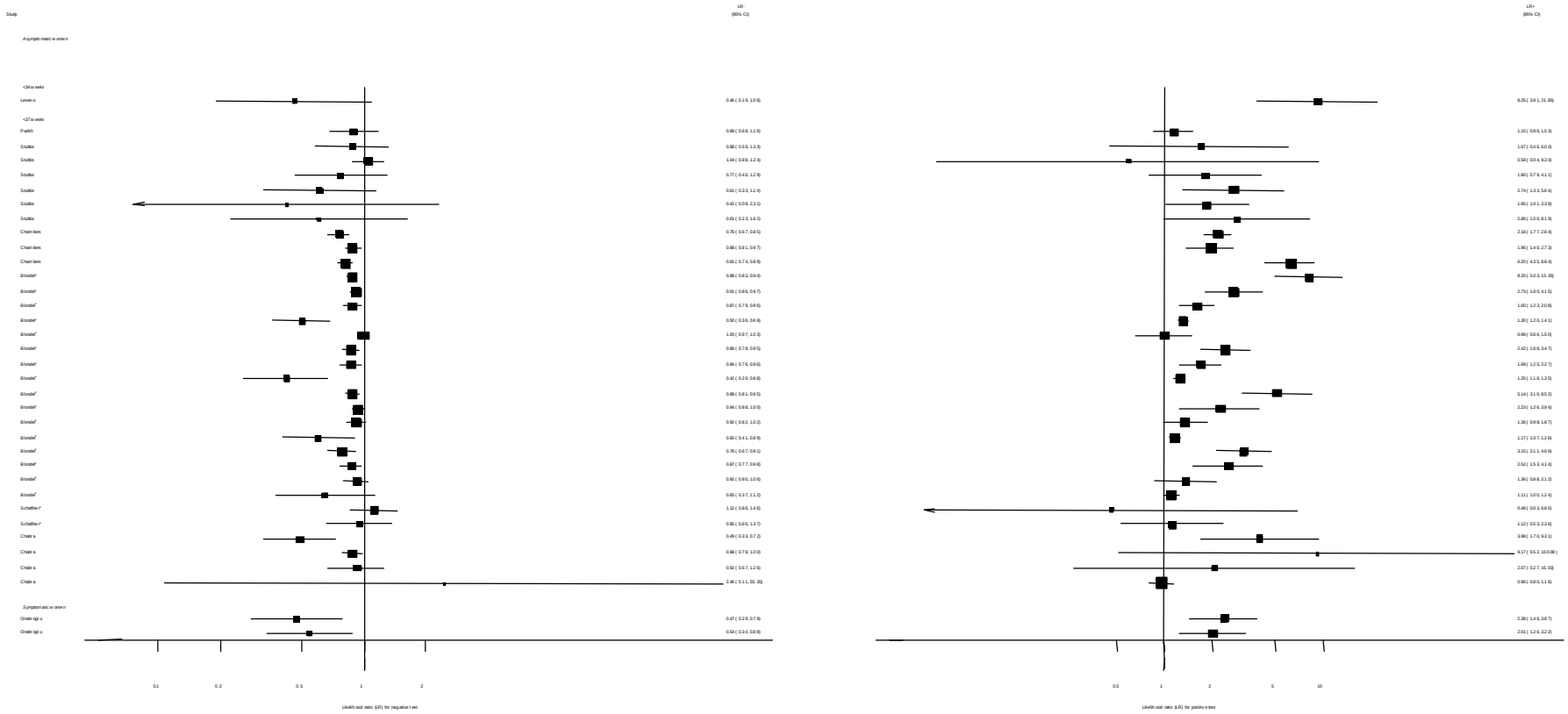


Figure 9 Forest plots of likelihood ratios (LR's) of digital examination in predicting spontaneous preterm birth as a predictor of spontaneous preterm birth



Cervico-vaginal fetal fibronectin (fFN)

Cervico-vaginal fetal fibronectin (fFN) is a glycoprotein, present in trace quantity that is usually undetectable in the cervical vaginal secretion. Higher quantity has been purported to be an indication of imminent labour onset. The test is readily available in the form of commercial rapid test kit. A cotton swab is used to collect samples of cervico-vaginal secretions during a speculum examination. The result is either positive (fFN is present), or negative (fFN is not present) obtained within 10 – 15 minutes of performing the test. These commercial preparations used positivity threshold of 50ng/mL.

Study characteristics and quality

There were 58 primary studies (n = 22,905 women) on the accuracy of bedside cervico-vaginal fetal fibronectin testing, comprising of 18 studies on asymptomatic antenatal women (n = 18,696) and 40 studies on symptomatic women with presented with threatened preterm labour (n = 4,209). Table 14 summarizes each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour. The studies' enrolment ranged from 20 to 6,508 women[76;77] with a median of 147 women in asymptomatic population and from 26 to 725 women[78;79] with a median of 86 women in symptomatic women. All the included studies had used cervico-vaginal fetal fibronectin specimen taken either from the posterior fornix or the cervix. There were three studies in asymptomatic women[80-82] and five studies in symptomatic women that fulfil the definition of high quality test accuracy studies.[78;83-86] The methodological quality of the included primary studies is summarized in Figure 10. There were seven and fifteen studies that reported the accuracy of the test for predicting spontaneous preterm birth before 34[76;81;87-91] and 37 weeks' gestation[76;77;80;82;87;88;90;92-99] respectively in asymptomatic women. For symptomatic women presenting with threatened preterm labour, eighteen studies[79;83;85;86;100-113] reported the accuracy of the test in predicting spontaneous preterm birth

within 7-10 days of testing in addition to 8 studies that reported birth before 34[86;108;114-119] and 31 studies that reported birth before 37 weeks' gestation.[78;79;83;84;86;96;97;99;101-103;105;107-109;111;113;116-118;120-130]

Accuracy of fFN in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, the range of LR+ was from 2.57 (95% CI 2.07 - 3.19) to 86.60 (95% CI 6.26 - 1198.92) with a summary LR+ of 7.65 (95% CI 3.93 to 14.86) (χ2 heterogeneity test 0.00073) and the range of LR- was from 0.28 (95% CI 0.05 – 1.52) to 0.80 (95% CI 0.52 – 1.24) with a summary LR- of 0.80 (95% CI 0.73 – 0.88) (χ2 heterogeneity test p = 0.082) (Figure 11). For predicting spontaneous preterm birth before 37 weeks' gestation, the range of LR+ was from 0.43 (95% CI 0.07 – 2.78) to 26.38 (95% CI 1.73 – 402.99) with a summary LR+ of 3.17 (95% CI 2.00 – 5.02) (χ2 heterogeneity test p = 0.00021) and the range of LR- was from 0.28 (95% CI 0.03 – 3.07) to 1.20 (95% CI 0.93 -1.54) with a summary LR- of 0.87 (95% CI 0.77 – 0.97) (χ2 heterogeneity test p = 0.00037) (Figure 12). Figure 13 and Figure 14 showed plot of sensitivities and specificities and their summary estimates for the accuracy of fFN in predicting spontaneous preterm birth before 34 and 37 weeks' gestation respectively. Individual test accuracy results from the included studies for asymptomatic women can be found in Table 15.

Accuracy of fFN in symptomatic women

For predicting spontaneous preterm birth within 7 – 10 day of testing, the range of LR+ was from 2.12 (95% CI 1.05 – 4.28) to 9.29 (95% CI 5.06 – 17.06) with a summary LR+ of 4.10 (95% CI 3.37 – 4.98) (χ2 heterogeneity test p = 0.0021) and the range of LR- from 0.09 (95% CI 0.01 – 0.58) to 0.59 (95% CI 0.25 – 1.39) with a summary LR- of 0.35 (95% CI 0.27 – 0.46) (χ2 heterogeneity test = 0.042) (Figure 15). For predicting spontaneous preterm birth before 34 weeks' gestation, the range of LR+ was from 1.57 (95% CI 0.53 – 4.60) to 5.70 (95% CI 2.88 – 11.28) with a summary LR+ of 3.58 (95% CI 2.56 – 5.00) (χ2 heterogeneity

test p = 0.052) and the range of LR- from 0.12 (95% CI 0.02 – 0.79) to 0.91 (95% CI 0.69 – 1.20) with summary LR- of 0.34 (95% CI 0.17 – 0.68) (χ2 heterogeneity test p = 0.0020) (Figure 16). For predicting spontaneous preterm birth before 37 weeks' gestation the range of LR+ was from 1.00 (95% CI 0.44 - 2.30)[78] to 14.36 (95% CI 5.81 - 35.47)[111] with summary LR+ of 3.62 (95% 3.02 - 4.33) (χ2 heterogeneity test p = 0.00021) and the range of LR- from 0.08 (95% CI 0.01 - 0.54)[118] to 1.00 (95% 0.44 - 2.30)[78] with a summary LR- of 0.50 (95% 0.43 - 0.59) (χ2 heterogeneity test p = 0.00019) (Figure 17). Figure 18, Figure 19 and Figure 20 showed plot of sensitivities and specificities and their summary estimates for the accuracy of fFN in predicting spontaneous preterm birth within 7-10 days of testing and before 34 and 37 weeks' gestation respectively in symptomatic women. Figure 21 showed absence of large studies with higher level of accuracy missing in the funnel plot analysis for studies of the accuracy of fFN in predicting spontaneous preterm birth within 7 – 10 days of testing in symptomatic women. Figure 22 did not show asymmetry in the funnel plot analysis of the accuracy of fFN in predicting spontaneous preterm birth before 37 weeks' gestation in symptomatic women. Individual test accuracy results from the included studies for symptomatic women can be found in Table 16.

Figure 10 Methodological quality of studies included in the systematic review of accuracy of bedside test for cervico-vaginal fetal fibronectin in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies

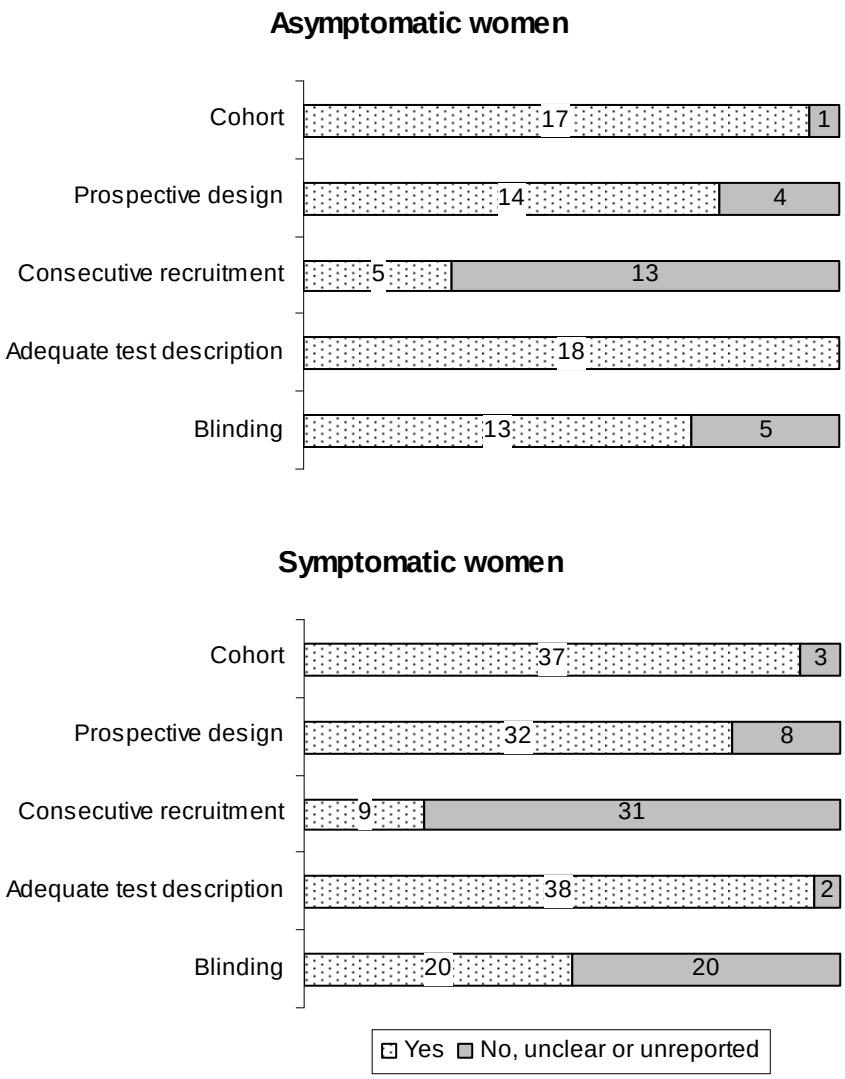
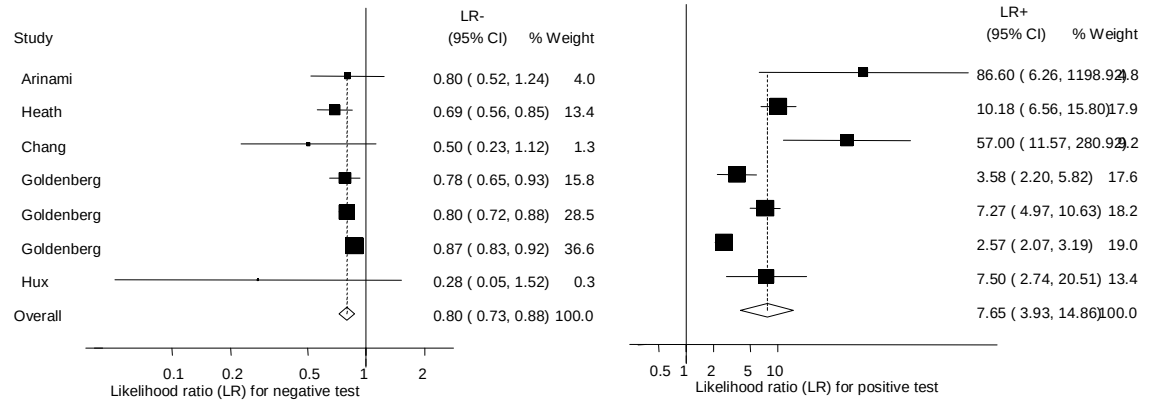
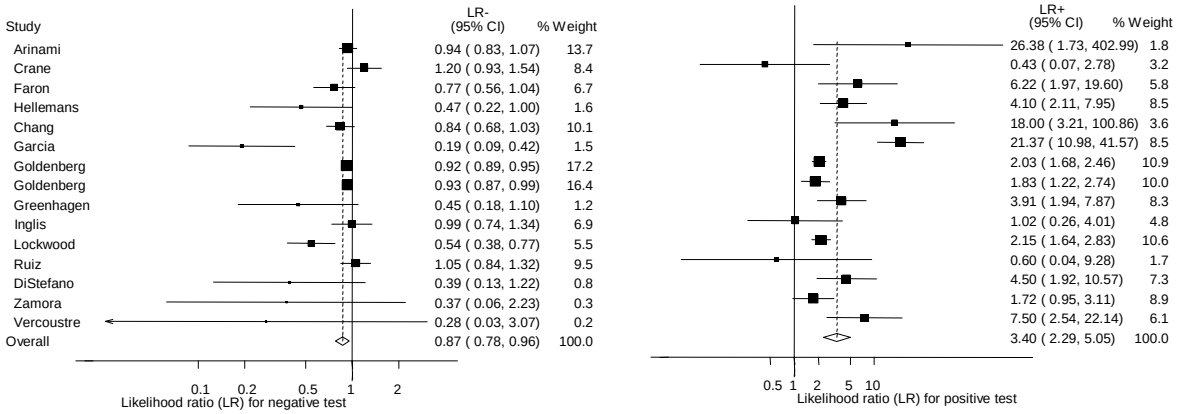


Figure 11 Forest plots of likelihood ratios (LR's) for cervico-vaginal fetal fibronectin bedside testing on asymptomatic antenatal women as a predictor of spontaneous preterm birth before 34 weeks' gestation*+



*Studies are arranged in descending order of methodological quality
+$\chi 2$ heterogeneity test p = 0.00073 for LR+ and p = 0.082 for LR-

Figure 12 Forest plots of likelihood ratios (LR's) for cervico-vaginal fetal fibronectin bedside testing on asymptomatic antenatal women as a predictor of spontaneous preterm birth before 37 weeks' gestation*+



*Studies are arranged in descending order of methodological quality
+$\chi 2$ heterogeneity test p = 0.00021 for LR+ and p = 0.00037 for LR-

Figure 13 Plot of sensitivity against specificity including summary values of the accuracy of cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 34 weeks' gestation

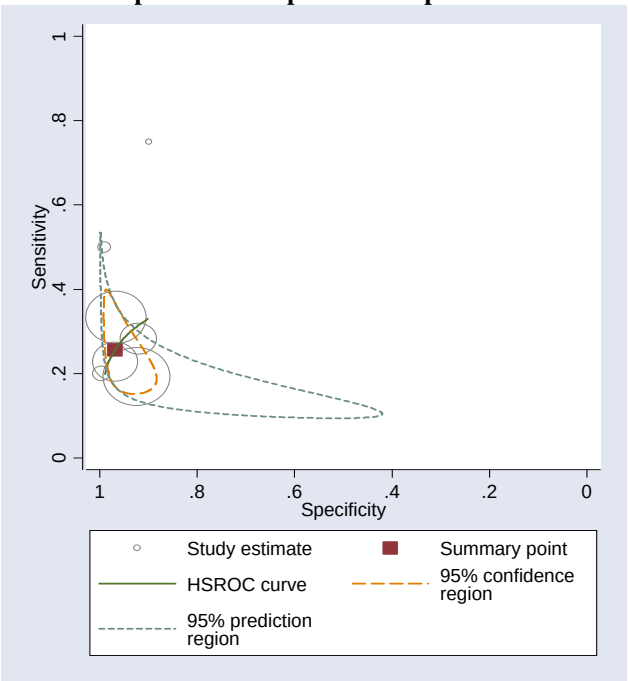


Figure 14 Plot of sensitivity against specificity including summary values of the accuracy of cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 37 weeks' gestation

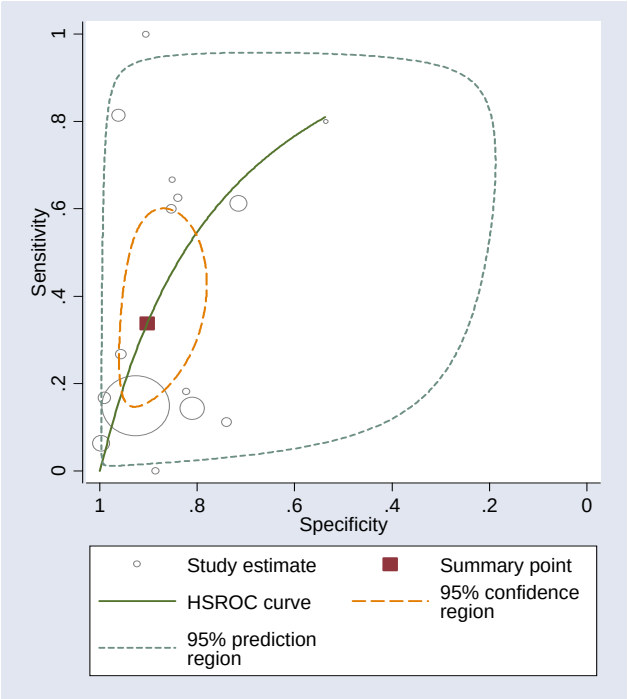
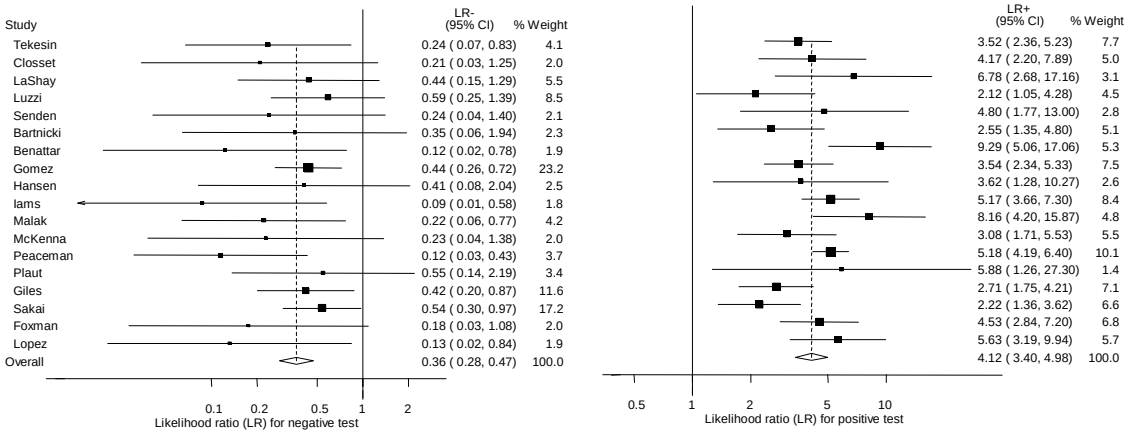
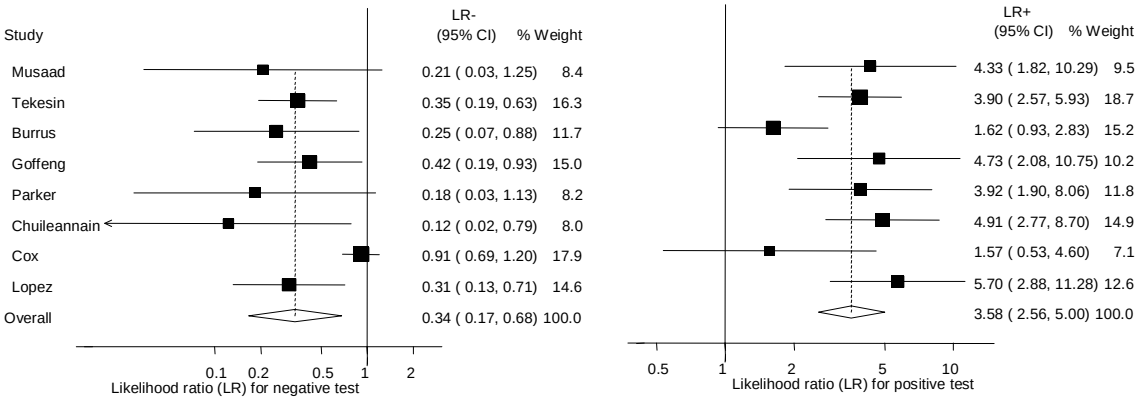


Figure 15 Forest plots of likelihood ratios (LR's) for cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth within 7-10 days of testing*+



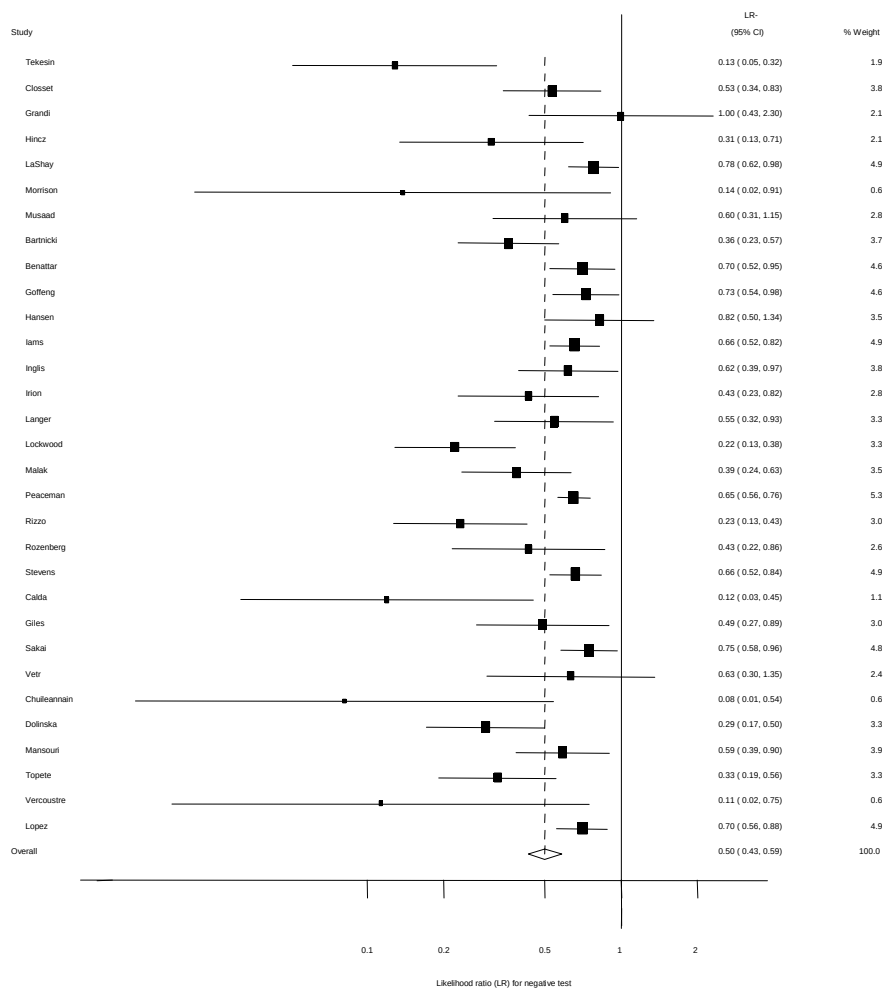
*Studies are arranged in descending order of methodological quality
+$\chi 2$ heterogeneity test p = 0.0021 for LR+ and p = 0.424 for LR-

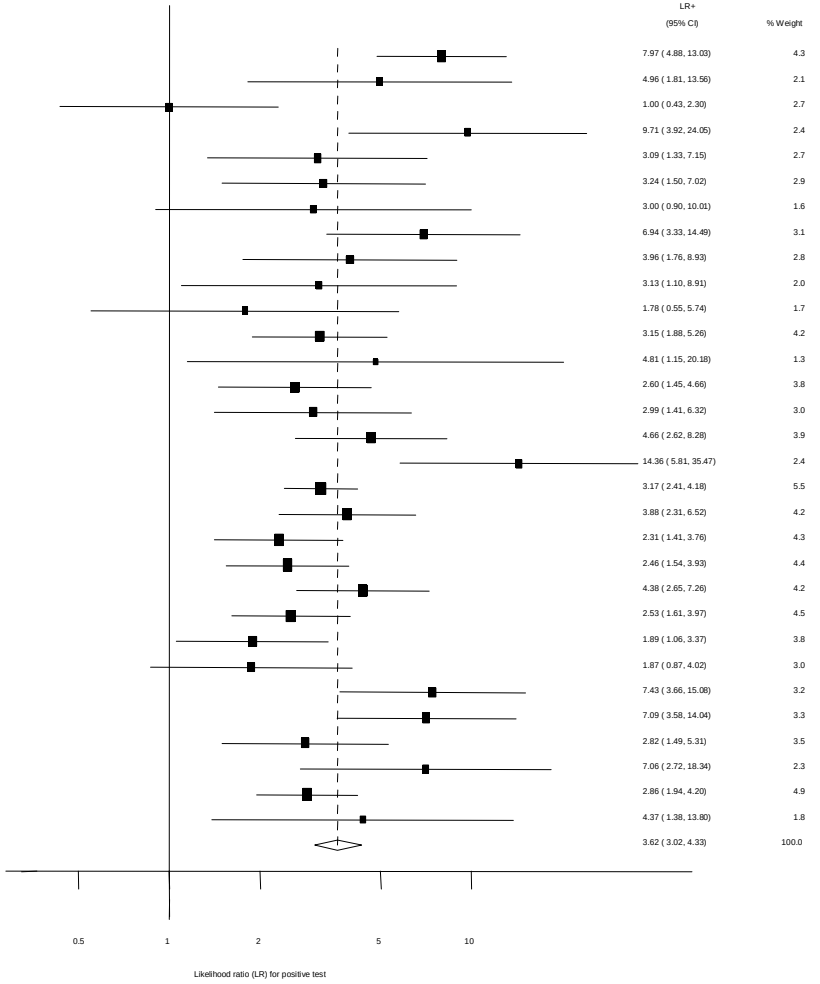
Figure 16 Forest plots of likelihood ratios (LR's) for cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 34 weeks' gestation*+



*Studies are arranged in descending order of methodological quality
+$\chi 2$ heterogeneity test p = 0.052 for LR+ and p = 0.0020 for LR-

Figure 17 Forest plots of likelihood ratios (LR's) for cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 37 weeks' gestation*+





*Studies are arranged in descending order of methodological quality
+$\chi 2$ heterogeneity test p = 0.00021 for LR+ and p = 0.000 for LR-

Figure 18 Plot of sensitivity against specificity including summary values of the accuracy of cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth within 7-10 days of testing

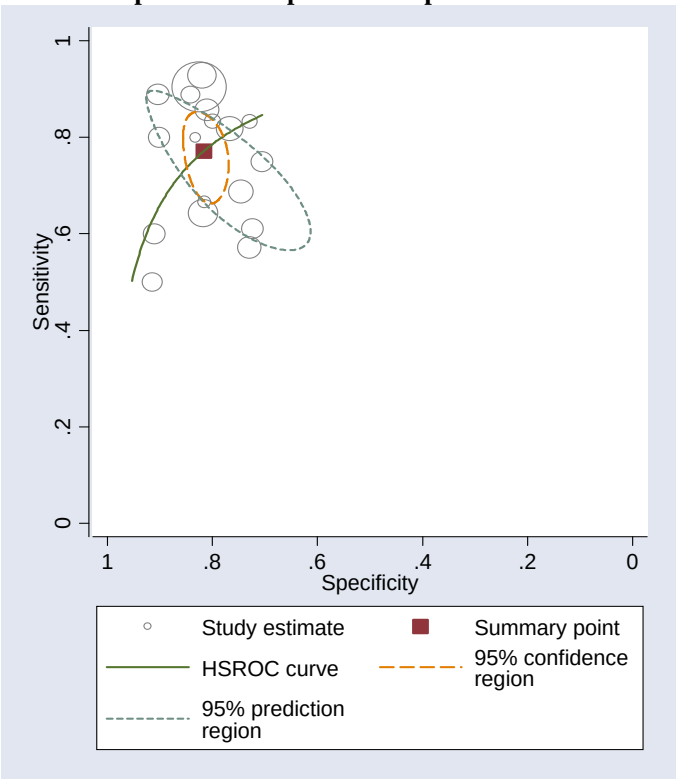


Figure 19 Plot of sensitivity against specificity including summary values of the accuracy of cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 34 weeks' gestation

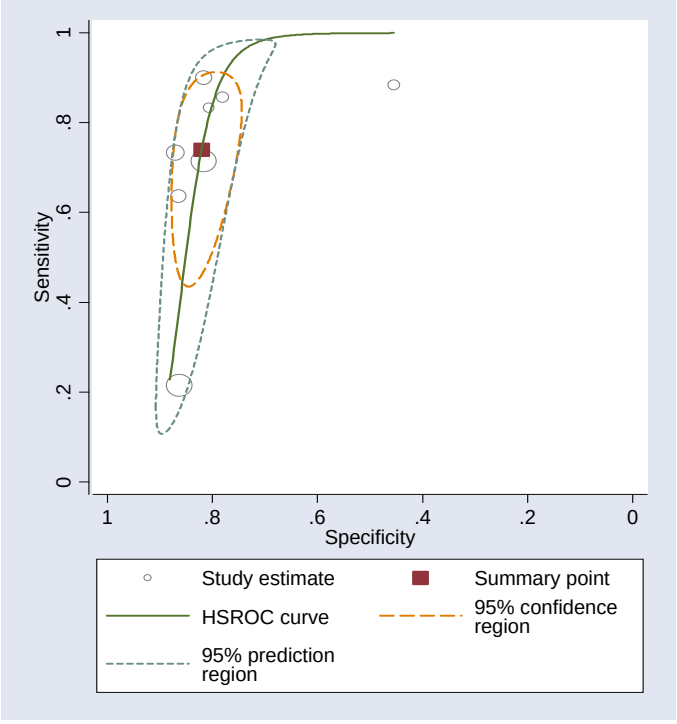


Figure 20 Plot of sensitivity against specificity including summary values of the accuracy of cervico-vaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 37 weeks' gestation

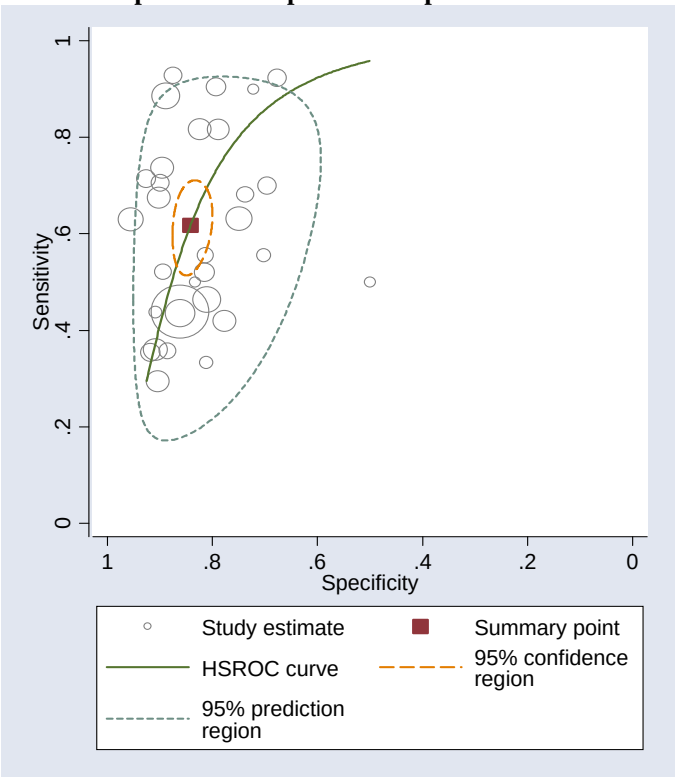


Figure 21 Funnel plot analysis of accuracy studies evaluating the accuracy of cervico-vaginal fetal fibronectin in symptomatic women in predicting spontaneous preterm birth within 7-10 days of testing

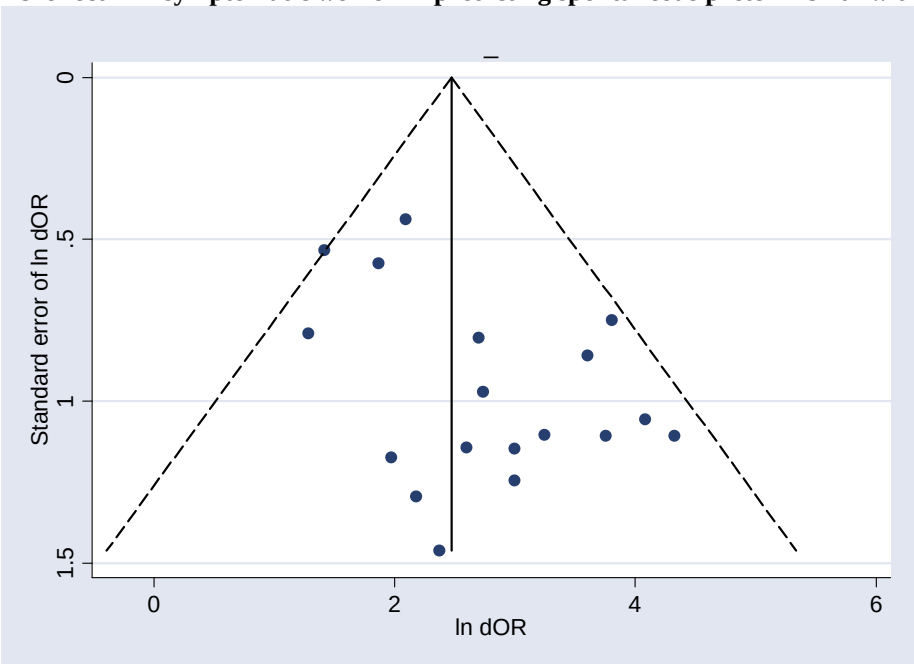
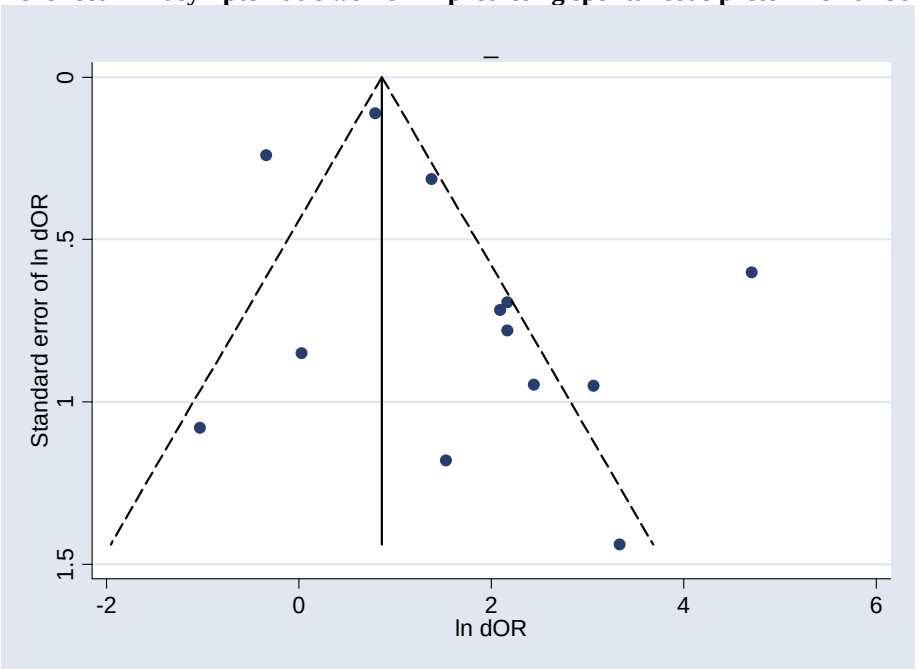


Figure 22 Funnel plot analysis of accuracy studies evaluating the accuracy of cervico-vaginal fetal fibronectin in asymptomatic women in predicting spontaneous preterm birth before 37 weeks' gestation



Cervico-vaginal prolactin

During pregnancy, prolactin is produced by the decidua (in addition to the maternal adenohypophysis and the fetal pituitary. Disruption of the decidua-membrane matrix during labour whether preterm or term, may allow the secreted prolactin to leak to the cervix and vagina where it would be available for detection. It is purported that detection of this cervico-vaginal prolactin is a reliable predictor of the onset of spontaneous preterm labour and hence spontaneous preterm birth.[131] A cotton swab is used to collect samples of cervico-vaginal secretions during a speculum examination, which was then sent for laboratory assay.

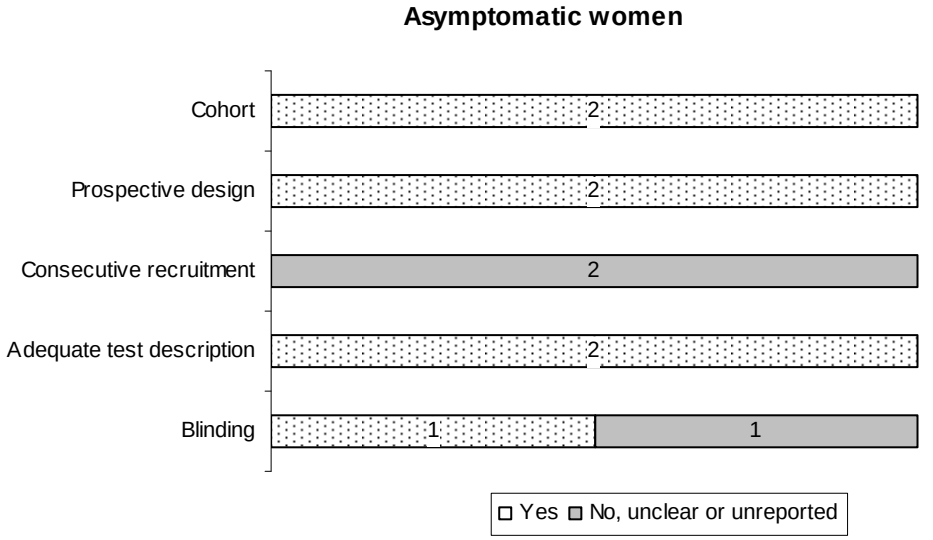
Study characteristics and quality

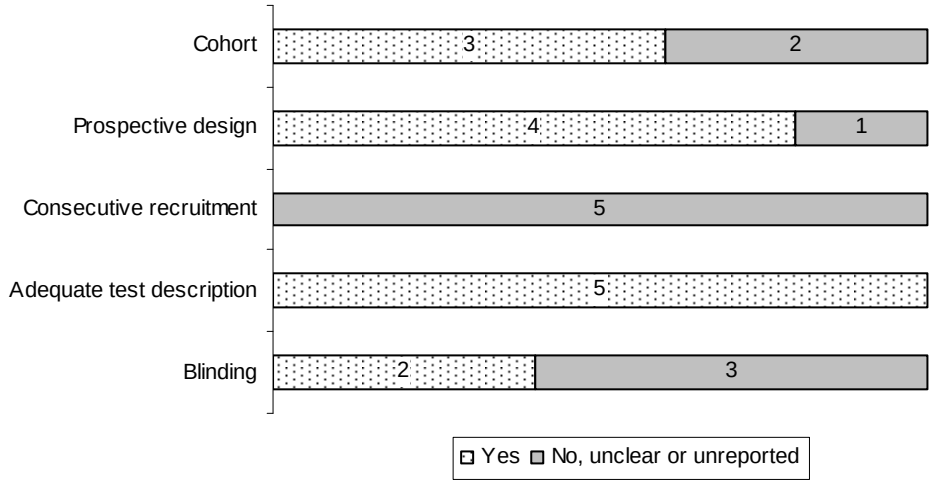
There were 5 primary studies, 2 evaluating the test in asymptomatic women population (n = 80)[131;132] and 5 evaluating the test in symptomatic women (n = 265),[131-135] presenting with threatened preterm labour, including two studies that evaluated the test in both populations.[131;132] The study enrolment ranged from 35[132] to 66 women.[135] In asymptomatic women, the test was carried between 24 and 32 weeks' gestation. The studies' enrolment for asymptomatic women ranged from 35 to 66 women[132;135] with a median of 40 women.[131] Only two studies, both in symptomatic women, used the same threshold of abnormality of 2.0 ng/ml.[131;134] The remaining studies used 1.5 ng/ml,[132] 1.8 ng/ml,[133] and 50 ng/ml thresholds.[135] All the studies evaluated cervico-vaginal prolactin test on a single occasion rather than as a serial test.

None of the studies reported consecutive enrolment and only 3 studies, one in asymptomatic population[131] and two in symptomatic population[131;134] reported blinding. The methodological quality of the included primary studies is summarized in Figure 23. None of the studies fulfilled the definition of ideal quality test accuracy study design. One study each reported outcome of spontaneous preterm birth before 34 weeks'[131] and 37 weeks' gestation.[132] One study reported outcome within 7 days of testing,[131] 3 studies reported outcome before 34

weeks' gestation[131;132;134] and all studies reported outcome before 37 weeks' gestation in symptomatic women.[131-135] Information on individual study characteristics can be found in Table 17, which summarizes each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour.

Figure 23 Methodological quality of studies included in the systematic review of accuracy of cervico-vaginal prolactin in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies





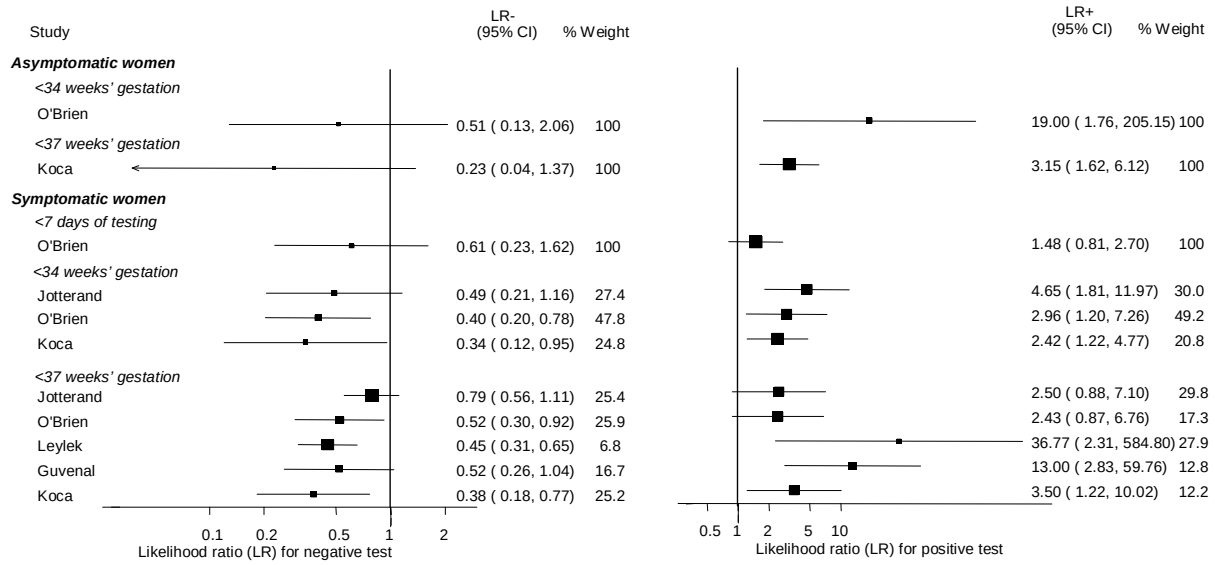
Accuracy of cervico-vaginal prolactin in asymptomatic women

In the single study evaluating the test on asymptomatic women for predicting spontaneous preterm birth before 34 weeks' gestation, LR+ was 19.00 (95% CI 1.76 - 205.15) and LR- was 0.51 (95% CI 0.13 - 2.06)[131] while before 37 weeks' gestation the LR was 3.15 (95% CI 1.62 - 6.12) and LR- was 0.23 (95% CI 0.038 - 1.37)[132] (Figure 24). The accuracy measures of the test in predicting spontaneous preterm births in asymptomatic women are summarized in Table 18.

Accuracy of cervico-vaginal prolactin in symptomatic women

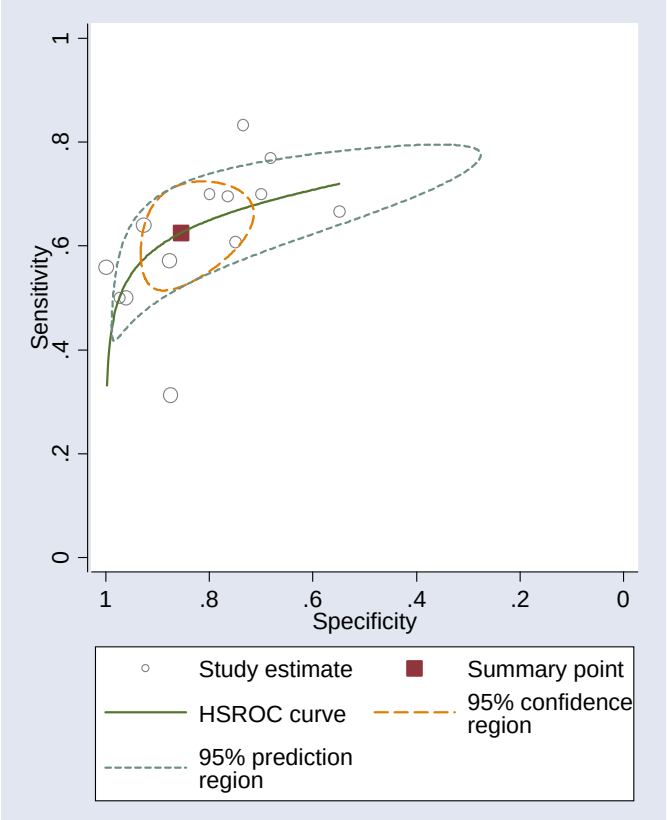
For predicting spontaneous preterm birth within 7days of testing, LR+ was 1.48 (95% CI 0.81 - 2.70) and LR- was 0.61 (95% CI 0.23 - 1.62) (Figure 24). The accuracy for predicting spontaneous preterm birth before 34 weeks' gestation ranged from LR+ 2.42 (95% CI 1.22 - 4.77) and LR- 0.34 (95% CI 0.12 - 0.95)[132] to LR+ 4.65 (95% CI 1.81 - 11.97) and LR- 0.49 (95% CI 0.21 - 1.16).[134] Jotterand *et al*[134] represented the largest higher quality available. The accuracy for predicting spontaneous preterm birth before 37 weeks' gestation ranged from LR+ 2.43 (95% CI 0.87 - 6.76) and LR- 0.52 (95% CI 0.30 - 0.92)[131] to LR+ 36.77 (95% CI 2.31 - 584.80) and LR- 0.45 (95% CI 0.31 - 0.65)[135] (Figure 24). The largest higher quality study (Jotterand *et al*)[134] however had LR+ 2.50 (95% CI 0.88 - 7.10) and LR- 0.79 (95% CI 0.56 - 1.11) for this reference standard. Heterogeneity assessment of the LR's did not reveal significant graphical or statistical heterogeneity of the accuracy results except for either positive or negative test results in predicting spontaneous preterm birth before 34 and 37 weeks' gestation in symptomatic women. The accuracy measures of the test in predicting spontaneous preterm births in symptomatic women are summarized in Table 18.

Figure 24 Forest plots of likelihood ratios (LR's) of rapid test for cervico-vaginal prolactin as a predictor of spontaneous preterm birth according to population and outcome gestations*+



*Studies are arranged in descending order of methodological quality
+$\chi 2$ heterogeneity test for 34 weeks' gestation p = 0.54 for LR+ and p = 0.86 for LR-, and for 37 weeks' gestation p = 0.13 for LR+ and p = 0.16 for LR-

Figure 25 Plot of sensitivity against specificity including summary values of the accuracy of cervico-vaginal prolactin testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 37 weeks' gestation



Cervico-vaginal phIGFBP-1

The phosphorylated form of insulin-like growth factor binding protein 1 (phIGFBP-1) is produced by placental decidual cells. It is released and leaks into the cervix during the onset of parturition, whether term or preterm, and thus has been purported as a reliable predictor of the onset of preterm labour and hence spontaneous preterm birth. The novel test is an immune-chromatographic dipstick test based on monoclonal antibodies that detects the presence of phosphorylated form of IGFBP-1 release from the decidual cells. The test is readily available in the form of a commercial rapid test kit.[136] A cotton swab is used to collect samples of cervico-vaginal secretions during a speculum examination. The result is either positive (phIGFBP-1 is present) (threshold exceeded 30μg/L), or negative (phIGFBP-1 less than 30μg/L) obtained within 10 – 15 minutes of performing the test.

Study characteristics and quality

There were 10 primary studies, involving altogether, a total of 568 women. One potentially eligible study for inclusion was excluded because data was unobtainable.[137] Table 19 summarizes each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women (1 study)[138] and women with symptoms of threatened preterm labour (9 studies).[136-146] The single study included on asymptomatic antenatal population had targeted the test, which was performed 3 weekly between 24 to 34 weeks' gestation, at women who has previous spontaneous preterm birth. The studies' enrolment ranged from 32 – 135 women, with a median of 46 women.

Only one study reported consecutive enrolment[139] and only two studies reported blinding to test results and or reference standards.[140;144] Otherwise all studies used cohort of pregnant women, where all except two reported prospective data collection design,[145;146] and with one exception,[145] had provided adequate test description. The methodological quality of the included primary studies is summarized in Figure 26. The only study on asymptomatic

women had reported spontaneous preterm birth before 37 weeks' gestation as the reference standard. For studies on symptomatic women, all studies have reported birth before 37 weeks' gestation as their reference standards. Additionally, 3 studies also reported birth within 48 hours of testing,[139;140;144] 4 studies reported birth within 7 days of testing,[139;140;143;144] and 3 studies reported birth before 34 weeks' gestation.[136;143;144]

Accuracy of phIGFBP-1 in asymptomatic women

In the single study evaluating the test on asymptomatic women for predicting spontaneous preterm birth before 37 weeks' gestation, LR+ was 4.17 (95% confidence interval (CI) 2.44 - 7.13) and LR- was 0.21 (95% CI 0.08 - 0.51).[138]

Accuracy of phIGFBP-1 in symptomatic women

For predicting spontaneous preterm birth within 48 hours of testing, summary LR+ was 2.53 (95% CI 1.17 – 5.48) and summary LR- was 0.32 (95% CI 0.15 – 0.66) (Figure 27). There were two studies of equal size and representing higher quality studies giving a summary LR+ 1.73 (95% CI 0.92 - 3.25) and summary LR- 0.59 (95% CI 0.24 - 1.45).[139;144] The accuracy for predicting spontaneous preterm birth within 7 days of testing was shown in Figure 28, where the summary LR+ was 3.29 (95% CI 2.24 – 4.83) and summary LR- was 0.20 (95% CI 0.10 – 0.41). For this reference standard (i.e. spontaneous preterm birth within 7 days of testing), the summary LR+ 2.83 (95% CI 1.57 - 5.09) and summary LR- 0.371 (95% CI 0.13 - 1.04) as there were two higher quality studies of equal size.[139;144] The accuracy for predicting spontaneous preterm birth before 34 weeks' gestation was shown in Figure 29, where the summary LR+ was 2.96 (95% CI 2.02 – 4.33) and summary LR- was 0.22 (95% CI 0.08 – 0.64). The largest higher quality study had LR+ 4.15 (95% CI 1.43 - 11.99) and LR- 0.31 (95% CI 0.03 - 3.38).[144] Summary LR+ for predicting spontaneous preterm birth before 37 weeks' gestation was 4.26 (95% CI 2.54 – 7.17) and summary LR- was 0.28 (95% CI 0.20 – 0.38) (Figure 30). The highest quality study has LR+ 3.87 (95% CI 1.54 - 9.72) and LR- 0.33

(95% CI 0.15 - 0.71) for this outcome.[144] Heterogeneity assessment of the likelihood ratios did not reveal significant graphical or statistical heterogeneity for most of the accuracy results except for positive test results in predicting spontaneous preterm birth before 37 weeks' gestation in this clinically similar group of women. The accuracy measures of the test in predicting spontaneous preterm births in symptomatic women were summarized in Table 20.

Figure 26 Methodological quality of studies included in the systematic review of accuracy of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

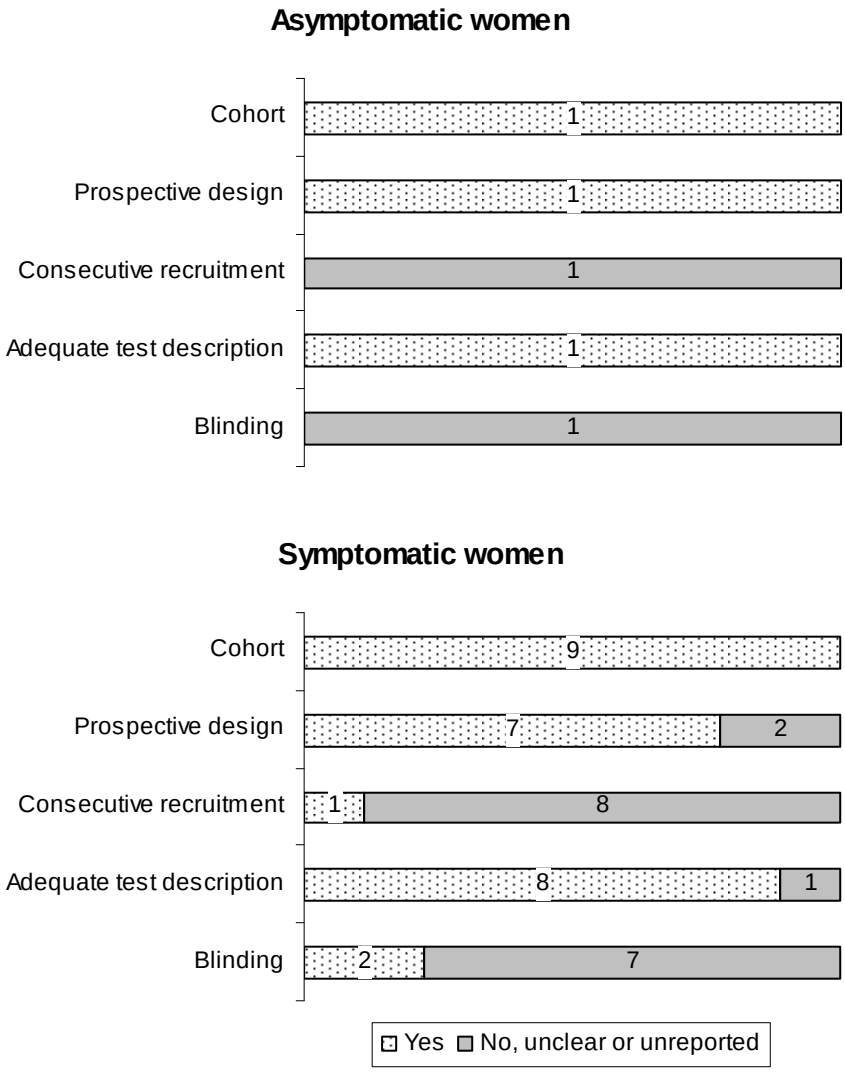
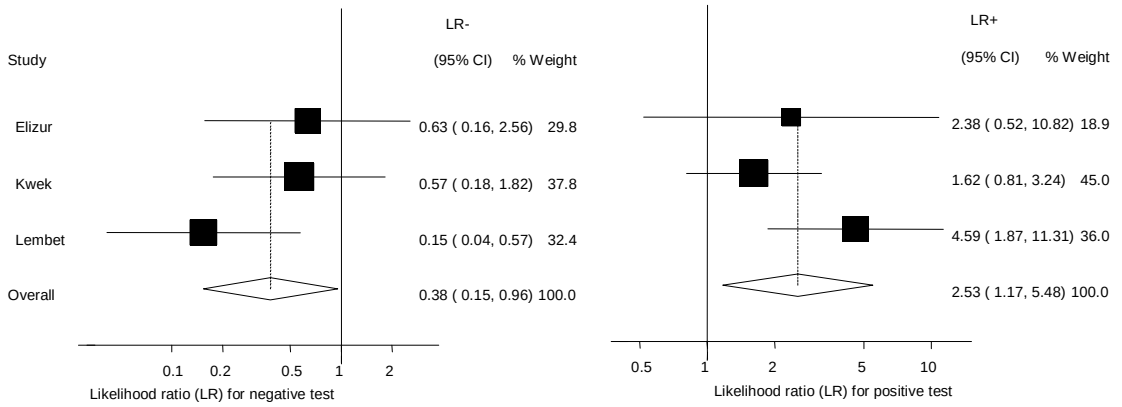
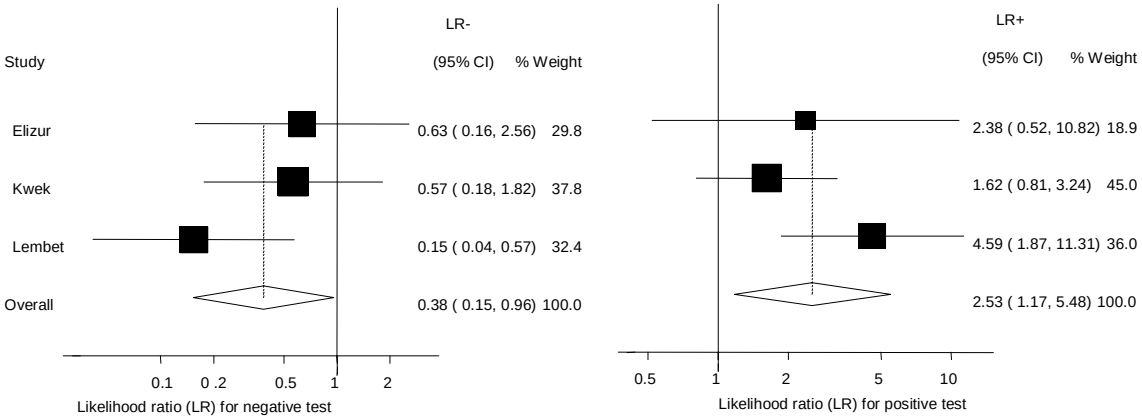


Figure 27 Forest plots of likelihood ratios (LR's) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth within 48 hours of testing*+



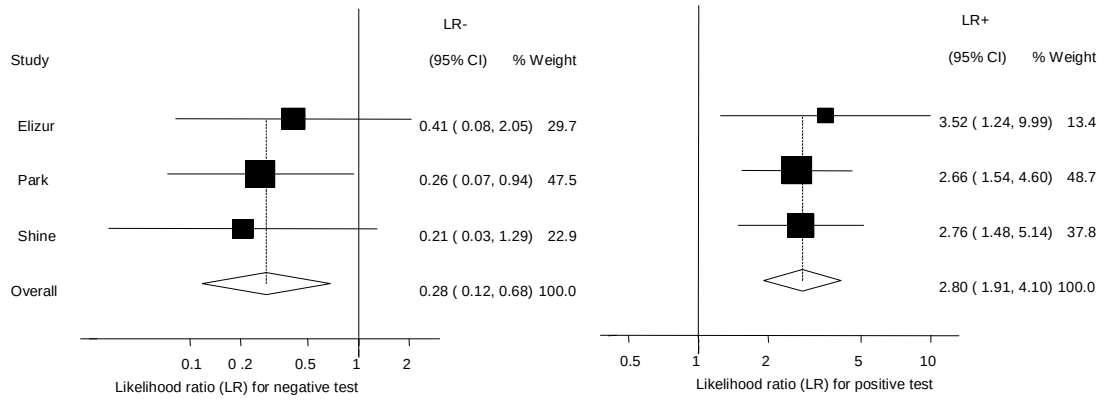
*Studies are arranged in descending order of methodological quality
+χ2 heterogeneity test p = 0.150 for LR+ and p = 0.22 for LR-

Figure 28 Forest plots of likelihood ratios (LR's) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth within 7 days of testing*+



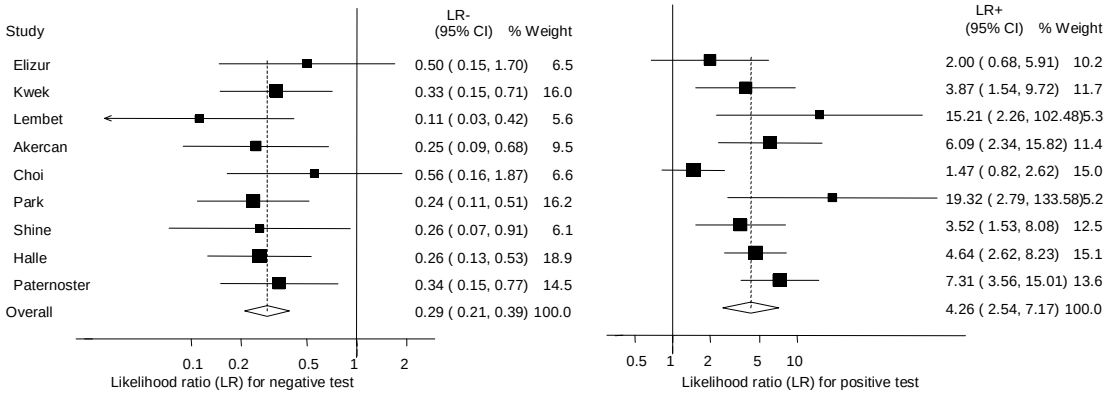
*Studies are arranged in descending order of methodological quality
+χ2 heterogeneity test p = 0.57 for LR+ and p = 0.29 for LR-

Figure 29 Forest plots of likelihood ratios (LR's) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth before 34 weeks' gestation*+



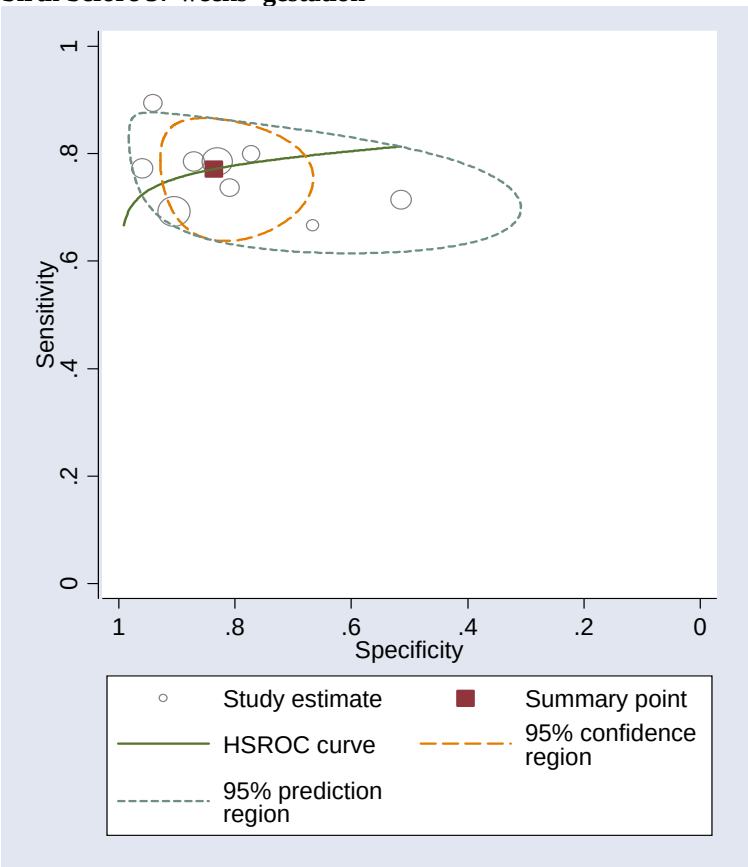
*Studies are arranged in descending order of methodological quality
+χ2 heterogeneity test p = 0.76 for LR+ and p = 0.85 for LR-

Figure 30 Forest plots of likelihood ratios (LR's) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth before 37 weeks' gestation*+



*Studies are arranged in descending order of methodological quality
+χ2 heterogeneity test p = 0.0037 for LR+ and p = 0.79 for LR-

Figure 31 Plot of sensitivity against specificity including summary values of the accuracy of phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 37 weeks' gestation



Serum α-fetoprotein (MSAFP)

A high level of maternal serum α-fetoprotein (MSAFP) in the first half of pregnancy has been associated with prematurity for the past three decades. However its utility as a serum marker for predicting spontaneous preterm birth has never been fully evaluated in a systematic review despite it being commonly used as a screening test for fetal neural tube defect and as an integral part of screening for trisomy 21.

Study characteristics and quality

There were 20 primary accuracy articles that met the selection criteria, all in asymptomatic women. Table 21 summarises each study's salient features.[147-165] One citation contributed to two separate studies and results.[150] The most common testing gestation was in the mid-trimester (14-28 weeks). The threshold at which studies commonly reported their results were 2.0 and 2.5 MoMs. The commonest reference standard was spontaneous preterm birth before 37 weeks' gestation with only 5 studies reporting spontaneous preterm birth before 34 weeks' gestation.[148;151;153;154;162] The methodological quality of the included primary studies is summarised in Figure 32 where it is shown that all the included studies were missing one or more ideal quality features.

Accuracy of maternal serum α-fetoprotein (MSAFP) in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation MSAFP with a most commonly used threshold of 2.5 MoM, had a range of LR+ from 3.03 (95% CI 2.30 – 4.01)[154] to 4.99 (95% CI 3.97 – 6.28)[162] and a range of LR- from 0.14 (95% CI 0.02 – 0.91)[154] to 0.95 (95% CI 0.94 – 0.97).[162] Waller et al represented the higher quality study available.[162]

For predicting spontaneous preterm birth before 37 weeks' gestation MSAFP, two thresholds used more commonly than others i.e. 2.0 MoM and 2.5 MoM. With threshold of 2.0 MoM, it had a range of LR+ from 0.97 (95% CI 0.51 – 1.85)[158] to 4.21 (95% CI 3.47 -5.09)[159] and a range of LR- from 0.45 (95% CI 0.20 – 1.02)[147] to 1.01 (95% CI 0.86 – 1.17).[158] The higher

quality study from Tanaka et al had LR+ 1.63 (95% CI 0.81 – 3.27) and LR- 0.96 (95% CI 0.89 – 1.03).[160] With a threshold of 2.5 MoM, LR+ ranged from 1.50 (95% CI 1.03 – 2.17)[157] to 70.23 (95% CI 21.78 – 226.38) and LR- form 0.34 (95% CI 0.17 – 0.69)[154] to 0.99 (95% CI 0.97 – 1.00).[156] Morssink et al represented the higher quality study available.[156] Figure 33 and Figure 35 summarized the accuracy of both thresholds in predicting spontaneous preterm birth. Individual accuracy results are summarized in Table 22.

Figure 32 Methodological quality of studies included in the systematic review of accuracy of maternal serum α-fetoprotein in predicting spontaneous preterm birth among asymptomatic antenatal women. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

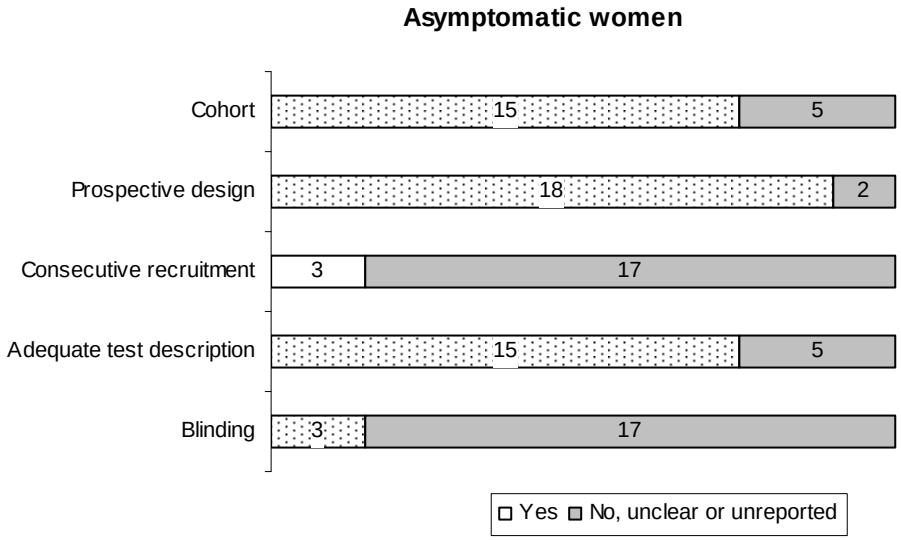
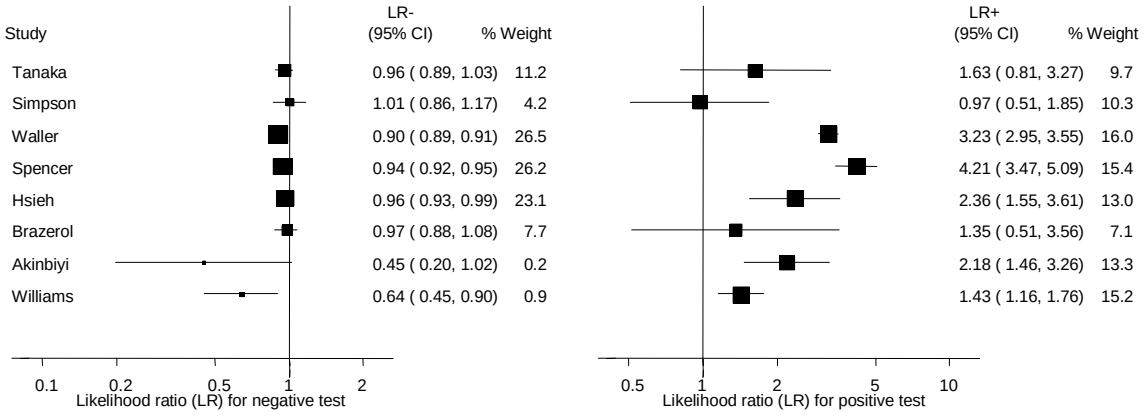


Figure 33 Forest plots of likelihood ratios (LR's) of maternal serum α-fetoprotein (MSAFP) in asymptomatic women (threshold of 2.0 MoM) as a predictor of spontaneous preterm birth before 37 weeks' gestation*



* Studies are arranged in descending order of methodological quality

Figure 34 Plot of sensitivity against specificity including summary values of the accuracy of maternal serum α-fetoprotein (MSAFP) in asymptomatic women (threshold of 2.0 MoM) as a predictor of spontaneous preterm birth before 37 weeks' gestation

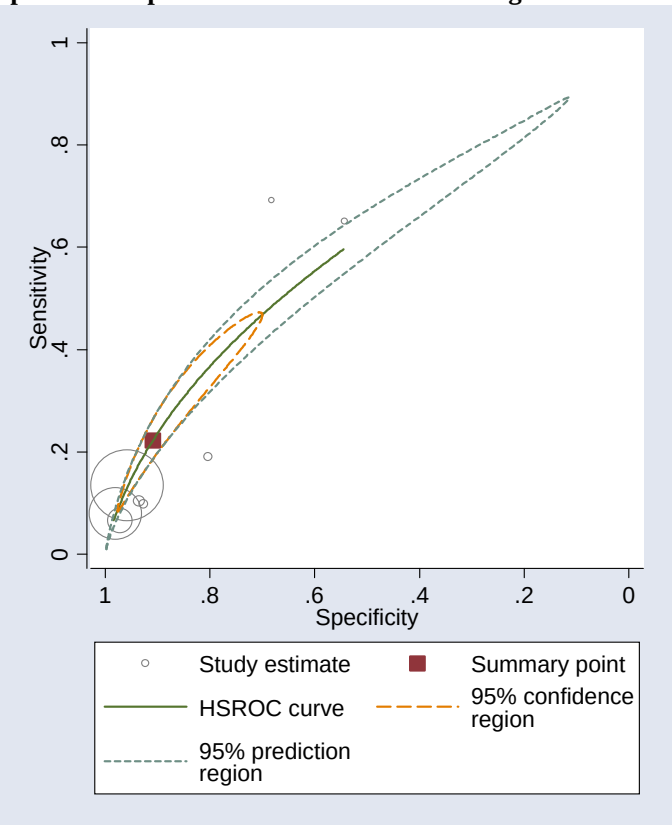
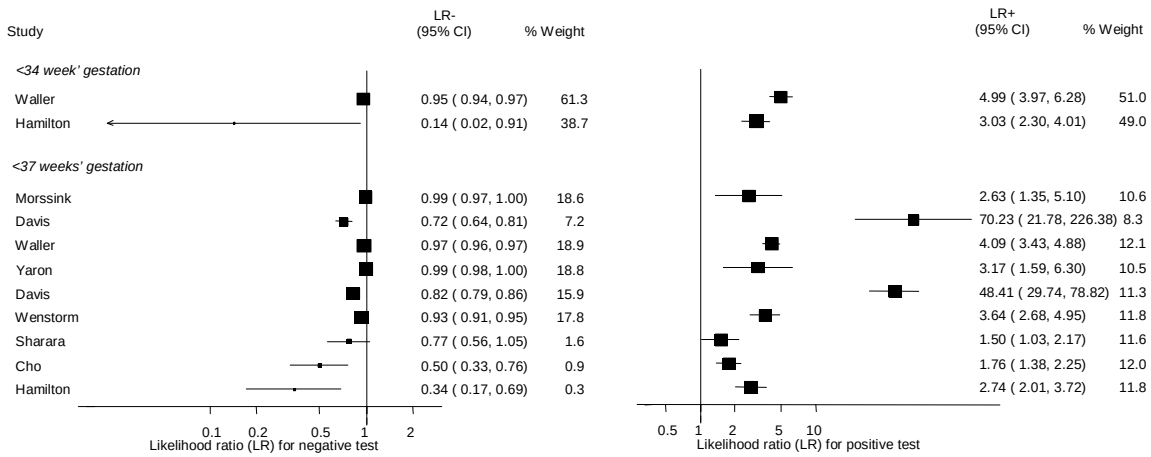
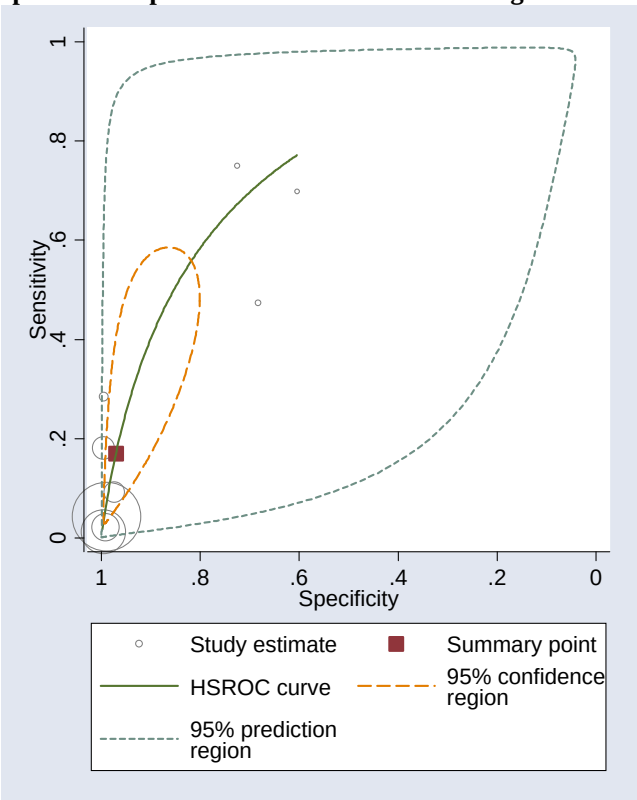


Figure 35 Forest plots of likelihood ratios (LR's) of maternal serum α-fetoprotein (MSAFP) in asymptomatic women (threshold of 2.5 MoM) as a predictor of spontaneous preterm birth before 34 and 37 weeks' gestation*



* Studies are arranged in descending order of methodological quality

Figure 36 Plot of sensitivity against specificity including summary values of the accuracy of maternal serum α-fetoprotein (MSAFP) in asymptomatic women (threshold of 2.5 MoM) as a predictor of spontaneous preterm birth before 37 weeks' gestation



Serum relaxin

Relaxin is a peptide hormone produced by the corpus luteum and known to soften and ripen the human cervix. Hyper-relaxinemia has been associated with prematurity.[166] Therefore it is purported that measurement of maternal serum relaxin may predict the impending preterm labour that leads to spontaneous preterm birth.

Study characteristics and quality

There were five primary studies on the accuracy of maternal serum relaxin measurements; four were on asymptomatic women (n=3549)[153;166-168] while one on symptomatic women with threatened preterm labour (n=34).[169] One study evaluated the test's serial testing accuracy in predicting spontaneous preterm birth in asymptomatic women.[166] Table 23 summarizes each study's salient features.

There were no studies included within the systematic review of the accuracy of maternal serum relaxin testing in predicting spontaneous preterm births that fulfil the ideal definition of high quality test accuracy studies either in asymptomatic or symptomatic women. Blinding was absent in all but one study.[168] However, all studies have adequate test description report. The methodological quality of the included primary studies is summarized in Figure 37.

Accuracy of maternal serum relaxin in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation serum relaxin had an LR+1.60 (95% CI 1.24 - 2.06) and LR- 0.84 (95% CI 0.74 - 0.95).[153] For predicting spontaneous preterm birth before 37 weeks' gestation serum relaxin had an LR+ 1.21 (95% CI 0.73 - 2.10) and LR- 0.74 (95% CI 0.29 - 1.95).[166] These studies represented the largest higher quality studies for the respective outcomes. The accuracy results are summarized in Figure 38. Individual accuracy results are summarized in Table 24.

Accuracy of maternal serum relaxin in symptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, maternal serum relaxin had an LR+ of LR+ 1.48 (95% CI 0.26 - 8.31) and LR- 0.861 (95% CI 0.38 - 1.96) and before 37 weeks' gestation it had LR+ 0.80 (95% CI 0.19 - 3.31) and LR- 1.07 (95% CI 0.72 - 1.57) Figure 38).[169] Individual accuracy results for symptomatic women can be found in Table 24.

Figure 37 Methodological quality of studies included in the systematic review of accuracy of maternal serum relaxin in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

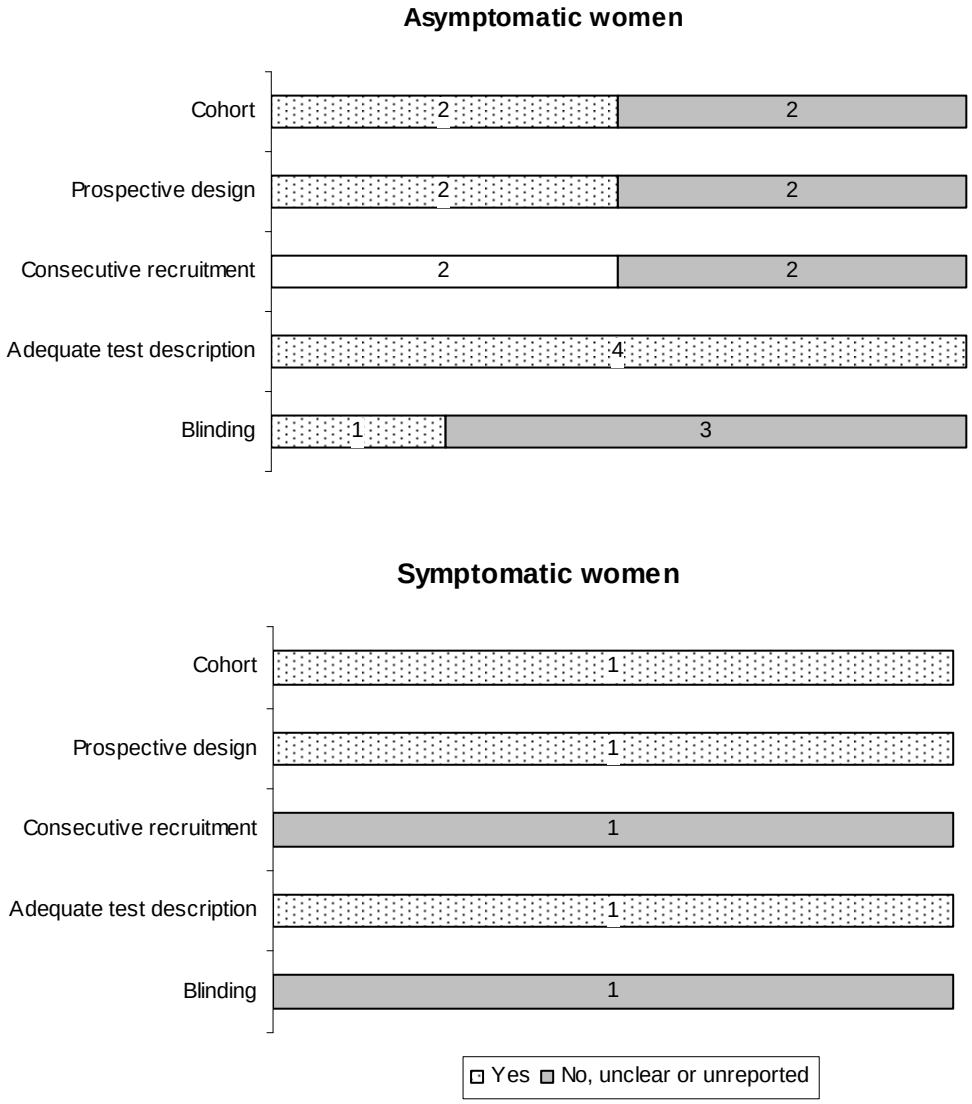
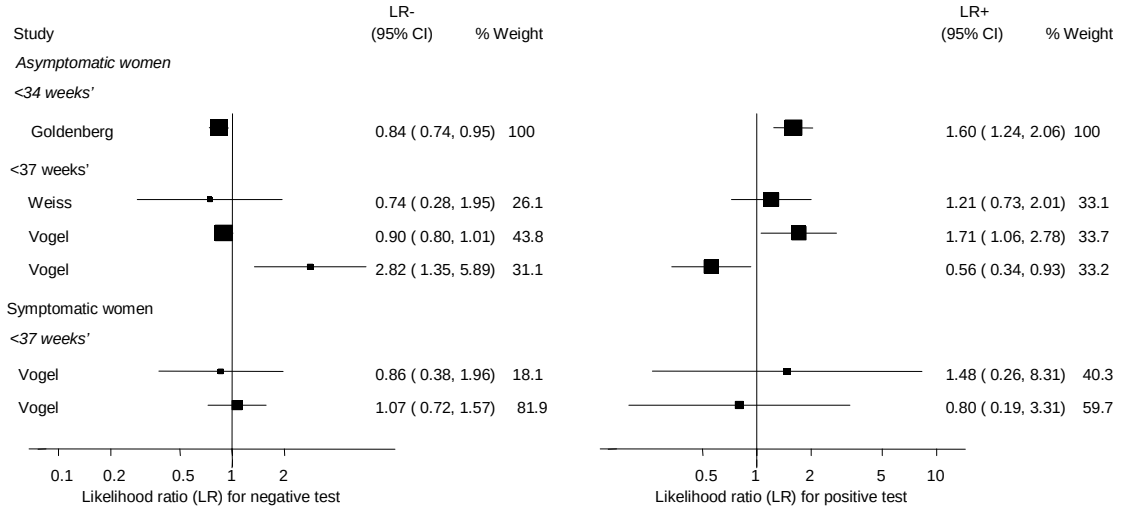


Figure 38 Forest plots of likelihood ratios (LR's) of maternal serum relaxin measurement in predicting spontaneous preterm birth stratified according to population and outcomes*



*Studies are arranged in descending order of methodological quality

Serum corticotrophin releasing hormone (CRH)

Corticotrophin-releasing hormone (CRH) is a peptide produced by the hypothalamus that in pregnancy is also produced by the placenta. Its role in pregnancy has been postulated to as one of the primary endocrine mediators of parturition and possibly also of fetal development. Its rise in the maternal serum has been observed to precede the development of labour and therefore its measurement was purported to predict spontaneous preterm birth.

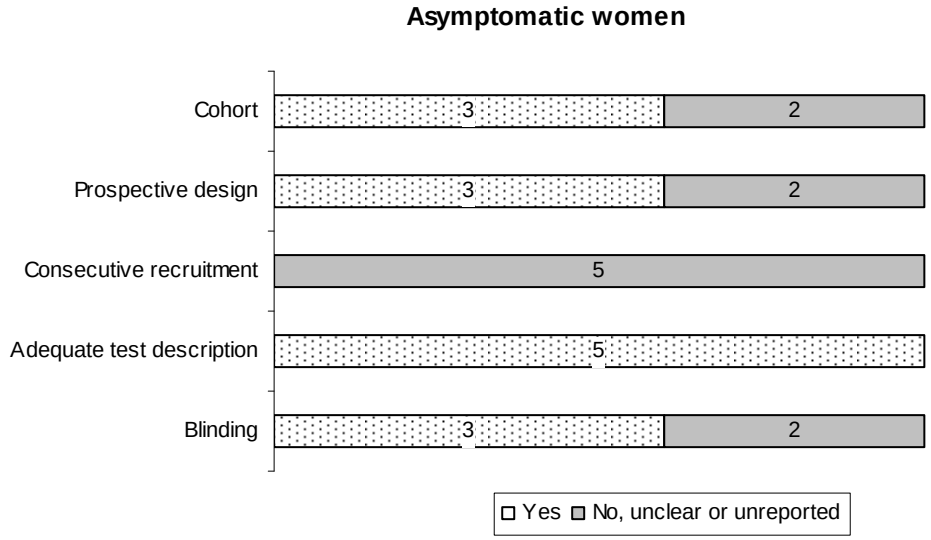
Study characteristics and quality

There were 6 primary studies (n = 5,034 women) on the accuracy of CRH testing, comprising of 5 studies on asymptomatic antenatal women (n = 4,940)[153;170-173] and 1 studies on symptomatic women with presented with threatened preterm labour (n = 94).[174] Table 25 summarizes each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour. One study was not included because it included multiple gestations in its population and iatrogenic preterm birth in its outcome.[175] The studies' enrolment for asymptomatic women ranged from 181 to 2,929 women[153;171] with a median of 396 women.[170]

There were no studies included within the systematic review of the accuracy of CRH testing in predicting spontaneous preterm births that fulfil the ideal definition of high quality test accuracy studies either in asymptomatic or symptomatic women. None of the studies in both population reported using consecutive enrolment of women into the study. However, all studies have adequate test description report. Retrospective and case-control study design was used in two studies in asymptomatic women.[153;171] Blinding of carers to the results of CRH tests were absent from two studies on asymptomatic women.[170;172] The methodological quality of the included primary studies is summarized in Figure 39.

Only two studies used the same threshold of abnormality, one each on asymptomatic and symptomatic women, of greater than 90th percentile value. Four studies, including the lone study on symptomatic women, used CRH as a single test,[171-174] whilst the remaining utilized it as a serial test. For asymptomatic women, one study used spontaneous preterm birth before 32 weeks' gestation, [153] 34 weeks' gestation,[173] two each used 35 weeks' gestation,[153;171] and 37 weeks' gestation as the reference standard.[170;172]

Figure 39 Methodological quality of studies included in the systematic review of accuracy of CRH in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies



Accuracy of CRH in asymptomatic women

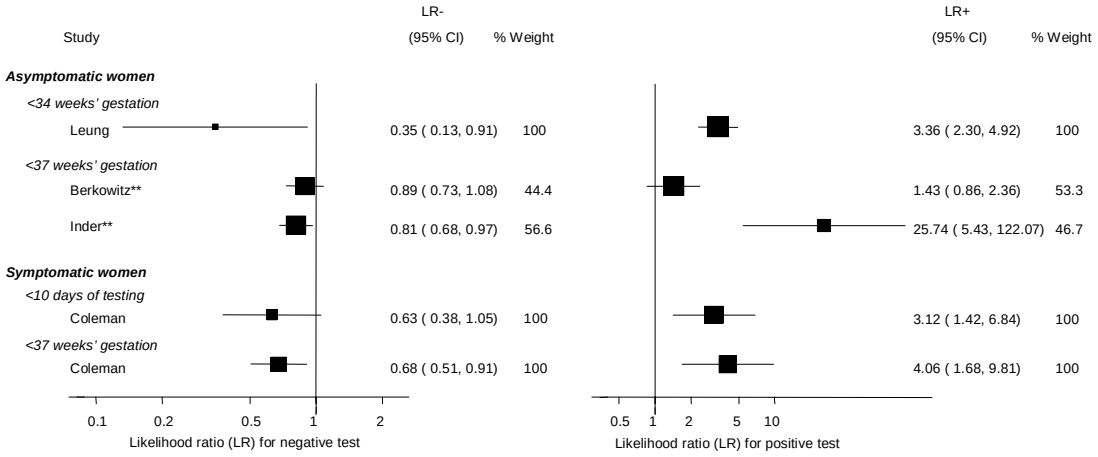
For predicting spontaneous preterm birth before 34 weeks' gestation, a single CRH testing had an LR+ of 3.36 (95% CI 2.30 - 4.92) and LR- of 0.35 (95% CI 0.13 - 0.91).[173] For predicting spontaneous preterm birth before 37 weeks' gestation, CRH had a range of LR+ from 1.43 (95% CI 0.86 - 2.36) to 25.74 95% CI 5.428 - 122.07) and LR- from 0.81 (95% CI 0.68 - 0.97) to 0.89 (95% CI 0.74 - 1.08) (Figure 40).[170;172] The largest higher quality study of

the reference standard was from Berkowitz *et al.*[170] Individual accuracy results can be found in Table 26.

Accuracy of CRH in symptomatic women

For predicting spontaneous preterm birth within 10 days of testing, CRH had an LR+ of 3.12 (95% CI 1.42 - 6.84) and LR- of 0.63 (95% CI 0.38 - 1.05). For predicting spontaneous preterm birth before 37 weeks' gestation, it had an LR+ of and LR- of 0.68 (95% CI 0.51 - 0.91) (Figure 40). Individual accuracy results can be found in Table 26.

Figure 40 Forest plots of likelihood ratios (LR's) of CRH in predicting spontaneous preterm birth within 7-10 days of testing and 37 weeks' gestation in symptomatic women and before 34 and 37 weeks' gestation strain asymptomatic women*



*Studies are arranged in descending order of methodological quality
**Serial testing

β-human chorionic gonadotrophin (β-hcg)

The hormone β-hcg manufactured by the feto-placental unit is known to be present in high concentrations in the amniotic fluid and maternal serum during pregnancy. Disruption of the chorion and the decidua as occurs when onset of labour was imminent has been postulated as the mechanism for testing for the presence of the cervico-vaginal secretions,[133] in addition to its presence in the maternal serum.[155] Measurement of β-hcg can be done either by taking maternal blood serum sample during asymptomatic antenatal period usually as part of 'triple test' to screen for Down syndrome or a cotton-tipped swab of cervico-vaginal secretions specimen obtained from speculum examination.

Study characteristics and quality

There were 23 primary articles, in which 19 evaluated the use of mid-trimester maternal serum hcg as a predictor of spontaneous preterm birth (n = 177,730 women)[151;152;155;156;159;160;165;176-187] while an article evaluated it in early first trimester (n = 169),[188] and three articles evaluated cervico-vaginal hcg as a predictor of spontaneous preterm birth in women who presented with symptoms of threatened preterm labour (n = 248).[133;189;190] Table 27 summarises each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and symptomatic women with threatened preterm labour.

None of the studies fulfilled ideal quality study design. There were nine case-control studies in asymptomatic[159;176;177;180-184;186] and one in symptomatic women.[133] Four studies in asymptomatic women reported consecutive enrolments,[151;160;185;187] while none was reported in symptomatic women. There were thirteen retrospective studies in asymptomatic women[152;155;159;165;176;177;180-184;186;188] while all the studies in symptomatic women were prospective. None of the studies on asymptomatic women reported blinding and only one

study in symptomatic women reported it.[190] The methodological quality of the included primary studies is summarized in Figure 41.

Most of the study in asymptomatic women reported their thresholds in terms of multiples of median (MoM), except for three studies,[179;185;188] which used percentiles. The commonest threshold used was 2.0 MoM, above of which abnormal was defined. The three studies that evaluated cervico-vaginal hcg had used 25 – 27 mIU/ml to define their thresholds for an abnormal result. Except for three studies in asymptomatic women, which used birth before 32 weeks'[151;179] and 34 weeks' gestation,[185] the remainder used birth before 37 weeks' gestation as their reference standard. One study reported birth within 7 days of testing in symptomatic women,[189] while the remainders reported before 37 weeks' gestation as their reference standard. There was graphical (Figure 42) and statistical evidence of heterogeneity in the accuracy results ($\chi 2$ heterogeneity test p = 0.00017 for LR+ and $\chi 2$ heterogeneity test p = 0.00011 for LR-) for studies using the commonest clinical characteristics (asymptomatic women, mid-trimester testing gestation, threshold of 2.0 MoM and birth before 37 weeks' gestation as the reference standard).

Accuracy of β-hcg in asymptomatic women

Maternal mid-trimester serum β-hcg, which used threshold of 2.0 MoM showed variable accuracy in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic women. The likelihood ratio for positive tests (LR+) ranged from 0.92 (95% confidence interval (CI) 0.77 - 1.11)[187] to 3.76 (95% CI 2.56 - 5.52)[184] and for negative tests, LR- ranged from 0.50 (95% CI 0.28 - 0.88)[182] to 1.30 (95% CI 0.79 - 2.12)[187] (Figure 42). The largest better quality study reported LR+ 2.77 (95% CI 2.07 - 3.69) and LR- 0.984 (95% CI 0.98 - 0.99) when first percentile was used as threshold to define abnormality.[179] Figure 44 showed plot of sensitivities and specificities and their summary estimates for the accuracy of β-hcg in asymptomatic woman in predicting spontaneous preterm birth. Figure 45 funnel plot analysis

showed asymmetry indicating presence of publication or related biases. The individual accuracy results for asymptomatic women are summarized in Table 28.

Accuracy of β-hcg in symptomatic women

In a study that reported birth within 7 days of testing, the LR+ was 6.07 (95% confidence interval (CI) 3.07 - 11.99) and LR- was 0.04 (95% CI 0.01 - 0.16).[189] Summary LR+ for birth before 37 weeks' gestation was 2.11(95% CI 1.61 - 2.77) ($\chi 2$ heterogeneity test p = 0.42) and summary LR- was 0.45 (95% CI 0.31 - 0.66) ($\chi 2$ heterogeneity test p = 0.57) (Figure 43). The largest higher quality study has LR+ 2.19 (95% CI 1.35 - 3.57) and LR- 0.51 (95% CI 0.30 - 0.85).[190] The individual accuracy results for symptomatic women are summarized in Table 28.

Figure 41 Methodological quality of studies included in the systematic review of accuracy of human chorionic gonadotrophin in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

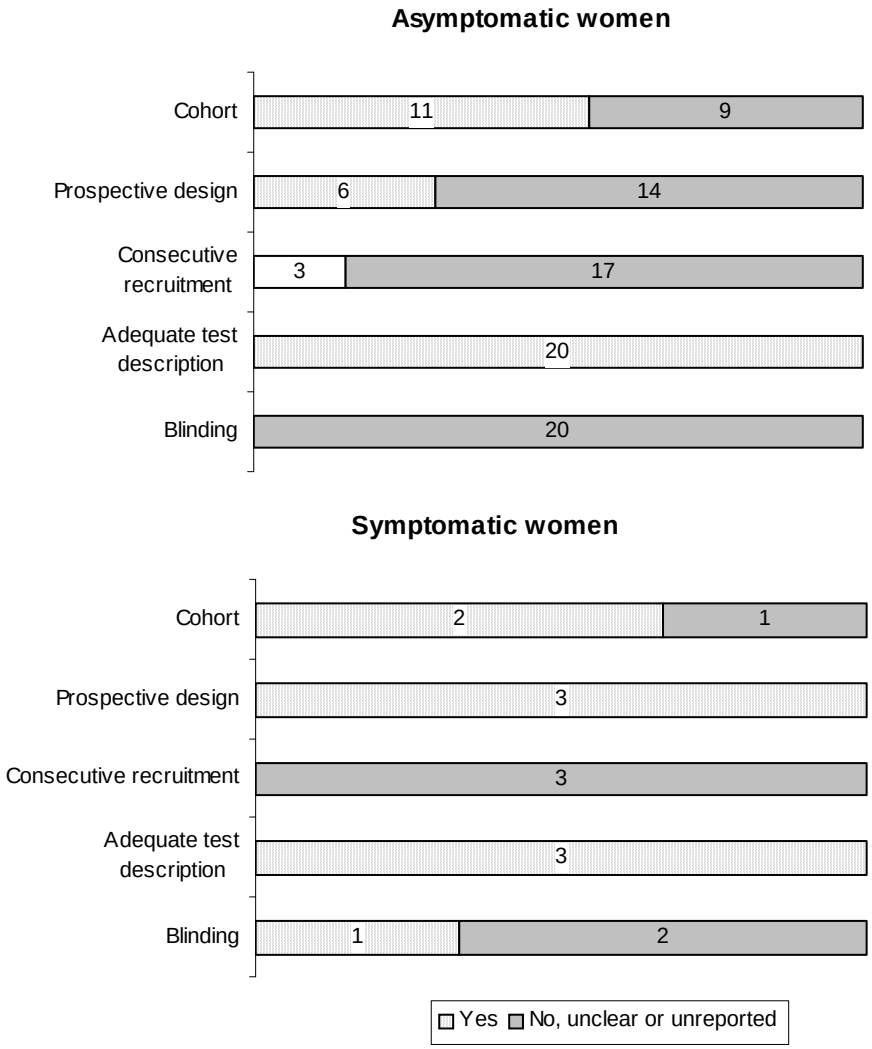
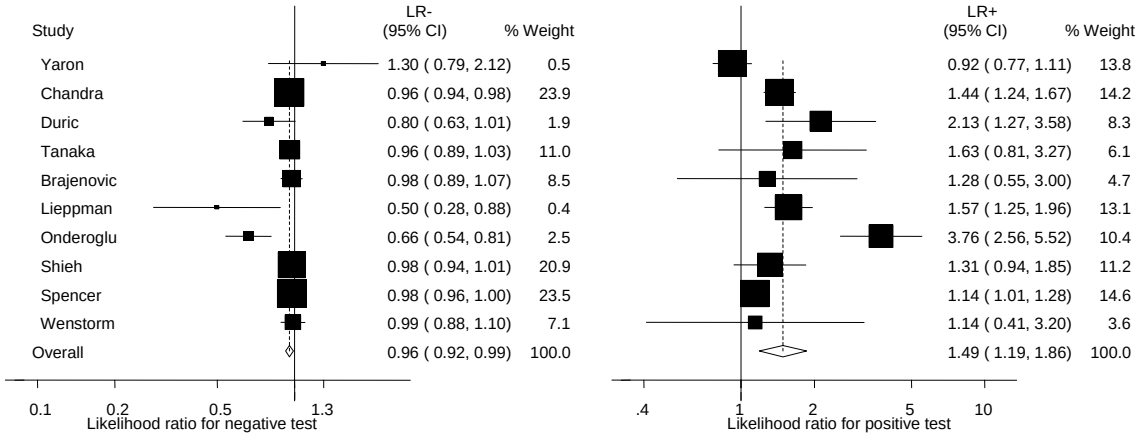
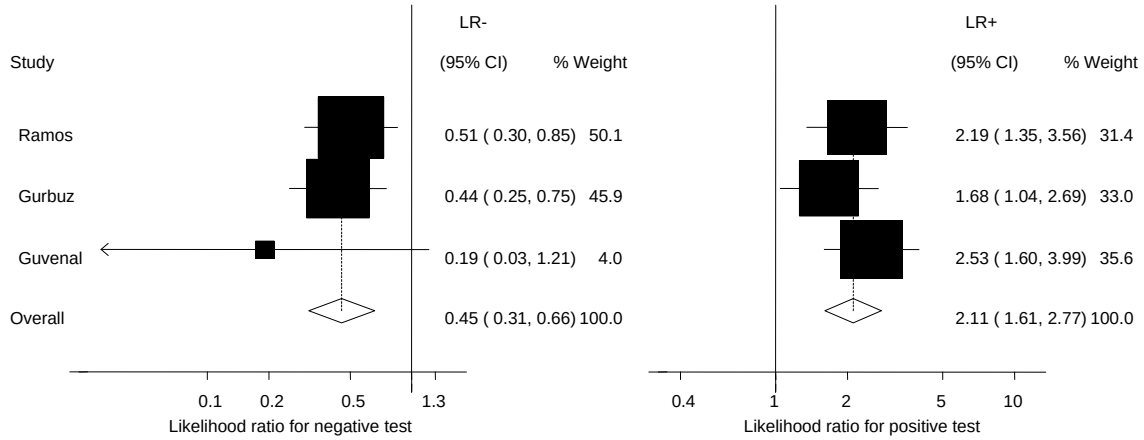


Figure 42 Forest plots of likelihood ratios (LR's) of serum β-human chorionic gonadotrophin (β-hcg) testing in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation*+



χ2 heterogeneity test p = 0.0022 for LR+ and χ2 heterogeneity test p = 0.0049 for LR-

Figure 43 Forest plots of likelihood ratios (LR's) of cervico-vaginal β-human chorionic gonadotrophin (β-hcg) testing in symptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation*+



χ2 heterogeneity test p = 0.42 for LR+ and χ2 heterogeneity test p = 0.57 for LR-

Figure 44 Plot of sensitivity against specificity including summary values of serum β-human chorionic gonadotrophin (β-hcg) testing in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation

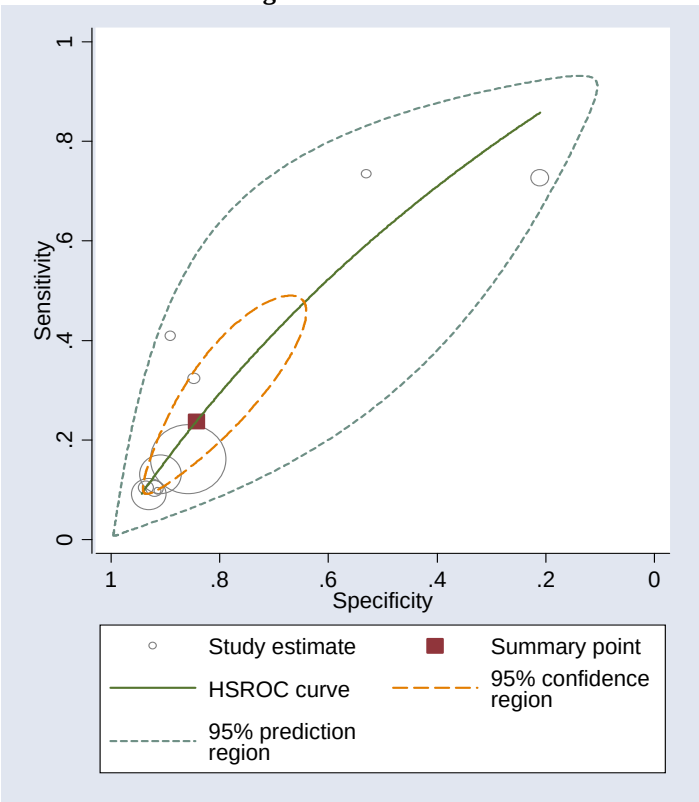
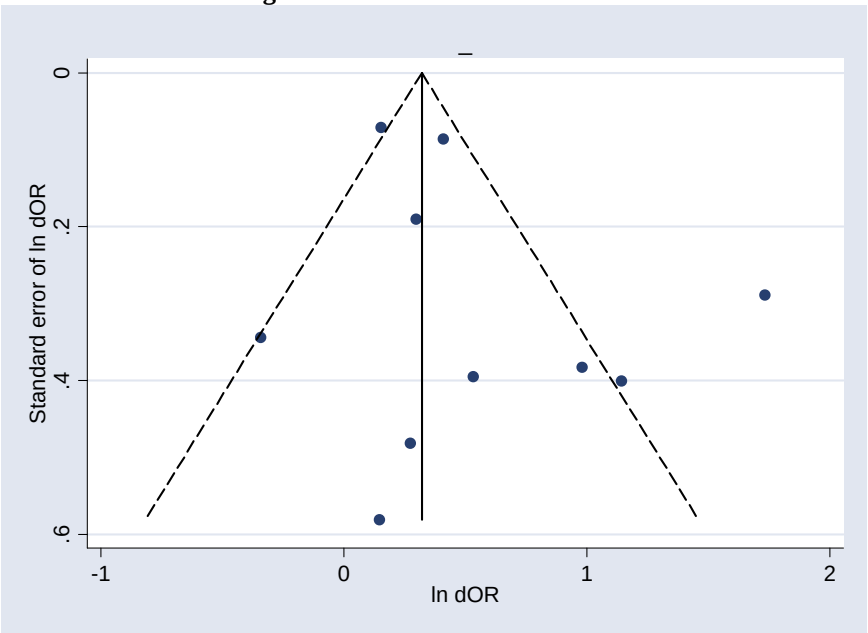


Figure 45 Funnel plot analysis of accuracy studies evaluating the accuracy of serum β-human chorionic gonadotrophin (β-hcg) testing in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation



Estriol

Estriol is produced by both mother and fetus in pregnancy. There is a surge in the maternal levels of estriol, which occurs several weeks prior to the onset of spontaneous labour. Measurement of either salivary and serum estriol was thus purported to be a predictor of spontaneous preterm birth.[191]

Study characteristics and quality

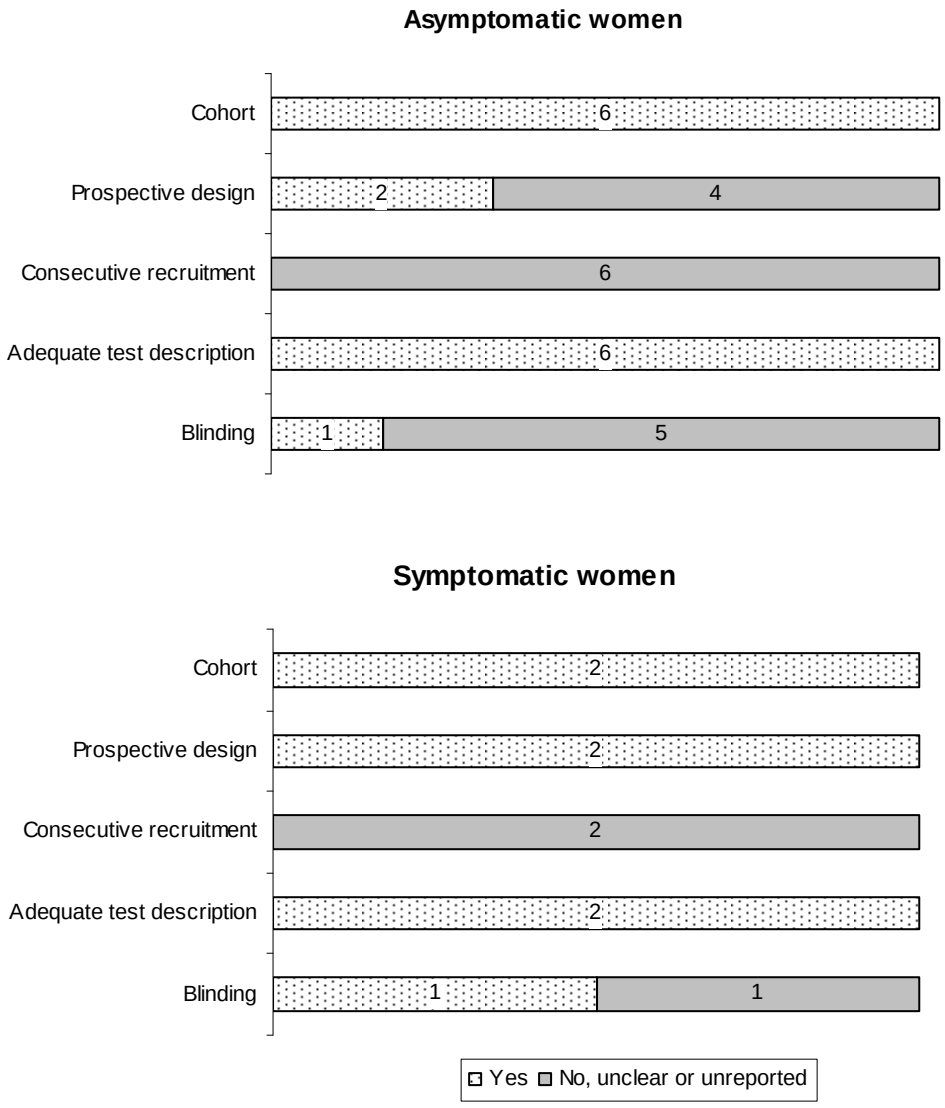
There were 7 primary studies (n = 60,722 women) on the accuracy of estriol testing as predictor of spontaneous preterm birth, comprising of 6 studies on asymptomatic antenatal women (n = 60,417)[151;152;165;192-194] and 2 studies on symptomatic women with presented with threatened preterm labour (n = 305).[191;192] Table 29 summarizes each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour. The studies' enrolment for asymptomatic women ranged from 399 to 33,145 women[151;194] with a median of 601 women,[192] while that of symptomatic women ranged from 115 to 190 women.[191;192] Two studies evaluated salivary estriol[191;192] while the remaining evaluated maternal serum estriol.[151;152;165;193;194] One study contributed to both asymptomatic and symptomatic population.[192]

There were no studies included within the systematic review of the accuracy of estriol testing in predicting spontaneous preterm births that fulfil the ideal definition of high quality test accuracy studies either in asymptomatic or symptomatic women. None of the studies in both population reported using consecutive enrolment of women into the study. However, all studies have adequate test description report. Retrospective data collection was used in three studies in asymptomatic women.[152;165;194] Blinding of carers to the results of estriol tests were absent from five studies on asymptomatic women[151;152;165;193;194] and one study on

symptomatic women.[191] The methodological quality of the included primary studies is summarized in Figure 46.

Three studies used the same threshold of abnormality of 0.75 MoM in asymptomatic women[152;193;194] while the two studies in symptomatic women used 2.1 ng/ml as their thresholds.[191;192] Two studies in asymptomatic women used 0.5 MoM as their thresholds[151;165] and one study in symptomatic women explored the accuracy of 1.4 ng/ml threshold cut-off in predicting spontaneous preterm birth.[192] One study in asymptomatic women evaluated the accuracy of repeat test in predicting spontaneous preterm birth.[192] For asymptomatic women, one study used spontaneous preterm birth before 32 weeks' gestation,[151] whilst the remaining reported 37 weeks' gestation as the reference standard. In symptomatic women, one study reported birth within 14 days of testing while another reported 37 weeks' gestation.

Figure 46 Methodological quality of studies included in the systematic review of accuracy of estriol in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies



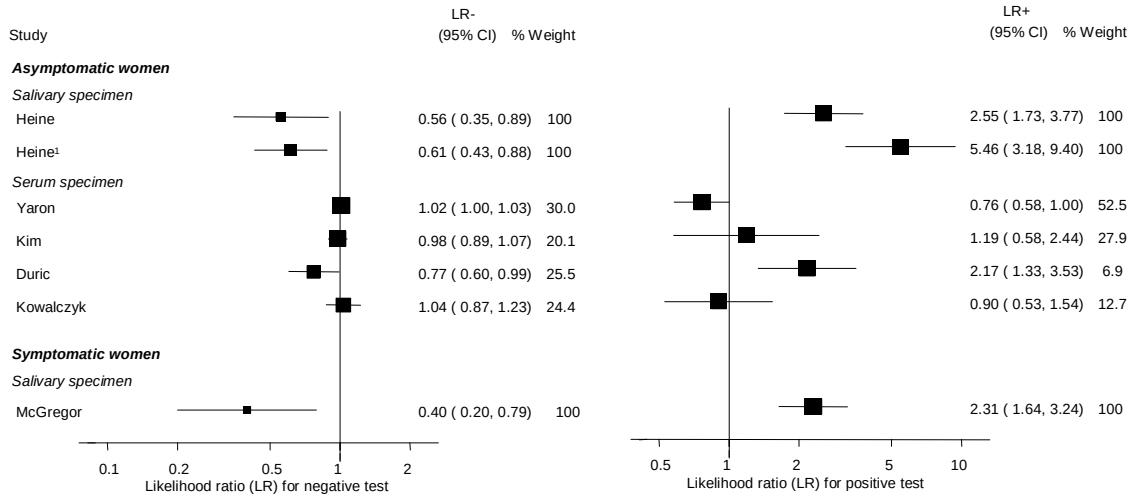
Accuracy of estriol in asymptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, a single salivary estriol testing had an LR+ 2.55 (95% CI 1.73 - 3.77) and LR- of 0.56 (95% CI 0.35 - 0.89) while a repeat test, where one positive result indicated positivity had an LR+ of 5.46 (95% CI 3.18 - 9.40) and LR- of 0.61 (95% CI 0.43 - 0.88) (Figure 47).[192] For predicting spontaneous preterm birth before 37 weeks' gestation, serum estriol test had a range of LR+ from 0.76 (95% CI 0.58 - 1.00) to 2.17 (95% CI 1.33 - 3.53) and LR- from 0.77 (95% CI 0.60 - 0.99) to 1.02 (95% CI 1.00 - 1.04) (Figure 47).[152;165] Estimates from Yaron *et al*[165] and Kim *et al*[193] represented the largest higher quality studies of the reference standard, with commonly used thresholds of 0.75 MoM and 0.5 MoM respectively. There was no study which reported spontaneous preterm birth before 34 weeks' gestation. Individual accuracy results can be found in Table 30.

Accuracy of estriol in symptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, salivary estriol had an LR+ of 2.31 (95% CI 1.64 - 3.24) and LR- of 0.40 (95% CI 0.20 - 0.79) (Figure 47).[191] There is no study evaluating serum estriol in predicting spontaneous preterm birth in symptomatic women. Individual accuracy results can be found in Table 30.

Figure 47 Forest plots of likelihood ratios (LR's) of salivary and serum estriol in predicting spontaneous preterm birth before 37 weeks' gestation for asymptomatic and symptomatic women*



*Studies are arranged in descending order of methodological quality
1. Repeat testing within 7 days of the first test

C-reactive protein (CRP)

C-reactive protein (CRP) is an acute phase reactant associated with presence of systemic infections and may be, if raised, an indicator of risk for spontaneous preterm birth. It is an easily detectable and reliably measured serological marker obtained from a sample of maternal serum from venepuncture or amniotic fluid from amniocentesis. It is produced by the hepatocytes in response to the circulating inflammatory cytokines released by the presence of infections.[195]

Study characteristics and quality

There were 13 primary articles, involving altogether, a total of 2,142 women.[195-207] summarises each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour and route of testing i.e. either amniotic sample from an amniocentesis or blood serum from venepuncture. Two studies reported on CRP measurement in amniotic fluid among asymptomatic women obtained at mid-trimester gestation,[200;205] whilst remaining studies used maternal blood plasma serum level of CRP obtained either at mid-trimester gestation for asymptomatic women or at presentation for women whom presented with symptoms of threatened preterm labour. The study population ranged from 34 – 506 women, with a median of 69 women. Table 31 summarized the individual study characteristics.

Only one study reported prospective data collection design[205] and only seven of the thirteen included studies reported consecutive enrolment.[195;196;199;201;204;205;207] Most of the studies had provided adequate test description but blinding was evident in only four studies.[195;196;200;201] The methodological quality of the included primary studies is summarised in Figure 48. There was no uniform test threshold used, which ranged from 1 ng/ml to 110 ng/ml, in the included studies. The most commonly used reference standard for asymptomatic women was birth before 37 weeks' gestation, with one study reporting birth before 34 weeks' gestation,[200]

while for symptomatic women with threatened preterm labour, they were birth within 7 days of testing,[196;198;201;207] 34 weeks' and 37 weeks' gestation.

Accuracy of CRP in asymptomatic women

In one study of amniotic fluid CRP level obtained at mid-trimester for predicting preterm birth before 34 weeks' gestation, the LR+ was 2.63 (95% Confidence interval (CI) 1.85 - 3.75) and LR- was 0.29 (95% CI 0.08 - 0.99).[200] In another study, for predicting spontaneous preterm birth before 37 weeks' gestation, the LR+ was 4.37 (95% CI 3.03 – 6.29) and LR- was 0.09 (95% CI 0.01 to 0.60).[205] In three studies of maternal plasma CRP level measurement on asymptomatic women at mid-trimester for predicting preterm birth before 37 weeks' gestation the range of LR+ was 1.55 (95% CI 1.22 – 2.13) to 2.06 (95% CI 1.29 to 3.29) and that of LR- was 0.77 (95% CI 0.65 – 0.91) to 0.86 (95% CI 076 – 0.98).[202;203;206] Summary LR+ for the accuracy of maternal serum level of CRP measurement in predicting spontaneous preterm birth before 37 weeks' gestation was 1.73 (95% CI 1.38 - 2.16) (heterogeneity test $\chi 2 = 1.06$, $p = 0.59$) and LR- was 0.83 (95% CI 0.76 - 0.91) ($\chi 2 = 1.20$, $p = 0.55$) (Figure 49). The accuracy of CRP test in predicting spontaneous preterm births in asymptomatic women is summarized in Table 32 and Table 33.

Accuracy of CRP in symptomatic women

In four studies of maternal plasma CRP level measurement on women with threatened preterm labour for predicting preterm birth within 7 days of testing, the range of LR+ was 1.35 (95% CI 0.71 – 2.55) to 34.36 (95% CI 4.86 – 243.09) and that of LR- was 0.17 (95% CI 0.05 – 0.62) to 0.89 (95% CI 0.69 – 1.15).[196;198;201;207] Summary LR+ for the accuracy of maternal serum level CRP measurement in predicting spontaneous preterm birth within 7 days of testing in symptomatic women with threatened preterm labour was 4.538 (95% CI 1.48 - 13.91) ($\chi 2$ heterogeneity test $p = 0.0017$) and summary LR- was 0.296 (95% CI 0.08 - 1.15) ($\chi 2$ heterogeneity test $p = 0.00021$) (Figure 50). A study on maternal measurement plasma

CRP level in women symptomatic with threatened preterm labour used 34 weeks' gestation had an LR+ of 6.75 (95% CI 1.34 – 34.00) and an LR- of 0.66 (0.38 – 1.14).[199] In four studies of maternal plasma CRP level measurement on women with threatened preterm labour for predicting preterm birth before 37 weeks' gestation, the range of LR+ was 1.67 (95% CI 0.76 – 3.66) to 4.20 (95% CI 1.10 – 15.98) and that of LR- was 0.47 (95% CI 0.25 – 0.87) to 0.76 (95% CI 0.48 – 1.21).[195-197;204] Summary LR+ for spontaneous preterm birth before 37 weeks' gestation was 2.29 (95% CI 1.57 - 3.35) ($\chi 2$ heterogeneity test p=0.66) and summary LR- was 0.60 (95% CI 0.46 - 0.79) ($\chi 2 = 2.23$, p=0.53) (Figure 51). Cammu's[196] result represented the largest higher quality study. Figure 52 showed plot of sensitivities and specificities and their summary estimates for serum CRP in symptomatic women predicting spontaneous preterm birth within 7days of testing. The accuracy of CRP test in predicting spontaneous preterm births in symptomatic women who presented with threatened preterm labour is summarized in Table 32 and Table 33.

Figure 48 Methodological quality of studies of C-reactive protein in predicting spontaneous preterm birth included in the systematic review. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

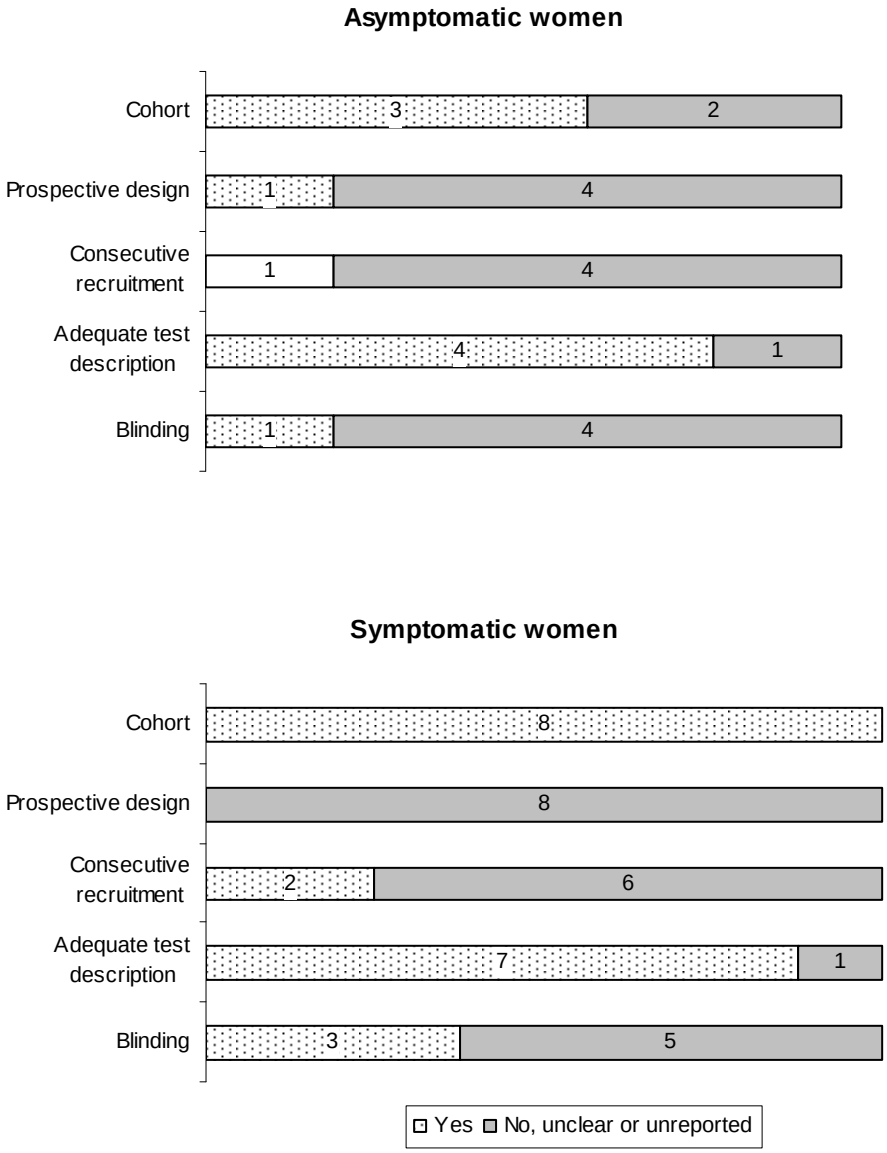
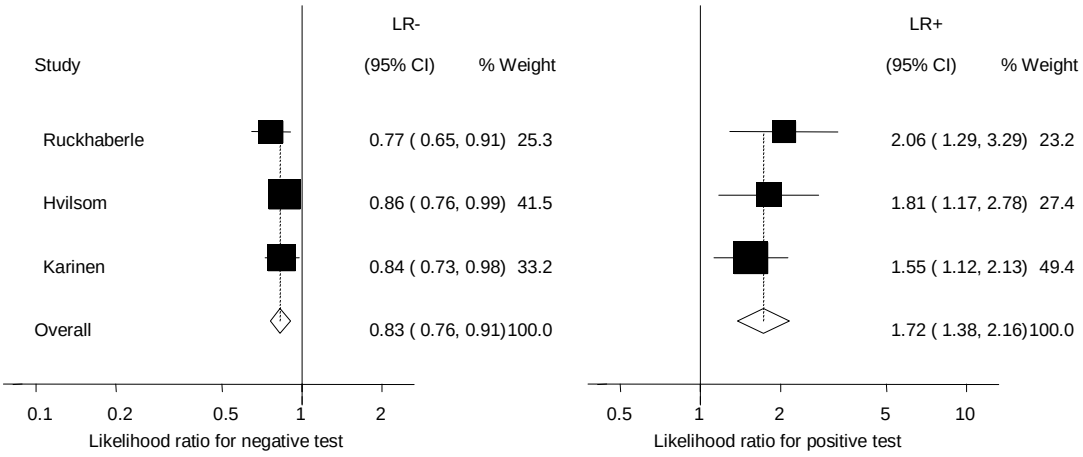
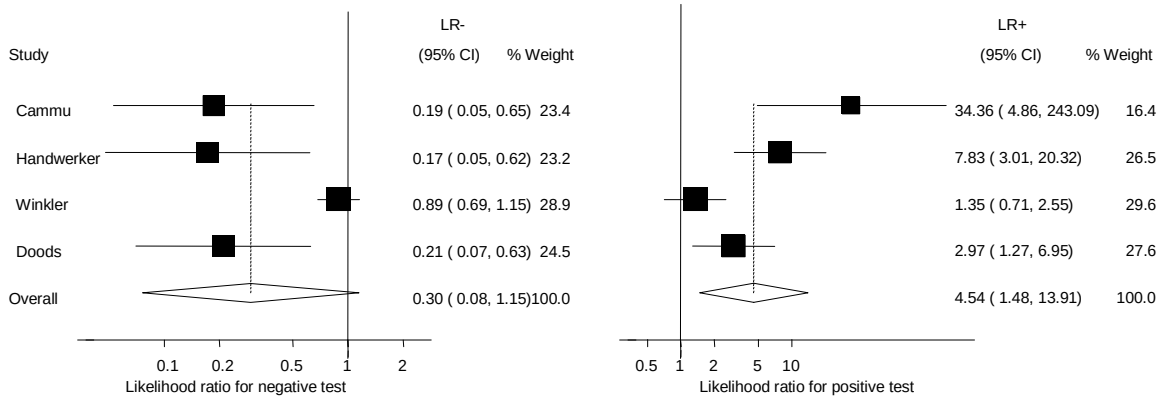


Figure 49 Forest plots of likelihood ratios (LR's) of the accuracy of mid-trimester maternal serum CRP level measurement in asymptomatic women for predicting spontaneous preterm birth before 37 weeks' gestation*+



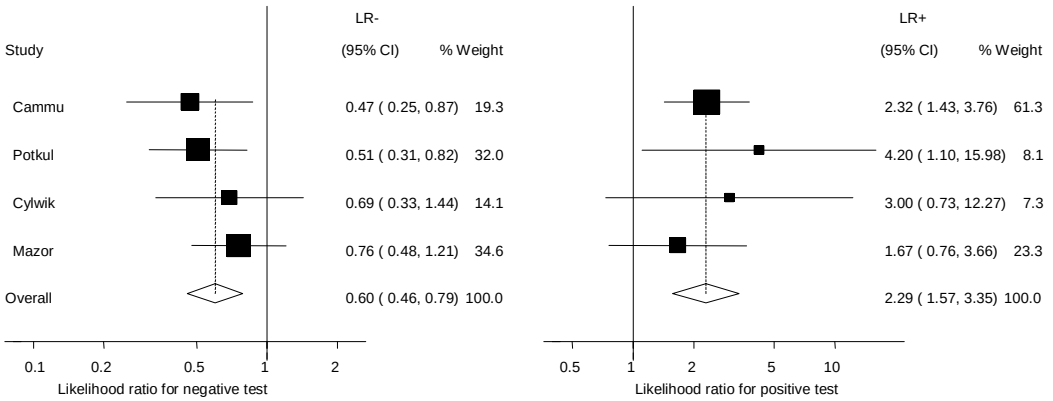
*χ2 heterogeneity test p = 0.59 for LR+ and p = 0.55 for LR-
+Studies are arranged in descending order of methodological quality

Figure 50 Forest plots of likelihood ratios (LR's) of the accuracy of maternal serum CRP level measurement in symptomatic women with threatened labour for predicting spontaneous preterm birth within 7 days of testing*+



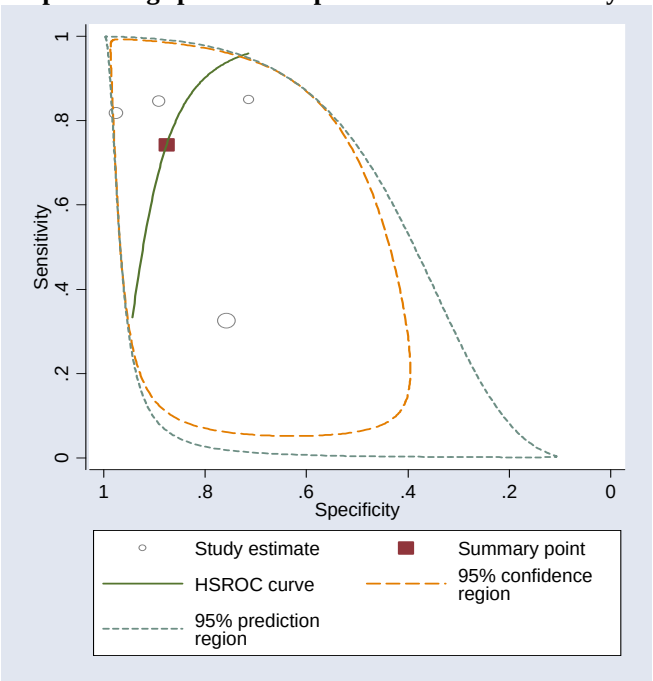
*χ2 heterogeneity test p = 0.0017 for LR+ and p = 0.00021 for LR-
+Studies are arranged in descending order of methodological quality

Figure 51 Forest plots of likelihood ratios (LR's) for maternal serum CRP level measurement in symptomatic women with threatened labour for predicting spontaneous preterm birth before 37 weeks' gestation*+



*$\chi 2$ heterogeneity test p = 0.66 for LR+ and p = 0.53 for LR-
+Studies are arranged in descending order of methodological quality

Figure 52 Plot of sensitivity against specificity including summary values of the maternal serum measurement of C-reactive protein (CRP) studies in symptomatic women with threatened preterm labour for predicting spontaneous preterm birth within 7 days of testing



Interleukin-6 (IL6)

Interleukin 6 (IL6) is a protein compound produced in response to presence of inflammation usually in response to presence of an infection. It can be found in amniotic fluid, cervical secretion and in maternal blood serum. Their presence or increasing values have been purported to predict spontaneous preterm birth in symptomatic women who presented with threatened preterm labour.[208]

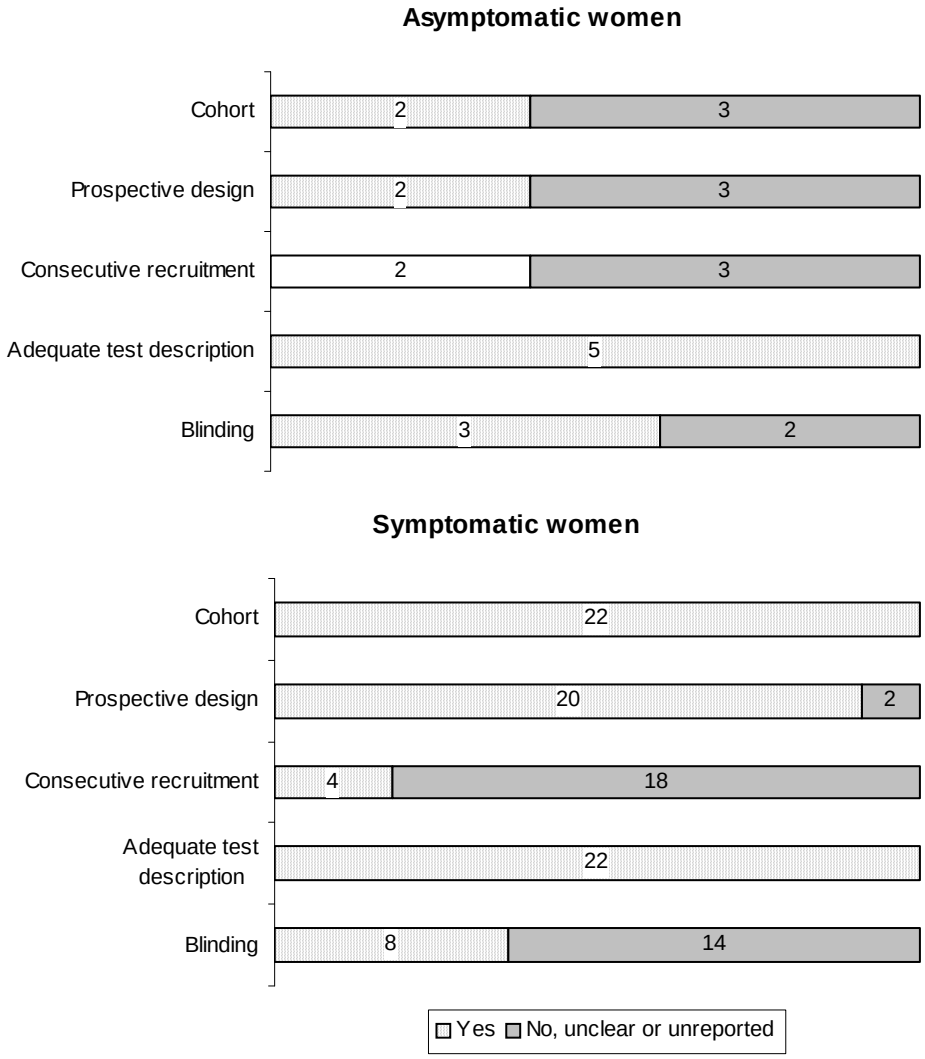
Study characteristics and quality

There were 26 primary studies (n = 2,594 women) on the accuracy of IL6 testing in predicting spontaneous preterm birth. However one study,[209] which evaluated cervical IL6 as predictor of spontaneous preterm birth in women who presented with symptoms of threatened preterm labour were excluded as the author was not able to provide the data within the time constraint of the thesis. The number of women enrolled ranged from 73[96] to 290[210] with a median of 161 in asymptomatic women [211] and from 18[114] to 146[208] with a median of 73 in symptomatic women.[96] There were 12 studies evaluating amniotic level of IL6, two in asymptomatic women[210;212] and ten in symptomatic women[114;208;213-220] as a predictor for spontaneous preterm birth. There were 10 studies evaluating cervical IL6, three in asymptomatic women[96;211;221] and seven in symptomatic women[83;96;222-226] as predictor of spontaneous preterm birth in women. One study evaluated serial testing of cervical IL6 in asymptomatic women.[211] There were six studies, all in symptomatic women who presented with threatened preterm labour, which evaluated serum IL6 as a predictor for spontaneous preterm birth.[225;227-231] Two studies provided information to more than one categories of either population[96] or type of IL6 specimen.[225] Table 34 summarized individual study characteristics.

Three studies fulfilled the ideal definition of high quality test accuracy studies.[96;211;217] All studies in both asymptomatic and symptomatic women provided adequate test description. However, out of 20 studies on symptomatic women, most were lacking in reporting of

consecutive enrolment with only three studies reported consecutive enrolment[96;217;223] and blinding of test results, where only eight studies reported it.[83;96;114;214;215;217;228;229] The methodological quality of the included primary studies is summarized in Figure 53. No two studies had reported using the same threshold. Three studies on asymptomatic women reported birth before 37 weeks' gestation as their reference standard[96;210;211] and one each for birth before 34 weeks'[212] and 35 weeks' gestation.[221] For symptomatic women, one study reported spontaneous preterm birth within 24 hours,[231] five studies within 48 hours[114;213;215;228;230] and four studies reported birth within 5 - 7 days of testing,[216;226;229;232] while the remainder reported birth before 35-37 weeks' gestation.[83;96;208;214;217-220;223;225]

Figure 53 Methodological quality of studies included in the systematic review of accuracy of interleukin-6 (IL6) in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.



Accuracy of IL6 in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, a single amniotic fluid IL6 measurement had a range of LR+ of 2.65 (95% CI 1.37 - 5.14) [210] to 2.95 (95% CI 0.96 - 9.04)[212] (χ2 heterogeneity test p = 0.87) and LR- of 0.84 (95% CI 0.62 - 1.13)[212] to 0.91 (95% CI 0.84 - 0.98)[210] (χ2 heterogeneity test p = 0.57) (Figure 54). For predicting spontaneous preterm birth before 37 weeks' gestation, a single amniotic fluid IL6 measurement had an LR+ of 1.91 (95% CI 0.99 - 3.67) and LR- of 0.95 (95% CI 0.90 - 1.00) (Figure 54),[210] the latter represented the largest higher quality study available for amniotic fluid IL6 in asymptomatic women for predicting spontaneous preterm birth before 34 and 37 weeks' gestation.[210] Serial testing of cervical IL6 in asymptomatic women had an LR+ of 3.34 (95% CI 1.96 - 5.70) and LR- of 0.59 (0.42 - 0.83) for predicting spontaneous preterm birth before 37 weeks' gestation.[211] Single testing of cervical IL6 in asymptomatic women had a range of LR+ from 0.564 (95% CI 0.08 - 3.97) [96] to 2.08 (95% CI 1.10 - 3.96)[221] and a range of LR- from 0.88 (95% CI 0.80 - 0.98)[221] to 1.08 (95% CI 0.87 - 1.35)[96] for predicting spontaneous preterm birth before 37 weeks' gestation (χ2 heterogeneity test p = 0.14 for LR+ and p = 0.003 for LR-) where the two studies represented the largest higher quality study available for cervical IL6 in asymptomatic women for preterm birth before 37 weeks' gestation for single and serial testings.[96;211]. Figure 54 summarized the accuracy results for amniotic fluid IL6 in predicting spontaneous preterm birth in asymptomatic women. There is no information on birth before 34 weeks' gestation using cervical IL6 testing. Individual accuracy results can be found in Table 35.

Accuracy of IL6 in symptomatic women

For predicting spontaneous preterm birth within 7 – 10 days of testing, cervical IL6 had a range of LR+ from 2.40 (95% CI 1.37 - 4.23)[224] to 4.01 (95% CI 2.02 - 7.96)[226] and a range of LR- from 0.12 (95% CI 0.01 - 1.72)[224] to 0.66 (95% CI 0.51 - 0.85),[226] where the latter

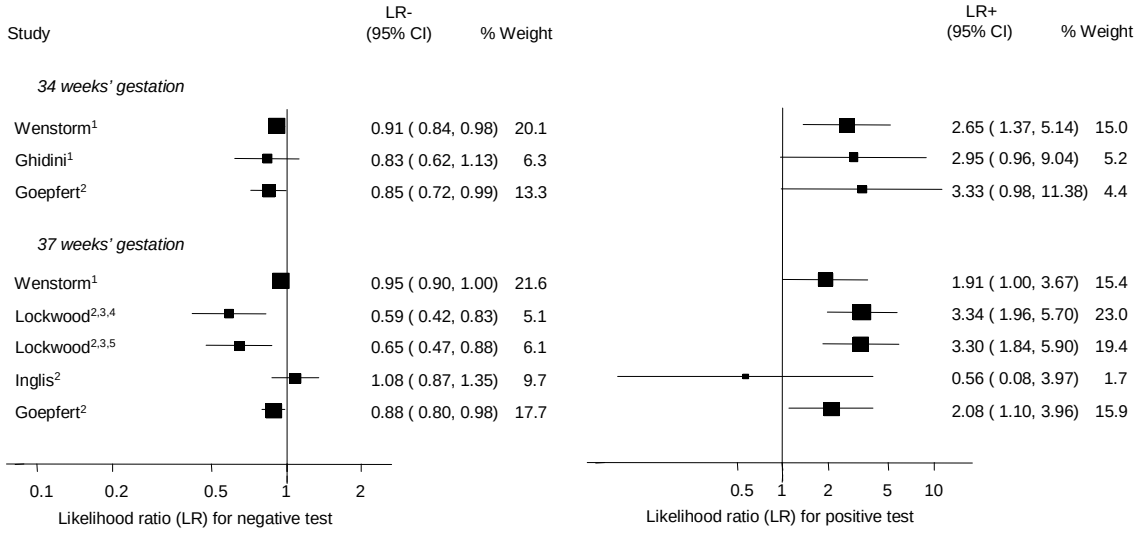
represented the largest higher quality cervical IL6 study available in symptomatic women for predicting spontaneous preterm birth within 7-10 days of testing.[226] Amniotic fluid measurement of IL6 had a range of LR+ from 2.43 (95% CI 1.36 - 4.36)[216] to 7.01 (95% CI 2.75 - 17.90)[215] and a range of LR- from 0.17 (95% CI 0.06 - 0.49)[215] to 0.24 (0.09 - 0.61)[216] LR estimates from Greci et al,[215] the largest higher quality study for this reference standard. Serum measurement of IL6 had an LR+ of 3.34 (95% CI 1.48 - 7.53) and LR- of 0.44 (95% CI 0.30 - 0.66).[230] The accuracy results for the different types of IL6 sources are shown in Figure 55.

For predicting spontaneous preterm birth before 34 weeks' gestation (Figure 56), amniotic fluid IL6 had an LR+ of 7.44 (95% CI 2.01 - 27.52) and LR- of 0.14 (95% CI 0.06 - 0.36).[216] For predicting spontaneous preterm birth before 34 weeks' gestation, cervical IL6 had a range of LR+ from 2.63 (95% CI 1.44 - 4.79)[224] to 4.92 (95% CI 1.80 - 13.46) and LR- from 0.097 (95% CI 0.01 - 1.45)[224] to 0.74 (95% CI 0.63 - 0.87);[226] the latter represented the largest higher quality study of cervical IL6 in this reference standard. Serum IL6 had an LR+ of 1.44 (95% CI 0.86 - 2.41) and LR- of 0.59 (95% CI 0.22 - 1.58) for predicting spontaneous preterm birth before 34 weeks' gestation.[228]

For predicting spontaneous preterm birth before 37 weeks' gestation, amniotic fluid IL6 had a range of LR+ from 4.92 (95% CI 1.26 - 19.29)[219] to 28.62 (95% CI 1.78 - 461.04)[217] and LR- from 0.05 (95% CI 0.003 - 0.76)[220] to 0.66 (95% CI 0.54 - 0.80),[217] the latter represented the largest higher quality study for this reference standard. For the same reference standard, cervical IL6 had a range of LR+ from 1.83 (95% CI 0.79 - 4.25)[96] to 14.0 (95% CI 2.03 - 96.62)[225] and LR- from 0.10 (95% CI 0.01 - 1.45)[224] to 1.29 (95% CI 0.75 - 2.20) (Figure 56).[83] Estimates from Inglis *et al*[96] represented the sole ideal quality study within this sub-group of reference standard of spontaneous preterm birth before 37 weeks' gestation. Serum IL6 had an LR+ of 1.13 (95% CI 0.55 - 2.32) and LR- of 0.92 (95% CI 0.54 - 1.56).[225] Figure

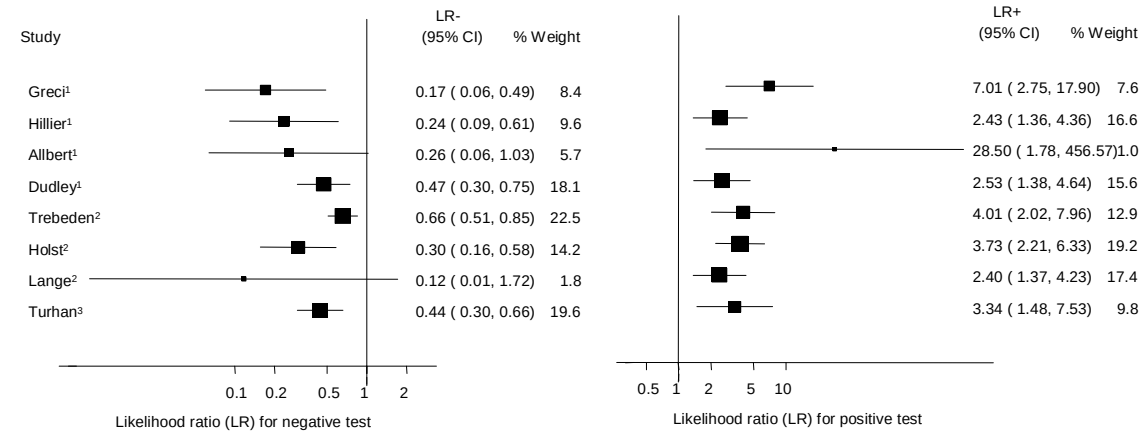
57 showed plot of sensitivities and specificities and their summary estimates for the accuracy of amniotic and cervical fluid in symptomatic women in predicting spontaneous preterm births within 7 days of testing.The accuracy of IL6 in predicting spontaneous preterm birth in asymptomatic and symptomatic women was summarized in Table 35.

Figure 54 Forest plots of likelihood ratios (LR's) of amniotic fluid interleukin-6 (IL6) measurement as a predictor of spontaneous preterm birth before 34 and 37 weeks' gestation in asymptomatic women*+



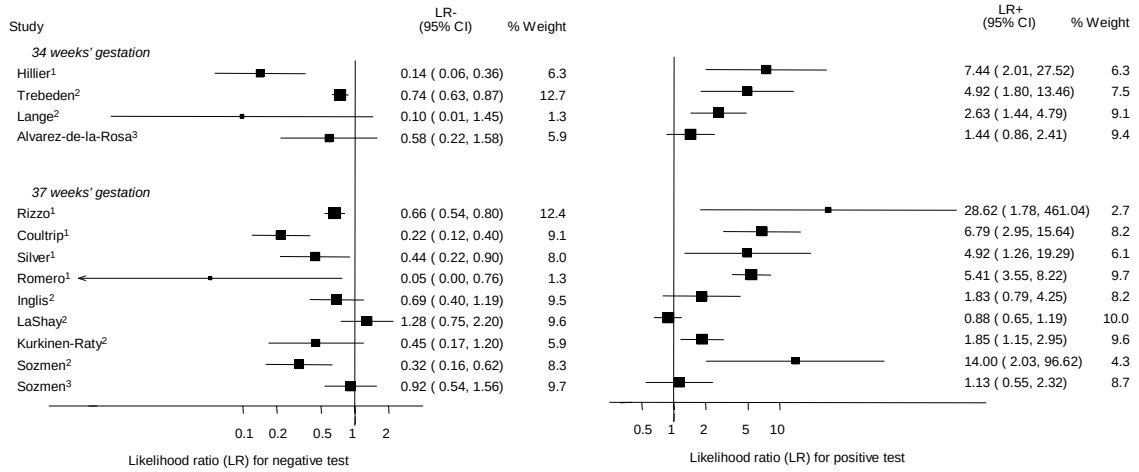
*Studies are arranged in descending order of methodological quality for each type of test
+For individual thresholds see Table x
1. Amniotic fluid measurement of IL6, 2. Cervico-vaginal measurements of IL6, 3. Serial measurement (repeated after 3-4 weeks interval), 4. Threshold 250 pg/ml, 5. Threshold 125 pg/ml

Figure 55 Forest plots of likelihood ratios (LR's) of IL6 measurement from amniotic fluid and cervical specimen as a predictor of spontaneous preterm birth within 7 - 10 days of testing in symptomatic women*



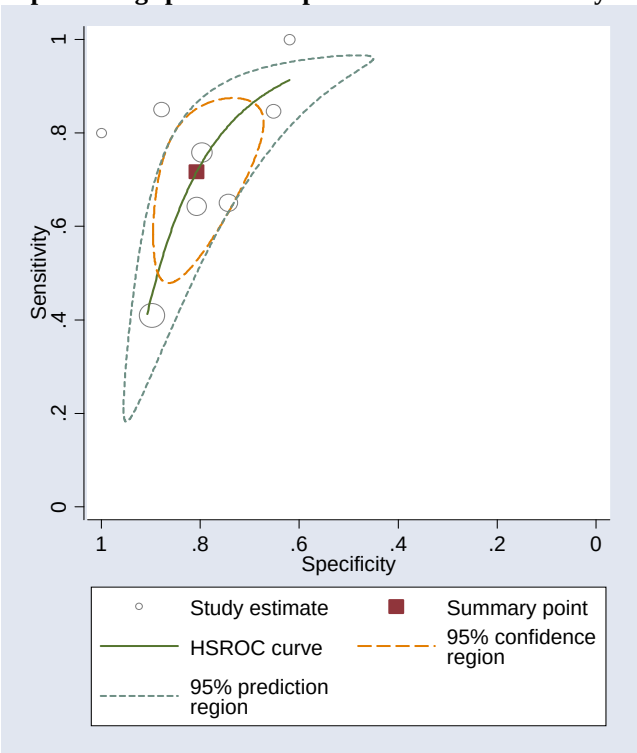
*Studies are arranged in descending order of methodological quality for each type of test
1. Amniotic fluid measurement of IL6, 2. Cervico-vaginal measurements of IL6, 3. Serum measurement of IL6

Figure 56 Forest plots of likelihood ratios (LR's) of IL6 measurement from amniotic fluid, cervical swab and serum specimen as a predictor of spontaneous preterm birth before 34 and 37 weeks' gestation*



*Studies are arranged in descending order of methodological quality for each type of test
1. Amniotic fluid measurement of IL6, 2. Cervico-vaginal measurements of IL6, 3. Serum measurement of IL6

Figure 57 Plot of sensitivity against specificity including summary values of the accuracy of amniotic fluid and cervico-vaginal interleukin – 6 (IL6) studies in symptomatic women with threatened preterm labour in predicting spontaneous preterm birth within 7 days of testing



Interleukin-8 (IL8)

Similar to IL6, interleukin-8 (IL8) is a protein compound produced in response to presence of inflammation usually in response to presence of an infection. It can be found in amniotic fluid, cervical secretion and in maternal blood serum. Their presence in cervico-vaginal secretion[209] or increasing values in maternal serum[213] have been purported to predict spontaneous preterm birth in symptomatic women who presented with threatened preterm labour.

Study characteristics and quality

There were 5 primary studies, involving altogether, a total of 568 women. Three potentially eligible studies for inclusion were excluded because their data were unobtainable.[209;231;233] Table 36 summarizes each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women (2 studies)[234;235] and women with symptoms of threatened preterm labour (3 studies).[213;222;223] One of the included studies on asymptomatic antenatal population had the test performed 2 weekly between 24 to 28 weeks' gestation.[235] Except for one study,[213] the remaining studies evaluated IL8 in cervico-vaginal specimen.

None of the studies fulfilled the ideal definition of high quality test accuracy studies. Blinding and consecutive enrolment were absent from four studies – none of the studies on symptomatic women reported blinding[213;222;223] and only one study, in symptomatic women, reported consecutive enrolment.[223] All studies in both asymptomatic and symptomatic women provided adequate test description. The methodological quality of the included primary studies is summarized in Figure 58. No two studies had reported using the same threshold, which varied widely. The two studies on asymptomatic women reported birth before 37 weeks' gestation as their reference standard but one of them[235] additionally reported birth before 32 and 34 weeks' gestation and had performed their performed their test serially with a

two-weekly interval. For symptomatic women, one study reported spontaneous preterm birth within 24 hours,[231] five studies within 48 hours[114;213;215;228;230] and four studies reported birth within 5 - 7 days of testing,[216;226;229;232] while the remainder reported birth before 35-37 weeks' gestation.[83;96;208;214;217-220;223;225] There were insufficient number of studies for statistical heterogeneity analysis to be conducted in the case of IL8.

Accuracy of IL8 in asymptomatic women

In the single study that evaluated the test for predicting spontaneous preterm birth before 34 weeks' gestation on asymptomatic women but which serial testing of cervical IL8 was used, LR+ was 2.23 (95% CI 1.46 - 3.41) and LR- 0.69 (0.50 - 0.97).[235] For predicting spontaneous preterm birth before 37 weeks' gestation, the LR+ ranged from 1.38 (95% CI 1.04 - 1.81)[235] to LR+ 2.75 (95% CI 1.68 - 4.52)[234] while LR- from 0.68 (95% CI 0.49 - 0.95)[234] to 0.91 (95% CI 0.82 - 1.01),[235] where the latter represented the largest higher quality study available for the population. Figure 59 showed the forest plots of the accuracy of the IL8 test in predicting spontaneous preterm birth. Individual accuracy measures of the test are summarized in Table 37.

Accuracy of IL8 in symptomatic women

For predicting spontaneous preterm birth within 48 hours of testing, LR+ was 36.00 (95% CI 2.30 - 564.54) and LR- 0.10 (95% CI 0.007 - 1.42).[213] The accuracy for predicting spontaneous preterm birth within 7 days of testing was shown in Figure 59, where the LR+ ranged from 2.34 (95% CI 1.42 - 3.84) (cervical IL8)[232] to 28.5 (95% CI 1.78 - 456.57) (amniotic fluid IL8)[213] and LR- ranged from 0.26 (95% CI 0.06 - 1.03) (amniotic fluid IL8)[213] to 0.52 (95% CI 0.32 - 0.84) (cervical IL8).[232] LR+ from Holst *et al*[232] represented the largest higher quality study. For predicting spontaneous preterm birth before 37 weeks gestation, LR+ was 1.4 (95% CI 0.83 - 2.35) and LR- 0.67 (95% CI 0.30 - 1.50).[223] Figure 59 showed

the forest plots of the accuracy of the IL8 test in predicting spontaneous preterm birth. Individual accuracy measures of the test are summarized in Table 37.

Figure 58 Methodological quality of studies included in the systematic review of accuracy of test for interleukin-8 (IL8) in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

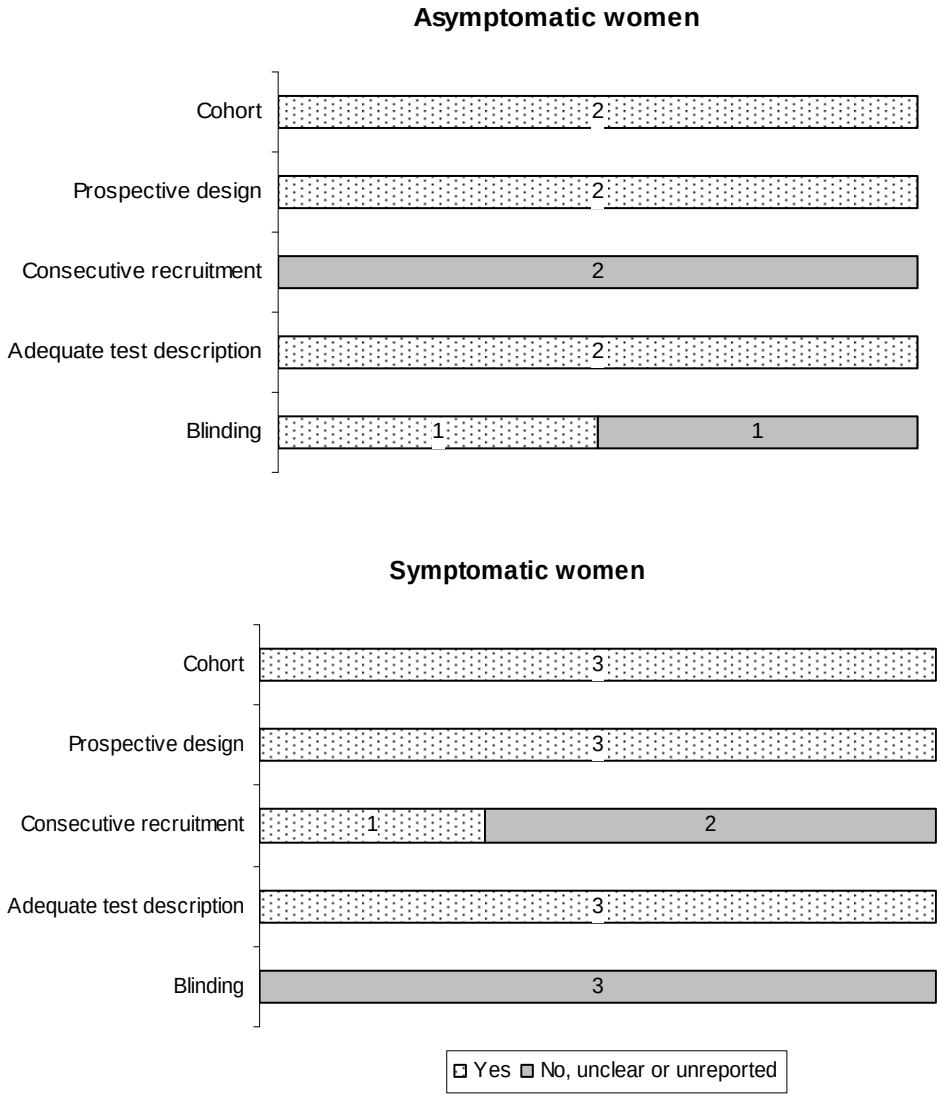
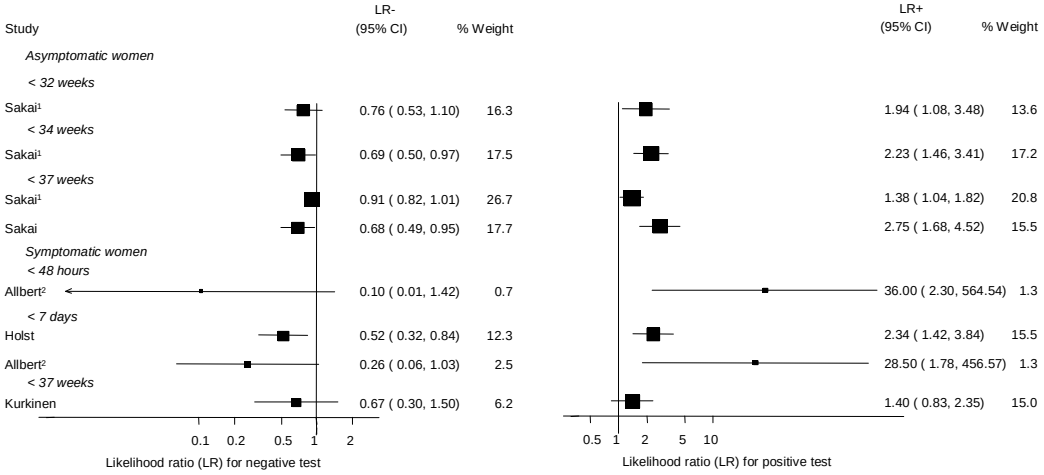


Figure 59 Forest plots of likelihood ratios (LR's) of interleukin-8 (IL8) measurement from amniotic fluid and cervical specimen as a predictor of spontaneous preterm birth stratified according to population and outcome*



*Studies are arranged in descending order of methodological quality and unless otherwise stated, were single testing, using samples obtained from cervico-vaginal swabs
1. Serial testing. 2. Amniotic fluid specimen.

Matrix metalloproteases-9 (MMP-9)

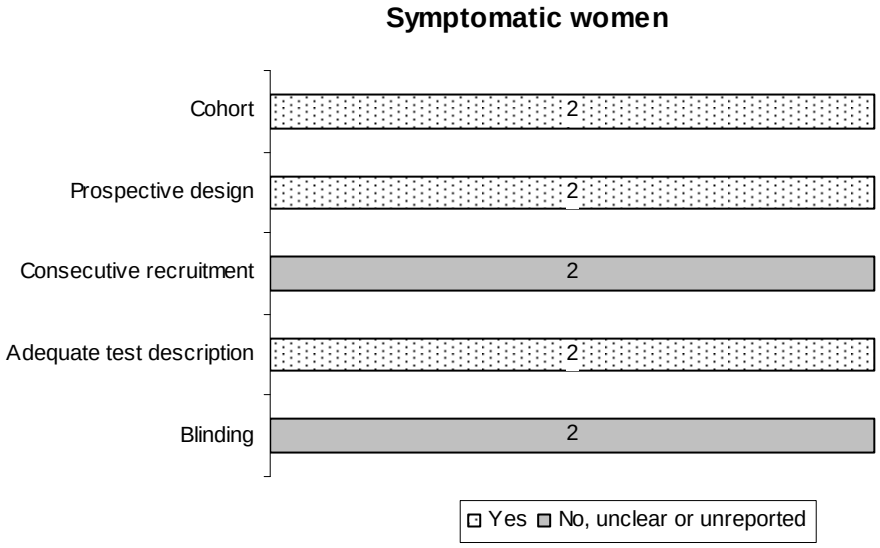
During pregnancy, MMP-9 is produced by the decidua, chorion and amnion. Its expression is increased in the choriodecidual membranes during active labour. It is purported that during the process of labour, which involved the disruption of decidua-membrane interface, measurement of MMP-9 may served as marker for impending preterm labour that lead to spontaneous preterm birth.[236]

Study characteristics and quality

There were 2 primary studies (n = 35) on the accuracy of MMP-9 testing, both were on symptomatic women with threatened preterm labour. One study evaluated MMP-9 in maternal plasma (n = 15)[236] while the other (n = 20) evaluated it in maternal plasma and urine specimens.[237] There were no study on asymptomatic women. Table 38 summarizes each study's salient features.

There were no studies included within the systematic review of the accuracy of MMP-9 testing in predicting spontaneous preterm births that fulfil the ideal definition of high quality test accuracy studies either in asymptomatic or symptomatic women. None of the studies in both population reported using consecutive enrolment of women into the study or blinding of test results to carers or assessors. However, all studies have adequate test description report. The methodological quality of the included primary studies is summarized in Figure 60.

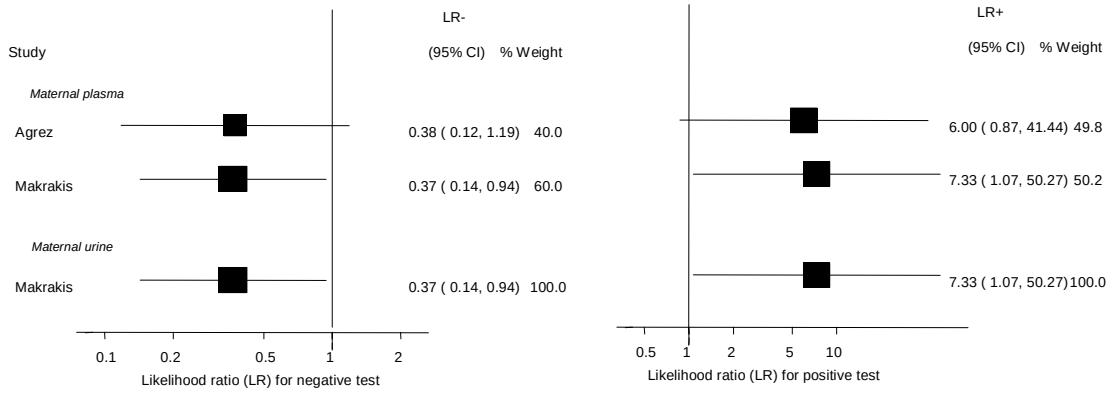
Figure 60 Methodological quality of studies included in the systematic review of accuracy of matrix metalloproteases-9 (MMP-9) in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.



Accuracy of MMP-9 in symptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, maternal plasma MMP-9 had an LR+ of 7.33 (95% CI 1.07 - 50.27)[236] and an LR- of 0.37 (95% CI 0.14 - 0.94)[237] while maternal urinary MMP-9 had a range of LR+ from 6.00 (95% CI 0.87 - 41.44) to 7.33 (95% CI 1.07 - 50.27)[237] and LR- from 0.37 (95% CI 0.14 - 0.94)[237] to LR- of 0.38 (95% CI 0.12 - 1.19) (Figure 61).[236] Estimates from Makrakis *et al*[237] represented the largest higher quality study for this reference standard. Individual accuracy results for symptomatic women can be found in Table 39.

Figure 61 Forest plots of likelihood ratios (LR's) of MMP-9 in predicting spontaneous preterm birth before 37 weeks' gestation in symptomatic women*



*Studies are arranged in descending order of methodological quality

Periodontal assessment

Periodontal health care is provided for free at the point of delivery to pregnant women within the UK. It examines the oral cavities for signs of periodontal disease (e.g. periodontitis), which has been purported to predispose to spontaneous preterm birth.[238]

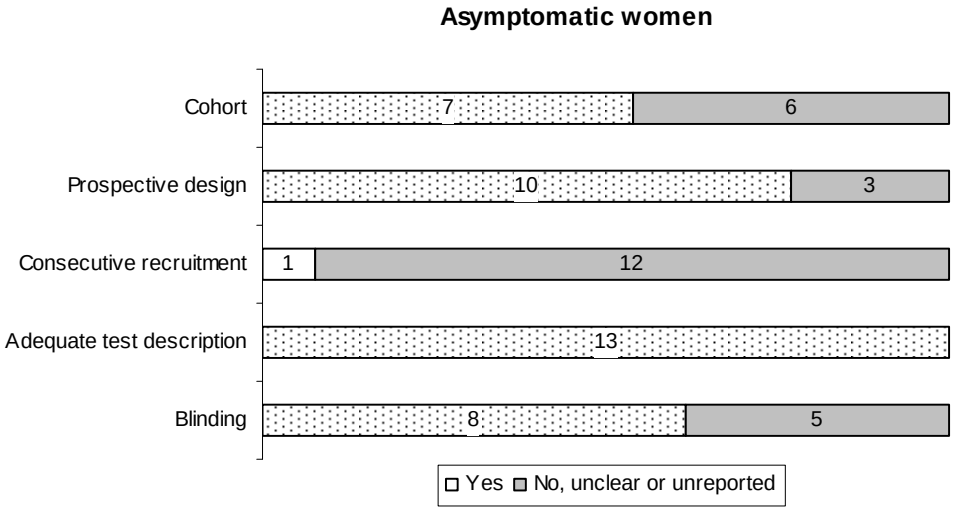
Study characteristics and quality

There were 13 primary articles evaluating the accuracy of the state of antenatal periodontal health in asymptomatic women or in the immediate postnatal period as predictor of spontaneous preterm birth (n = 3,900 women).[238-250] The number of women enrolled ranged from 36[240] to 1,313[238] with a median of 128. Two studies published their preliminary results (n = 176 women), full results of which were not available at the time of writing.[242;249] The accuracy of one study was not evaluated further as data was not extractable from the publication and the corresponding author was not able to provide it within the time scale of this thesis.[244] There was no study evaluating the accuracy of periodontal assessment as a predictor of spontaneous preterm birth in women who presented with threatened preterm labour. Table 40 summarises each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and symptomatic women with threatened preterm labour.

None of the studies fulfilled ideal quality study designs. There were ten studies that reported prospective data collection[238-242;244;246-248;250] and six that reported case-control design.[239;241;243;245;247;249] Consecutive enrolment was only evident in one study.[238] Blinding was reported in eight studies.[238;239;241;244;246-249] Overall, there were adequate reports of test description from the studies. The methodological quality of the included primary studies is summarised in Figure 62.

All but one study assessed women's periodontal status for presence of periodontitis. The one study assessed women's antibodies serology for *Prophyromonas gingivalis*, the predominant organism implicated in periodontitis in general population.[239] Seven studies performed their periodontal assessment in 2nd trimester[238-240;242;244;246;250] while six studies performed theirs within 2 - 5 days of delivery.[241;243;245;247-249] There were as many criteria for determining periodontitis as the number of studies. No two studies had used the same criteria for determining periodontitis. Except for two studies, which used 32 weeks' gestation,[241;246] most studies had used 37 weeks' gestation as their reference standard.

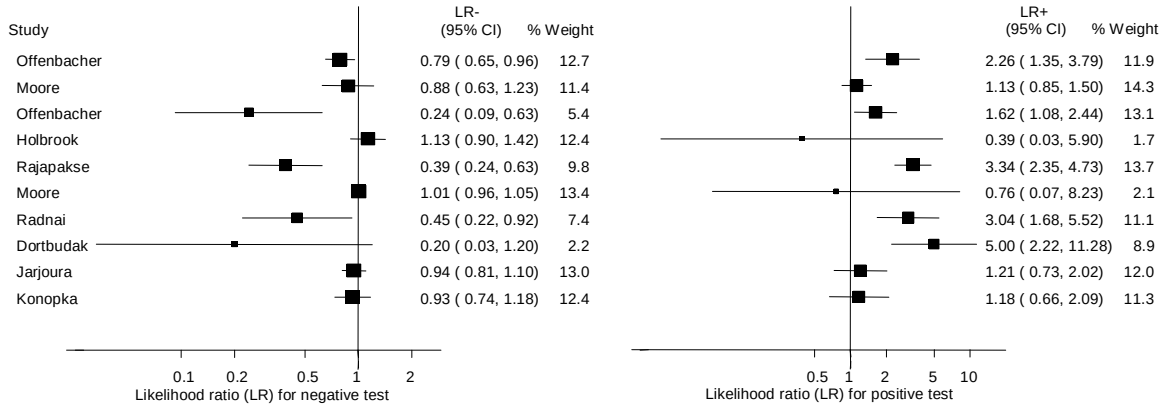
Figure 62 Methodological quality of studies included in the systematic review of accuracy of periodontal health status in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.



Accuracy of periodontal assessment in asymptomatic women

The presence of periodontal disease showed variable accuracy in predicting spontaneous preterm birth (Figure 63). The likelihood ratio for positive tests (LR+) ranged from 0.38 (95% confidence interval (CI) 0.04 - 3.33)[247] to 5.00 (95% CI 2.22 - 11.28)[240] and the LR- ranged from 0.22 (95% CI 0.09 - 0.57)[248] to 1.13 (95% CI 0.90 - 1.42).[242] The largest higher quality study reported LR+ 2.26 (95% CI 1.35 - 3.79) and LR- 0.79 (95% CI 0.65 - 0.96).[238] Figure 64 showed of sensitivity against specificity including summary values of the accuracy of periodontal health status in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic women. Funnel plot analysis (Figure 65) showed presence of asymmetry indicating presence of publication or related biases. Individual accuracy result of the state of periodontal health in predicting spontaneous preterm birth in asymptomatic women was summarized in Table 41. Meta-analysis was not performed because of the clinical heterogeneity in the criteria defining periodontal disease.

Figure 63 Forest plots of likelihood ratios (LR's) of periodontal health status in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic women*



*Studies are arranged in descending order of methodological quality

Figure 64 Plot of sensitivity against specificity including summary values of the accuracy of periodontal health status in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic women

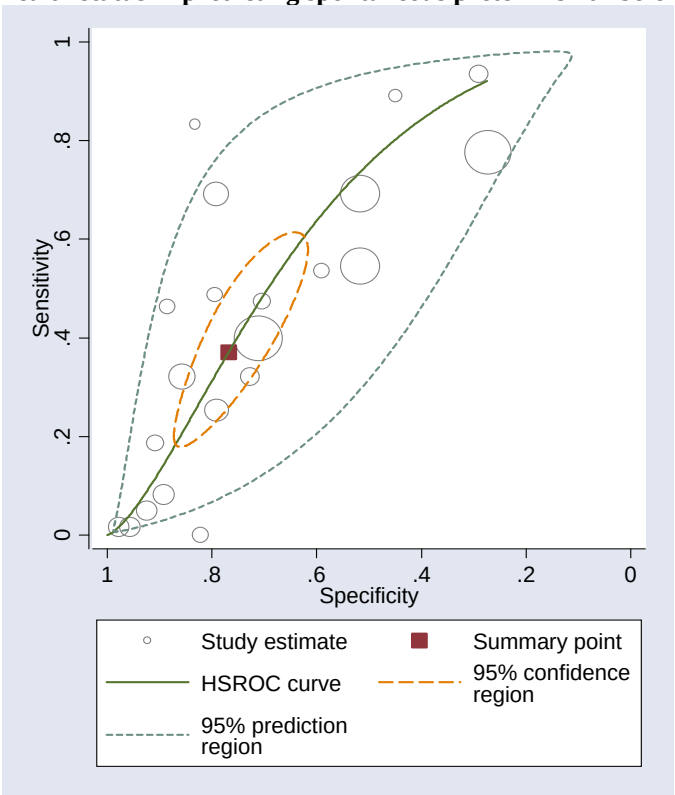
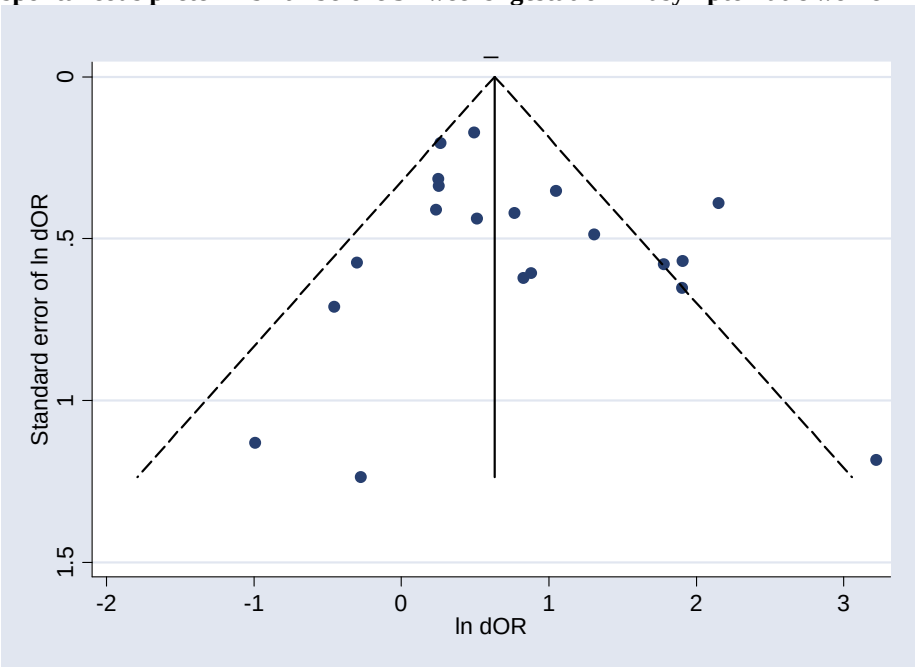


Figure 65 Funnel plot analysis of accuracy studies evaluating periodontal health status in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic women



Asymptomatic bacteriuria assessment

Screening for asymptomatic bacteriuria has been a routine component of an antenatal care. Its finding has been purported to increase the risk of spontaneous preterm birth. The usual specimen obtained was a mid-stream urine specimen sent for bacterial culture and sensitivity analysis. In light of recognised contribution of vaginal colonization in development of spontaneous preterm labour, there is even a call to re-evaluate the usefulness of screening for asymptomatic bacteriuria.[251] One systematic review had been done before.[252]

Study characteristics and quality

There were 26 studies (n=66,824) evaluating the accuracy of screening for asymptomatic bacteriuria in predicting spontaneous preterm birth.[253-278] Three of the included studies (n=11,520) evaluated the accuracy of asymptomatic Group B Streptococcus bacteriuria exclusively.[265;266;277] All the studies had used birth before 37 weeks' gestation as their outcome measurement. Table 42 summarized the characteristic of the included studies.

None of the studies fulfilled the criteria for an ideal quality study, specifically blinding was absent from all the studies. Only 6 and 9 studies used consecutive enrolment[262;265;266;269;274;278] and prospective data collection respectively.[262;265;266;268;269;274;275;278] Figure 66 summarized the methodological quality of the included studies.

Accuracy of asymptomatic bacteriuria in asymptomatic women

Screening for asymptomatic bacteriuria showed a variable accuracy in predicting spontaneous preterm birth before 37 weeks' gestation (Figure 67). LR+ ranged from 0.10 (95% CI 0.01 - 1.70)[256] to 3.83 (95% 2.22 - 6.59)[260] while LR- ranged from 0.43 (95% CI 0.19 - 0.94) to 1.17 (95% CI 0.64 - 2.13)[254] for asymptomatic bacteriuria. For asymptomatic GBS bacteriuria, LR+ ranged from 1.52 (95% CI 0.80 - 2.86)[277] to 2.69 (95% CI 1.51 - 4.76)[266] and LR- ranged from 0.96 (95% CI 0.88 - 1.04)[265] to 0.99 (95% CI 0.98 - 1.01).[277] The higher quality study available reported LR+ 2.63 (95% CI 1.54 - 4.50) and LR- 0.96 (95% CI 0.92 - 0.99) was

from Wren *et al*[278]. Figure 68 showed plot of sensitivities and specificities and their summary estimates for the accuracy of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation. Figure 69 did not show asymmetry in the funnel plot analysis of the accuracy of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation. Individual accuracy data is summarized in Table 43.

Figure 66 Methodological quality of studies included in the systematic review of accuracy of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth among asymptomatic antenatal women. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

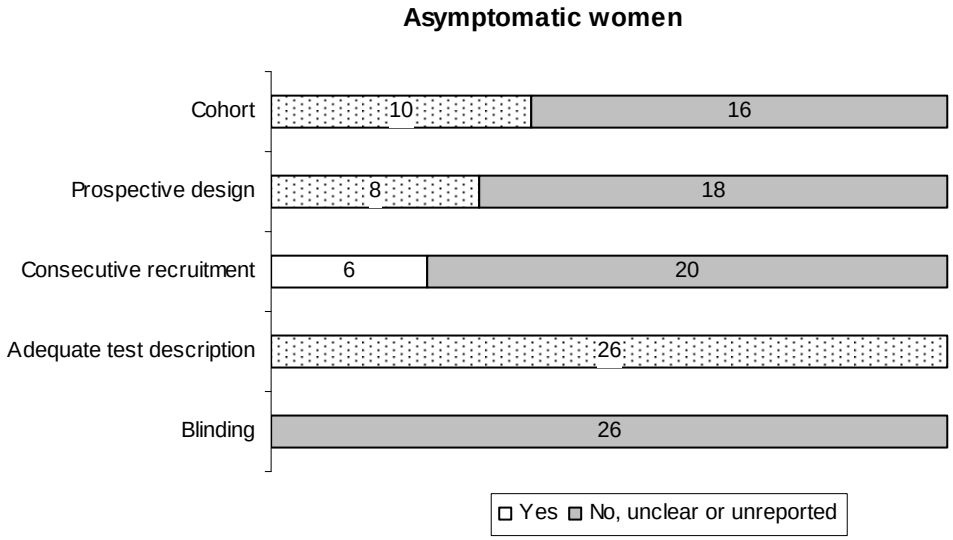
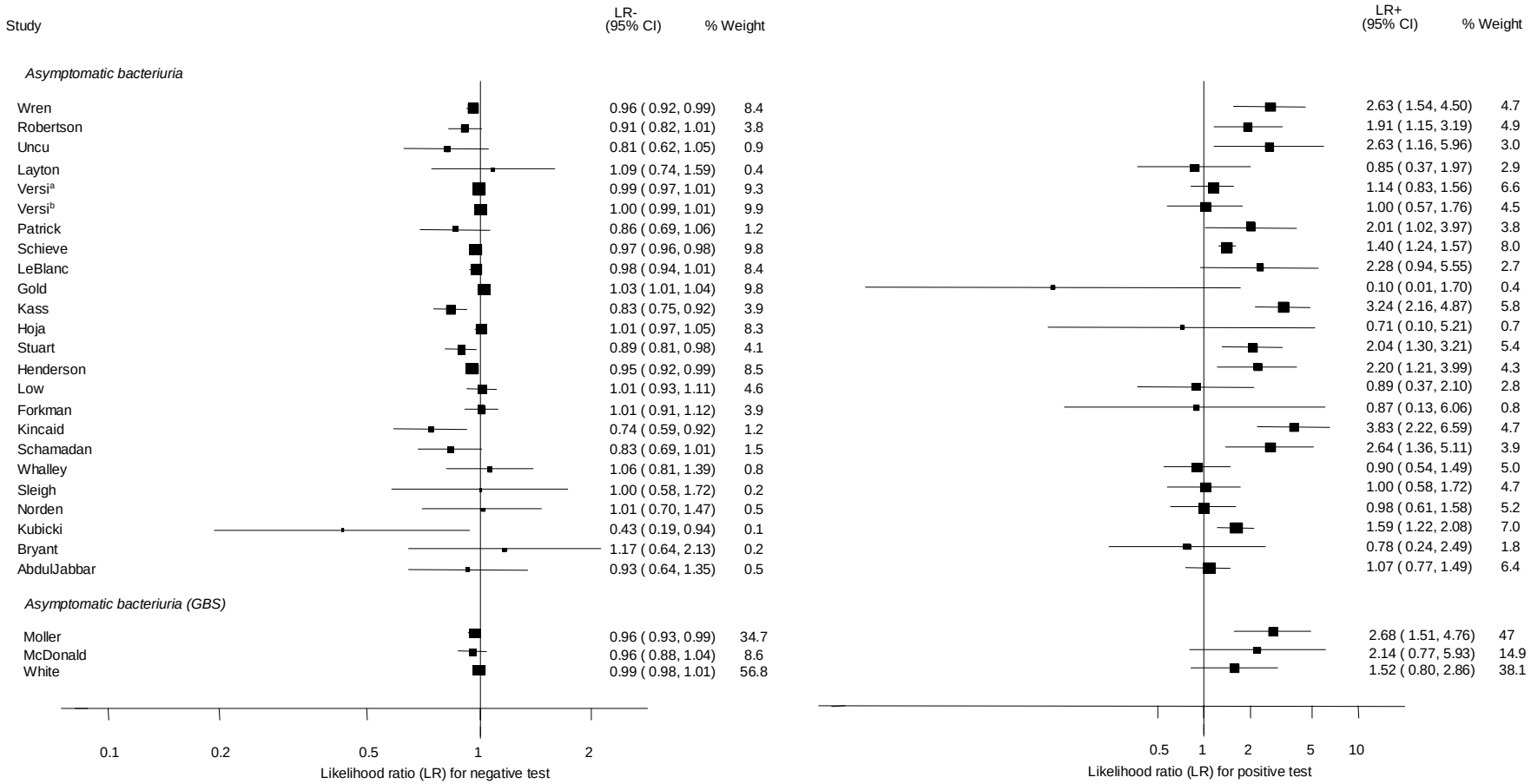


Figure 67 Forest plots of likelihood ratios (LR's) of asymptomatic bacteriuria assessment in asymptomatic women as a predictor of spontaneous preterm birth before 37 weeks' gestation stratified according to the type of asymptomatic bacteriuria*



*Studies are in descending order of quality
a. Caucasian population, b. Bangladeshi population
$\chi 2$ heterogeneity test for asymptomatic bacteriuria p = 0.0019 for LR+ and p = 0.0026 for LR-; for asymptomatic bacteriuria (GBS) p = 0.42 for LR+ and p = 0.16 for LR-

Figure 68 Plot of sensitivity against specificity including summary values of the accuracy of asymptomatic bacteriuria assessment in asymptomatic women as a predictor of spontaneous preterm birth before 37 weeks' gestation

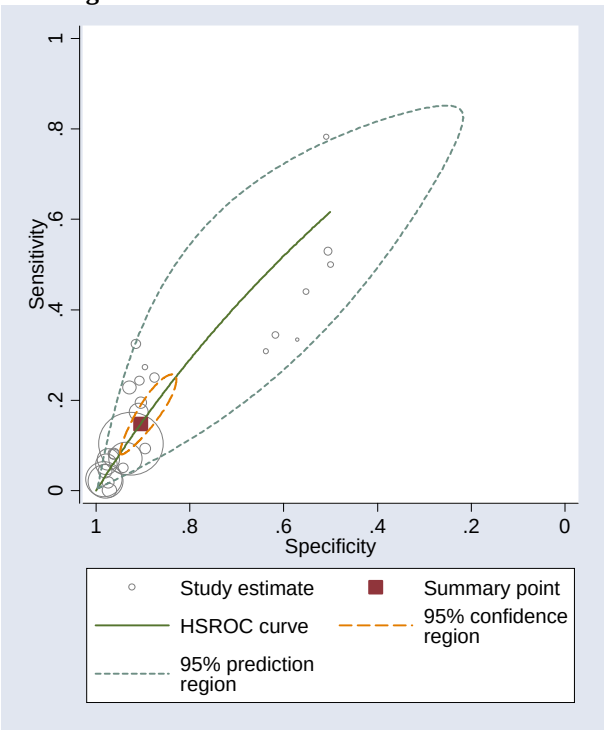
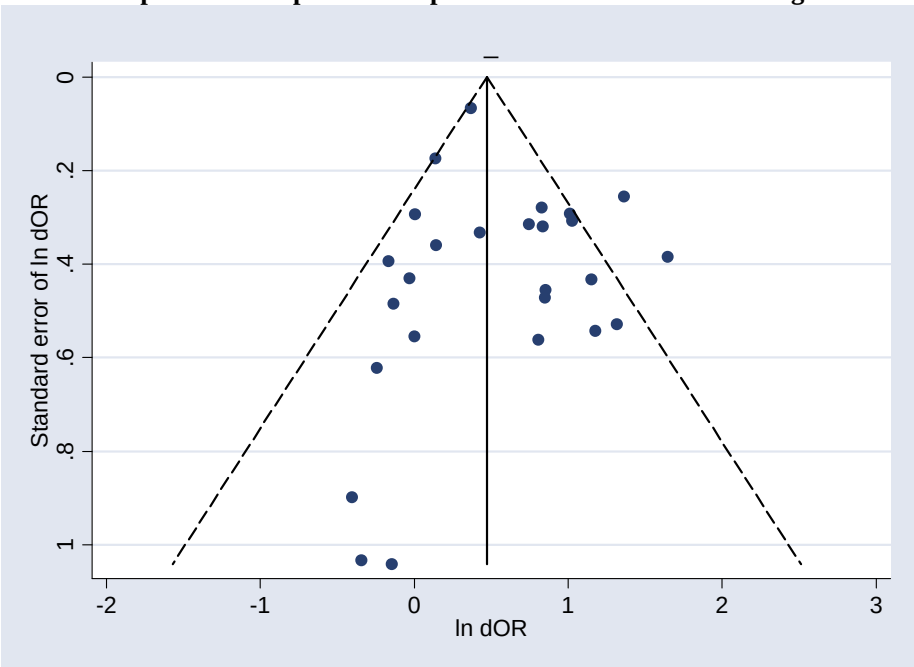


Figure 69 Funnel plot analysis of the accuracy of asymptomatic bacteriuria assessment in asymptomatic women as a predictor of spontaneous preterm birth before 37 weeks' gestation



Bacterial vaginosis (BV)

BV is a condition in women where the normal balance of bacteria in the vagina is disrupted and replaced by an overgrowth of anaerobic bacteria. The condition has been purported to predispose to spontaneous preterm birth. The condition can be tested by taking high vaginal swab specimen during speculum examination for either clinical evaluation (Amsel criteria),[279] Gram staining (Nugent[280] or Spiegel[281] criteria), or standard microbiological culture.

Study characteristics and quality

There were 25 primary studies (n = 35,652 women) on the accuracy of BV testing, comprising of 17 studies on asymptomatic antenatal women (n = 33,628)[92;282-298] and 8 studies on symptomatic women who presented with threatened preterm labour (n = 2,024)[232;299-305]. Table 44 summarizes each study's salient features, stratified according to population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour. The studies' enrolment ranged from 103 to 12,937 women[282;284] with a median of 646 women in asymptomatic population and from 87 to 753 women[232;299] with a median of 211 women.

There were no studies included within the systematic review of the accuracy of BV testing in predicting spontaneous preterm births that fulfil the ideal definition of high quality test accuracy studies. Blinding of carers to the results of BV tests were often absent from studies on asymptomatic[282;285-290] and symptomatic women.[232;299;301-303] For symptomatic women, six studies had used case-control design to assess the accuracy of BV testing in predicting spontaneous preterm births in symptomatic women.[232;299;301;303-305] The methodological quality of the included primary studies is summarized in Figure 70.

The commonly used criterion to diagnose BV was Gram staining using Nugent's criteria in the included studies, otherwise the other two methods that were used infrequently included

Gram staining using Spiegel's[232;301;305] and bedside diagnosis using Amsel's clinical criteria.[92;283;290;303] Three studies evaluated the accuracy or serial BV testing in asymptomatic pregnant women for predicting spontaneous preterm births[289;291;292] while the remainders evaluated a single BV testing, usually performed at mid-trimester.[92;282;284-287;289;291-295]

One study in asymptomatic antenatal women collected data for prediction of spontaneous preterm births at 23 – 26 weeks' gestation but which was not published.[284] Otherwise, most studies reported births before 37 weeks' gestation as their reference standards with two exceptions; a study used birth before 32 and 34 weeks' gestation as their reference standard[287] whilst another study used birth 35 weeks' gestation as its reference standard.[288] Similarly, for symptomatic women, the most commonly used reference standard was births before 37 weeks' gestation, except for 3 studies that reported births within 7 days of testing and before 33 weeks' gestation,[300] birth before 34 weeks' gestation[232] and births before 35 weeks' gestation.[302] One studies reported birth within 7 days of testing.[300]

Accuracy of BV in asymptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, a *single* BV testing (using Nugent's criterion) had a range of LR+ from 0.49 (95% CI 0.07 - 3.16) to 5.31 (95% CI 3.84 - 7.33) with a summary LR+ of 1.77 (95% CI 1.03 to 3.03) (χ2 heterogeneity test p = 0.0033) and a range of LR- from 0.32 (95% CI 0.23 – 0.43) to 1.15 (95% CI 0.90 – 1.48) with a summary LR- of 0.80 (95%CI 0.69 – 0.93) (χ2 heterogeneity test p = 0.0029) (Figure 71). LR+ 0.80 (95% CI 0.38 - 1.72) and LR- 1.04 (95% CI 0.92 - 1.17) represented LR from the sole ideal quality study.[285] For predicting spontaneous preterm birth before 37 weeks' gestation, *serial* BV testing (using Nugent's criterion) had a range of LR+ from 1.15 (95% CI 0.67 - 1.96) to 1.92 (95% 0.63 – 5.92) with a summary LR+ of 1.38 (95% CI 0.92 – 2.07) (χ2 heterogeneity test p = 0.56) and a range of LR- from 0.87 (95% 0.49 – 1.56) to 0.94 (95% 0.85 -1.04) with a summary LR- of 0.94 (95% 0.86 – 1.02) (χ2 heterogeneity test p = 0.96)

(Figure 72). The largest higher quality study has LR+ 1.92 (95% CI 0.63 - 5.92) and LR- 0.93 (95% CI 0.79 - 1.10).[292] For predicting spontaneous preterm birth before 37 weeks' gestation, a *single* BV testing (using Amsel's clinical criterion) had a range of LR+ from 0.87 (95% CI 0.48 – 1.59)[283] to 1.62 (95% CI 0.44 – 5.91)[92] (χ2 heterogeneity test p = 0.67) and LR- from 0.90 (95% CI 0.63 – 1.29)[92] to 1.02 (95% CI 0.93 – 1.12) (χ2 heterogeneity test p = 0.79) (Figure 75).[283] Figure 73 showed plot of sensitivities and specificities and their summary estimates for the accuracy of a single 2nd trimester BV testing using Nugent's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation while Figure 74 did not show asymmetry in the funnel plot analysis in this group. Individual accuracy results can be found in Table 45.

Accuracy of BV in symptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, BV testing (using Nugent's criterion) had a range of LR+ from 0.91 (95% CI 0.57 - 1.45) to 1.86 (95% CI 1.31 - 2.65) with a summary LR+ of 1.28 (95% CI 0.72 to 2.20) (χ2 heterogeneity test p = 0.04) and a range of LR- from 0.89 (95% CI 0.84 – 0.95) to 1.04 (95% CI 0.87 – 1.23) with a summary LR- of 0.95 (95%CI 0.86 – 1.05) (χ2 heterogeneity test p = 0.10) (Figure 76). For predicting spontaneous preterm birth before 37 weeks' gestation, BV testing (using Spiegel's criterion) had a range of LR+ from 1.00 (95% 0.76 – 1.32) to 3.68 (95% CI 1.13 - 11.97) with a summary LR+ of 1.30 (95% CI 0.95 – 1.77) (χ2 heterogeneity test p = 0.25) and a range of LR- from 0.66 (95% 0.46 – 0.96) to 1.00 (95% 0.73 -1.36) with a summary LR- of 0.94 (95% 0.87 – 1.01) (χ2 heterogeneity test p = 0.04) (Figure 76). Individual accuracy results can be found in Table 45.

Figure 70 Methodological quality of studies included in the systematic review of accuracy of bacterial vaginosis (BV) testing in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

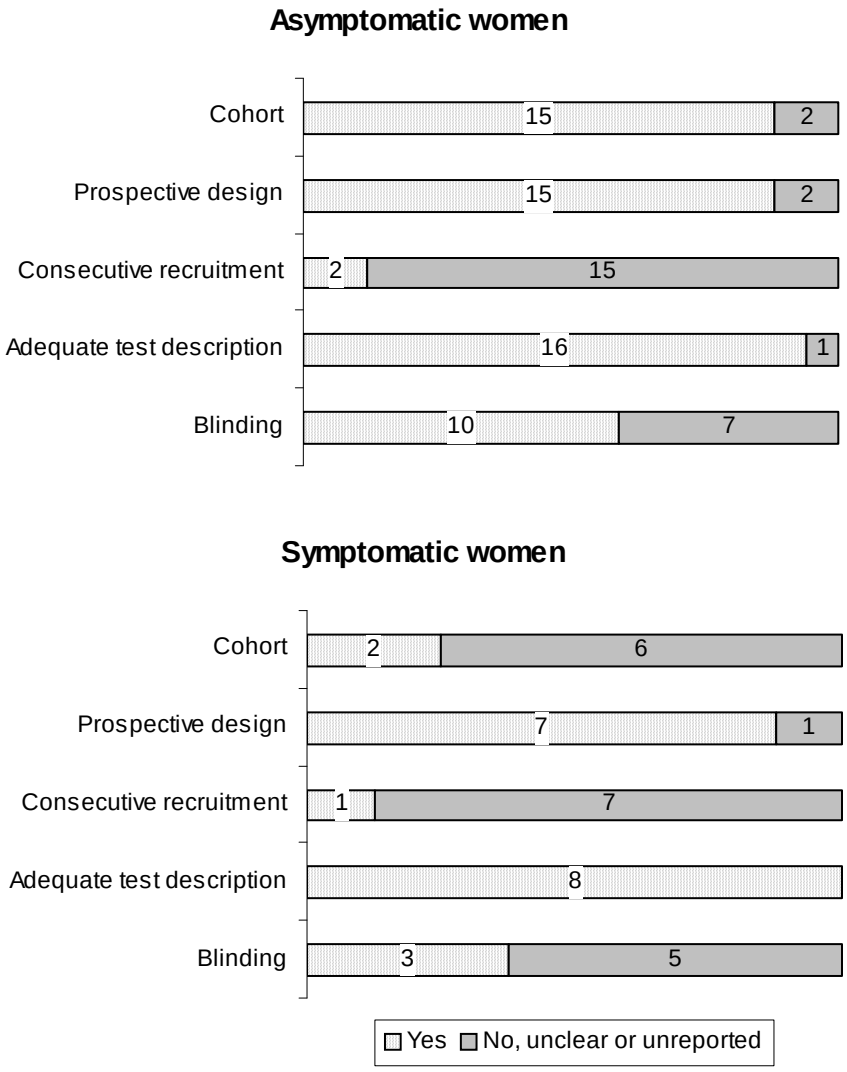
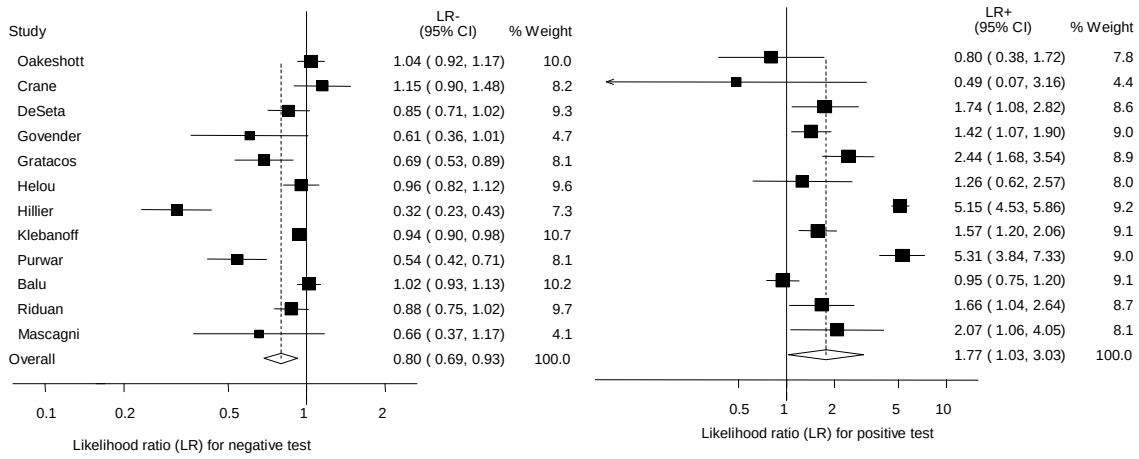
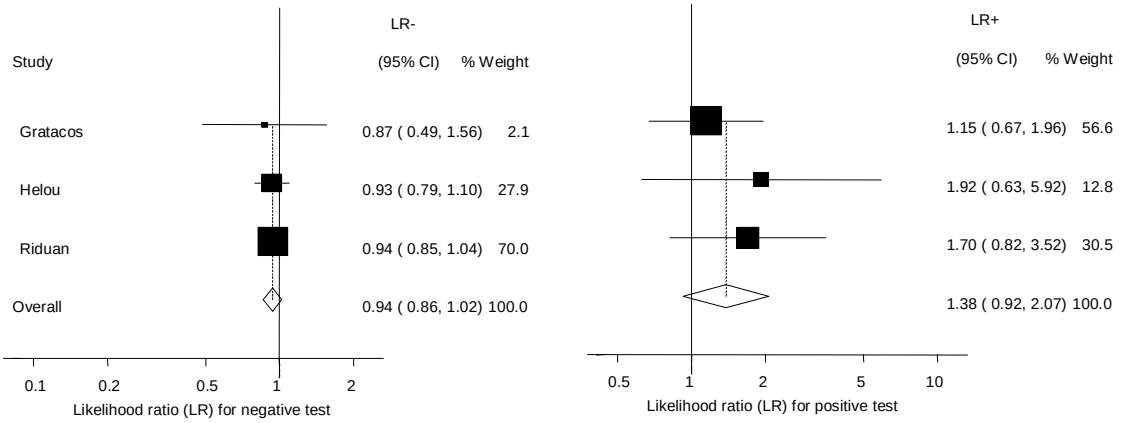


Figure 71 Forest plots of likelihood ratios (LR's) of a single 2nd trimester bacterial vaginosis (BV) testing using Nugent's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation



$\chi 2$ heterogeneity test for Nugent's criteria p = 0.0033 for LR+ and p = 0.0029 for LR-

Figure 72 Forest plots of likelihood ratios (LR's) of serial bacterial vaginosis (BV) testing using Nugent's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation



$\chi 2$ heterogeneity test for Nugent's criteria p = 0.56 for LR+ and p = 0.96 for LR-

Figure 73 Plot of sensitivity against specificity including summary values of the accuracy of a single 2nd trimester bacterial vaginosis (BV) testing using Nugent's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation

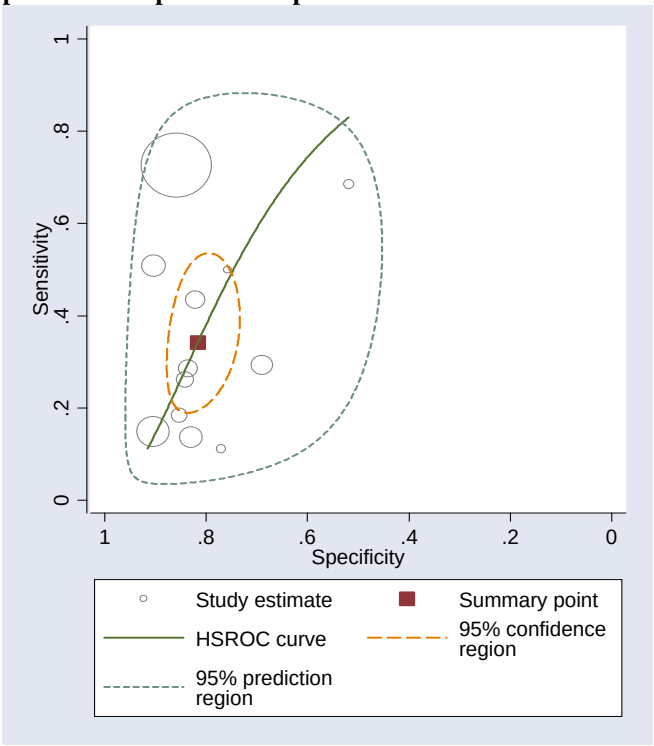


Figure 74 Funnel plot analysis of accuracy studies evaluating the accuracy of a single 2nd trimester bacterial vaginosis (BV) testing using Nugent's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation

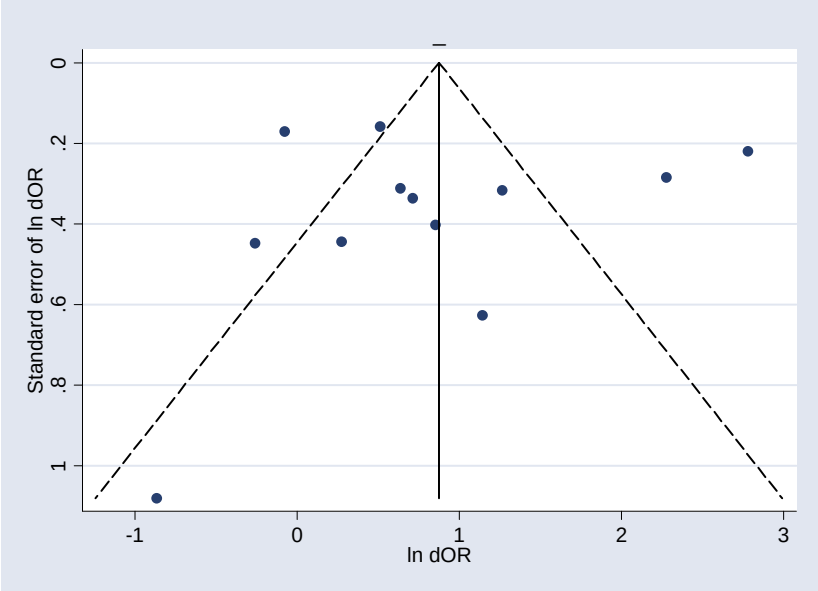
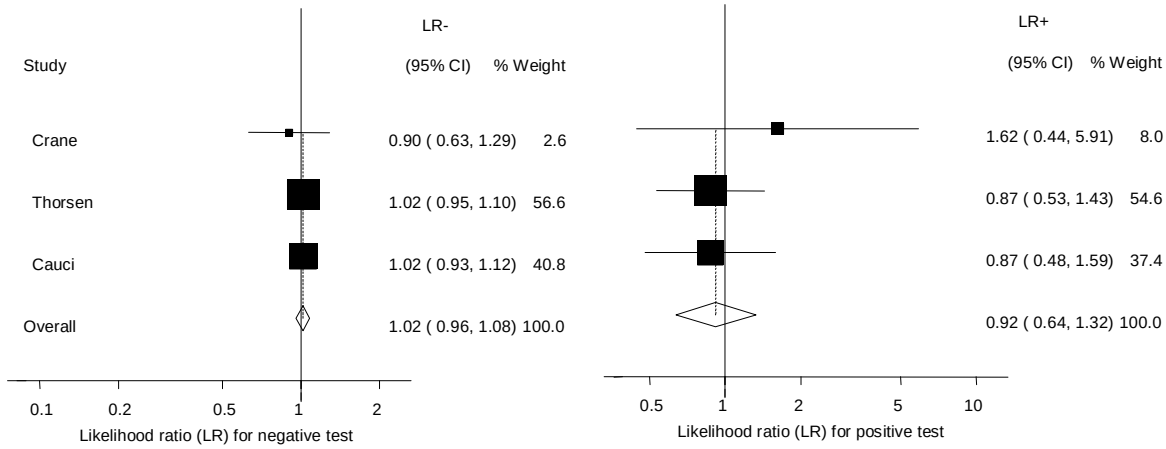
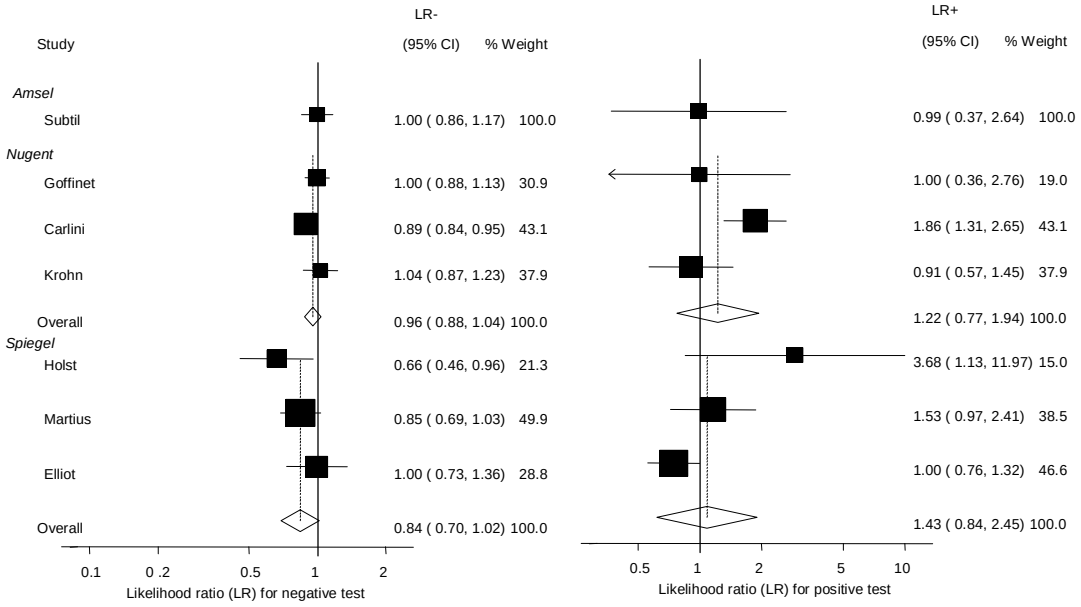


Figure 75 Forest plots of likelihood ratios (LR's) of a single 2nd trimester bacterial vaginosis (BV) testing using Amsel's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation



$\chi 2$ heterogeneity test for Nugent's criteria p = 0.67 for LR+ and p = 0.79 for LR-

Figure 76 Forest plots of likelihood ratios (LR's) of bacterial vaginosis (BV) testing in symptomatic women as a predictor of spontaneous preterm birth before 37 weeks' gestation



$\chi 2$ heterogeneity test for Nugent's criteria p = 0.04 for LR+ and p = 0.10 for LR-; for Spiegel's criteria p = 0.25 for LR+ and p = 0.04 for LR-

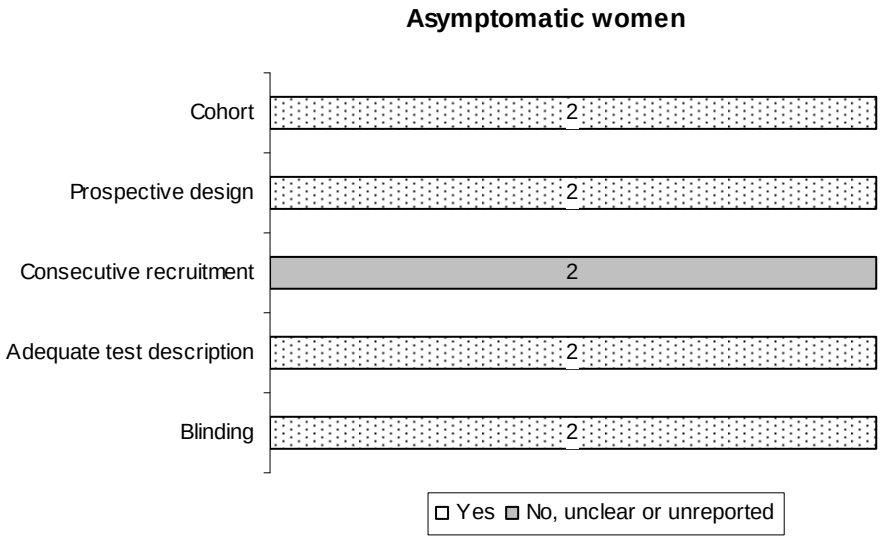
Mammary stimulation test

Antenatal mammary stimulation test is a provocative test of uterine contractility, which purported to identify asymptomatic women at high risk for spontaneous preterm birth. The presence of easily provoked uterine contractility supposed to be an indication of higher risk of spontaneous preterm birth.

Study characteristics and quality

There were 2 studies evaluating mammary stimulation test, both in asymptomatic antenatal women (n = 341).[306;307] Both studies enrolled their population at the early third trimester. One study evaluated the accuracy in predicting spontaneous preterm birth before 34 weeks' gestation[307] while both evaluated the accuracy for prediction before 37 weeks' gestation. None of the studies fulfilled the criteria for ideal quality study with consecutive enrolment being absent from both studies. Figure 77 summarizes the methodological quality of the included study. Both studies used the same test threshold. Individual study characteristics can be found in Table 46

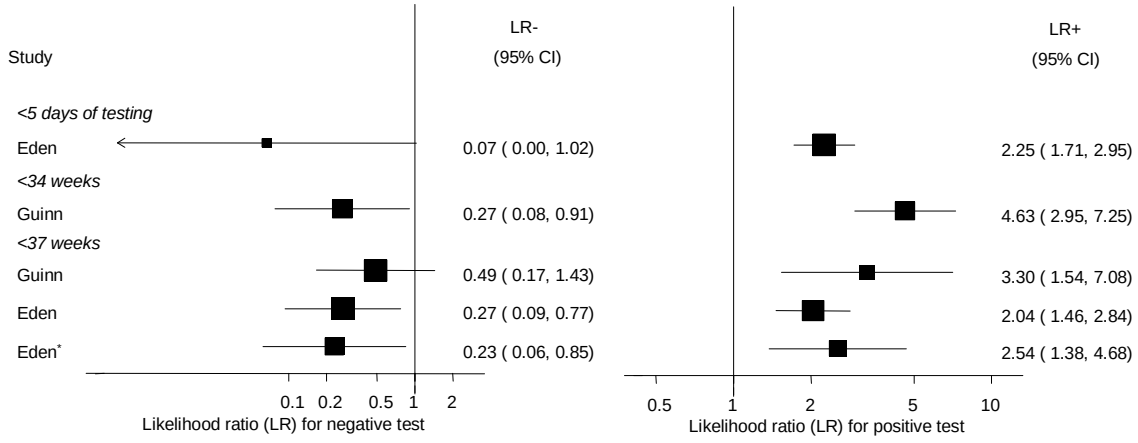
Figure 77 Methodological quality of studies included in the systematic review of accuracy of mammary stimulation test in asymptomatic women for predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.



Accuracy of mammary stimulation test in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, mammary stimulation test had an LR+ 4.63 (95% CI 2.95 - 7.25) and LR- 0.27 (0.08 - 0.91).[307] For predicting spontaneous preterm birth before 37 weeks' gestation mammary stimulation test had a range of LR+ from 2.04 (95% CI 1.45 - 2.84)[306] to 3.30 (95% CI 1.54 – 7.08)[307] and LR- from 0.23 (0.06 – 0.85)[306] for those with high Creasy risk score to 0.49 (0.17 – 1.43) (Figure 78).[307] The largest higher quality study was Guinn *et al*.[307] Individual accuracy results can be found in Table 47.

Figure 78 Forest plots of likelihood ratios (LR's) of mammary stimulation test as a predictor of spontaneous preterm birth in asymptomatic women stratified according to outcome



*High-risk women according Creasy' risk scoring system

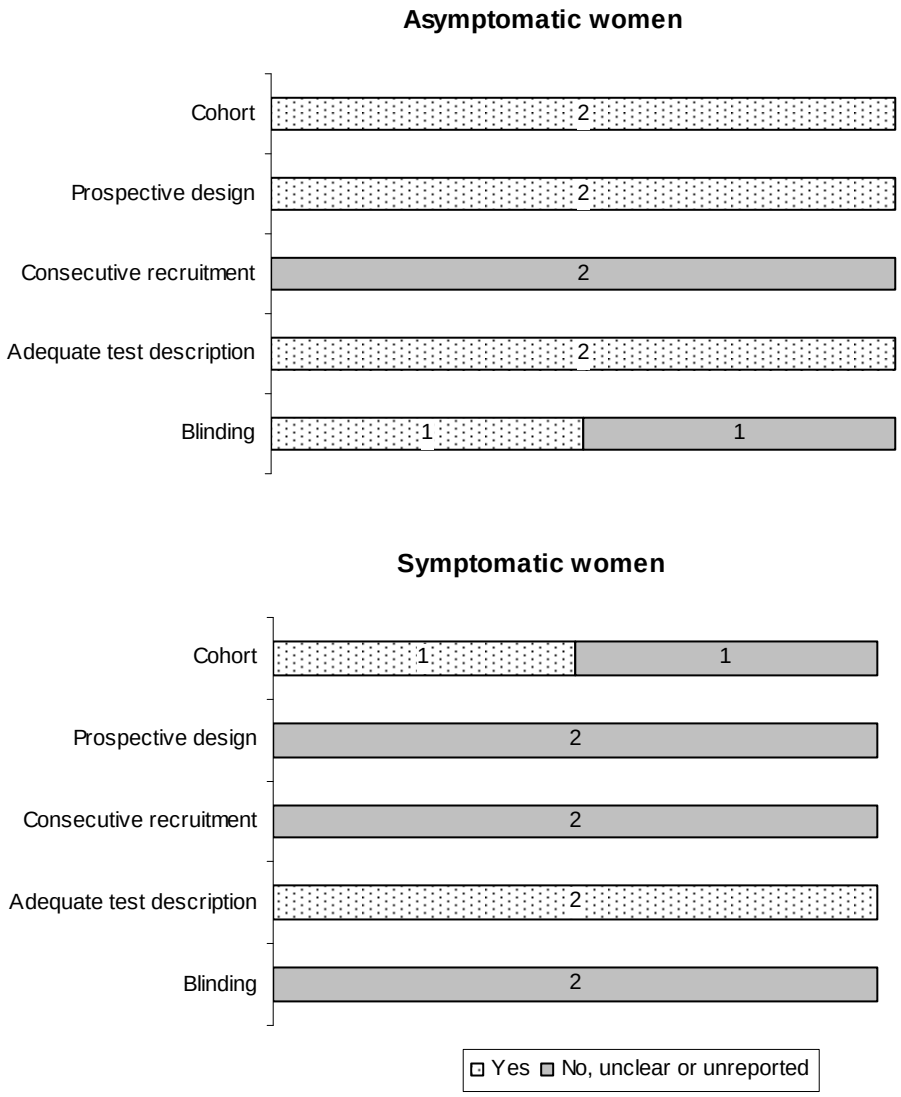
Uterine activity monitoring

Presence of increasingly co-ordinated, frequent and progressively stronger uterine activities often preceded the development of labour. It was thus purported that if uterine activities may be monitored, advance warning of impending onset of labour, whether at term or specifically preterm may be predicted.

Study characteristics and quality

There were 4 studies evaluating uterine activities, 2 asymptomatic antenatal women (n = 370) and 2 in symptomatic women with threatened preterm labour (n = 114).[69;308-310] 3 studies utilized tocograph while 1 utilized emerging technology electromyographic recording of uterine activities.[310] There was no consensus on threshold defining abnormality. Aside from one study which used birth before 35 weeks' gestation as its outcome,[69] the remaining study used birth before 37 weeks' gestation. None of the studies fulfilled the criteria for ideal quality study, consecutive enrolment was absent from any of the studies and blinding were absent from three studies. Figure 79 summarizes the methodological quality of the included study. Individual study characteristics are summarized in Table 48.

Figure 79 Methodological quality of studies included in the systematic review of of home uterine activity monitoring in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.



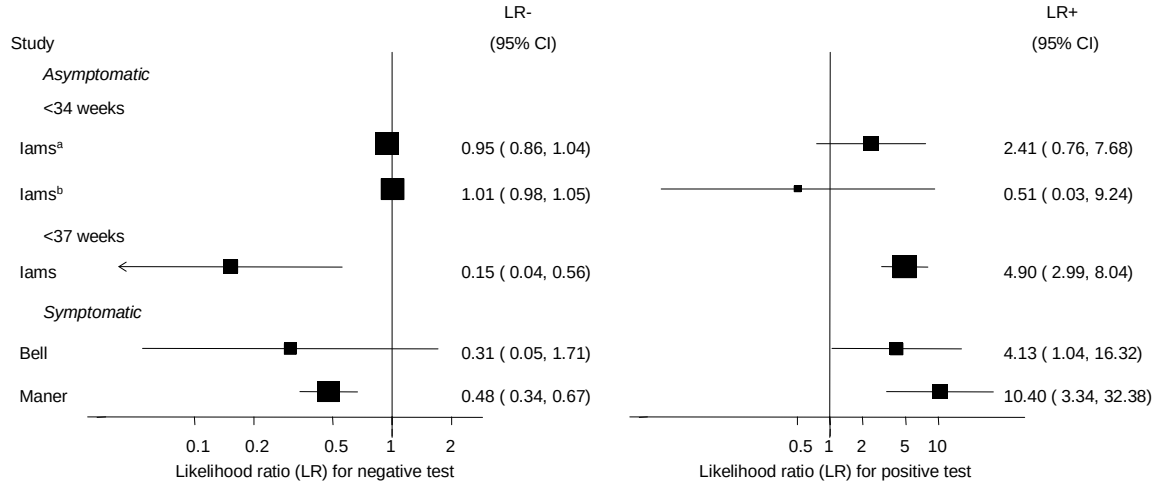
Accuracy of uterine activity monitoring in asymptomatic women

For predicting spontaneous preterm birth, uterine activity monitoring had a range of LR+ from 0.51 (95% CI 0.03 - 9.24)[69] when the threshold was set for detection of significant uterine activities during the day time, to 4.90 (95% CI 2.99 - 8.04)[309] when 4 significant contractions were detected within an hour period, and a range of LR- from 0.15 (95% CI 0.04 - 0.56)[309] when 4 significant contractions were detected within an hour period to 1.01 (95% CI 0.98 - 1.05)[69] for detection of significant uterine activities during the day time. The higher quality study from Iams *et al* has LR+ 2.41 (95% CI 0.76 - 7.68) and LR- 0.95 (95% CI 0.86 - 1.04).[69] Figure 80 summarized the accuracy results while Table 49 showed individual accuracy results for each study.

Accuracy of uterine activity monitoring in symptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, uterine activity monitoring had a range of LR+ from 4.13 (95% CI 1.04 - 16.32)[308] to 10.40 (95% CI 3.34 - 32.38)[310] and a range of LR- from 0.31 (95% CI 0.05 - 1.71)[308] to 0.48 (95% CI 0.34 - 0.67)[310] when using tocographic and electromyographic recording respectively. Bell *et al* represented the higher quality study available.[308] Figure 80 summarized the accuracy results while Table 49 showed individual accuracy results for each study.

Figure 80 Forest plots of likelihood ratios (LR's) of uterine activity monitoring as a predictor of spontaneous preterm birth before 37 weeks' gestation* stratified according to populations



a. Uterine activities at night-time, b. uterine activities in day-time
*. Unless otherwise stated

Rheobase

Rheobase in the context of a test to predict spontaneous preterm birth is measurement of the minimum strength of an electrical stimulus (electrical current) of that is able to cause excitation of a muscle, e.g. tibialis anterior muscle in symptomatic women with threatened preterm labour, which would show a higher threshold compared to a quiescent uterus. Mass electrical uterine activities in a genuine spontaneous labour would require greater electrical current to generate muscular excitation in genuine case of threatened preterm labour (compared to the relatively smaller current required when uterus is quiescent) and hence the purported ability of rheobase to predict spontaneous preterm birth in symptomatic women with threatened preterm labour by measuring these greater electrical current.

Study characteristics and quality

There was only one study evaluating rheobase in symptomatic women with threatened preterm labour (n = 176).[311] Two different thresholds were evaluated (2.8 and 3.4 mA) and outcome of spontaneous preterm birth before 37 weeks' gestation was used. The study characteristics can be found Table 50. Methodological quality was summarized in Figure 81.

Accuracy of rheobase measurement in symptomatic women

Depending on the thresholds being used, rheobase had an LR+ that ranged from 2.29 (95% CI 1.50 to 3.52) when 2.8 mA was used to 2.36 (95% CI 1.73 to 3.20) when 3.4 mA was used, and an LR- that ranged from 0.36 (95% CI 0.19 to 0.66) when 3.4 mA was used to 0.60 (95% CI 0.41 to 0.88) when 2.8 mA was used (Figure 82). Individual accuracy results were summarized in Table 51.

Figure 81 Methodological quality of studies included in the systematic review of accuracy of rheobase testing in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies

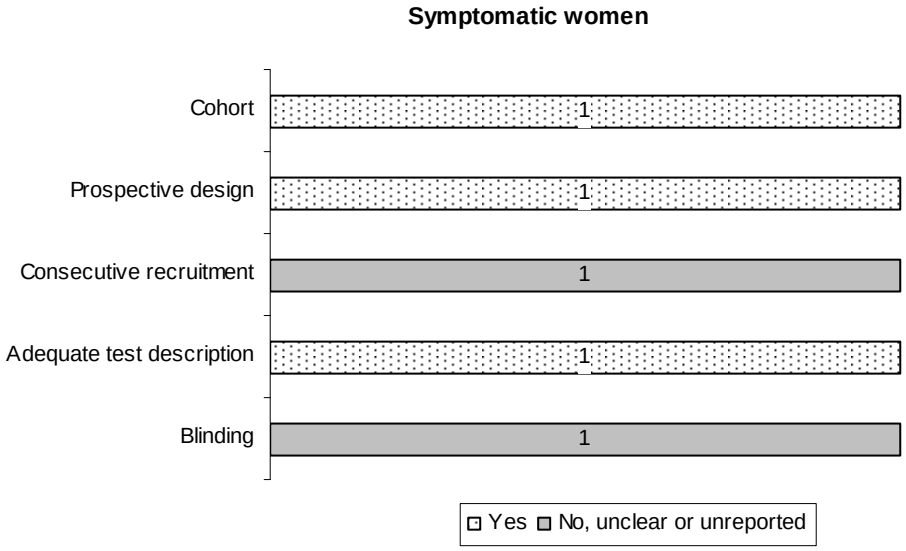
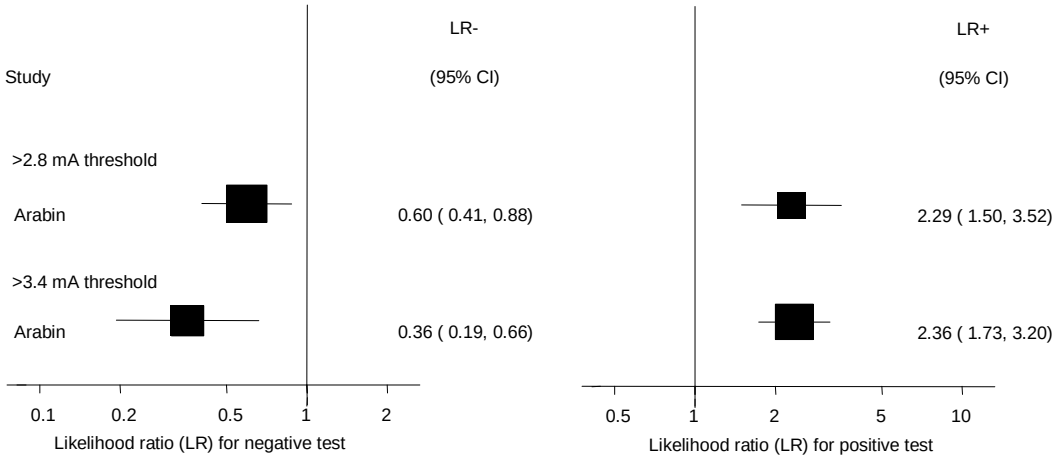


Figure 82 Forest plots of likelihood ratios (LR's) of rheobase measurement as a predictor of spontaneous preterm birth in symptomatic women stratified according to thresholds



Absence of fetal breathing movements on ultrasound

A decrease in fetal breathing movements observed during a 20 minutes observation with real-time ultrasound at the time of admission for threatened preterm labour has been purported to be a predictor of progression to spontaneous preterm birth.[312]

Study characteristics and quality

There were 8 primary accuracy articles that met the selection criteria, which included a total of 328 women.[85;312-318] (Table 52). All of them evaluated fetal breathing movements for a sustained period of 15-20 seconds in a 30-45 minute period with real time ultrasound. The absence of breathing movements, defined when no sustained fetal breathing movements were noted in the time period, indicated a positive result. In all the studies, the test was carried out once, on the delivery suite, at the time of admission. All the studies were of small size, with enrolment ranging from 24[312] to 70[318] women. One study fulfilled the ideal quality criteria.[85] Methodological quality was summarized in Figure 83.

Accuracy of absence of fetal breathing movement in symptomatic women

For predicting preterm birth within 48 hours (Figure 84) and within 7 days of testing (Figure 85), there was a wide variation in the accuracy results. Statistical heterogeneity was not detected in the accuracy results of positive test for birth within 7 days of testing ($\chi 2$ heterogeneity test $p = 0.57$) and of negative test for birth within 48 hours of testing ($\chi 2$ heterogeneity test $p=0.64$). However, within each reference standard sub-group, the studies were of variable methodological quality and heterogeneity was present for the corresponding negative and positive LR's respectively. The ideal quality study from Senden et al,[85] showed a LR+ of 4.00 (95% confidence interval (CI) 0.73 - 21.84) and a LR- of 0.67 (95% CI 0.32 - 1.38) for predicting spontaneous preterm birth within 7 days of testing (Figure 85). For predicting preterm birth within 48 hours of testing, where the studies were lacking in one or

more ideal quality features, the LR for a positive test estimated from a better quality study was LR+ 16.08 (95% CI 5.22 - 49.55) and for a negative test of LR- 0.16 (95% CI 0.05 - 0.58)[318] (Figure 84). Figure 86 Individual accuracy results from the included studies are summarized in Table 53.

Figure 83 Methodological quality of studies included in the systematic review of the accuracy of fetal breathing movements in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.

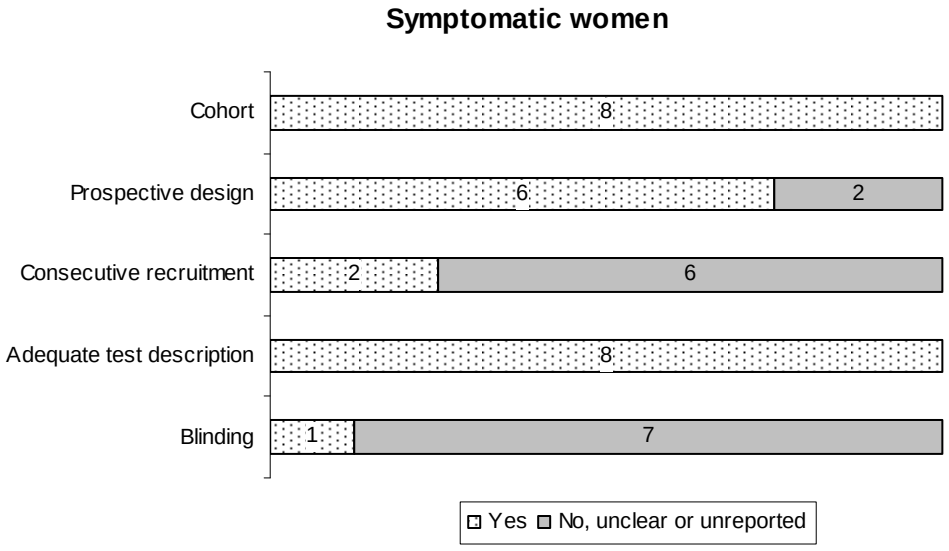
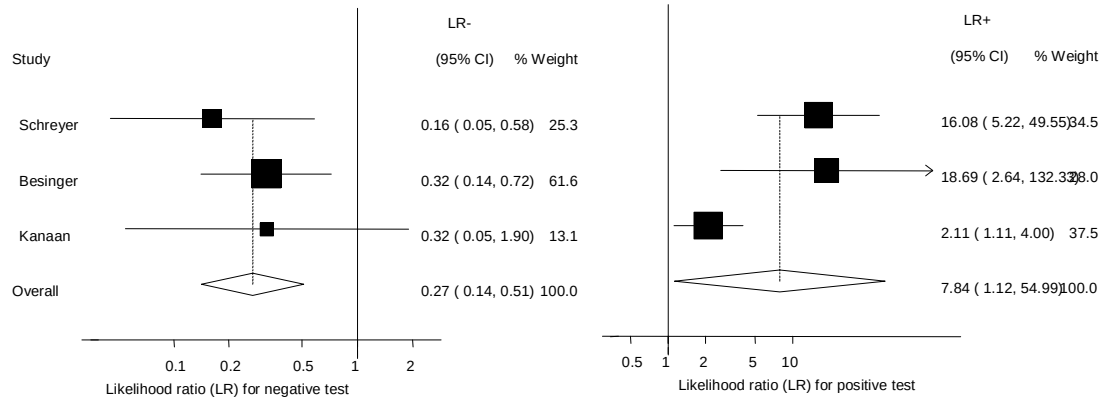
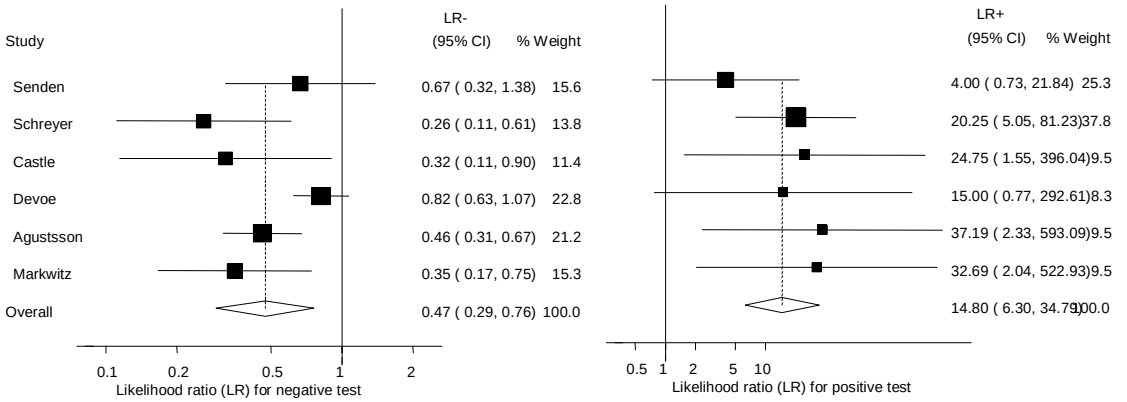


Figure 84 Forest plots of likelihood ratios (LR's) for the absence of fetal breathing movements in predicting spontaneous preterm birth within 48 hours of testing in women presenting with threatened preterm labour*



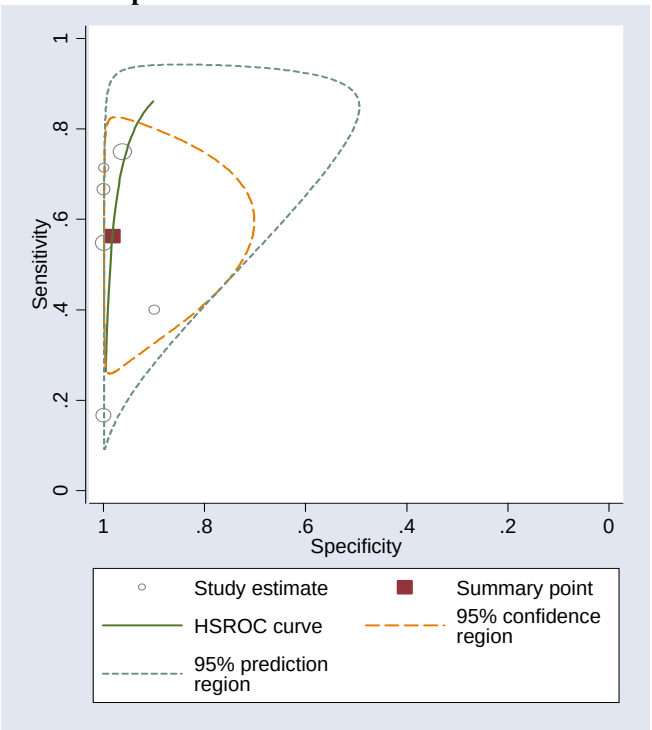
*$\chi 2$ heterogeneity test = 17.44, p = 0.00 for LR+ and $\chi 2$ = 0.89, p = 0.64 for LR-
+Studies are arranged in descending order of methodological quality

Figure 85 Forest plots of likelihood ratios (LR's) for the absence of fetal breathing movements in predicting spontaneous preterm birth within 7 days of testing in women presenting with threatened preterm labour*



*$\chi 2$ heterogeneity test = 3.84, p = 0.57 for LR+ and $\chi 2$ = 21.10, p = 0.0013 for LR-
+Studies are arranged in descending order of methodological quality

Figure 86 Plot of sensitivity against specificity including summary values of the absence of fetal breathing movements in predicting spontaneous preterm birth within 7 days of testing in women presenting with threatened preterm labour



Cervical ultrasound assessment

Antenatal cervical length shortening[319] and opening of the internal os (funnelling)[320] has been purported to increase the risk in asymptomatic women and the likelihood of spontaneous preterm birth in women who presented with threatened spontaneous preterm labour.

Study characteristics and quality

There were a total of 31 studies comprising 13 primary studies on asymptomatic women (n = 21555 women)[59;321-332] and 19 primary studies (n = 2849 women)[57;75;106;223;235;333-347] on symptomatic women with threatened preterm labour evaluating the accuracy of transvaginal ultrasound measurement of cervical length in predicting spontaneous preterm birth. Table 54 and Table 55 summarized individual study characteristics of the included studies of cervical length measurement in predicting spontaneous preterm birth, evaluating antenatal asymptomatic women and women with threatened preterm labour respectively.

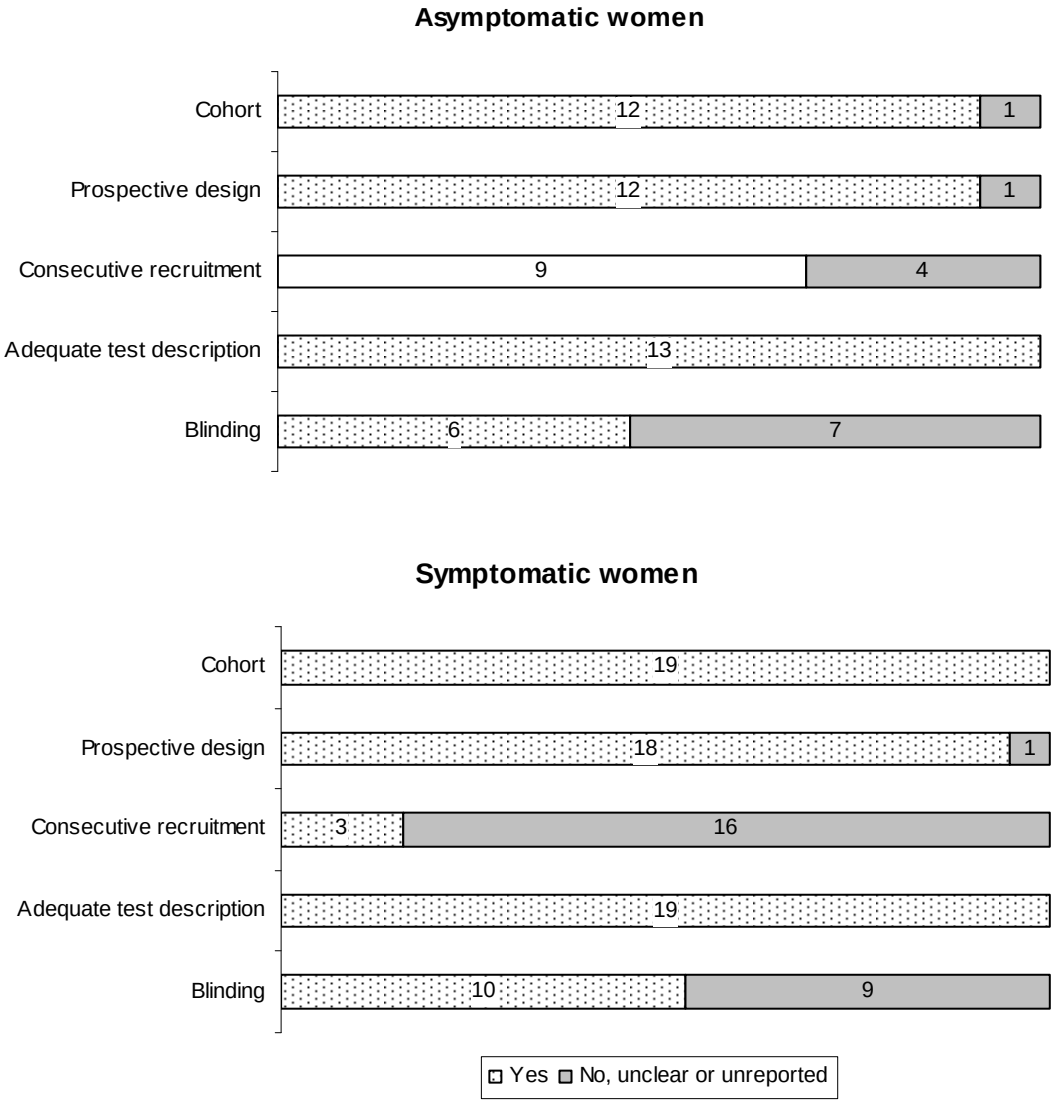
Additionally, there were 11 studies, comprising 6 primary studies on asymptomatic women (n = 12855 women)[319;322;326;327;329;331] and 5 primary studies (n = 509 women)[223;320;333;337;340] on the accuracy of symptomatic women with threatened preterm labour evaluating the accuracy of transvaginal ultrasound assessment and measurement of cervical funnelling in predicting spontaneous preterm birth. Table 56 summarized individual study characteristics of the included studies of cervical funnelling assessment in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour.

There was a wide variation in gestation at which ultrasound cervical length measurement was carried out in asymptomatic antenatal women and the definition for thresholds of abnormality. The most common gestation at which ultrasound measurement of cervical length was carried was in the late second trimester, between 20 – 24 weeks' gestation. The most common

threshold used in asymptomatic women was 25mm at this gestation and was evaluated in 2 ideal quality studies.[319;322] The outcome frequently used by studies on asymptomatic women was 37 weeks' gestation but amongst ideal quality studies, the outcome frequently used was spontaneous preterm birth before 34 weeks' gestation. Among symptomatic women, the most common threshold used was 15mm and the most common outcome used was spontaneous preterm birth within 7 days of testing using this threshold.

There were 5 studies on asymptomatic women[322;323;326;328;332] and 2 studies on symptomatic women on cervical length measurement that fulfilled ideal definition of high quality study[333;337] and 3 studies on asymptomatic women[319;322;326] and 2 studies on symptomatic women evaluating cervical funnelling that fulfilled ideal definition of high quality study.[333;337] The methodological quality of the included primary studies is summarized in Figure 87.

Figure 87 Methodological quality of studies included in the systematic review of accuracy of cervical length in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.



Accuracy of cervical length and funnelling in asymptomatic women

When cervical length measurement was performed before 20 weeks' gestation using a threshold of 25 mm (commonest threshold evaluated at this gestation) for predicting spontaneous preterm birth before 34 weeks' gestation, it had sLR+ of 13.38 (95% CI 6.90 - 25.96) (χ2 heterogeneity test p = 0.07) and sLR- of 0.80 (95% CI 0.71 - 0.90) (χ2 heterogeneity test p = 0.91).[322;326;328] Figure 88 showed forest plot of ideal quality studies for cervical length measurement before 20 weeks' gestation in predicting spontaneous preterm birth before 34 weeks' gestation in asymptomatic antenatal women. When performed between 20 -24 weeks' gestation, again using a threshold of 25mm (commonest threshold evaluated at this gestation) it had sLR+ 4.68 (95% CI 3.64 - 6.03) (χ2 heterogeneity test p = 0.54) and sLR- 0.68 (95% CI 0.60 - 0.78) (χ2 heterogeneity test p = 0.93).[319;322] Cervical funnelling screening in asymptomatic had variable LR's depending on the chosen threshold (some studies did not indicate their threshold, merely indicating presence of the 'funnelling' appearance on ultrasound imaging) (Figure 92). LR+ 4.63 (95% CI 3.31 - 6.48) and LR- 0.79 (95% CI 0.71 - 0.87) from Iams *et al* using 5mm protrusion of amniotic membrane into the cervical canal as their threshold as predictor for spontaneous preterm birth before 34 weeks' gestation represented higher quality study available for this threshold and reference standard.[319]

There was no more than a single study of small sample size for any of the evaluated threshold for cervical measurement performed before 20 weeks' gestation in predicting spontaneous preterm birth before 37 weeks (Figure 90). When cervical length was measured between 20 – 24 weeks' gestation for predicting before 37 week's gestation (Figure 91) using threshold of 32.5mm, it had an LR+ of 3.99 (95% CI 2.84 - 5.62) and LR- of 0.33 (95% CI 0.17 - 0.66).[332] Individual accuracy results are summarized in Table 57 and Table 59.

Accuracy of cervical length and funnelling in symptomatic women

For predicting spontaneous preterm birth within 48 hours of testing, cervical length measurement in symptomatic women with threatened preterm labour had a variable LR's depending on the threshold abnormality chosen (Figure 93). LR+ 6.43 (95% CI 5.17 - 8.00) and LR- 0.027 (95% CI 0.0017 - 0.42) from Tsoi *et al* represented higher quality study available for the relatively more common threshold used (15 mm) and reference standard (birth within 48 hours of testing).[346] For predicting spontaneous preterm birth within 7 days of testing, cervical length measurement in symptomatic women with threatened preterm labour had a variable LR's depending on the threshold abnormality chosen (Table 58). Figure 94 showed the forest plot of LR's for the most commonly used threshold (<15mm) for the reference standard of spontaneous preterm birth within 7 days of testing. LR+ 8.61 (95% CI 6.65 - 11.14) and LR- 0.026 (95% CI 0.0038 - 0.182) from Tsoi *et al* represented higher quality study available for the aforementioned threshold and reference standard.[346]

For predicting spontaneous preterm birth before 34 weeks' gestation, cervical length measurement in symptomatic women with threatened preterm labour had a variable LR's depending on the threshold abnormality chosen (Table 58). Figure 95 showed the forest plot of LR's for the most commonly used threshold (<30mm) for the reference standard of spontaneous preterm birth before 34 weeks' gestation. LR+ 1.879 (95% CI 1.36 – 2.59) and LR- 0.30 (95% CI 0.083 – 1.07) from Crane *et al* represented the ideal quality study available for the aforementioned threshold and reference standard.[333] For predicting spontaneous preterm birth before 37 weeks' gestation, cervical length measurement in symptomatic women with threatened preterm labour had a variable LR's depending on the threshold abnormality chosen (Figure 95). LR+ 3.36 (95% CI 1.73 - 6.54) and LR- 0.35 (95% CI 0.17 - 0.70) from Gomez *et* al with threshold of <18mm and LR+ 2.29 (1.68 - 3.12 & LR- 0.29 (95% CI 0.15 - 0.58) from Crane *et al* with threshold of <30mm represented ideal quality

study available for the reference standard.[333] Cervical funnelling screening in symptomatic had variable LR's depending on the chosen threshold (some studies did not indicate their threshold, merely indicating presence of the funnelling appearance on ultrasound imaging) (Figure 97). LR+ 4.70 (95% CI 1.90 - 11.66) and LR- 0.61 (95% CI 0.34 - 1.10) for predicting spontaneous preterm birth before 34 weeks' gestation and LR+ 2.53 (95% CI 1.02 - 6.25) and LR- 0.86 (95% CI 0.71 – 1.03) for predicting spontaneous preterm birth before 37 weeks' gestation from Crane *et al* using the presence of 'V-shaped' ultrasonographic appearance as threshold for funnelling represented ideal quality study available for this threshold and reference standard in symptomatic women. [333] Individual accuracy results for cervical length and funnelling measurement symptomatic women can be found in Table 58 and Table 59.

Figure 88 Forest plots of likelihood ratios (LR's) from ideal quality studies for cervical length measurement before 20 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 34 weeks' gestation in asymptomatic antenatal women

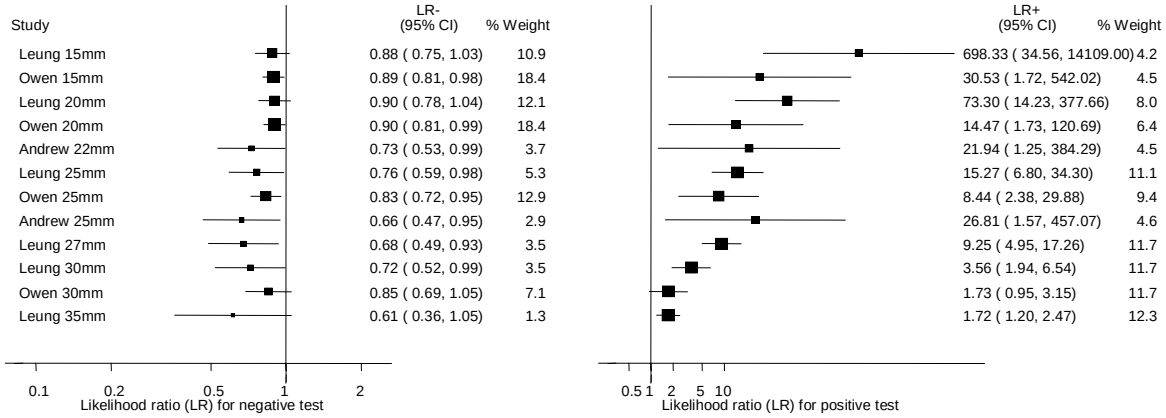


Figure 89 Forest plots of likelihood ratios (LR's) from ideal quality studies for cervical length measurement between 20 - 24 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 34 weeks' gestation in asymptomatic antenatal women

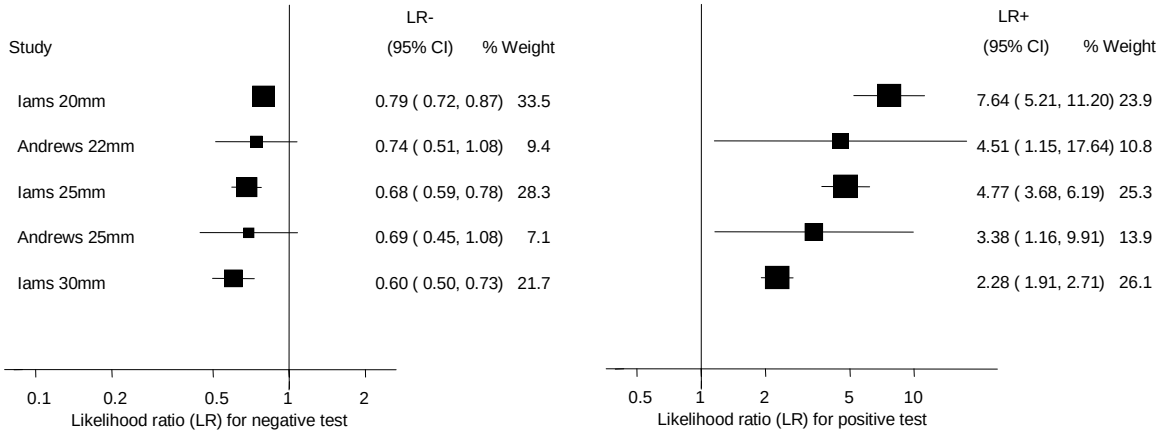


Figure 90 Forest plots of likelihood ratios (LR's) from ideal quality studies for cervical length measurement before 20 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic antenatal women

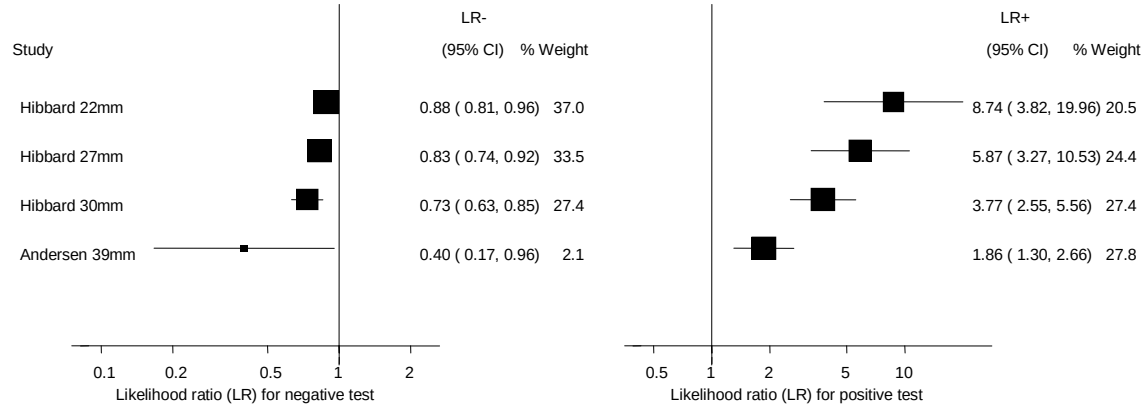


Figure 91 Forest plots of likelihood ratios (LR's) from ideal quality studies for cervical length measurement between 20 – 24 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic antenatal women

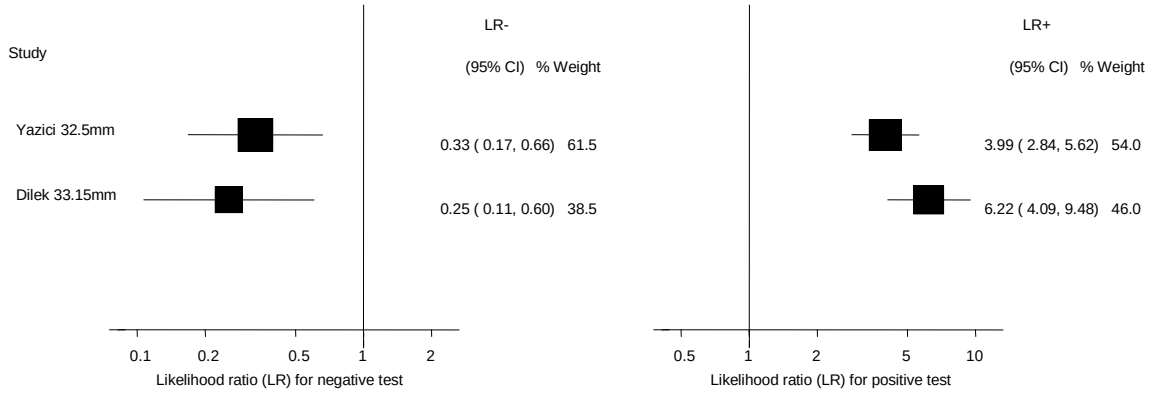
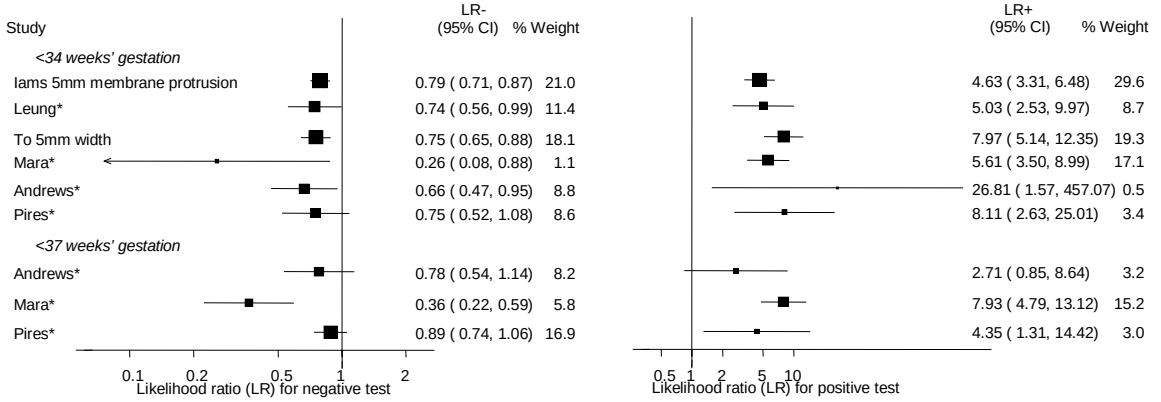


Figure 92 Forest plots of likelihood ratios (LR's) for cervical funnelling between 20 – 24 weeks' gestation in predicting spontaneous preterm birth stratified according to reference standards (outcomes) in asymptomatic antenatal women



+ Studies are arranged in descending order of quality *Any definition of funnelling unless otherwise stated

Figure 93 Forest plots of likelihood ratios (LR's) from ideal quality studies for cervical length measurement in predicting spontaneous preterm birth within 48 hours of testing in symptomatic women with threatened preterm labour

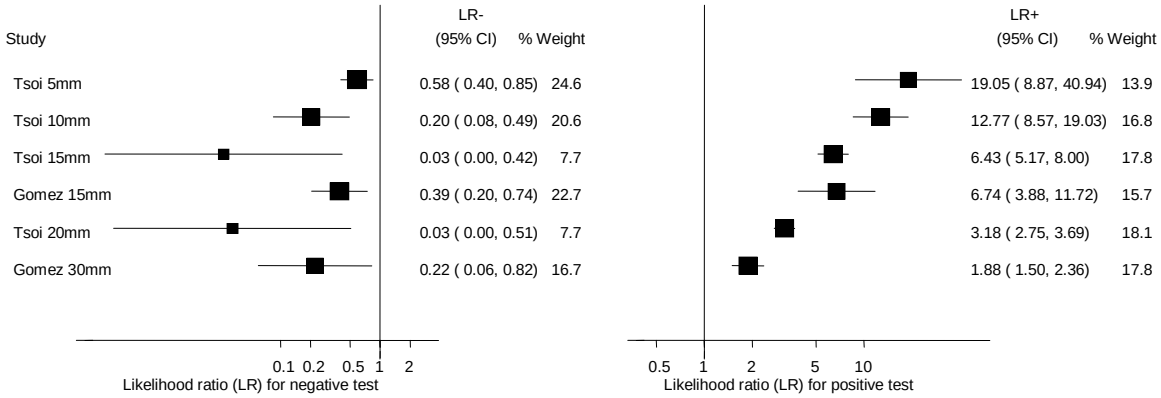
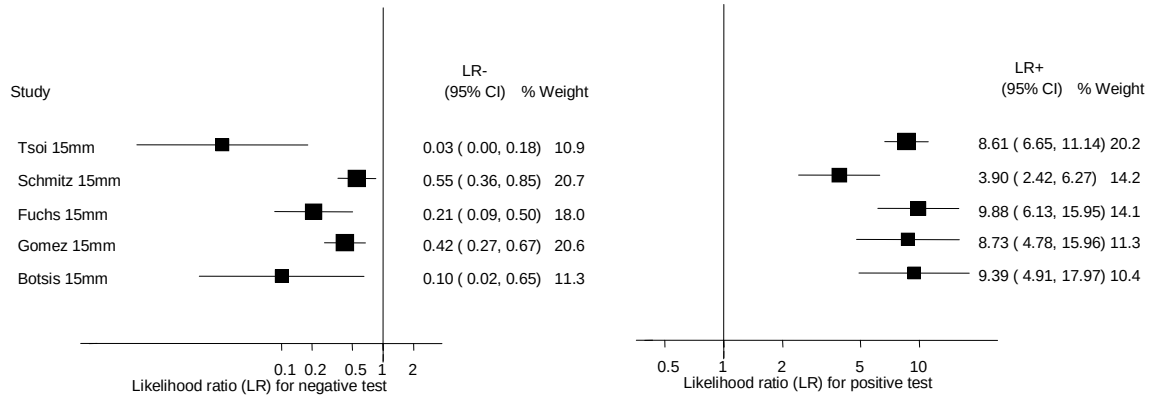
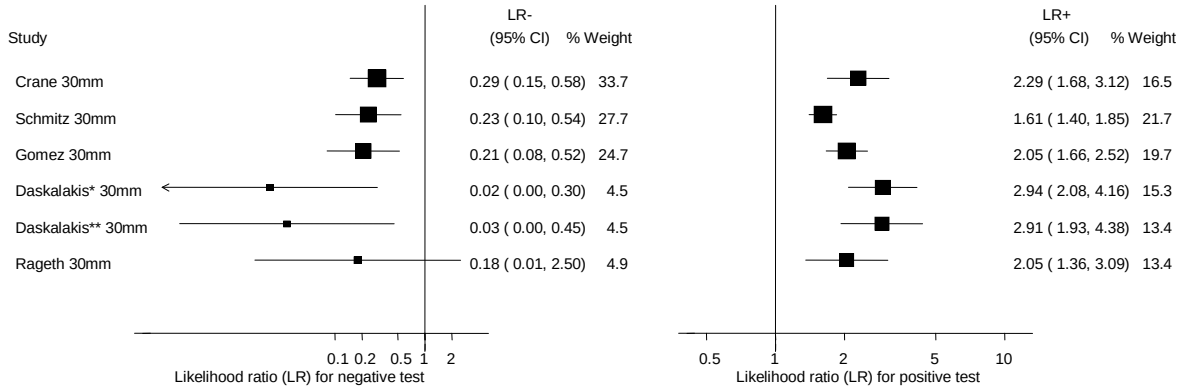


Figure 94 Forest plots of likelihood ratios (LR's) for cervical length measurement utilizing commonly chosen threshold (15mm) in predicting spontaneous preterm birth within 7 days of testing in symptomatic women with threatened preterm labour[+]



+ Studies are arranged in descending order of quality

Figure 95 Forest plots of likelihood ratios (LR's) for cervical length measurement utilizing commonly chosen threshold (30mm) in predicting spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour[+]



+ Studies are arranged in descending order of quality

Figure 96 Forest plots of likelihood ratios (LR's) from ideal quality studies for cervical length measurement in predicting spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour

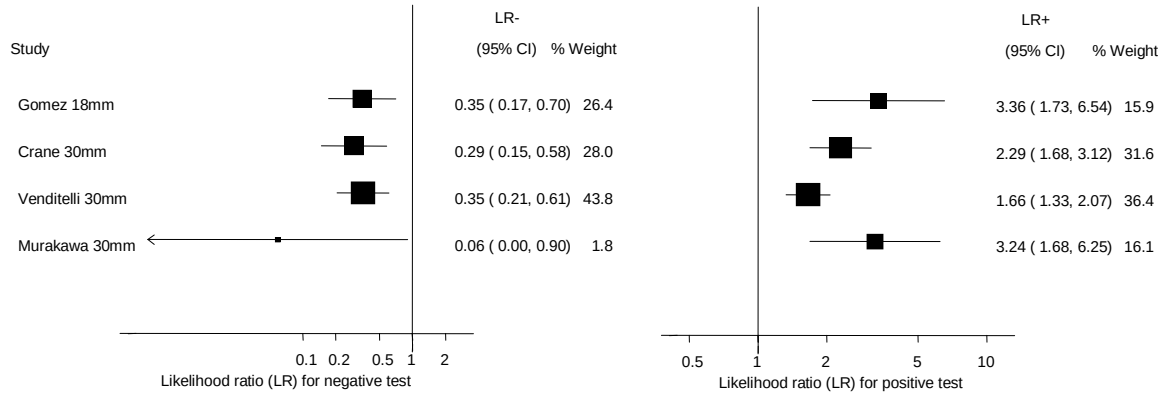
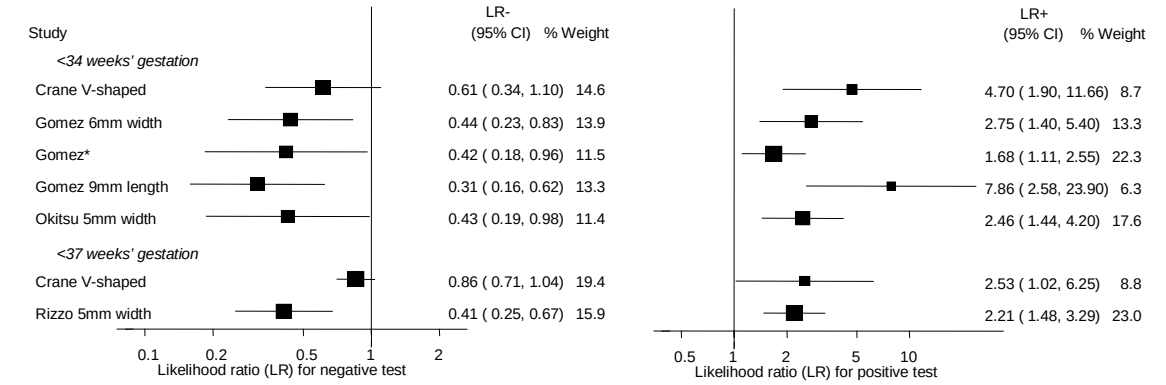


Figure 97 Forest plots of likelihood ratios (LR's) for cervical funnelling between 24 – 36 weeks' gestation in predicting spontaneous preterm birth stratified according to reference standards (outcomes) in symptomatic women with threatened preterm labour



Studies are arranged in descending order of quality *Any definition of funnelling unless otherwise stated

Chapter 5 Overview and summary of test accuracy results

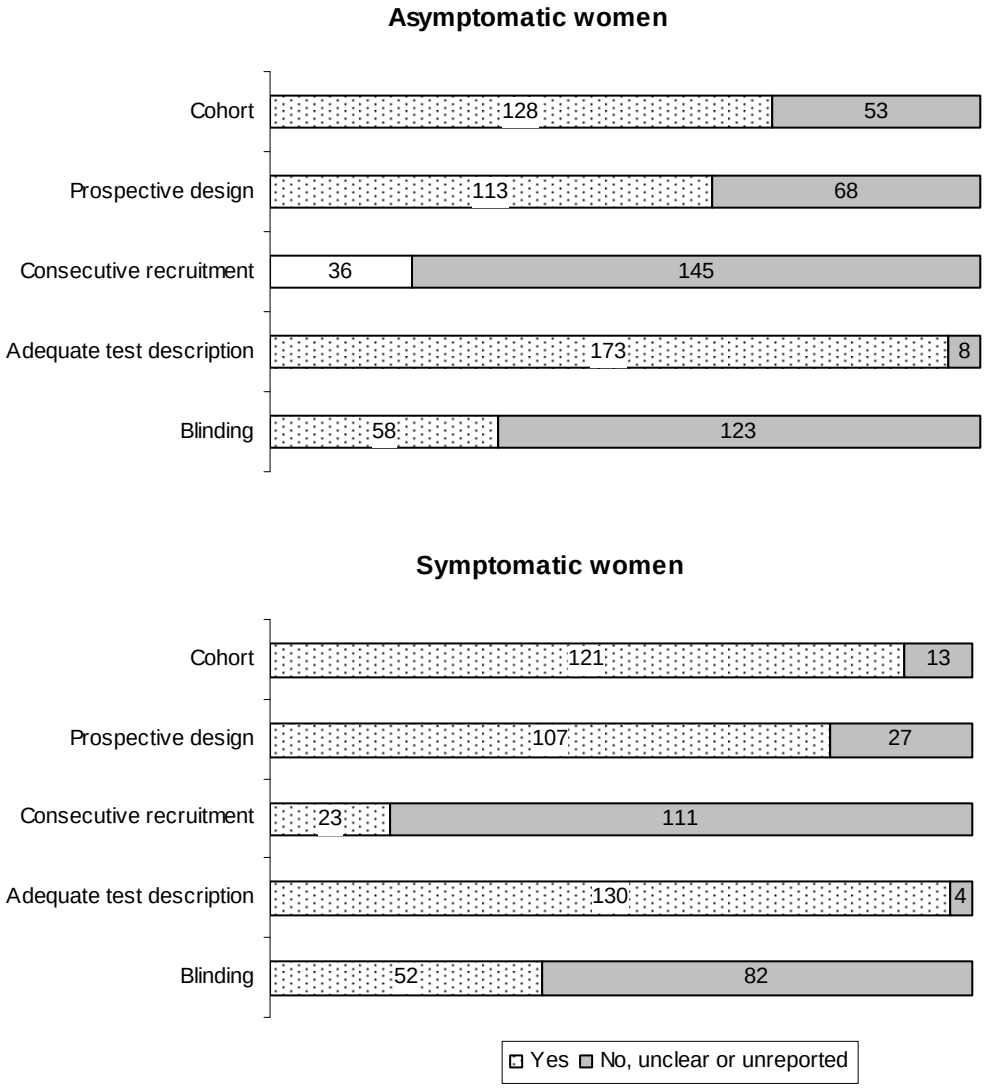
There were a large number of studies reviewed but not many promising tests were identified. The numbers of studies for most test were small and of poor quality with few exceptions. The median number of studies was 5 (range 0 - 26) for asymptomatic and was 2 (range 0 - 40) for symptomatic women. It was planned *a-priori* to perform meta-analysis only for highest quality studies to improve the validity of the results. This meant that the number of tests meta-analyzable were small (cervico-vaginal fetal fibronectin and cervical ultrasound) and the number of studies per meta-analysis was similarly small (median = 3), introducing imprecision in estimation of accuracy for these tests.

The overall quality of studies within reviews was variable. There were deficiencies in many areas of methodology (Figure 98) but two quality items, consecutive enrolment and blinding, were more frequently unreported than the other items. No test had universally high quality data, but in some tests e.g. fibronectin, cervico-vaginal phIGFBP-1 or cervical length, a number of high quality studies was available. Overall quality of test accuracy studies in symptomatic women tend to be better than those in asymptomatic women ($\chi 2$ test $p \leq 0.001$). The interpretations of the accuracy data on all tests were negatively affected by poor reporting and potential threats to validity identified in assessment of study quality. Although the reviews were restricted to singleton pregnancies, some of the included studies where they have not specifically recruited singleton pregnancies were suspected to have included patients across other clinical risk spectrum (e.g. multiple pregnancies). There could be thus, when assessing the published results, uncertainties about the reported predictive ability of the test.

In evaluation of many tests, the limited number of quality studies and the limited number of cases with preterm birth per study seriously constrained conclusions. As spontaneous preterm birth has lower prevalence particularly for important outcomes such as birth before 34 weeks'

gestation or birth with 48 hours of presentation, the small absolute numbers of affected cases introduced imprecision(i.e. by increasing the variance and therefore widen the calculated confidence intervals).

Figure 98 Summary of methodological quality of studies included in the systematic review of accuracy of rheobase testing in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies*

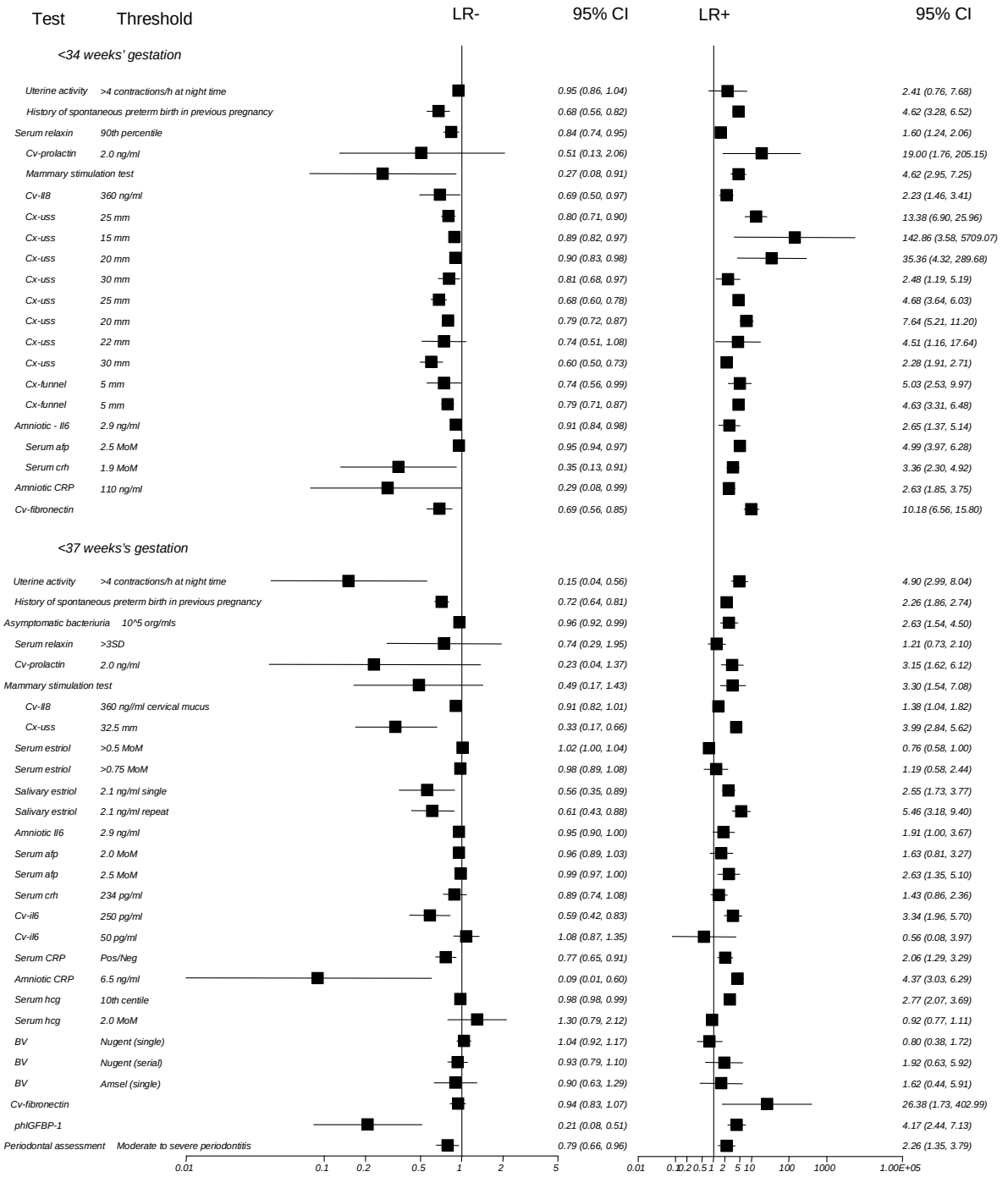


*Some studies are reported twice because of their contributions to multiple reviews

The main accuracy results are summarised in Figure 99, Figure 100 and Figure 101 representing prediction of spontaneous preterm birth before 34 and 37 weeks' gestation in asymptomatic women, within 48 hours and 7 days of testing, and before 34 and 37 weeks' gestation in symptomatic women respectively. For most of the tests evaluated, results were not pooled due to lack of high quality studies. Where studies were pooled, random effects model were used. This method accounts for statistical heterogeneity that is left unexplained after attempts to identify its sources, where feasible. It produced a more conservative estimate of the confidence intervals.

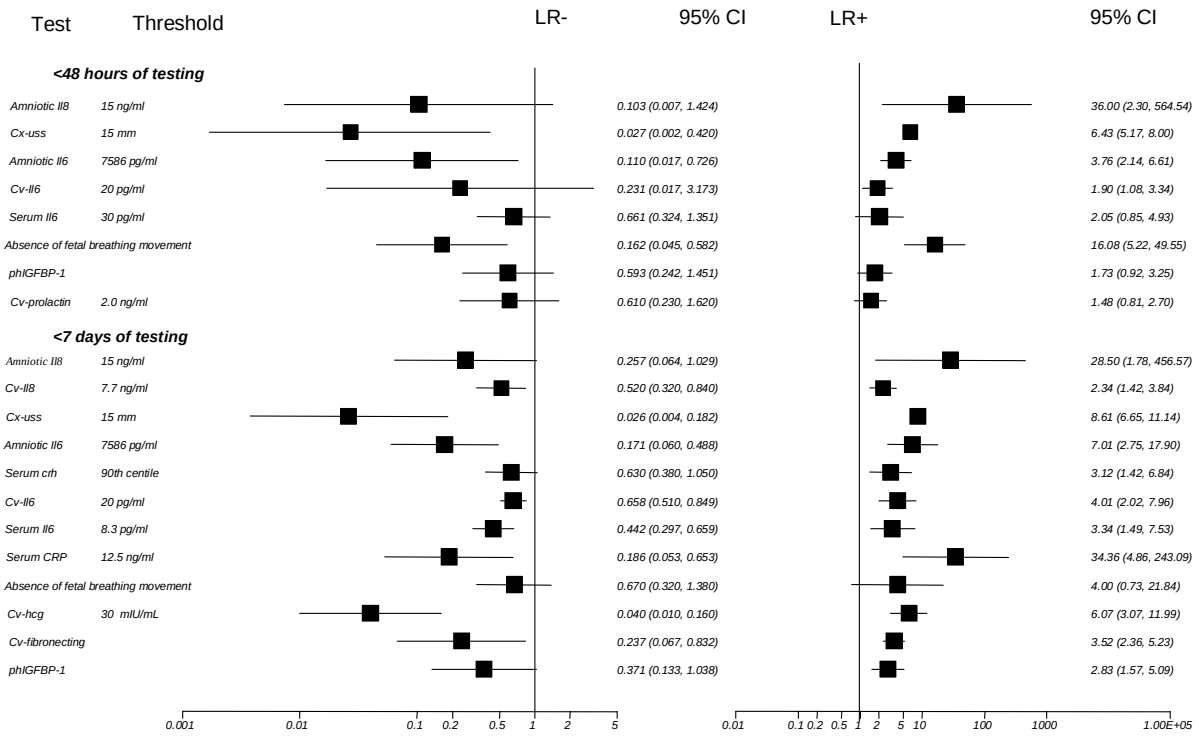
The forest plots below summarize tests' accuracies for the 22 tests for the asymptomatic (for predicting birth before 34 and 37 weeks' gestation) and symptomatic (for predicting birth within 48 hours and 7 days of testing and before 34 and 37 weeks' gestation) population. The more the LR values depart away from 1.0 the greater the change they would bring in post-test probability. As proposed by Jaeschke *et al*,[46] a useful test should at least have an accuracy of LR+ >5.0 and LR- <0.2. These estimates require at least a moderate disease prevalence for post-test probabilities to show substantial change from pre-test probabilities. In this situation, when a test produces a positive result it will predict with greater likelihood the later development of the condition i.e. spontaneous preterm birth. When the test result is negative, it would provide reassurance that the condition will not likely develop later. Clinically, however, most tests tend to have a greater usefulness for either LR+ or LR-, not both together. This trade-off was apparent from the accuracy reviews. Considering the point estimates of LR's, screening for spontaneous preterm birth in asymptomatic antenatal women tended to be more useful for a positive test result compared to a negative test result, i.e. LR+ tended to be further away from 1.0. This meant that it was unlikely that negative test result would rule out the likelihood of spontaneous preterm birth confidently. In symptomatic women, similarly, there was a predominance of more useful LR+ results compared to LR- results.

Figure 99 Summary forest plots of likelihood ratios (LR's) of various tests accuracy as a predictor of spontaneous preterm birth in asymptomatic women stratified according to reference standards (outcome of spontaneous preterm birth before 34 and 37 weeks' gestation), tests and selected thresholds[*]



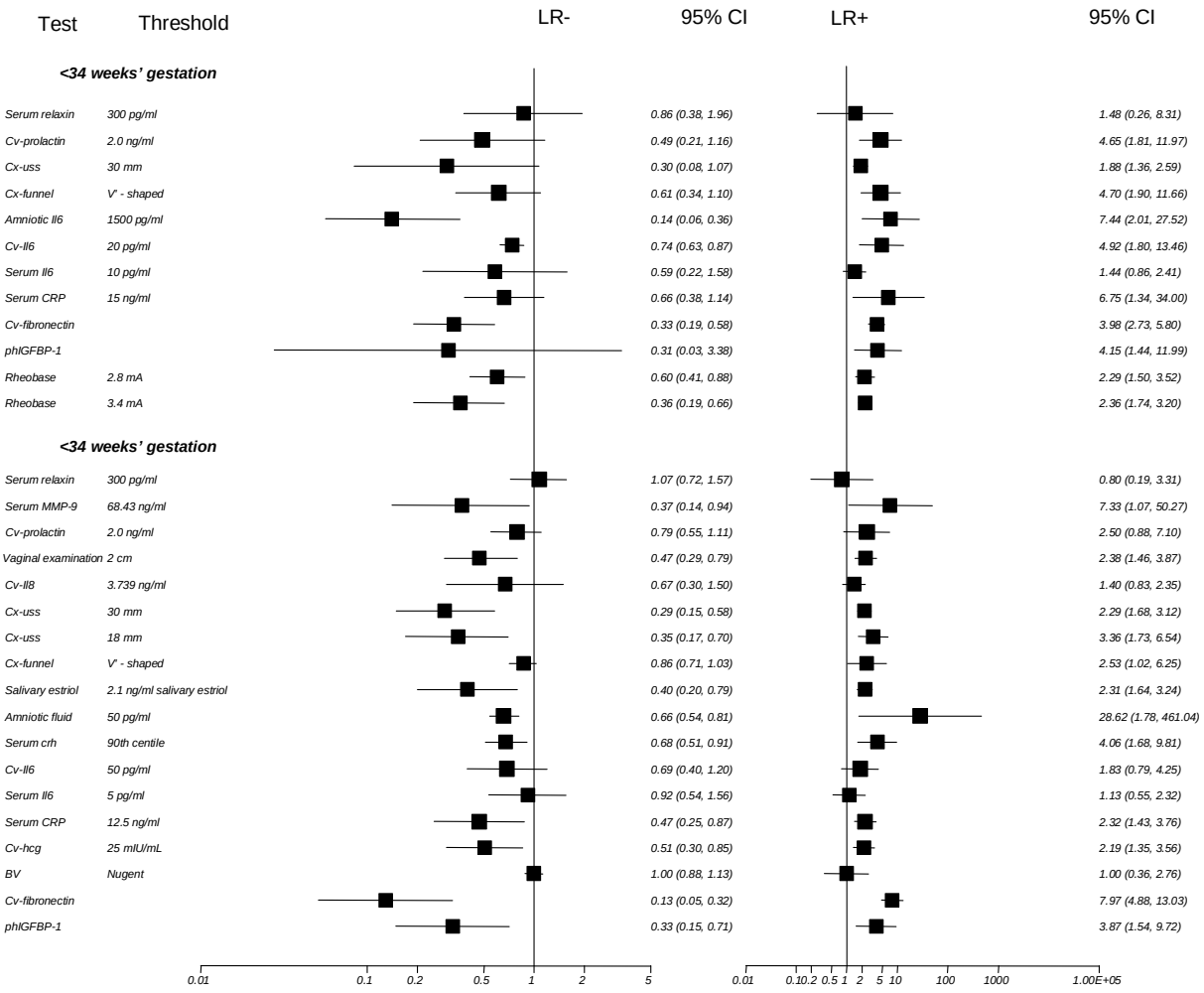
*LR values above are those that were based on results of highest quality studies.

Figure 100 Summary forest plots of likelihood ratios (LR's) of various tests accuracy as a predictor of spontaneous preterm birth in symptomatic women stratified according to reference standards (outcome spontaneous preterm birth within 48 hours and 7 days of testing), tests and selected thresholds*



*LR values above are those that were based on results of highest quality studies.

Figure 101 Summary forest plots of likelihood ratios (LR's) of various tests accuracy as a predictor of spontaneous preterm birth in symptomatic women stratified according to reference standards (outcome spontaneous preterm birth before 34 and 37 weeks' gestation), tests and selected thresholds*



*LR values above are those that were based on results of highest quality studies.

Screening typically involves use of a confirmatory test after initial testing, prior to institution of an intervention. This was not the case in this research thesis where testing was used to identify a risk group in which preventative interventions (both intensive monitoring and or treatments) will be employed directly after test results are known. In this situation, for a test to serve as a good tool for screening, it should perform well.[46] However, given that there is often a trade-off between LR+ and LR-, the balance between LR+ and LR- that is preferable depends largely on the outcomes of the disease and costs (including potential mortality and morbidity) associated with the intervention(s). The consequences of false positive results include both costs of intensive monitoring and treatment associated morbidity, and costs among otherwise normal women. Thus it is important that LR+ is suitably high, since erroneously providing interventions to falsely positive cases leads to unwarranted inconvenience, expense and morbidity when the likelihood of spontaneous preterm birth does not change compared to the background risk due to low LR+ values. Given the consequences of false negative results (both costs and morbidity of cases of spontaneous preterm birth resulting due to lack of treatment), it is important that LR- is suitably low. This is because erroneously withholding effective interventions from falsely negative results lead to excessive morbidity and expense in the face of spontaneous preterm birth. If available effective interventions are convenient, inexpensive, and without adverse effects (to both mother and child), it is better to have the accuracy trade-offs in favour of LR- i.e. a test with a low LR- than a high LR+ and *vice-versa*.

Figure 99, Figure 100 and Figure 101 demonstrate that considering the point estimates of and imprecision in the LR's, most tests perform either poorly or the level of their performance is uncertain (i.e. with a wide confidence intervals). A few tests in asymptomatic antenatal women reached LR+ >5, putting them in the useful tests category in predicting spontaneous preterm birth. These were ultrasonographic cervical length and funnelling measurement, and

cervico-vaginal fetal fibronectin screening. For LR-, only two tests in asymptomatic women had an LR- <0.2. These were detection of uterine contractions (by home uterine monitoring device) and amniotic fluid CRP measurement. In symptomatic women with threatened preterm labour, there were more tests with LR+ >5 compared to asymptomatic women. These were absence of fetal breathing movements, cervical length and funnelling, amniotic fluid IL6, serum CRP for predicting spontaneous preterm birth within 48 hours or 7 days of testing; and MMP-9, amniotic fluid IL6, cervico-vaginal fetal fibronectin and cervico-vaginal hcg testing for predicting spontaneous preterm birth before 34 or 37 weeks' gestation. For symptomatic women with threatened preterm labour: measurement of cervico-vaginal IL8, cervico-vaginal hcg, cervical length measurement, absence of fetal breathing movement, amniotic fluid IL6, and serum CRP all showed LR- <0.2 for predicting spontaneous preterm birth within 48 hours or 7 days of testing. Only cervico-vaginal fetal fibronectin and amniotic fluid IL6 had an LR- <0.2 in predicting spontaneous preterm birth before 34 or 37 weeks' gestation. Depending on level of effectiveness of various interventions and their associated inconvenience, costs and morbidity, a threshold analysis (a subject for further research) will be required to determine which thresholds of accuracy are required to make testing cost-effective in prevention of spontaneous preterm birth. Tabular summary of the tests' accuracies for the respective reference standards can be found as Table 3 – Table 8.

Table 3 Summary of tests' accuracy results for predicting spontaneous preterm birth before 34 weeks' gestation in asymptomatic antenatal women

Test (threshold)	No. of studies	LR+ (95% CI)	LR- (95% CI)
Cervical length (15mm @14-20 weeks)	3	142.86 (3.58 - 5709.07)	0.89 (0.82 - 0.97)
Cervical length (20mm @14-20 weeks)	3	35.36 (4.32 - 289.68	0.90 (0.83 - 0.98)
Cervico-vaginal prolactin (2.0ng/ml)	5	19.00 (1.76 - 205.15)	0.51 (0.13 - 2.06)
Cervical length (25mm @14-20 weeks)	3	13.38 (6.90 - 25.96	0.80 (0.71 - 0.90)
Cervico-vaginal fetal fibronectin	7	10.18 (6.56 - 15.80	0.69 (0.56 - 0.85)
Cervical length (20mm @20-24 weeks)	2	7.64 (15.21 - 1.20)	0.79 (0.72 - 0.87)
Cervical funnelling (5mm @16-20 weeks)	1	5.03 (2.53 - 9.97)	0.74 (0.56 - 0.99)
Serum α-fetoprotein (2.5 MoM)	9	4.99 (3.97 - 6.28)	0.95 (0.94 - 0.97)
Cervical length (25mm 20-24)	2	4.68 (3.64 - 6.03)	0.68 (0.60 - 0.78)
Cervical funnelling (5mm @20-24 weeks)	1	4.63 (3.31 - 6.48)	0.79 (0.71 - 0.87)
History of spontaneous preterm birth	10	4.62 (3.28 - 6.52)	0.68 (0.56 - 0.82)
Mammary stimulation test	2	4.62 (2.95 - 7.25)	0.27 (0.08 - 0.91)
Cervical length (22mm @20-24 weeks)	5	4.51 (1.16 - 17.64	0.74 (0.51 - 1.08)
Serum CRH (1.9MoM)	5	3.36 (2.30 - 4.92)	0.35 (0.13 - 0.91)
Amniotic fluid IL6 (2.9ng/ml)	2	2.65 (1.37 - 5.14)	0.91 (0.84 - 0.98)
Amniotic fluid CRP (110ng/ml)	1	2.63 (1.85 - 3.75)	0.29 (0.08 - 0.99)
Cervical length (30mm @14-20 weeks)	3	2.48 (1.19 - 5.19)	0.81 (0.68 - 0.97)
HUAM (≥4 contractions/h at night time)	1	2.41 (0.76 - 7.68)	0.95 (0.86 - 1.04)
Cervical length (30mm @20-24)	5	2.28 (1.91 - 2.71)	0.60 (0.50 - 0.73)
Cervico-vaginal IL8 (360ng/ml)	4	2.23 (1.46 - 3.41)	0.69 (0.50 - 0.97)
Serum relaxin (90th centile)	5	1.60 (1.24 - 2.06)	0.84 (0.74 - 0.95)

Table 4 Summary of tests' accuracy results for predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic antenatal women

Test (threshold)	No. of studies	LR+ (95% CI)	LR- (95% CI)
Cervico-vaginal fetal fibronectin	15	26.38 (1.73 - 402.99)	0.94 (0.83 - 1.07)
Salivary estriol (serial)	2	5.46 (3.18 - 9.40)	0.61 (0.43 - 0.88)
HUAM (≥4 contractions/h at night time)	3	4.90 (2.99 - 8.04)	0.15 (0.04 - 0.56)
Amniotic fluid CRP (6.5ng/ml)	3	4.37 (3.03 - 6.29)	0.09 (0.01 - 0.60)
phIGFBP-1	1	4.17 (2.44 - 7.13)	0.21 (0.08 - 0.51)
Cervical length (32.5mm @20-24 weeks)	1	3.99 (2.84 - 5.62)	0.33 (0.17 - 0.66)
Cervico-vaginal IL6 (250pg/ml)	3	3.34 (1.96 - 5.70)	0.59 (0.42 - 0.83)
Mammary stimulation test	2	3.30 (1.54 - 7.08)	0.49 (0.17 - 1.43)
Cervico-vaginal prolactin (2.0ng/ml)	5	3.15 (1.62 - 6.12)	0.23 (0.04 - 1.37)
Serum β-hcg (10th centile)	2	2.77 (2.07 - 3.69)	0.98 (0.98 - 0.99)
Asymptomatic bacteriuria testing	26	2.63 (1.54 - 4.50)	0.96 (0.92 - 0.99)
Serum α-fetoprotein (2.5MoM)	9	2.63 (1.35 - 5.10)	0.99 (0.97 - 1.00)
Salivary estriol (single)	2	2.55 (1.73 - 3.77)	0.56 (0.35 - 0.89)
Moderate to severe periodontitis	13	2.26 (1.35 - 3.79)	0.79 (0.66 - 0.96)
History of spontaneous preterm birth	10	2.26 (1.86 - 2.74)	0.72 (0.64 - 0.81)
Serum CRP (positive or negative)	1	2.06 (1.29 - 3.29)	0.77 (0.65 - 0.91)
Bacterial vaginosis (Nugent serial)	3	1.92 (0.63 - 5.92)	0.93 (0.79 - 1.10)
Amniotic fluid il6 (2.9ng/ml)	2	1.91 (1.00 - 3.67)	0.95 (0.90 - 1.00)
Serum α-fetoprotein (2.0MoM))	9	1.63 (0.81 - 3.27)	0.96 (0.89 - 1.03)
Bacterial vaginosis (Amsel single)	3	1.62 (0.44 - 5.91)	0.90 (0.63 - 1.29)
Serum CRH (234 pg/ml)	5	1.43 (0.86 - 2.36)	0.89 (0.74 - 1.08)
Cervico-vaginal IL8 (360ng/ml)	4	1.38 (1.04 - 1.82)	0.91 (0.82 - 1.01)
Serum relaxin (>3SD)	5	1.21 (0.73 - 2.10)	0.74 (0.29 - 1.95)
Serum estriol (<0.75MoM)	5	1.19 (0.58 - 2.44)	0.98 (0.89 - 1.08)
Serum β-hcg (2.0MoM)	10	0.92 (0.77 - 1.11)	1.30 (0.79 - 2.12)
Bacterial vaginosis (Nugent single)	12	0.80 (0.38 - 1.72)	1.04 (0.92 - 1.17)
Serum estriol (<0.5MoM)	5	0.76 (0.58 - 1.00)	1.02 (1.00 - 1.04)
Cervico-vaginal IL6 (50pg/ml)	3	0.56 (0.08 - 3.97)	1.08 (0.87 - 1.35)

Table 5 Summary of tests' accuracy results for predicting spontaneous preterm birth within 48 hours of testing in symptomatic women with threatened preterm labour

Test (threshold)	No. of studies	LR+ (95% CI)	LR- (95% CI)
Amniotic fluid IL8 (15ng/ml)	4	36.00 (2.30 - 564.54)	0.10 (0.01 - 1.42)
Absence of fetal breathing movement	3	16.08 (5.22 - 49.55)	0.16 (0.05 - 0.58)
Cervical length (15mm)	2	6.43 (5.17 - 8.00)	0.03 (0.00 - 0.42)
Amniotic fluid IL6 (7.5ng/ml)	10	3.76 (2.14 - 6.61)	0.11 (0.02 - 0.73)
Serum IL6 (30pg/ml)	5	2.05 (0.85 - 4.93)	0.66 (0.32 - 1.35)
Cervico-vaginal IL6 (20pg/ml)	7	1.90 (1.08 - 3.34)	0.23 (0.02 - 3.17)
phIGFBP-1	3	1.73 (0.92 - 3.25)	0.59 (0.24 - 1.45)

Table 6 Summary of tests' accuracy results for predicting spontaneous preterm birth within 7 – 10 days of testing in symptomatic women with threatened preterm labour

Test (threshold)	No. of studies	LR+ (95% CI)	LR- (95% CI)
Serum CRP (12.5ng/ml)	4	34.36 (4.86 - 243.09)	0.19 (0.05 - 0.65)
Amniotic fluid IL8 (15ng/ml)	4	28.50 (1.78 - 456.57)	0.26 (0.06 - 1.03)
Cervical length (15mm)	6	8.61 (6.65 - 11.14)	0.03 (0.00 - 0.18)
Amniotic fluid IL6 (7.5ng/ml)	10	7.01 (2.75 - 17.90)	0.17 (0.06 - 0.49)
Cervico-vaginal β-hcg (30mIU/ml)	3	6.07 (3.07 - 11.99)	0.04 (0.01 - 0.16)
Cervico-vaginal IL6 (20pg/ml)	7	4.01 (2.02 - 7.96)	0.66 (0.51 - 0.85)
Absence of fetal breathing movement	6	4.00 (0.73 - 21.84)	0.67 (0.32 - 1.38)
Cervico-vaginal fetal fibronectin	18	3.52 (2.36 - 5.23)	0.24 (0.07 - 0.83)
Serum IL6 (8.30pg/ml)	5	3.34 (1.49 - 7.53)	0.44 (0.30 - 0.66)
Serum CRH (90th centile)	1	3.12 (1.42 - 6.84)	0.63 (0.38 - 1.05)
phIGFBP-1	3	2.83 (1.57 - 5.09)	0.37 (0.13 - 1.04)
Cervico-vaginal IL8 (7.7ng/ml)	4	2.34 (1.42 - 3.84)	0.52 (0.32 - 0.84)
Cervico-vaginal prolactin (2.0ng/ml)	5	1.48 (0.81 - 2.70)	0.61 (0.23 - 1.62)

Table 7 Summary of tests' accuracy results for predicting spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour

Test (threshold)	No. of studies	LR+ (95% CI)	LR- (95% CI)
Amniotic fluid IL6 (1500pg/ml)	10	7.44 (2.01 - 27.52)	0.14 (0.06 - 0.36)
Serum CRP (15ng/ml)	1	6.75 (1.34 - 34.00)	0.66 (0.38 - 1.14)
Cervico-vaginal IL6 (20pg/ml)	7	4.92 (1.80 - 13.46)	0.74 (0.63 - 0.87)
Cervical funnelling (V-shaped)	1	4.70 (1.90 - 11.66)	0.61 (0.34 - 1.10)
Cervico-vaginal prolactin (2.0ng/ml)	5	4.65 (1.81 - 11.97)	0.49 (0.21 - 1.16)
phIGFBP-1	3	4.15 (1.44 - 11.99)	0.31 (0.03 - 3.38)
Cervico-vaginal fetal fibronectin	8	3.98 (2.73 - 5.80)	0.33 (0.19 - 0.58)
Cervical length (30mm)	4	1.88 (1.36 - 2.59)	0.30 (0.08 - 1.07)
Serum relaxin (300pg/ml)	5	1.48 (0.26 - 8.31)	0.86 (0.38 - 1.96)
Serum IL6 (10pg/ml)	5	1.44 (0.86 - 2.41)	0.59 (0.22 - 1.58)

Table 8 Summary of tests' accuracy results for predicting spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour

Test (threshold)	No. of studies	LR+ (95% CI)	LR- (95% CI)
Amniotic fluid IL6 (50pg/ml)	10	28.62 (1.78 - 461.04)	0.66 (0.54 - 0.81)
Cervico-vaginal fetal fibronectin	31	7.97 (4.88 - 13.03)	0.13 (0.05 - 0.32)
Serum MMP-9 (68.43ng/ml)	2	7.33 (1.07 - 50.27)	0.37 (0.14 - 0.94)
Serum CRH (90th centile)	1	4.06 (1.68 - 9.81)	0.68 (0.51 - 0.91)
phIGFBP-1	9	3.87 (1.54 - 9.72)	0.33 (0.15 - 0.71)
Cervical length (18mm)	1	3.36 (1.73 - 6.54)	0.35 (0.17 - 0.70)
Cervical funnelling (V-shaped)	1	2.53 (1.02 - 6.25)	0.86 (0.71 - 1.03)
Cervico-vaginal prolactin (2.0ng/ml)	5	2.50 (0.88 - 7.10)	0.79 (0.55 - 1.11)
Digital vaginal examination (2cm dilatation)	10	2.38 (1.46 - 3.87)	0.47 (0.29 - 0.79)
Rheobase (>3.4 mA)	1	2.36 (1.74 - 3.20)	0.36 (0.19 - 0.66)
Serum CRP (12.5ng/ml)	4	2.32 (1.43 - 3.76)	0.47 (0.25 - 0.87)
Salivary estriol (2.1ng/ml)	2	2.31 (1.64 - 3.24)	0.40 (0.20 - 0.79)
Cervical length (30mm)	3	2.29 (1.68 - 3.12)	0.29 (0.15 - 0.58)
Rheobase (>2.8mA)	1	2.29 (1.50 - 3.52)	0.60 (0.41 - 0.88)
Cervico-vaginal β-hcg (25mIU/ml)	3	2.19 (1.35 - 3.56)	0.51 (0.30 - 0.85)
Cervico-vaginal IL8 (50pg/mL)	7	1.83 (0.79 - 4.25)	0.69 (0.40 - 1.20)
Cervico-vaginal IL8 (3.739ng/ml)	4	1.40 (0.83 - 2.35)	0.67 (0.30 - 1.50)
Serum IL6 (5pg/ml)	5	1.13 (0.55 - 2.32)	0.92 (0.54 - 1.56)
Bacterial vaginosis (Nugent)	8	1.00 (0.36 - 2.76)	1.00 (0.88 - 1.13)
Serum relaxin (300pg/ml)	5	0.80 (0.19 - 3.31)	1.07 (0.72 - 1.57)

Chapter 6 Discussion

Methodological quality of the reviews undertaken for the thesis

The strength of the inferences derived from this thesis depends upon the rigor of the methodology and the reliability of the accuracy estimates. In undertaking the research for this thesis, all contemporaneous criteria for performing a quality systematic review were followed (Chapter 3). A range of databases were searched and no language restriction was applied. Cognizant of the fact that reviews of test accuracy studies are often fraught with difficulty due to poor methodological quality of the primary studies, each of the selected studies were scrutinised for their methodological quality. However, some of the methodological issues that have empirically been shown to overestimate accuracy such as the absence of test descriptions and the use of different reference tests were generally not applicable to the studies selected for review due to the clinical nature of spontaneous preterm birth.

Limitations arising from problems with primary data

The interpretations of the accuracy data on tests are affected by threats to validity identified in assessment of study quality (Figure 98). Only a few tests had been evaluated and reported in studies which met generally accepted definition of ideal study design as defined in the method section, both in asymptomatic and symptomatic women. The following tests were evaluated in at least one ideal quality study: cervical length and funnelling, IL6, and cervico-vaginal fetal fibronectin in asymptomatic women, with the addition of absence of fetal breathing movement in symptomatic women. The overall quality of studies within reviews was variable with deficiencies in many areas of methodology (Figure 98). Association between design quality components and diagnostic performance has been empirically studied.[42;348] It cannot be stressed enough that before any measures of test accuracy (whatever their magnitude) count as scientific evidence, it would require adequate reporting of the study's population (clinical spectrum), design and execution in evaluating the test's accuracy. Idealistic

expectations of the level of detail that should be provided in the literature of the primary studies including adherence to the current standards of reporting for diagnostic studies, were perhaps unrealistic given that initiatives to improve test accuracy study design and its subsequent reporting are only recent phenomena.

In evaluating many of included studies for the reviews, blinding and consecutive enrolment, in particular, were often either unreported or were not part of the study design. The extent to which these deficiencies have impact on accuracy estimates depends on a number of factors. In both asymptomatic antenatal women and symptomatic women with threatened preterm labour, there is a time interval between (screening) testing and potential outcome of spontaneous preterm birth. In this situation, the absence of blinded assessment may lead to alteration(s) of usual antenatal care that would affect the outcome i.e. spontaneous preterm birth, which in turn would influence the final accuracy estimates. This is known as 'treatment paradox'[349] where test positive women given effective treatments leading to prevention of spontaneous preterm birth, makes an otherwise reasonable test appears inaccurate.

Lack of consecutive enrolment may have resulted in differing clinical spectrum of women being enrolled in the study, leading to a spectrum bias potentially influencing the final accuracy estimates. Spectrum bias refers to the possibility that a test's LR+ and/or LR- may vary in groups of patients with differing risks of spontaneous preterm birth. In other words, spectrum bias refers to variation across subgroups, (or, to use the technical term, effect measure modification). This effect can be minimized, not withstanding the inherent study design and reporting inadequacy, by constraining the inclusion criteria for the reviews to singleton and low-risk pregnancies.

Where studies were available, absence of primary data in key areas (e.g. description of population, threshold, or outcome) limited the ability to extract and explore the data as

completely as would have been desired. As an example, some studies reported mean ± SD for non-Gaussian distributions of index test results and did not provide 2x2 tables. Such study had to be excluded from the review. Attempts to minimize this problem by writing to the corresponding author(s) for the required data met with variable results: An initial (usually via e-mail) communiqué followed by another a week later in case of non-response. Generally, co-operation was obtained but for some, their work commitment schedules meant that they were not able to extend co-operation where they would have otherwise liked to. In some circumstances, data were no longer available, accessible or simply no response was forthcoming. Only after this approach was exhausted, were the studies excluded that would otherwise have met the inclusion criteria. Indeed, from the preceding discussion, better quality primary test accuracy studies with better reporting would have improved the assessment of the test accuracy.

This discussion would be remiss without touching on the issue of interpreting a test's accuracy in light of information obtained by any preceding test(s), which has so far been overlooked in diagnostic research. Diagnostic confounding, which refers to one or more tests having predictive abilities that are related to each other and the outcome, such that it is difficult to assess the independent prediction from each of the tests on the diagnosis of the outcome can occur in this situation. Additionally, it remains to be elucidated whether the very act of performing some the tests within the vaginal and cervical milieu (e.g. cervical digital examination, transvaginal ultrasound scanning or obtaining samples for subsequent assays) may contribute to the cascading process that manifest eventually as spontaneous preterm birth. This thesis did not assess these emerging issues. There may or may not be increased accuracy when two or more tests were combined in the prediction of spontaneous preterm birth depending on the overlap of information between test. These issues may only be optimally dealt with by multivariable analysis of the primary studies or Individual Patient

Data (IPD) meta-analyses. Such an analysis would generate probabilities of spontaneous preterm birth for patient characteristics and test results to obtain a predictive probability for each profile, e.g. the probability of spontaneous preterm birth from a cervical length measurement in a nulliparous obese woman. If no multivariable analysis is planned, such confounding may be attenuated by selection of patient groups that are as homogeneous as possible with respect to their other characteristics (e.g. patient history and obstetric risk profile in multiparous women). However, such an approach is difficult given the large amount of clinical information that usually exists (e.g. age, parity, and co-morbidities to name a few).

Limitations arising from review methods

The accuracy review was carried out using a comprehensive search strategy so as to minimise the risk of missing tests and studies. Nevertheless the amount of research identified per test was often of variable quality and insufficient to produce precise estimates of accuracy in either or both groups of populations of asymptomatic antenatal women and symptomatic women with threatened preterm labour. For both asymptomatic women and symptomatic women populations, only three tests had >20 accuracy studies: asymptomatic bacteriuria (26 studies), serum β-hcg (20 studies) and serum α-fetoprotein for asymptomatic women (20 studies); cervico-vaginal fetal fibronectin (58 studies), cervical length and funnelling (42 studies), and IL6 (22 studies) for symptomatic women. Where there was scarcity of primary studies, it was not surprising that some of the LR estimates were affected by imprecision. Thus when assessing their results about the range of reported predictive ability (accuracy) of the tests especially when there was only a small number of studies with small sample size in each could not be ascertain with a high degree of confidence.

Thus far, the thesis in carrying the systematic reviews had already made explicit the deficiencies in the quality of studies (see above). In light of this, it would have been preferred to base any inferences on high quality studies e.g. ideal quality features in asymptomatic

antenatal women population, using a single threshold and outcome (reference standard). To that end, it was planned *a-priori* subgroup analyses according to study quality within predefined populations and outcomes. However, due to the low number of included studies per test or per specific threshold, compounded by oft lack of reporting clarity, such subgroup analyses were often not possible or had insufficient power. In cases where it had been possible e.g. cervico-vaginal fetal fibronectin and cervical length measurement, their subgroup analyses were based on small number of studies.

Variation in test thresholds for determining abnormality meant that generating summaries of findings was not straightforward. For some tests e.g. cervical ultrasound measurement of either length or funnelling, the same study may have provided estimates from different thresholds. This precluded valid statistical comparison of these indices due to violation of the principle that the compared study samples should be statistically independent. For some other tests e.g. CRP and interleukins, none of the studies had used the same thresholds, thus limiting the ability to compare and infer the accuracy estimates obtained. In these situations, a systematic attempt (see methods section) was made at translating results in a summary ROC space into clinically relevant information. For pooling test results that can be pooled, a random effects approach was used where unexplained statistical heterogeneity is formally taken into account. Detailed exploration of reasons for heterogeneity was constrained largely because poor reporting and the small number of studies per test would have rendered use of explorative statistical methods such as meta-regression underpowered. If the pooled results amalgamate heterogeneous individual estimates, these should be interpreted with caution. In situations where it was not sensible to pool given the absence of high quality studies, an arbitrarily chosen accuracy estimates from the largest higher quality study available for the particular test would have been shown for comparison. The thesis conservative method and judgement, given the uncertain impact of these study design issues on the magnitudes of the

accuracy estimates, would likely to have generated summaries of the best available results for clinical interpretation.

Limitations arising from things not done (omissions)

For some tests where only few studies (e.g. rheobase (1 study), mammary stimulation test (2 studies), MMP-9 (2 studies)) were found, besides reporting their individual accuracy estimates no meaningful analyses could be carried out. It had been expected, at the inception of the thesis research, that there would be some studies on the accuracy of abdominal palpation for uterine contractions in symptomatic women with threatened preterm labour as a predictor for spontaneous preterm birth. However within the extensive literature searches, no studies were found on this aspect of physical examination, which forms the cornerstone of daily clinical practice. For some tests, and this has to be borne in mind, researchers were only just beginning to make headway in evaluating their accuracies where the relevant studies were only just emerging (e.g. periodontal assessment, serum relaxin, phIGFBP-1). Additionally as understanding of the aetiology, physiology and pathology of spontaneous preterm birth evolves, more tests would appear that may not have been included in the current review.

Interpretation of the findings

Typically, confirmatory test usually follows the initial screening, before institution of therapy. In the research for this thesis, this is not the case. Screening is used to identify a risk group that may benefit from preventative interventions (e.g. intensive monitoring and treatments), which will be employed directly when screening results are known, and without further confirmatory test(s). Screening and tests, which offer high LR+ have the potential to minimise unwarranted inconvenience, expense and morbidity associated with false positive results, which led to unnecessary interventions; while those, which offer low LR- have the potential to minimise unwarranted inconvenience, expense and morbidity associated with false negative results, which led to spontaneous preterm births. Additionally, tests that detect changes of the

final common pathway of spontaneous preterm labour (irrespective of the initial stimulus e.g. be it sub-clinical infection or a cervical structural abnormality) e.g. cervical shortening/funnelling or vaginal fibronectin are more likely to be accurate than screening e.g. for infection. Once these tests become positive it may be less likely that an intervention would be effective.

Given the quality, level and precision of the accuracy evidence, the thesis found that no single test emerged as a front runner neither in predicting spontaneous preterm births when the test result was positive nor to exclude it when the test result was negative. On a few occasions, this was due to imprecision of the LR estimates i.e. given a useful LR point estimate; its CI's should not be wide enough so as to make the LR less useful due to its imprecision. For example absence of fetal breathing movement had an LR+ 6.08 (95% CI 5.22 - 49.55) which would have made it a useful test in predicting spontaneous preterm birth within 48 hours testing when the result is positive. However, it had and LR- 0.16 (95% CI 0.05 - 0.58) where the upper limit of its confidence would have made it less than a useful test when the test result is negative. Had the estimate of the LR- including its CI's be <0.2, absence of fetal breathing movement would have been a useful test indeed. It may well be that no single screening or testing modality would suffice in the prediction of spontaneous preterm birth and that an IPD to better delineate the accuracy of test combinations has to be considered in the absence of a novel accurate test.

Recommendations for practice

How, and before, accuracy results from this thesis are considered for incorporation into clinical practice, there are several factors to be appraised. They include dealing with challenges relating to the systematic review process (covered above), patient acceptance and preferences as well as cost-effectiveness' analysis of any interventions (taking account both the tests' and interventions' benefits and harmful side-effects to both mother and fetus

(newborn)). Notwithstanding such challenges, one such consideration for application of thesis is modelling the integration of accuracy results with results from effectiveness studies to derive corresponding number needed to treat (NNTreat) and number needed to test (NNTest), which will aid and inform decision making. Of patients' acceptance and preference, the issues have not been explored in the literature especially in relation to more invasive tests yet potentially accurate (e.g. amniotic fluid measurement of interleukins). One of the key issues concerning screening or predictive tests for spontaneous preterm birth is that, if available effective interventions are convenient, inexpensive, and without particular risk of harm or side effects, it is better to have tests with better LR- than LR+ values. It is worth speculating that in preventing spontaneous preterm birth, it may be difficult from a clinical and patient perspective to distinguish between false positive and false negative results and so from this perspective the optimal screening or testing modality will be one which minimizes both false positive (i.e. the test showed a high LR+) and false negative (i.e. the test showed a low LR-) results. Where screening and or testing have low LR- than high LR+, they are unlikely to improve cost-effectiveness when used in combination with cheap, safe and effective treatments. Similarly, where screening and or testing have higher LR+ it will minimize the unwarranted cost, complications from exposure of women and the fetus to treatments. Depending on the cost-effectiveness' analysis, there is a small risk of overlooking potentially accurate screening or testing modalities in the face of cheap, safe and effective interventions to prevent spontaneous preterm birth. Data provided in Figure 99 - Figure 101 would be ideal for consideration into a cost-effectiveness' future research analysis because it provided the most robust estimates, which was either derived from meta-analysis of ideal quality studies or from the largest higher quality study available for the particular test. Such a cost-effective analysis would have shown the level of LR+ and LR- that would be required to make testing cost-effective in prevention of spontaneous preterm birth. Until such a consideration (i.e. cost-

effectiveness), there are no practical recommendations for clinicians for prevention of spontaneous preterm birth with testing performed before preventative treatment, beyond stating, which of those available tests that are accurate and are thus worthy for further considerations.

Table 9 Testing among symptomatic pregnant women for risk of spontaneous preterm birth and number of women needed to be tested and treated with antenatal maternal administration of corticosteroids to prevent respiratory distress syndrome before 34 weeks' gestation for anticipated birth within 7 days of testing, based on a prevalence of spontaneous preterm birth of 4.5%, risk of respiratory distress syndrome (RDS) of 53% and relative risk treatment effect of corticosteroids of 0.66[1]

	Probability of spontaneous preterm birth after testing positive (%)	Probability of RDS without treatment (%)[2]	Probability of RDS after treatment (%)	NNTreat[3]	NNTest[4]
No test, no treatment	–	2.4	2.4	–	–
No test, treat all	–	2.4	1.6	123	–
Test all, treat positives					
Serum CRP	61.8	32.8	21.6	9	112
Cervical length (15mm)	28.9	15.3	10.1	19	48
Amniotic fluid IL6 (7.5ng/ml)	24.8	13.2	8.7	22	56
Cervico-vaginal HCG (30mIU/mL)	22.2	11.8	7.8	25	49
Absence of fetal breathing movement	15.9	8.4	5.9	29	65
Cervico-vaginal fetal fibronectin	14.2	7.5	5.6	39	58
phIGFBP-1	11.8	6.2	4.1	48	95

1. Risk of RDS at this gestation was derived from Usher et al[350] and Sinclair et al[351] while that of corticosteroids treatment effect was derived from Roberts et al.[352]
2. Further detail for the calculation for probability of RDS can be found from Honest et al.[23]
3. Number needed to treat (NNTreat) to prevent one additional case of an adverse outcome was calculated by 1/(post-test disease probability after tested positive – probability of disease after tested positive & received treatment).
4. Number needed to test (NNTest) to prevent one additional case of an adverse outcome with the treatment of test positive case was calculated by 1/(true positives as a proportion of population (TP) – (TP * RR)).

Recommendations for research

- New more robustly designed test accuracy studies are required to develop tests that have superior LR- values.
- Such studies should evaluate the added value of new test using multivariable analyses and include cost-effectiveness' analysis taking into account subsequent interventions together with both tests and interventions benefits and side-effects profile as well as women's acceptance and preference.
- Where such studies are not forthcoming, individual patient data (IPD) of test accuracy meta-analysis should be considered as an alternative.

Chapter 7 Conclusions

There are a number of promising tests identified by this thesis in spite of the aforementioned provisos and limitation. For asymptomatic women, only testing for asymptomatic bacteriuria, cervico-vaginal fibronectin, assessment for periodontitis and bacterial vaginosis, and serum β-hcg were evaluated in more than 10 studies while for symptomatic women, aside from fetal fibronectin, and amniotic fluid IL6 which has been evaluated in 31 and 10 studies respectively, the remainder have only been evaluated in a handful of studies. Some tests were able to achieve high predictive value when positive, but at the expense of compromised low predictive value when negative. Only a few tests reached LR+ point estimates >5. In asymptomatic antenatal women these were ultrasonographic cervical funnelling and length measurement, cervico-vaginal prolactin and cervico-vaginal fetal fibronectin screening for predicting spontaneous preterm birth before 34 weeks' gestation. In this group, tests with LR- point estimates approaching <0.2 were detection of uterine contraction (by mammary stimulating test) and amniotic fluid CRP measurement. In symptomatic women with threatened preterm labour tests with LR+ point estimate >5 were absence of fetal breathing movements, cervical length measurement, amniotic fluid IL6 and IL8, serum CRP and

cervico-vaginal hcg (for predicting birth within 2-7 days of testing); and serum CRP, amniotic fluid IL6, and MMP-9, cervico-vaginal fetal fibronectin and cervico-vaginal hcg (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation). In this group tests with LR- point estimate <0.2 were measurement of cervico-vaginal hcg, cervical length measurement, absence of fetal breathing movement, amniotic fluid IL6 and IL8, and serum CRP (for predicting birth within 2 - 7 days of testing); and cervico-vaginal fetal fibronectin and amniotic fluid IL6 (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation).

The prominence of the detection of absence of fetal breathing movement, cervical funnelling and cervical length measurement provide a stronger impetus for a universal provision for high quality ultrasound machine in labour wards for predicting spontaneous preterm birth among women with a viable pregnancy who present with threatened preterm labour to direct management (e.g. administration of tocolysis, corticosteroids and in-utero transfer). Nevertheless, provision for round the clock trained personnel to perform such a scan in the interim is a challenge. Additionally, the feasibility and acceptability to mothers and health providers of such tests including more invasive (but potentially more accurate amniotic fluid assessment of IL6 and 8) strategies needs to be explored. Rigorous evaluation is needed of tests with minimal cost (i.e. tests that are 'inexpensive') or invasiveness whose initial assessments suggest that they may have high levels of accuracy. Similarly, there is a need for high quality, adequately powered randomized controlled trials to investigate whether interventions are indeed effective in reducing (in asymptomatic women) and/or delaying (in symptomatic women with threatened preterm labour) spontaneous preterm birth. In future, an economic model (cost-effectiveness) should be developed which considers not just spontaneous preterm birth, but other related outcomes, particularly those relevant to the infant like perinatal death and shorter and longer term outcomes amongst survivors. Such a

modelling project should make provision for primary data collection on the safety of interventions and their associated costs.

Appendices

Appendices

Appendix I - List of tests

List of tests for predicting spontaneous preterm birth

Type of tests or investigation	Predictive and diagnostic tests for preterm birth	Last updated
History	Previous history of either spontaneous preterm birth*	
Examination	Abdominal palpation+	
	Cervical digital examination+	
Biochemistry	Cervico-vaginal glycoproteins: Interleukins (IL-6, IL-8)+ β-hcg+ Fetal fibronectin*+ Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1)+	2001
	Serum glycoproteins: α-fetoprotein, human chorionic gonadotrophin (as part of Down's screening)*	
	Endocrine hormones: Salivary estriol+ Corticotrophin releasing hormone+	
	Inflammatory markers (serum): C-reactive protein*+ Matrix metalloprotease (MMP)+ Interleukins*+	
Microbiology	Detection of bacterial vaginosis*+ Periodontal screening* Midstream urine culture*+	2002 2006 1989
Physiological	Uterine activity monitoring* Rheobase+ Mammary stimulation test+	
Ultrasound scan	Absence of fetal breathing movements+	2003
	Measurement of cervical length*+	2003

*Test applied on asymptomatic women
+Test applied on symptomatic women

Appendix II - Search strategies

MEDLINE (Ovid Gateway). 2000-2005/Aug week 1. 10th August 2005.

186 records were retrieved.

1. Meta-Analysis/
2. Review-Literature/
3. meta analysis.pt.
4. review literature.pt.
5. (meta analy$ or metaanaly$ or meta-analy$).tw.
6. (systematic adj4 (review$ or overview$)).tw.
7. (data adj synthesis).ti,ab.
8. (published adj studies).ti,ab.
9. (data adj extract$).ti,ab.
10. or/1-9
11. letter.pt.
12. comment.pt.
13. editorial.pt.
14. 11 or 12 or 13
15. Animal/
16. Human/
17. 15 not (15 and 16)
18. 10 not (14 or 17)
19. Labor, Premature/
20. ((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
21. ((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
22. ((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
23. (premature adj3 (labor or labour or parturition)).ti,ab.
24. Fetal Membranes, Premature Rupture/
25. ((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
26. (PROM or PPROM).ti,ab.
27. or/19-26
28. 18 and 27

MEDLINE (Ovid Gateway). 2002/April-2005/Sep week 1. 20th September 2005.

2858 records were retrieved in MEDLINE and 184 records were retrieved in MEDLINE In-Process & Other Non-Indexed Citations.

1. Labor, Premature/
2. ((premature or preterm or pre term) adj3 birth$).ti,ab.
3. ((premature or preterm or pre term) adj3 deliver$).ti,ab.
4. ((preterm or pre term) adj3 (labor or labour)).ti,ab.
5. (premature adj3 (labor or labour or parturition)).ti,ab.
6. or/1-5
7. exp Socioeconomic Factors/
8. Social Class/
9. Ethnic Groups/
10. risk factors/
11. Life Style/
12. exp Substance-Related Disorders/
13. exp smoking/
14. Pregnancy, High-Risk/
15. Pregnancy in Adolescence/
16. exp Pregnancy, Multiple/
17. Pregnancy Complications/
18. Parity/
19. Reproductive History/
20. Fetal Membranes, Premature Rupture/
21. Cervix Incompetence/
22. exp Abdominal Pain/
23. Uterine Contraction/
24. Uterine Hemorrhage/
25. Cervical Ripening/
26. Treponema pallidum/
27. Neisseria gonorrhoeae/
28. Chlamydia trachomatis/
29. exp Sexually Transmitted Diseases, Bacterial/
30. exp Bacteroidaceae Infections/
31. exp Chlamydiaceae Infections/
32. exp Herpes Genitalis/
33. Vaginosis, Bacterial/
34. mobiluncus/

35. Streptococcus agalactiae/
36. Mycoplasma hominis/
37. Trichomonas vaginalis/
38. Bacteroides Infections/
39. Gardnerella vaginalis/
40. Bacteriuria/
41. Granuloma Inguinale/
42. exp Mycoplasmatales Infections/
43. exp Neisseriaceae Infections/
44. exp Treponemal Infections/
45. exp Staphylococcal Infections/
46. exp Streptococcal Infections/
47. Ureaplasma Infections/
48. exp Lactobacillus/
49. exp Urinary Tract Infections/
50. exp "Diagnostic Techniques, Obstetrical and Gynecological"/
51. exp Diagnostic Equipment/
52. exp Diagnostic Imaging/
53. Diagnostic Tests, Routine/
54. exp Reagent Kits, Diagnostic/
55. exp Ultrasonography, Prenatal/
56. Medical History Taking/
57. Risk Assessment/
58. exp Physical Examination/
59. Uterine Monitoring/
60. exp Culture Techniques/
61. exp Body Constitution/
62. Body Temperature/
63. exp fever/
64. Palpation/
65. exp Corpus Luteum Hormones/
66. Relaxin/
67. exp Prostaglandins/
68. exp Estrogens/
69. exp Inhibins/
70. exp Estradiol/
71. exp Estriol/
72. exp Estrone/
73. exp Estrogen Receptor Modulators/
74. exp Receptors, Estrogen/
75. exp Prostaglandin Antagonists/
76. exp Receptors, Prostaglandin/
77. exp Leukotrienes/
78. exp Thromboxanes/
79. exp Collagenases/
80. Fetal Proteins/
81. Fibronectins/
82. exp Acute-Phase Proteins/
83. exp Immunoproteins/
84. Platelet-Derived Growth Factor/
85. Tumor Necrosis Factor-alpha/
86. Chorioamnionitis/
87. Esterases/
88. exp Cytokines/
89. exp Amniotic Fluid/
90. exp Leukocytes/
91. Saliva/
92. exp Biological Markers/
93. Corticotropin-Releasing Hormone/
94. (risk factor$ or socioeconomic factor$ or socioeconomic status).ti,ab.
95. (occupation$ or socioeconomic or ethnic or ethnicity or manual work or long hours).ti,ab.
96. (cocaine or heroin or narcotics or crack or dope or cannabis or substance abuse$ or addiction).ti,ab.
97. (substance disorder$ or smoking or tobacco or alcohol$ or lifestyle$ or life-style$).ti,ab.
98. (low adj3 pregnancy adj3 weight).ti,ab.
99. high parity.ti,ab.
100. (early adj3 bleeding adj3 pregnancy).ti,ab.
101. vaginal bleeding.ti,ab.
102. ((uterine or antepartum) adj3 (hemorrhage or haemorrhage)).ti,ab.
103. (abdominal pain or uterine contraction$).ti,ab.
104. (pyrexia or febrile or fever).ti,ab.
105. (short adj3 pregnancies).ti,ab.
106. (interpregnancy interval$ or inter-pregnancy interval$).ti,ab.
107. (older women or elderly women).ti,ab.
108. (adolescent$ or teenage$).ti,ab.
109. (clinical histor$ or patient histor$ or patient record$ or pregnan$ histor$ or birth histor$ or reproductive histor$).ti,ab.
110. (obstetric histor$ or previous preterm or repeat preterm).ti,ab.

111. (premature adj3 rupture adj3 membrane$).ti,ab.
112. Chorioamnionitis.ti,ab.
113. (estriol or plasma crf or vaginal infection$).ti,ab.
114. ((biophysical or biochemical) adj3 marker$).ti,ab.
115. (bishop$ adj1 (score or scores)).ti,ab.
116. (cervical adj1 (change$ or length or measurement)).ti,ab.
117. (endocervical adj1 (effacement or assessment or examination)).ti,ab.
118. (cervical adj1 (effacement or assessment or state or examination$)).ti,ab.
119. (risk scor$ or physical examination$).ti,ab.
120. (physical exam or physical exams or cervical dilation or (cervix adj3 length)).ti,ab.
121. (dilation adj3 cervix).ti,ab.
122. tocodynamo$.ti,ab.
123. (uterine tocography or uterine anomal$ or tocometry).ti,ab.
124. ((cervical or cervix) adj3 (abnormal$ or incompetence or incompetent)).ti,ab.
125. ((cervical or cervix) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
126. ((vaginal or endovaginal or transvaginal or obstetric) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
127. (uterine activity or huam or uterine excitability).ti,ab.
128. ((myometrial or myometrium) adj3 excitability).ti,ab.
129. ((oncofetal or c-reactive) adj3 protein$).ti,ab.
130. fibronectin.ti,ab.
131. (asymptomatic bacteriuria or genital tract infection$).ti,ab.
132. (leucocyte esterase$ or cytokines).ti,ab.
133. (culture$ adj3 (amniotic or blood or genital or vaginal or cervical or urine)).ti,ab.
134. (timp or collagenase or relaxin or tissue inhibitor$).ti,ab.
135. plasma corticotropin releasing hormone$.ti,ab.
136. (estrogen or oestrogen or progestogen).ti,ab.
137. (glucose concentration$ adj3 amniotic).ti,ab.
138. (zinc adj3 amniotic).ti,ab.
139. or/7-138
140. exp "Sensitivity and Specificity"/
141. ROC Curve/
142. Logistic Models/
143. Likelihood Functions/
144. exp Diagnostic Errors/
145. (predictive value$ or reproducibility or logistic regression).ti,ab.
146. (ability adj3 predict$).ti,ab.
147. (logistic model$ or sroc or roc or positive rate or positive rates).ti,ab.
148. (likelihood ratio$ or negative rate or negative rates).ti,ab.
149. (receiver operating characteristic or correlation or correlated).ti,ab.
150. ((tests or test) adj3 accuracy).ti,ab.
151. (curve or curves or test outcome).ti,ab.
152. ((pretest or pre-test or posttest or post-test) adj3 probabilities).ti,ab.
153. diagnosis.ti,ab.
154. or/140-153
155. 6 and 139 and 154
156. 6 and 139
157. Animals/
158. Humans/
159. 157 not (157 and 158)
160. 155 not 159
161. 156 not 159
162. (200204$ or 200205$ or 200206$ or 200207$ or 200208$ or 200209$ or 200210$ or 200211$ or 200212$).ed.
163. (2003$ or 2004$ or 2005$).ed.
164. 162 or 163
165. 161 and 164

EMBASE (Ovid Gateway). 2002/Mar-2005/week 38. 20th September 2005.

4004 records were retrieved.

1. Premature Labor/
2. ((premature or preterm or pre term or pre-term) adj3 birth$).ti,ab.
3. ((premature or preterm or pre term or pre-term) adj3 deliver$).ti,ab.
4. ((preterm or pre term or pre-term) adj3 (labor or labour)).ti,ab.
5. (premature adj3 (labor or labour or parturition)).ti,ab.
6. Premature Fetus Membrane Rupture/
7. ((premature or preterm or pre term or pre-term) adj3 rupture$).ti,ab.
8. (PROM or PPROM).ti,ab.
9. or/1-8
10. exp socioeconomics/
11. Social Class/
12. Risk Factor/
13. exp "Ethnic and Racial Groups"/
14. Smoking/
15. exp Addiction/

16. Substance Abuse/
17. lifestyle/
18. High Risk Pregnancy/
19. Adolescent Pregnancy/
20. parity/
21. ANAMNESIS/
22. Pregnancy Disorder/
23. exp Pregnancy Complication/
24. Obstetric Hemorrhage/
25. Premature Fetus Membrane Rupture/
26. Abdominal Pain/
27. Uterus Contraction/
28. exp Uterine Complication/
29. Uterus Bleeding/
30. Fever/
31. exp Estrogen/
32. Relaxin/
33. Treponema Pallidum/
34. Neisseria Gonorrhoeae/
35. Streptococcus Agalactiae/
36. Mycoplasma Hominis/
37. Chlamydia Trachomatis/
38. Trichomonas Vaginalis/
39. bacteroides/
40. Vaginitis/
41. mobiluncus/
42. Gardnerella Vaginalis/
43. exp Multiple Pregnancy/
44. Uterine Cervix Incompetence/
45. Uterine Cervix Ripening/
46. Fetoprotein/
47. Fibronectin/
48. Bacteriuria/
49. exp Diagnostic Procedure/
50. exp Laboratory Diagnosis/
51. Virus Diagnosis/
52. Venereal Disease Reaction Test/
53. Transvaginal Echography/
54. equipment/
55. Diagnostic Imaging/
56. Test Strip/
57. Reagent/
58. ultrasound/
59. Diagnostic Test/
60. Risk Assessment/
61. exp Physical Examination/
62. exp examination/
63. Home Monitoring/
64. exp Urogenital System Examination/
65. Clinical Observation/
66. Fetus Monitoring/
67. Esterase/
68. exp Tissue Culture/
69. exp Cytokine/
70. Acute Phase Protein/
71. exp Immunoglobulin/
72. Platelet Derived Growth Factor/
73. Tumor Necrosis Factor/
74. Sex Hormone/
75. Progesterone/
76. Inhibin/
77. Estradiol/
78. Estriol/
79. Estrone/
80. exp Estrogen Receptor/
81. exp Prostaglandin Receptor Blocking Agent/
82. exp Leukotriene/
83. exp Thromboxane/
84. Collagenase/
85. Body Constitution/
86. exp "Physical Constitution and Health"/
87. exp Body Temperature/
88. palpation/
89. exp Sexually Transmitted Disease/
90. exp bacteroides/
91. chlamydiaceae/

92. Granuloma Inguinale/
93. mycoplasmatales/
94. Gram Negative Infection/
95. neisseriaceae/
96. Bacterial Infection/
97. Staphylococcus Infection/
98. Streptococcus Infection/
99. exp lactobacillus/
100. Genital Herpes/
101. exp Urinary Tract Infection/
102. exp Chorioamnionitis/
103. exp Amnion Fluid/
104. exp leukocyte/
105. saliva/
106. Biological Marker/
107. Blood Analysis/
108. Blood Culture/
109. exp urinalysis/
110. Amnion Fluid Analysis/
111. Image Analysis/
112. Saliva Analysis/
113. Sputum Analysis/
114. exp assay/
115. exp Chemical Analysis/
116. Corticotropin Releasing Factor/
117. (risk factor$ or socioeconomic factor$ or socioeconomic status).ti,ab.
118. (occupation$ or socioeconomic or ethnic or ethnicity or manual work or long hours).ti,ab.
119. (cocaine or heroin or narcotics or crack or dope or cannabis or substance abuse$ or addiction).ti,ab.
120. (substance disorder$ or smoking or tobacco or alcohol$ or lifestyle$ or life-style$).ti,ab.
121. (low adj3 pregnancy adj3 weight).ti,ab.
122. high parity.ti,ab.
123. (early adj3 bleeding adj3 pregnancy).ti,ab.
124. vaginal bleeding.ti,ab.
125. ((uterine or antepartum) adj3 (hemorrhage or haemorrhage)).ti,ab.
126. (abdominal pain or uterine contraction$).ti,ab.
127. (pyrexia or febrile or fever).ti,ab.
128. (short adj3 pregnancies).ti,ab.
129. (interpregnancy interval$ or inter-pregnancy interval$).ti,ab.
130. (older women or elderly women).ti,ab.
131. (adolescent$ or teenage$).ti,ab.
132. (clinical histor$ or patient histor$ or patient record$ or pregnan$ histor$ or birth history$ or reproductive history$).ti,ab.
133. (obstetric histor$ or previous preterm or repeat preterm).ti,ab.
134. (premature adj3 rupture adj3 membrane$).ti,ab.
135. Chorioamnionitis.ti,ab.
136. (estriol or plasma crf or vaginal infection$).ti,ab.
137. ((biophysical or biochemical) adj3 marker$).ti,ab.
138. (bishop$ adj1 (score or scores)).ti,ab.
139. (cervical adj1 (change$ or length or measurement)).ti,ab.
140. (endocervical adj1 (effacement or assessment or examination)).ti,ab.
141. (cervical adj1 (effacement or assessment or state or examination$)).ti,ab.
142. (risk scor$ or physical examination$).ti,ab.
143. (physical exam or physical exams or cervical dilation or (cervix adj3 length)).ti,ab.
144. (dilation adj3 cervix).ti,ab.
145. tocodynamo$.ti,ab.
146. (uterine tocography or uterine anomal$ or tocometry).ti,ab.
147. ((cervical or cervix) adj3 (abnormal$ or incompetence or incompetent)).ti,ab.
148. ((cervical or cervix) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
149. ((vaginal or endovaginal or transvaginal or obstetric) adj3 (ultrasound or ultrasonography or sonography)).ti,ab.
150. (uterine activity or huam or uterine excitability).ti,ab.
151. ((myometrial or myometrium) adj3 excitability).ti,ab.
152. ((oncofetal or c-reactive) adj3 protein$).ti,ab.
153. fibronectin.ti,ab.
154. (asymptomatic bacteriuria or genital tract infection$).ti,ab.
155. (leucocyte esterase$ or cytokines).ti,ab.
156. (culture$ adj3 (amniotic or blood or genital or vaginal or cervical or urine)).ti,ab.
157. (timp or collagenase or relaxin or tissue inhibitor$).ti,ab.
158. plasma corticotropin releasing hormone$.ti,ab.
159. (estrogen or oestrogen or progestogen).ti,ab.
160. (glucose concentration$ adj3 amniotic).ti,ab.
161. (zinc adj3 amniotic).ti,ab.
162. or/10-161
163. Diagnostic Error/
164. Diagnostic Accuracy/
165. Diagnostic Value/
166. Differential Diagnosis/
167. Quantitative Diagnosis/

168. exp Statistical Analysis/
169. Discriminant Analysis/
170. statistics/
171. Statistical Model/
172. reliability/
173. variance/
174. Receiver Operating Characteristic/
175. Multiple Regression/
176. (predictive value$ or reproducibility or logistic regression).ti,ab.
177. (ability adj3 predict$).ti,ab.
178. (logistic model$ or sroc or roc or positive rate or positive rates).ti,ab.
179. (likelihood ratio$ or negative rate or negative rates).ti,ab.
180. (receiver operating characteristic or correlation or correlated).ti,ab.
181. ((tests or test) adj3 accuracy).ti,ab.
182. (curve or curves or test outcome).ti,ab.
183. ((pretest or pre-test or posttest or post-test) adj3 probabilities).ti,ab.
184. diagnosis.ti,ab.
185. (sensitivity or specificity).ti,ab.
186. or/163-185
187. 9 and 162 and 186
188. 9 and 162
189. exp animal/
190. Nonhuman/
191. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
192. 189 or 190 or 191
193. exp human/
194. 192 not (192 and 193)
195. 187 not 194
196. 188 not 194
197. (2002$ or 2003$ or 2004$ or 2005$).em.
198. 196 and 197

BIOSIS (DIALOG). 2002/June-2005/Sep. 22nd September 2005.

1071 records were retrieved.

s (premature or preterm)(3n)birth? ?
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor? ? or socioeconomic(w)factor? ?
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding
s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction? ?
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval? ?
s pregnancy(3n)multiple
s pregnancy(3n)complication? ?
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder? ? or smoking or tobacco or alcohol? or lifestyle? ?
s estriol or plasma(w)crf or vaginal(3n)infection? ?
s (biophysical or biochemical)(3w)marker? ?
s bishop?(w)score? ?
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record? ?
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test? ?)
s uterine(3n)activity or huam or uterine(3n)excitability
s (myometrial or myometrium)(3n)excitability

s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w)infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)
s timp or collagenase or relaxin or tissue(w)inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen
s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53
s s54/2002-2005

PASCAL (DIALOG). 2002/June-2005/Sep. 22nd September 2005.

456 records were retrieved.

s (premature or preterm)(3n)birth? ?
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor? ? or socioeconomic(w)factor? ?
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding
s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction? ?
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval? ?
s pregnancy(3n)multiple
s pregnancy(3n)complication? ?
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder? ? or smoking or tobacco or alcohol? or lifestyle? ?
s estriol or plasma(w)crf or vaginal(3n)infection? ?
s (biophysical or biochemical)(3w)marker? ?
s bishop?(w)score? ?
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record? ?
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test? ?)
s uterine(3n)activity or huam or uterine(3n)excitability
s (myometrial or myometrium)(3n)excitability
s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w)infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)
s timp or collagenase or relaxin or tissue(w)inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen
s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53

s s54/2002-2005

Science Citation Index (SCI) (DIALOG). 2002/June-2005/Sep. 22nd September 2005.

643 records were retrieved.

s (premature or preterm)(3n)birth? ?
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor? ? or socioeconomic(w)factor? ?
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding
s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction? ?
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval? ?
s pregnancy(3n)multiple
s pregnancy(3n)complication? ?
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder? ? or smoking or tobacco or alcohol? or lifestyle? ?
s estriol or plasma(w)crf or vaginal(3n)infection? ?
s (biophysical or biochemical)(3w)marker? ?
s bishop?(w)score? ?
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record? ?
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test? ?)
s uterine(3n)activity or huam or uterine(3n)excitability
s (myometrial or myometrium)(3n)excitability
s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w)infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)
s timp or collagenase or relaxin or tissue(w)inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen
s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53
s s54/2002-2005

Inside Conferences (DIALOG). 2002/June-2005/Sep. 22nd September 2005.

12 records were retrieved.

s (premature or preterm)(3n)birth? ?
s (premature or preterm)(3n)deliver?
s (premature or preterm)(3n)(labo?r or parturition)
s risk(w)factor? ? or socioeconomic(w)factor? ?
s low(3w)pregnancy(3w)weight
s high(w)parity
s early(3n)bleeding(3n)pregnancy
s vaginal(3n)bleeding

s (uterine or antepartum)(3w)(hemorrhag? or haemorrhag?)
s abdominal(w)pain or uterine(w)contraction? ?
s pyrexia or febrile
s short(3n)between(3n)pregnancies
s interpregnancy(w)interval? ?
s pregnancy(3n)multiple
s pregnancy(3n)complication? ?
s pregnancy(3n)(high(w)risk)
s pregnancy(3n)(adolescen? or teenage?)
s (older or elderly)(n)women
s occupation? or socioeconomic or ethnic or ethnicity or manual(w)work or long(w)hours
s cocaine or heroin or narcotics or crack or dope or cannabis or substance(w)abuse
s substance(w)disorder? ? or smoking or tobacco or alcohol? or lifestyle? ?
s estriol or plasma(w)crf or vaginal(3n)infection? ?
s (biophysical or biochemical)(3w)marker? ?
s bishop?(w)score? ?
s cervical(w)(change? or length or measurement)
s endocervical(w)(effacement or assessment)
s cervical(w)(effacement or assessment or state)
s medical(w)histor? or clinical(w)histor? or patient(w)histor? or patient(w)record? ?
s obstetric(w)histor? or previous(w)preterm or repeat(w)preterm
s risk(w)scor? or risk(w)assessment
s physical(w)examination? or cervical(w)dilation or cervix(3n)length
s dilation(3n)cervix
s uterine(w)tocography or uterine(w)anomal? or tocometry
s (cervical or cervix)(3n)(abnormal? or incompetence or incompetent)
s (cervical or cervix)(3n)(ultrasound or ultrasonography)
s (vaginal or endovaginal or transvaginal or obstetric)(3n)(ultrasound or ultrasonography)
s diagnostic(n)(technique? or equipment or test? ?)
s uterine(3n)activity or huam or uterine(3n)excitability
s (myometrial or myometrium)(3n)excitability
s (oncofetal or c-reactive)(w)(protein?)
s fibronectin?
s sexually(w)transmitted(w)disease?
s asymptomatic(w)bacteriuria or genital(w)tract(w)infection?
s chlamydia or gonorrhea or herpes
s leucocyte(w)esterase? or cytokines
s culture?(3n)(amniotic or blood or genital or vaginal or cervical)
s timp or collagenase or relaxin or tissue(w)inhibitor?
s plasma(w)corticotropin(w)releasing(w)hormone?
s estrogen or oestrogen or progestogen
s (glucose(w)concentration?)(n)amniotic
s zinc(n)amniotic
s s1:s3
s s4:s51
s s52 and s53
s s54/2002-2005

Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL). Cochrane Library, Issue 2:2002-3:2005. 20th September 2005.

1 new protocol was identified in CDSR and 144 records were retrieved in CENTRAL.

Labor, Premature (MeSH)
(premature or preterm or pre*term) NEAR/3 birth
(premature or preterm or pre*term) NEAR/3 deliver*
(preterm or pre*term) NEAR/3 (labour or labor)
premature NEAR/3 (labour or labor or parturition)
Fetal Membranes, Premature Rupture (MeSH)
(premature or preterm or pre*term) NEAR/3 ruptur*
PROM or PPROM
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
Socioeconomic Factors (MeSH)
Social Class (MeSH)
Risk Factors (MeSH)
Ethnic Groups (MeSH)
Smoking (MeSH)
Life Style(MeSH)
Substance-Related Disorders(MeSH)
Pregnancy, High-Risk (MeSH)
Parity (MeSH)
Reproductive History (MeSH)
Abdominal Pain (MeSH)
Pregnancy Complications (MeSH)
Uterine Contraction (MeSH)

Uterine Hemorrhage (MeSH)
Fever (MeSH)
Estriol (MeSH)
Relaxin (MeSH)
Treponema pallidum (MeSH)
Neisseria gonorrhoeae (MeSH)
Streptococcus agalactiae (MeSH)
Mycoplasma hominis (MeSH)
Chlamydia trachomatis (MeSH)
Trichomonas vaginalis (MeSH)
Bacteroides Infections (MeSH)
Vaginosis, Bacterial (MeSH)
Mobiluncus (MeSH)
Gardnerella vaginalis (MeSH)
Prostaglandins (MeSH)
Pregnancy, Multiple (MeSH)
Cervix Incompetence (MeSH)
Cervical Ripening (MeSH)
Fetal Proteins (MeSH)
Bacteriuria (MeSH)
Diagnostic Techniques, Obstetrical and Gynecological (MeSH)
Diagnostic Equipment (MeSH)
Diagnostic Imaging (MeSH)
Reagent Kits, Diagnostic (MeSH)
Ultrasonography, Prenatal (MeSH)
Diagnostic Tests, Routine (MeSH)
Medical History Taking (MeSH)
Risk Assessment (MeSH)
Physical Examination (MeSH)
Uterine Monitoring (MeSH)
Esterases (MeSH)
Cytokines (MeSH)
Immunoproteins (MeSH)
Platelet-Derived Growth Factor (MeSH)
Tumor Necrosis Factor-alpha (MeSH)
Gonadal Steroid Hormones (MeSH)
Corpus Luteum Hormones (MeSH)
Estrogens (MeSH)
Inhibins (MeSH)
Estradiol (MeSH)
Estrone (MeSH)
Receptors, Estrogen (MeSH)
Prostaglandin Antagonists (MeSH)
Receptors, Prostaglandin (MeSH)
Leukotrienes (MeSH)
Receptors, Thromboxane (MeSH)
Collagenases (MeSH)
Body Constitution (MeSH)
Body Temperature (MeSH)
Palpation (MeSH)
Sexually Transmitted Diseases, Bacterial (MeSH)
Bacteroidaceae Infections (MeSH)
Chlamydiaceae Infections (MeSH)
Granuloma Inguinale (MeSH)
Mycoplasmatales Infections (MeSH)
Neisseriaceae Infections (MeSH)
Treponemal Infections (MeSH)
Staphylococcal Infections (MeSH)
Streptococcal Infections (MeSH)
Ureaplasma Infections (MeSH)
Lactobacillus (MeSH)
Herpes Genitalis (MeSH)
Urinary Tract Infections (MeSH)
Chorioamnionitis (MeSH)
Amniotic Fluid (MeSH)
Leukocytes (MeSH)
Saliva (MeSH)
Biological Markers (MeSH)
Corticotropin-Releasing Hormone (MeSH)
(older or elderly) NEAR women
fibronectin* or tocodynamo* or (risk NEAR factor*) or (socioeconomic NEAR factor*)
low NEAR pregnancy NEAR weight
(high NEAR parity) or (early NEAR bleeding) or (vaginal NEAR bleeding) or (uterine or antepartum) NEAR hemorrhage or (abdominal NEAR pain) or (uterine NEAR contraction*) or pyrexia or febrile or fever or short NEAR/3 between NEAR/3 pregnancies

interpregnancy and interval* or occupation* or socioeconomic or ethnic or ethnicity or (manual NEAR work) or (long NEAR hours) or cocaine or heroin or narcotics or crack or dope or cannabis or (substance NEAR abuse) or smoking or tobacco or alcohol* or lifestyle* or estriol or (plasma NEAR crf) or (vaginal NEAR infection*)
(biophysical or biochemical) and marker* or bishop* and (score or scores) or cervical NEAR (change* or length or measurement) or endocervical NEAR (effacement or assessment) or cervical NEAR (effacement or assessment or state)
(clinical NEAR histor*) or (patient NEAR histor*) or (patient NEAR record*) or (obstetric NEAR histor*) or (previous NEAR preterm) or (repeat NEAR preterm) or (risk NEAR scor*) or (physical NEAR examination*) or (physical NEAR exam) or (physical NEAR exams) or (cervical NEAR dilation) or (cervix NEAR length) or dilation NEAR cervix
(uterine NEAR tocography) or (uterine NEAR anomal*) or tocometry or (cervical or cervix) NEAR (abnormal* or incompetence or incompetent) or (cervical or cervix) NEAR (ultrasound or ultrasonography) or (vaginal or endovaginal or transvaginal or obstetric) NEAR (ultrasound or ultrasonography) or uterine NEAR (activity or huam or excitability)
(myometrial or myometrium) NEAR excitability or (oncofetal or reactive) NEAR (protein*) or (asymptomatic NEAR bacteriuria) or (genital NEAR tract NEAR infection*) or leucocyte NEAR (esterase* or cytokines) or culture* NEAR (amniotic or blood or genital or vaginal or cervical)
timp or collagenase or relaxin or (tissue NEAR inhibitor*) or plasma NEAR corticotropin NEAR releasing NEAR hormone* or estrogen or oestrogen or progestogen or glucose NEAR concentration* NEAR amniotic or zinc NEAR amniotic
#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80
#81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101
#102 OR #103 OR #104 OR #105 OR #106

National Research Register (NRR). (Update Software). 2002:1-2005:3. 21st September 2005.

192 records were retrieved.

LABOR PREMATURE
((premature next birth) or (preterm next birth) or (preterm next birth))
((premature next deliver*) or (preterm next deliver*) or (preterm next deliver*))
((preterm next labour) or (preterm next labour))
((preterm next labor) or (preterm next labor))
((premature next labour) or (premature next labor) or (premature next parturition))
#1 or #2 or #3 or #4 or #5 or #6
SOCIOECONOMIC FACTORS
SOCIAL CLASS
RISK FACTORS
SMOKING
ETHNIC GROUPS
SUBSTANCERELATED DISORDERS
LIFE STYLE
PREGNANCY HIGHRISK
PREGNANCY IN ADOLESCENCE
PARITY
REPRODUCTIVE HISTORY
PREGNANCY COMPLICATIONS
FETAL MEMBRANES PREMATURE RUPTURE
ABDOMINAL PAIN
UTERINE CONTRACTION
UTERINE HEMORRHAGE
FEVER
ESTRIOL
RELAXIN
TREPONEMA PALLIDUM
NEISSERIA GONORRHOEAE
STREPTOCOCCUS AGALACTIAE
MYCOPLASMA HOMINIS
CHLAMYDIA TRACHOMATIS
TRICHOMONAS VAGINALIS
BACTEROIDES INFECTIONS
VAGINOSIS BACTERIAL
MOBILUNCUS
GARDNERELLA VAGINALIS
PROSTAGLANDINS
PREGNANCY MULTIPLE
CERVIX INCOMPETENCE
CERVICAL RIPENING
FETAL PROTEINS
BACTERIURIA
DIAGNOSTIC TECHNIQUES OBSTETRICAL AND GYNECOLOGICAL
DIAGNOSTIC EQUIPMENT

DIAGNOSTIC IMAGING
REAGENT KITS DIAGNOSTIC
ULTRASONOGRAPHY PRENATAL
DIAGNOSTIC TESTS ROUTINE
MEDICAL HISTORY TAKING
RISK ASSESSMENT
PHYSICAL EXAMINATION
UTERINE MONITORING
ESTERASES
CYTOKINES
TISSUE CULTURE
ACUTEPHASE PROTEINS
IMMUNOPROTEINS
PLATELETDERIVED GROWTH FACTOR
TUMOR NECROSIS FACTOR
CORPUS LUTEUM HORMONES
ESTROGENS
INHIBINS
ESTRADIOL
ESTRIOL
ESTRONE
ESTROGEN RECEPTOR MODULATORS
RECEPTORS ESTROGEN
PROSTAGLANDIN ANTAGONISTS
RECEPTORS PROSTAGLANDIN
LEUKOTRIENES
THROMBOXANES
COLLAGENASES
BODY CONSTITUTION
BODY TEMPERATURE
PALPATION
SEXUALLY TRANSMITTED DISEASES BACTERIAL
BACTEROIDACEAE INFECTIONS
CHLAMYDIACEAE INFECTIONS
GRANULOMA INGUINALE
MYCOPLASMATALES INFECTIONS
NEISSERIACEAE INFECTIONS
TREPONEMAL INFECTIONS
STAPHYLOCOCCAL INFECTIONS
STREPTOCOCCAL INFECTIONS
UREAPLASMA INFECTIONS
LACTOBACILLUS
HERPES GENITALIS
URINARY TRACT INFECTIONS
CHORIOAMNIONITIS
AMNIOTIC FLUID
LEUKOCYTES
SALIVA
BIOLOGICAL MARKERS
CORTICOTROPINRELEASING HORMONE
((older near women) or (elderly near women))
fibronectin*
((premature near rupture) near membrane*)
tocodynamo*
((risk near factor*) or (socioeconomic near factor*))
((low near pregnancy) near weight)
(high next parity)
((early near bleeding) near pregnancy)
(vaginal near bleeding)
((uterine near hemorrhage) or (antepartum near hemorrhage))
((abdominal next pain) or (uterine next contraction*))
((pyrexia or febrile) or fever)
((short near between) near pregnancies)
(interpregnancy and interval*)
(((((occupation* or socioeconomic) or ethnic) or ethnicity) or (manual next work)) or (long next hours))
(((((cocaine or heroin) or narcotics) or crack) or dope) or cannabis) or (substance next abuse))
(((((substance and disorder*) or smoking) or tobacco) or alcohol*) or lifestyle*)
((estriol or (plasma near crf)) or (vaginal near infection*))
((biophysical or biochemical) and marker*)
(bishop* and (score or scores))
((cervical near change*) or (cervical near length) or (cervical near measurement))
((endocervical near effacement) or (endocervical near assessment))
((cervical near effacement) or (cervical near assessment) or (cervical near state))
(((clinical near histor*) or (patient near histor*)) or (patient near record*))
(((obstetric near histor*) or (previous near preterm)) or (repeat near preterm))
((risk next scor*) or (physical next examination*))

((((physical next exam) or (physical next exams)) or (cervical next dilation)) or (cervix near length))
(dilation near cervix)
(((uterine near tocography) or (uterine near anomal*)) or tocometry)
((cervical near abnormal*) or (cervical near incompetence) or (cervical near incompetent))
((cervix near abnormal*) or (cervix near incompetence) or (cervix near incompetent))
((cervical near ultrasound) or (cervical near ultrasonography))
((cervix near ultrasound) or (cervix near ultrasonography))
((vaginal near ultrasound) or (ultrasound near endovaginal) or (transvaginal near ultrasound) or (obstetric near ultrasound) or (vaginal near ultrasonography) or (ultrasonography near endovaginal) or (transvaginal near ultrasonography) or (obstetric near ultrasonography))
((uterine near activity) or (uterine near huam) or (uterine near excitability))
((myometrial near excitability) or (myometrium near excitability))
((oncofetal near protein*) or ((c next reactive) near protein*)
((asymptomatic next bacteriuria) or (genital next tract next infection*))
((leucocyte next esterase*) or (leucocyte next cytokines))
((amniotic near culture*) or (blood near culture*) or (genital near culture*) or (vaginal near culture*) or (cervical near culture*))
(((timp or collagenase) or relaxin) or (tissue next inhibitor*))
(plasma next corticotropin next releasing next hormone*)
((estrogen or oestrogen) or progestogen)
((glucose next concentration*) near amniotic)
(zinc near amniotic)
(#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
(#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
(#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
(#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60)
(#61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80)
(#81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100)
(#101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120)
(#121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129 or #130 or #131 or #132 or #133 or #134 or #135 or #136 or #137 or #138 or #139)
(#141 or #142 or #143 or #144 or #145 or #146 or #147)
(#7 and #148)

MEDION. 2005. 27th September 2005.

8 records were retrieved. Separate searches were performed using the abstract, title and ICPC code fields.

ICPC code: W Pregnancy, childbearing, family planning

Abstract, Title: ‘premature’, ‘preterm’, ‘pre term’, ‘pre-term’

Appendix III - Data extraction pro-forma

Pro-forma for study inclusion and data extraction

Reviewer	Language	1st author	Publication year	
Data extraction				
Country				
Population	Asymptomatic	Symptomatic		
Study design	Cohort	Case-control	Can't tell	Others (state)
Data collection	Prospective	Retrospective	Can't tell	Others (state)
Enrolment	Consecutive	Arbitrary	Can't tell	Others (state)
Blinding	Yes	No	Can't tell	Others (state)
Test description	Yes	No	Can't tell	Others (state)
Inclusion criteria				
Exclusion criteria				
Testing gestation(s)				
Threshold(s)				
Reference standard(s)				
Sample size				

2x2 data extraction here (reproduce table as many times as required)

	Birth <48h/7d/34wks/37wks	Birth >48h/7d/34wks/37wks	Total
Test positive			
Test negative			

Appendix IV - Characteristics and results of individual included test accuracy studies

Table 10 Characteristic of studies on accuracy of maternal history of previous spontaneous preterm birth in predicting subsequent spontaneous preterm birth

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation	Threshold	Outcome (weeks' gestation)
Goldenberg[61]	1998	USA	1711	Cohort Prospective Test described	Singleton pregnancies	Placenta previa, congenital fetal anomaly	First antenatal appointment	Previous spontaneous preterm birth	<35, <37
Iams[62]	1998	USA	1282	Cohort Prospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth before 26, 31 or 36 weeks' gestation	37
Botsis[57]	2004	Greece	104	Cohort Prospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	36
Kristensen[63]	1995	Denmark	13764	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37
Berkowitz[56]	1998	USA	13197	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37
Carr-Hill[58]	1985	UK	6072[a] 1463[b]	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	One, two previous spontaneous preterm birth	37
deCarvalho[59]	2005	Brazil	1958	Cohort Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	34
Ancel[55]	1999	France	13292	Case-control Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37
Weidinger[64]	1974	Germany	911	Case-control Retrospective Test described	Singleton pregnancies		First antenatal appointment	One, two previous spontaneous preterm birth	37
deHaas[60]	1991	USA	420	Case-control Retrospective Test described	Singleton pregnancies		First antenatal appointment	Previous spontaneous preterm birth	37

a. One previous spontaneous preterm birth, b. Two previous spontaneous preterm births

Table 11 Individual accuracy results of maternal history of previous spontaneous preterm birth in predicting subsequent spontaneous preterm birth

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Goldenberg[61]	85	278	119	1229	0.42	0.35	0.49	0.82	0.80	0.83	2.26	1.86	2.74	0.72	0.64	0.81
Goldenberg[$61]	55	308	32	1316	0.63	0.52	0.73	0.81	0.79	0.83	3.33	2.76	4.03	0.45	0.34	0.60
Iams[+62]	15	83	67	1117	0.18	0.11	0.28	0.93	0.91	0.94	2.64	1.60	4.37	0.88	0.79	0.97
Iams[++62]	27	149	55	1051	0.33	0.23	0.44	0.88	0.86	0.89	2.65	1.88	3.74	0.77	0.66	0.89
Iams[+++62]	55	323	27	877	0.67	0.56	0.77	0.73	0.70	0.76	2.49	2.09	2.98	0.45	0.33	0.61
Botsis[57]	1	10	10	83	0.09	0.00	0.41	0.89	0.81	0.95	0.85	0.12	5.99	1.02	0.83	1.24
Kristensen[63]	55	433	241	13035	0.19	0.14	0.23	0.97	0.96	0.97	5.78	4.47	7.46	0.84	0.80	0.89
Berkowitz[56]	214	1049	465	11469	0.32	0.28	0.35	0.92	0.91	0.92	3.76	3.32	4.26	0.75	0.71	0.79
Carr-Hill[x58]	76	418	261	537	0.23	0.18	0.27	0.56	0.53	0.59	0.52	0.42	0.64	1.38	1.27	1.49
Carr-Hill[xx58]	8	17	57	1381	0.12	0.05	0.23	0.99	0.98	0.99	10.12	4.54	22.59	0.89	0.81	0.97
deCarvalho[59]	25	155	41	1737	0.38	0.26	0.51	0.92	0.90	0.93	4.62	3.28	6.52	0.68	0.56	0.82
Ancel[55]	850	526	4477	7439	0.16	0.15	0.17	0.93	0.93	0.94	2.42	2.18	2.68	0.90	0.89	0.91
Weidinger[x64]	73	18	370	450	0.16	0.13	0.20	0.96	0.94	0.98	4.28	2.60	7.06	0.87	0.83	0.91
Weidinger[xx64]	25	4	370	450	0.06	0.04	0.09	0.99	0.98	1.00	7.18	2.52	20.46	0.95	0.92	0.97
deHaas[60]	21	14	119	266	0.15	0.10	0.22	0.95	0.92	0.97	3.00	1.57	5.72	0.89	0.83	0.96

$ Spontaneous preterm birth <35 weeks' gestation
+ Previous spontaneous preterm birth before 26 weeks' gestation
++ Previous spontaneous preterm birth before 31 weeks' gestation
+++ Previous spontaneous preterm birth before 36 weeks' gestation
x One previous spontaneous preterm birth
xx Two previous spontaneous preterm birth

Table 12 Characteristics of test accuracy studies of digital examination in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and women symptomatic with threatened preterm labour

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Asymptomatic										
Leveno[70]	1986	USA	185	Cohort Prospective Consecutive Blinded Test described	Low risk pregnancy	x	26 - 30	Single	2cm dilated	<34
Parikh[72]	1961	India	463	Cohort Prospective Consecutive Test described	Singleton pregnancies	Pre-eclampsia, infection, placenta previa, previous history of miscarriages	24 - 36	Biweekly	Admit digit at internal os	<37
Iams	2002	USA	270	Cohort Prospective Blinded Test described	Singleton pregnancies	Women who had received or were scheduled to receive an ambulatory monitor or tocolytic medication or to undergo cerclage were complicated by placenta previa or a major fetal anomaly detected by ultrasonography. Women who did not have telephones were not enrolled, because the transmission of data collected by the monitoring system required a telephone.	<35	Quads	Bishop score changes	<35
Stubbs[74]	1986	USA	108	Cohort Prospective Blinded Test described	Singleton pregnancies	Uterine or fetal anomaly, previous history of IUGR, spontaneous preterm birth, or cone biopsy, PPROM, history of second trimester miscarriage	28, 32 and 34	Thrice	1cm internal os dilatation, 30% effacement	<37
Chambers[67]	1991	France	5066	Cohort Prospective Test described	Low risk pregnancy	x	28 and <37	Biweekly	< 1cm long cervix at 28 weeks, >1cm internal os dilatation before 37 weeks	<37

Blondel[66]	1990	France	3159	Cohort Prospective Test described	Singleton pregnancies able to attend antenatal clinic at 25 - 28 and 29 - 31 weeks' gestation, divided into nulliparous and multiparous groups	Unknown gestation, iatrogenic preterm delivery	25 – 28, 29 - 31	Twice	1cm internal os dilatation, 1cm long cervix, mid-position, soft cervix	<37
Newman[71]	1997	USA	2916	Cohort Prospective Test described	Singleton pregnancies	x	22 – 24, 26 - 29	Twice	Bishop score ≥4 or cervical score <1.5	<35
Schaffner[73]	1966	USA	83	Cohort Blinded Test described	All pregnant women seen at routine antenatal clinic between 28 - 32 weeks' gestation, divided into nulliparous and multiparous groups	Operative cervical procedure, threatened or chronic miscarriage, hormone administration during pregnancy, PPROM, previous CS, uncertain dates	28 - 32	Single	2-3cm dilated	<37
Chabra[68]	1991	India	75	Cohort Prospective Test described	Singleton pregnancies	Polyhydramnios, pre-eclampsia, vaginal bleeding, previous bad obstetrics history or history of preterm birth	28 - 28	Single	Central cervix position: ≥2.6, ≥1.5 cm long and posterior cervix position: ≥2.6, ≥1.5 cm long	<37
Symptomatic										
Onderoglu[75]	1997	Turkey	90	Cohort Prospective Blinded Test described	Singletons, intact membrane, cervical dilatation <3cm, absence of fetal and maternal complication		25 - 36	Single	>2cm dilated, >40% effacement	<37

Table 13 Individual accuracy results of digital examination in predicting spontaneous preterm birth stratified according to population of asymptomatic antenatal women and symptomatic women with threatened preterm labour

Authors	Testing gestation (weeks)	Threshold	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																		
Leveno[70]	26 - 30	2cm dilated	4	11	3	167	0.57	0.18	0.90	0.94	0.89	0.97	9.25	3.91	21.85	0.46	0.19	1.08
Parikh[72]	24 - 36	admit finger at internal os	28	174	29	232	0.49	0.36	0.63	0.57	0.52	0.62	1.15	0.86	1.53	0.89	0.68	1.16
Stubbs[74]	34	30% effacement	2	22	2	104	0.50	0.07	0.93	0.83	0.75	0.89	2.86	1.00	8.19	0.61	0.23	1.62
Stubbs[74]	32	30% effacement	5	23	5	103	0.50	0.19	0.81	0.82	0.74	0.88	2.74	1.33	5.64	0.61	0.33	1.14
Stubbs[74]	28	1cm internal os	2	15	6	85	0.25	0.03	0.65	0.85	0.76	0.91	1.67	0.46	6.04	0.88	0.59	1.33
Stubbs[74]	32	1cm internal os	4	28	6	98	0.40	0.12	0.74	0.78	0.70	0.85	1.80	0.79	4.11	0.77	0.46	1.29
Stubbs[74]	28	30% effacement	0	9	8	91	0.00	0.00	0.37	0.91	0.84	0.96	0.59	0.04	9.34	1.04	0.88	1.24
Stubbs[74]	34	1cm internal os	3	51	1	75	0.75	0.19	0.99	0.60	0.50	0.68	1.85	1.01	3.39	0.42	0.08	2.31
Chambers[67]	<37	1cm internal os	65	846	109	4046	0.37	0.30	0.45	0.83	0.82	0.84	2.16	1.77	2.64	0.76	0.67	0.85
Chambers[67]	28	1cm long cervix	29	487	109	4046	0.21	0.15	0.29	0.89	0.88	0.90	1.96	1.40	2.73	0.88	0.81	0.97
Chambers[67]	<37	Combined	30	146	109	4046	0.22	0.15	0.29	0.97	0.96	0.97	6.20	4.35	8.84	0.81	0.74	0.89
Blondel[a66]	29 - 31	1cm long cervix	26	228	92	2271	0.22	0.15	0.31	0.91	0.90	0.92	2.42	1.68	3.47	0.86	0.78	0.95
Blondel[a66]	25 - 28	1cm long cervix	22	149	140	2848	0.14	0.09	0.20	0.95	0.94	0.96	2.73	1.80	4.15	0.91	0.86	0.97
Blondel[a66]	25 - 28	mid-position cervix	45	520	117	2476	0.28	0.21	0.35	0.83	0.81	0.84	1.60	1.23	2.08	0.87	0.79	0.96
Blondel[a66]	29 - 31	mid-position cervix	34	427	84	2072	0.29	0.21	0.38	0.83	0.81	0.84	1.69	1.25	2.27	0.86	0.76	0.96
Blondel[a66]	29 - 31	1cm internal os	25	135	386	2071	0.06	0.04	0.09	0.94	0.93	0.95	0.99	0.66	1.50	1.00	0.97	1.03
Blondel[a66]	29 - 31	Soft cervix	103	1742	15	757	0.87	0.80	0.93	0.30	0.28	0.32	1.25	1.16	1.35	0.42	0.26	0.68
Blondel[a66]	25 - 28	1cm internal os	21	48	139	2950	0.13	0.08	0.19	0.98	0.98	0.99	8.20	5.03	13.35	0.88	0.83	0.94
Blondel[a66]	25 - 28	Soft cervix	130	1870	30	1129	0.81	0.74	0.87	0.38	0.36	0.39	1.30	1.20	1.41	0.50	0.36	0.69
Blondel[b66]	29 - 31	1cm long cervix	14	130	56	1509	0.20	0.11	0.31	0.92	0.91	0.93	2.52	1.53	4.14	0.87	0.77	0.98
Blondel[b66]	25 - 28	Soft	95	1434	21	616	0.82	0.74	0.88	0.30	0.28	0.32	1.17	1.07	1.28	0.60	0.41	0.89

Blondel[b66]	25 - 28	mid-position cervix	30	384	88	1664	0.25	0.18	0.34	0.81	0.79	0.83	1.36	0.98	1.87	0.92	0.82	1.02
Blondel[b66]	25 - 28	1cm long cervix	12	96	103	1955	0.10	0.06	0.18	0.95	0.94	0.96	2.23	1.26	3.94	0.94	0.88	1.00
Blondel[b66]	29 - 31	Soft cervix	59	1242	11	397	0.84	0.74	0.92	0.24	0.22	0.26	1.11	1.00	1.24	0.65	0.37	1.12
Blondel[b66]	29 - 31	1cm internal os	20	151	49	1489	0.29	0.19	0.41	0.91	0.89	0.92	3.15	2.11	4.69	0.78	0.67	0.91
Blondel[b66]	25 - 28	1cm internal os	17	59	98	1992	0.15	0.09	0.23	0.97	0.96	0.98	5.14	3.10	8.52	0.88	0.81	0.95
Blondel[b66]	29 - 31	mid-position cervix	16	292	50	1351	0.24	0.15	0.36	0.82	0.80	0.84	1.36	0.88	2.12	0.92	0.80	1.06
Schaffner[a73]	28 - 32	2-3cm dilated	0	12	5	56	0.00	0.00	0.52	0.82	0.71	0.91	0.46	0.03	6.85	1.12	0.86	1.46
Schaffner[b73]	28 - 32	2-3cm dilated	5	60	10	141	0.33	0.12	0.62	0.70	0.63	0.76	1.12	0.53	2.36	0.95	0.66	1.37
Chabra[68]	28	central 1.5cm long cervix	5	0	36	34	0.12	0.04	0.26	1.00	0.90	1.00	9.17	0.52	160.08	0.88	0.78	1.00
Chabra[68]	28	posterior 2.6 cm long cervix	1	4	6	54	0.14	0.00	0.58	0.93	0.83	0.98	2.07	0.27	16.03	0.92	0.67	1.26
Chabra[68]	28	central 2.6cm long cervix	24	5	17	29	0.59	0.42	0.74	0.85	0.69	0.95	3.98	1.70	9.31	0.49	0.33	0.72
Chabra[68]	28	posterior 1.5 cm long cervix	7	57	0	1	1.00	0.59	1.00	0.02	0.00	0.09	0.96	0.80	1.16	2.46	0.11	55.35
Symptomatic																		
Onderoglu[75]	25 - 36	2cm dilated cervix	21	16	11	42	0.66	0.47	0.81	0.72	0.59	0.83	2.38	1.46	3.87	0.47	0.29	0.79
Onderoglu[75]	25 - 36	40% effacement	20	18	12	40	0.63	0.44	0.79	0.69	0.55	0.80	2.01	1.26	3.22	0.54	0.34	0.88

Table 14 Characteristic of studies on the accuracy of bedside cervico-vaginal fetal fibronectin testing as a predictor of spontaneous preterm birth stratified according to study population of asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour

Authors	Year	n	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)*
Asymptomatic							
Ruiz[98]	2001	78	Cohort Prospective Test described	Asymptomatic women	<18 or >40 years old, Rh iso-immunization, multiple gestation, cervical cerclage, use of tocolytics agents in the current pregnancy, maternal medical disorders, non-English speaking, >28 weeks' gestation at enrolment, misses > 1 monthly antenatal check-up.	23 – 26, 27 – 30, and both times	<37
Arinami[87]	1999	438	Prospective Consecutive Test described	Singleton pregnancies without medical or obstetrical complications.	None stated	26-28	<34 weeks <37 weeks
Goldenberg[89]	1996	2929	Prospective Blind Test described	Singletons pregnancies.	Placenta previa. Fetal anomalies	22, 24, 26, 28, 30	<34 weeks
Goldenberg[90]	1997	1870	Prospective Blind Test described	Singleton pregnancies of women who are not randomised to treatment for Trichomonas vaginalis or Bacterial vaginosis.	None stated	8-22	<35 weeks
Goldenberg[76]	2000	6508	Prospective Blind Test described	Singletons pregnancies.	None stated	8-22	<28 weeks <32 weeks <35 weeks <37 weeks
Hux[91]	1995	54	Prospective Blind Test described	Intact membrane and undilated cervix.	Candida infection, fetal anomalies, vaginal bleeding, placenta previa, and threatened preterm labour.	26-29	<37 weeks
Heath[81]	2000	5146	Prospective Consecutive Blind Test described	Singletons pregnancies of women attending an inner city ante-natal clinic	Fetal abnormalities.	22-24	<33 weeks
Chang[88]	1997	234	Prospective Blind Test described	Singletons pregnancies without previous history of spontaneous preterm labour or birth Intact membrane.	Vaginal bleeding. Pre-eclampsia. Placenta previa. Uncertain date. Fetal anomaly	28	<34 weeks <37 weeks

Faron[80]	1997	155	Prospective Consecutive Blind Test described	All asymptomatic women in antenatal clinic with known gestation.	Vaginal bleeding	24-33	<37 weeks
Hellemans[82]	1995	133	Blind Consecutive Prospective Test described	Low risk singletons pregnancies. Intact membrane.	Placenta previa. Vaginal bleeding. Cervical dilatation >1cm or cervical cerclage. Threatened preterm labour <26 weeks, Unknown date.	26-36	<37 weeks
Garcia[94]	1999	263	Blind Prospective Test described	Low risk singletons Intact membrane.	Cerclage.	24-37	<32 weeks <37 weeks
Greenhagen[95]	1996	108	Blind Prospective Test described	Low risk singletons pregnancies. Intact membrane.	Previous history of spontaneous preterm labour or birth Vaginal bleeding. Fetal anomaly.	24-34	<37 weeks
DiStefano[93]	1999	60	Prospective Test described	Singletons pregnancies Intact membrane.	Previous history of spontaneous preterm labour or birth Vaginal bleeding. Fetal anomaly Cervical cerclage. Genital infection. Maternal or fetal complications during gestation &/or examination	24-36	<37 weeks
Crane[92]	1999	140	Blind Consecutive Prospective Test described	Singleton pregnancies. Intact membrane.	Cerclage. Fetal anomalies or death. Vaginal bleeding. Recently treated bacterial vaginosis.	20-24	<37 weeks
Inglis[96]	1994	73	Blind Prospective Test described	Intact membrane	Fetal anomalies, placenta previa, genital or urinary infection, use of antibiotics in the preceding 7 days	<37	<37 weeks
Lockwood[97]	1991	429	Blind Prospective Test described	Asymptomatic women from an inner city antenatal clinic.	Uncertain date, placenta previa, iatrogenic preterm delivery	24-37	<28 day <37 weeks
Vercoustre[99]	1996	58	Test described	Asymptomatic women	Coitus <24 hours and vaginal bleeding.	27-37	<37 weeks
Zamora[77]	2000	20	Blind Test described	Asymptomatic pregnant women Intact membrane.	Coitus <24 hours. Recent usage of vaginal pessary	28-36	<37 weeks

Symptomatic							
Luzzi[110]	2003	133	Cohort Consecutive Prospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Scheduled caesarean section, induced delivery within 21 days of testing.	24 - 35	<7, <14 and <21 days of testing
Tekesin[86]	2005	170	Cohort Consecutive Prospective Blinded Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Multiple gestations, cervical manipulations (examination, intercourse, ultrasound), vaginal bleeding, major fetal anomaly, PPROM, cervical cerclage, suspected fetal asphyxia	24 - 35	<7, <14, <21 days of testing and <34 and <37
Musaad[117]	2005	27	Cohort Consecutive Prospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Vaginal bleeding	24 - 33	<34, <37
Dolinska[126]	2005	115	Cohort Retrospective Test described	Singleton, preterm labour, intact membrane, < 3 cm cervical dilatation, no cerclage.	x	24 - 34	<37
Topete[121]	2004	74	Cohort Retrospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	x	24 - 34	<37
Foxman[104]	2004	139	Cohort Prospective	Preterm labour, intact membrane, < 3 cm cervical dilatation	x	x	<7
Hincz[122]	2002	82	Cohort Prospective Blinded Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	Cerclage, clinical criteria of intrauterine infection, vaginal bleeding, IUGR, pre-eclampsia	24 - 34	<37
Sakai[113]	2003	116	Cohort Test described	Preterm labour, intact membrane, < 4 cm cervical dilatation	PROM, multiple pregnancy, elective preterm delivery, pre-eclampsia, abruption, placenta previa, maternal medical conditions	20 - 36	<7 days of testing, and <37
Closset[103]	2001	61	Cohort Prospective Blinded Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	x	24 - 36	<7, <14, <21 days of testing, and <37
Gomez[106]	2005	215	Cohort Prospective Test described	Preterm labour, intact membrane, < 3 cm cervical dilatation	x	22 - 35	<48 hours, <7, <14 days of testing and <32, <35

Hansen[109]	2004	41	Cohort Prospective Test described	>16 years of age, preterm labour, < 3cm dilatation for primigravida and < 4cm for multiparous.	Multiple gestations, major fetal anomaly, vaginal bleeding, PPROM, cervical cerclage, suspected fetal asphyxia.	23 - 34	<7, <14 days of testing, and <37
Stevens[129]	2004	185	Cohort Prospective Test described	Preterm labour, intact membrane, ≥ 2cm dilatation, ≥ 50% effacement		24 - 34	<32, <37
LaShay[83]	2000	118	Cohort Consecutive Prospective Blind Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm.	Coitus or digital vaginal examination within 24 hours Vaginal bleeding Placenta previa Placental abruption Polyhydramnios Pre-eclampsia Known uterine or fetal abnormalities	24-34	<48 hours <7 days <37 weeks
Senden[85]	1996	49	Cohort Consecutive Prospective Blind Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <4 cm.	Vaginal bleeding. Clinical chorioamnionitis. Diabetes mellitus.	25-35	<7 days
Bartnicki[101]	1996	112	Cohort Prospective Blind Test described	Intact membrane, cervical dilatation <2 cm.		22-35	<7 days <14 days <21 days <28 days <34 weeks
Benattar[102]	1997	124	Cohort Prospective Blind Test described	Singletons and twin pregnancies. Intact membrane, cervical dilatation <3 cm.	Vaginal bleeding. Coitus < 24 hours.	24-36	<7 days <14 days <21 days <32 weeks <34 weeks
Malak[111]	1996	112	Cohort Prospective Blind Test described	Singletons pregnancies. Intact membrane. Cervical dilation < 2 cm.	Placenta previa. Vaginal bleeding. Coitus < 24 hours.	24-34	<7 days <14 days <21 days <37 weeks
McKenna[112]	1999	50	Cohort Consecutive Prospective Test described	Cervical dilation < 3 cm.	Coitus < 24 hours. Vaginal digital examination or transvaginal ultrasounds scan procedure. Cervical cerclage. Uterine anomalies. Placenta previa. Placental abruption.	22-34	<7 days <14 days <37 weeks

Peaceman[79]	1997	725	Cohort Prospective Blind Test described	Singleton, twin pregnancies and 1 triplet. Intact membrane. Cervical dilatation <3 cm.	Placenta previa. Cerclage. Trauma leading to preterm labour.	24-34	<7 days <14 days <37 weeks
Iams[107]	1995	192	Cohort Prospective Blind Test described	Intact membrane. Cervical dilation < 3 cm.	Placenta previa. Cerclage. Uterine anomalies. Vaginal bleeding.	24-34	<7 days <37 weeks
Giles[105]	2000	150	Cohort Prospective Test described	Intact membrane.	Vaginal bleeding. Coitus < 24 hours. Recent digital vaginal examination.	24-34	<7 days <36 weeks
Lopez[108]	2000	85	Cohort Retrospective	Singletons pregnancies. Intact membrane. Cervical dilation < 3 cm.	Uncertain date. Lost to follow up. Incomplete data.	24-35	<7 days 14 days <34 weeks <37 weeks
Cox (Abstract)[115]	1995	175	Test described	Intact membrane. Cervical dilatation < 3 cm.	None stated	24-34	<37 weeks
Chuileannain[118]	1998	50	Cohort Retrospective Test described	Singletons pregnancies. Intact membrane. Cervical dilation < 2 cm.	Placenta previa. Placental abruption. Cerclage. Fetal anomalies.	<34	<34 weeks
Goffeng[116]	1997	63	Cohort Consecutive Prospective Test described	Singletons pregnancies with intact membrane.	Pre-eclampsia. Uterine or cervical abnormalities. Placenta previa, placental abruption. Fetal anomalies. Diabetes mellitus.	23-34	<34 weeks <37 weeks
Parker[119]	1995	36	Cohort Prospective Blind Test described	Singletons pregnancies. Intact membrane. Cervical dilation < 2 cm.	Placenta previa. Placental abruption. Cerclage. Fetal anomalies. Coitus < 24 hours.	20-34	<34
Burrus[114]	1995	37	Cohort Prospective Blind Test described	Symptomatic women in their first pregnancy. Intact membrane Cervical dilatation <3 cm and changing, no contra-indication to tocolytic	Amnionitis. Placental abruption.	<34	<37 weeks

Grandi[78]	1996	26	Cohort Consecutive Prospective Blind Test described	Singletons pregnancies. Intact membrane. Cervical dilation < 2cm	Placenta previa. Placental abruption. Fetal anomalies. Coitus <24 hours, Iatrogenic preterm labour.	24-36	<37 weeks
Inglis[96]	1994	38	Cohort Prospective Blind Test described	Singletons pregnancies. Intact membrane.	Fetal anomalies. Placenta previa. Genital or urinary infection. Use of antibiotics in the preceding 7 days	<37	<37 weeks
Irion[123]	1995	64	Cohort Prospective Blind Test described	Intact membrane. Cervical dilation < 2 cm.	Fetal anomalies. Vaginal bleeding. Coitus < 24 hours. Iatrogenic preterm delivery.	24-36	<37 weeks
Langer[124]	1997	61	Cohort Prospective Blind Test described	Intact membrane.	Vaginal bleeding. Coitus < 24 hours. Progressive cervical dilatation. Abnormal fetal heart rate monitoring.	24-34	<37 weeks
Lockwood[97]	1991	117	Cohort Prospective Blind Test described	Intact membrane	Fetal anomalies. Placenta previa. Coitus < 24 hours. Intra-uterine growth restriction. Fetal distress. Previous pregnancy terminated due to severe pre-eclampsia.	25-35	<37 weeks
Morrison[84]	1993	28	Cohort Blind Consecutive Prospective Test described	Singleton pregnancies. Intact membrane.	Uterine or cervical abnormalities. Vaginal bleeding. Placenta previa. Suspected placental abruption. Coitus or douching <24 hours. Diabetes mellitus. Unknown date. Pre-eclampsia. <15 years old.	24-34	<37 weeks
Rizzo[127]	1997	106	Cohort Prospective Blind Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm.	Fetal or maternal complications. Urinary or genital infection. Use of antibiotic in the preceding 14 days	24-36	<37 weeks

Rozenberg[128]	1997	76	Cohort Prospective Blind Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <2 cm.	Gestation <24 or >34 weeks. Cerclage. Placenta previa. Placental abruption. Iatrogenic preterm delivery.	24-34	<37 weeks
Calda[120]	1995	84	Cohort Prospective Test described	Intact membrane.		24-34	<36 weeks
Mansouri[125]	1996	90	Cohort Retrospective Test described	Intact membrane.	Vaginal bleeding Coitus < 24 hours	24-34	<37 weeks
Vercoustre[99]	1996	86	Test described	Singleton pregnancies with threatened preterm labour	Coitus < 24 hours Vaginal bleeding	<37	<37 weeks
Vetr[130]	1996	46	Cohort Prospective Test described	Intact membrane.	Fetal anomalies Placenta previa Vaginal bleeding Intra-uterine growth restriction Fetal distress Diabetes mellitus Pre-eclampsia	25-36	<37 weeks

*unless otherwise state

Table 15 Individual accuracy results of cervico-vaginal fetal fibronectin (fFN) in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
<7 – 10 days																
Tekesin[86]	9	37	2	122	0.82	0.48	0.98	0.77	0.69	0.83	3.52	2.36	5.23	0.24	0.07	0.83
Closset[103]	5	11	1	44	0.83	0.36	1.00	0.80	0.67	0.90	4.17	2.20	7.89	0.21	0.03	1.25
LaShay[83]	3	10	2	103	0.60	0.15	0.95	0.91	0.84	0.96	6.78	2.68	17.16	0.44	0.15	1.29
Luzzi[110]	4	34	3	92	0.57	0.18	0.90	0.73	0.64	0.81	2.12	1.05	4.28	0.59	0.25	1.39
Senden[85]	4	4	1	20	0.80	0.28	0.99	0.83	0.63	0.95	4.80	1.77	13.00	0.24	0.04	1.40
Bartnicki[101]	3	33	1	79	0.75	0.19	0.99	0.71	0.61	0.79	2.55	1.35	4.80	0.35	0.06	1.94
Benattar[102]	8	11	1	104	0.89	0.52	1.00	0.90	0.84	0.95	9.29	5.06	17.06	0.12	0.02	0.78
Gomez[106]	18	34	10	153	0.64	0.44	0.81	0.82	0.76	0.87	3.54	2.34	5.33	0.44	0.26	0.72
Hansen[109]	2	7	1	31	0.67	0.09	0.99	0.82	0.66	0.92	3.62	1.28	10.27	0.41	0.08	2.04
Iams[107]	13	32	1	146	0.93	0.66	1.00	0.82	0.76	0.87	5.17	3.66	7.30	0.09	0.01	0.58
Malak[111]	8	10	2	92	0.80	0.44	0.97	0.90	0.83	0.95	8.16	4.20	15.87	0.22	0.06	0.77
McKenna[112]	5	13	1	35	0.83	0.36	1.00	0.73	0.58	0.85	3.08	1.71	5.53	0.23	0.04	1.38
Peaceman[79]	19	123	2	581	0.90	0.70	0.99	0.83	0.80	0.85	5.18	4.19	6.40	0.12	0.03	0.43
Plaut[100]	1	8	1	86	0.50	0.01	0.99	0.91	0.84	0.96	5.88	1.26	27.30	0.55	0.14	2.19
Giles[105]	11	34	5	100	0.69	0.41	0.89	0.75	0.66	0.82	2.71	1.75	4.21	0.42	0.20	0.87
Sakai[113]	11	27	7	71	0.61	0.36	0.83	0.72	0.63	0.81	2.22	1.36	3.62	0.54	0.30	0.97
Foxman[104]	6	25	1	107	0.86	0.42	1.00	0.81	0.73	0.87	4.53	2.84	7.20	0.18	0.03	1.08
Lopez[108]	8	12	1	64	0.89	0.52	1.00	0.84	0.74	0.92	5.63	3.19	9.94	0.13	0.02	0.84
<34 weeks																
Musaad[117]	5	5	1	21	0.83	0.36	1.00	0.81	0.61	0.93	4.33	1.82	10.29	0.21	0.03	1.25
Tekesin[86]	20	26	8	116	0.71	0.51	0.87	0.82	0.74	0.88	3.90	2.57	5.93	0.35	0.19	0.63
Burrus[114]	23	6	3	5	0.88	0.70	0.98	0.45	0.17	0.77	1.62	0.93	2.83	0.25	0.07	0.88
Goffeng[116]	7	7	4	45	0.64	0.31	0.89	0.87	0.74	0.94	4.73	2.08	10.75	0.42	0.19	0.93
Parker[119]	6	7	1	25	0.86	0.42	1.00	0.78	0.60	0.91	3.92	1.90	8.06	0.18	0.03	1.13
Chuileannain[118]	9	11	1	49	0.90	0.55	1.00	0.82	0.70	0.90	4.91	2.77	8.70	0.12	0.02	0.79
Cox[115]	3	22	11	139	0.21	0.05	0.51	0.86	0.80	0.91	1.57	0.53	4.60	0.91	0.69	1.20
Lopez[108]	11	9	4	61	0.73	0.45	0.92	0.87	0.77	0.94	5.70	2.88	11.28	0.31	0.13	0.71

<37 weeks																
Tekesin[86]	31	15	4	120	0.89	0.73	0.97	0.89	0.82	0.94	7.97	4.88	13.03	0.13	0.05	0.32
Closset[103]	12	4	11	34	0.52	0.31	0.73	0.89	0.75	0.97	4.96	1.81	13.56	0.53	0.34	0.83
Grandi[78]	4	9	4	9	0.50	0.16	0.84	0.50	0.26	0.74	1.00	0.43	2.30	1.00	0.43	2.30
Hincz[122]	10	5	4	63	0.71	0.42	0.92	0.93	0.84	0.98	9.71	3.92	24.05	0.31	0.13	0.71
LaShay[83]	10	8	24	76	0.29	0.15	0.47	0.90	0.82	0.96	3.09	1.33	7.15	0.78	0.62	0.98
Morrison[84]	9	5	1	13	0.90	0.55	1.00	0.72	0.47	0.90	3.24	1.50	7.02	0.14	0.02	0.91
Musaad[117]	5	3	5	15	0.50	0.19	0.81	0.83	0.59	0.96	3.00	0.90	10.01	0.60	0.31	1.15
Bartnicki[101]	27	7	13	65	0.68	0.51	0.81	0.90	0.81	0.96	6.94	3.33	14.49	0.36	0.23	0.57
Benattar[102]	9	9	16	90	0.36	0.18	0.57	0.91	0.83	0.96	3.96	1.76	8.93	0.70	0.52	0.95
Goffeng[116]	10	4	18	31	0.36	0.19	0.56	0.89	0.73	0.97	3.13	1.10	8.91	0.73	0.54	0.98
Hansen[109]	3	6	6	26	0.33	0.07	0.70	0.81	0.64	0.93	1.78	0.55	5.74	0.82	0.50	1.34
Iams[107]	27	18	35	112	0.44	0.31	0.57	0.86	0.79	0.92	3.15	1.88	5.26	0.66	0.52	0.82
Inglis[96]	7	2	9	20	0.44	0.20	0.70	0.91	0.71	0.99	4.81	1.15	20.18	0.62	0.39	0.97
Irion[123]	15	11	7	31	0.68	0.45	0.86	0.74	0.58	0.86	2.60	1.45	4.66	0.43	0.23	0.82
Langer[124]	10	8	8	35	0.56	0.31	0.78	0.81	0.67	0.92	2.99	1.41	6.32	0.55	0.32	0.93
Lockwood[97]	49	10	11	47	0.82	0.70	0.90	0.82	0.70	0.91	4.66	2.62	8.28	0.22	0.13	0.38
Malak[111]	17	5	10	109	0.63	0.42	0.81	0.96	0.90	0.99	14.36	5.81	35.47	0.39	0.24	0.63
Peaceman[79]	61	81	78	505	0.44	0.35	0.53	0.86	0.83	0.89	3.17	2.41	4.18	0.65	0.56	0.76
Rizzo[127]	40	12	9	45	0.82	0.68	0.91	0.79	0.66	0.89	3.88	2.31	6.52	0.23	0.13	0.43
Rozenberg[128]	14	17	6	39	0.70	0.46	0.88	0.70	0.56	0.81	2.31	1.41	3.76	0.43	0.22	0.86
Stevens[129]	32	20	37	86	0.46	0.34	0.59	0.81	0.72	0.88	2.46	1.54	3.93	0.66	0.52	0.84
Calda[120]	19	13	2	50	0.90	0.70	0.99	0.79	0.67	0.89	4.38	2.65	7.26	0.12	0.03	0.45
Giles[105]	12	33	7	99	0.63	0.38	0.84	0.75	0.67	0.82	2.53	1.61	3.97	0.49	0.27	0.89
Sakai[113]	26	12	36	42	0.42	0.30	0.55	0.78	0.64	0.88	1.89	1.06	3.37	0.75	0.58	0.96
Vetr[130]	5	11	4	26	0.56	0.21	0.86	0.70	0.53	0.84	1.87	0.87	4.02	0.63	0.30	1.35
Chuileannain[118]	13	7	1	49	0.93	0.66	1.00	0.88	0.76	0.95	7.43	3.66	15.08	0.08	0.01	0.54
Dolinska[126]	28	8	10	69	0.74	0.57	0.87	0.90	0.81	0.95	7.09	3.58	14.04	0.29	0.17	0.50
Mansouri[125]	13	12	12	53	0.52	0.31	0.72	0.82	0.70	0.90	2.82	1.49	5.31	0.59	0.39	0.90
Topete[121]	24	4	10	36	0.71	0.53	0.85	0.90	0.76	0.97	7.06	2.72	18.34	0.33	0.19	0.56
Vercoustre[99]	12	21	1	44	0.92	0.64	1.00	0.68	0.55	0.79	2.86	1.94	4.20	0.11	0.02	0.75
Lopez[108]	17	3	31	34	0.35	0.22	0.51	0.92	0.78	0.98	4.37	1.38	13.80	0.70	0.56	0.88

Table 16 Individual accuracy results of cervico-vaginal fetal fibronectin (fFN) in predicting spontaneous preterm birth among asymptomatic antenatal women

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
<34 weeks																
Arinami	1	1	4	432	0.20	0.01	0.72	1.00	0.99	1.00	86.60	6.26	1198.92	0.80	0.52	1.24
Heath	15	167	30	4934	0.33	0.20	0.49	0.97	0.96	0.97	10.18	6.56	15.80	0.69	0.56	0.85
Chang	3	2	3	226	0.50	0.12	0.88	0.99	0.97	1.00	57.00	11.57	280.92	0.50	0.23	1.12
Goldenberg	13	144	33	1680	0.28	0.16	0.43	0.92	0.91	0.93	3.58	2.20	5.82	0.78	0.65	0.93
Goldenberg	29	88	98	2714	0.23	0.16	0.31	0.97	0.96	0.97	7.27	4.97	10.63	0.80	0.72	0.88
Goldenberg	79	457	331	5641	0.19	0.16	0.23	0.93	0.92	0.93	2.57	2.07	3.19	0.87	0.83	0.92
Hux	3	5	1	45	0.75	0.19	0.99	0.90	0.78	0.97	7.50	2.74	20.51	0.28	0.05	1.52
<37 weeks																
Arinami	1	1	15	421	0.06	0.00	0.30	1.00	0.99	1.00	26.38	1.73	402.99	0.94	0.83	1.07
Crane	1	34	8	97	0.11	0.00	0.48	0.74	0.66	0.81	0.43	0.07	2.78	1.20	0.93	1.54
Faron	4	6	11	134	0.27	0.08	0.55	0.96	0.91	0.98	6.22	1.97	19.60	0.77	0.56	1.04
Hellemans	6	18	4	105	0.60	0.26	0.88	0.85	0.78	0.91	4.10	2.11	7.95	0.47	0.22	1.00
Chang	3	2	15	214	0.17	0.04	0.41	0.99	0.97	1.00	18.00	3.21	100.86	0.84	0.68	1.03
Garcia	22	9	5	227	0.81	0.62	0.94	0.96	0.93	0.98	21.37	10.98	41.57	0.19	0.09	0.42
Goldenberg	118	418	675	5297	0.15	0.12	0.18	0.93	0.92	0.93	2.03	1.68	2.46	0.92	0.89	0.95
Goldenberg	24	133	144	1569	0.14	0.09	0.21	0.92	0.91	0.93	1.83	1.22	2.74	0.93	0.87	0.99
Greenhagen	5	16	3	84	0.63	0.24	0.91	0.84	0.75	0.91	3.91	1.94	7.87	0.45	0.18	1.10
Inglis	2	11	9	51	0.18	0.02	0.52	0.82	0.70	0.91	1.02	0.26	4.01	0.99	0.74	1.34
Lockwood	30	108	19	272	0.61	0.46	0.75	0.72	0.67	0.76	2.15	1.64	2.83	0.54	0.38	0.77
Ruiz	0	8	6	62	0.00	0.00	0.46	0.89	0.79	0.95	0.60	0.04	9.28	1.05	0.84	1.32
DiStefano	4	8	2	46	0.67	0.22	0.96	0.85	0.73	0.93	4.50	1.92	10.57	0.39	0.13	1.22
Zamora	4	13	1	15	0.80	0.28	0.99	0.54	0.34	0.72	1.72	0.95	3.11	0.37	0.06	2.23
Vercoustre	1	6	0	58	1.00	0.03	1.00	0.91	0.81	0.96	7.50	2.54	22.14	0.28	0.03	3.07

Table 17 Characteristics of studies on test accuracy of cervico-vaginal prolactin in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Thresholds	Outcome (weeks' gestation)*
Asymptomatic										
O'Brien[131]	1994	USA	40	Cohort Prospective Blinded Test described	Asymptomatic antenatal women	Rupture of membrane, fetal anomalies, vaginal bleeding, contra-indication to tocolysis	24-32	Single	2.0 ng/ml	<34
Koca[132]	1999	Turkey	40	Cohort Prospective Test described	Singleton pregnancies, asymptomatic antenatal women	Rupture of membrane, fetal anomalies, contra-indication to tocolysis	24-32	Single	1.5 ng/ml	<37
Symptomatic										
Jotterand[134]	1997	France	64	Cohort Prospective Blinded Test described	Singleton pregnancies, threatened preterm labour	Rupture of membrane, fetal anomalies, vaginal bleeding, fetal distress, placenta previa, contra-indication to tocolysis	21-34	Single	2.0 ng/ml	<34, <37
O'Brien[131]	1994	USA	40	Cohort Prospective Blinded Test described	Threatened preterm labour	Rupture of membrane, fetal anomalies, vaginal bleeding, contra-indication to tocolysis	24-32	Single	2.0 ng/ml	Within 7 and 14 days of testing, <34, <37
Leylek[135]	1997	Turkey	66	Cohort Prospective Test described	Singleton pregnancies, threatened preterm labour		29-36	Single	50 ng/ml	Within 12 days of testing and <37
Koca[132]	1999	Turkey	35	Cohort Prospective Test described	Singleton pregnancies, threatened preterm labour	Rupture of membrane, fetal anomalies, contra-indication to tocolysis	24-32	Single	1.5 ng/ml	<34, <37
Guvenal[133]	2001	Turkey	60	Case-control Retrospective Test described	Singleton pregnancies, threatened preterm labour	Rupture of membrane, fetal anomalies, contra-indication to tocolysis, maternal hypertension, IUGR, fetal distress, placenta previa	24-36	Single	1.8 ng/ml	37

*Unless otherwise stated

Table 18 Individual accuracy results of cervico-vaginal prolactin measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour

Authors	Outcome	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																	
O'Brien[131]	34	1	1	1	37	0.50	0.01	0.99	0.97	0.86	1.00	19.00	1.76	205.15	0.51	0.13	2.06
Koca[132]	37	5	9	1	25	0.83	0.36	1.00	0.74	0.56	0.87	3.15	1.62	6.12	0.23	0.04	1.37
Symptomatic																	
O'Brien[131]	7	6	14	3	17	0.67	0.30	0.93	0.55	0.36	0.73	1.48	0.81	2.70	0.61	0.23	1.62
O'Brien[131]	34	16	4	7	13	0.70	0.47	0.87	0.76	0.50	0.93	2.96	1.20	7.26	0.40	0.20	0.78
Koca[132]	34	10	7	3	15	0.77	0.46	0.95	0.68	0.45	0.86	2.42	1.22	4.77	0.34	0.12	0.95
Jotterand[134]	34	4	7	3	50	0.57	0.18	0.90	0.88	0.76	0.95	4.65	1.81	11.97	0.49	0.21	1.16
O'Brien[131]	37	17	3	11	9	0.61	0.41	0.78	0.75	0.43	0.95	2.43	0.87	6.76	0.52	0.30	0.92
Leylek[135]	37	19	0	15	32	0.56	0.38	0.73	1.00	0.89	1.00	36.77	2.31	584.80	0.45	0.31	0.65
Koca[132]	37	14	3	6	12	0.70	0.46	0.88	0.80	0.52	0.96	3.50	1.22	10.02	0.38	0.18	0.77
Guvenal[133]	37	4	2	4	50	0.50	0.16	0.84	0.96	0.87	1.00	13.00	2.83	59.76	0.52	0.26	1.04
Jotterand[134]	37	5	6	11	42	0.31	0.11	0.59	0.88	0.75	0.95	2.50	0.88	7.10	0.79	0.56	1.11

Table 19 Characteristic of studies on the accuracy of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth stratified according to study population of asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour

Authors	Year	n	Study design	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Reference standards (weeks' gestation)*
Asymptomatic							
Bittar[138]	2001	53	Cohort Prospective Test described	Previous premature delivery, intact membrane, no vaginal bleeding, screened and treated for Trichomonas, Candida, N. gonorrhoea, C. trachomatis, Group B Streptococcus	Lost to follow-up	24 - 34, 3 weekly	<37
Symptomatic							
Shine[136]	2001	32	Cohort Prospective Test described	Threatened preterm labour, cervix < 2 cm dilated, intact membrane		24 - 36	<34 and <37
Lembet[140]	2002	36	Cohort Prospective Blinded Test described	Threatened preterm labour	Uterine anomaly, congenital fetal abnormality, intra-uterine growth restriction, pre-eclampsia, vaginal bleeding	20 - 36	<48 hours, <7 days, and <37
Choi[142]	2003	42	Cohort Prospective Test described	Threatened preterm labour		20 - 36	<37
Park[143]	2003	50	Cohort Prospective Test described	Threatened preterm labour, cervix < 3 cm dilated, intact membrane		24 - 34	<7 days, <34, and <37
Akercan[141;143]	2004	45	Cohort Prospective Test described	Threatened preterm labour	Pre-eclampsia, ruptured membrane, vaginal bleeding, intra-uterine growth restriction, congenital fetal abnormality, and uterine anomaly	24 - 36	<37
Kwek[139]	2004	47	Cohort Consecutive Prospective Test described	Threatened preterm labour	Antepartum haemorrhage, cervix >3 cm dilated, contra-indication to tocolysis, insertion of cervical cerclage	24 - 34	<48 hours, <7 days, and <36

Elizur[144]	2005	35	Cohort Prospective Blinded Test described	Threatened preterm labour		24 - 35	<48 hours, <7 days, <34, and <37
Halle[146]	1999	93	Cohort Test described	Threatened preterm labour		23 - 32	<37
Paternoster[145]	2005	135	Cohort	Threatened preterm labour	Pre-eclampsia, ruptured membrane, vaginal bleeding, intra-uterine growth restriction, congenital fetal abnormality, and uterine anomaly	Not stated	<37
Turnell[137]	2005	100	Cohort Consecutive	Threatened preterm labour		Not stated	<37

*Unless otherwise stated

Table 20 Individual accuracy results of bedside rapid test cervico-vaginal phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour

Authors	Year	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
48 hours									
Lembet[140]	2002	14	4	1	17	0.88 (0.62 - 0.98)	0.81 (0.58 - 0.95)	4.59 (1.87 - 11.31)	0.15 (0.04 - 0.57)
Kwek[139]	2004	4	14	2	20	0.67 (0.22 - 0.96)	0.59 (0.41 - 0.75)	1.62 (0.81 - 3.24)	0.57 (0.18 - 1.82)
Elizur[144]	2005	0	7	0	29	0.50 (0.01 - 0.99)	0.79 (0.63 - 0.90)	2.38 (1.52 - 10.82)	0.63 (0.16 - 2.56)
							Summary LR's	2.53 (1.17 – 5.48)	0.32 (0.15 – 0.66)
7 days									
Lembet[140]	2002	15	3	1	17	0.94 (0.70 - 1.00)	0.85 (0.62 - 0.97)	6.25 (2.19 - 17.88)	0.07 (0.01 - 0.49)
Park[143]	2003	11	10	2	27	0.85 (0.55 - 0.98)	0.73 (0.56 - 0.86)	3.13 (1.76 - 5.58)	0.21 (0.06 - 0.77)
Kwek[139]	2004	10	8	2	20	0.83 (0.52 - 0.98)	0.71 (0.51 - 0.87)	2.92 (1.54 - 5.52)	0.23 (0.06 - 0.84)
Elizur[144]	2005	0	7	0	29	0.50 (0.01 - 0.99)	0.79 (0.63 - 0.90)	2.38 (0.52 - 10.82)	0.63 (0.16 - 2.56)
							Summary LR's	3.29 (2.24 – 4.83)	0.20 (0.10 – 0.41)
34 weeks									
Shine[136]	2001	5	8	0	19	1.00 (0.48 - 1.00)	0.70 (0.50 - 0.86)	3.02 (1.64 - 5.56)	0.12 (0.01 - 1.72)
Park[143]	2003	9	12	2	27	0.82 (0.48 - 0.98)	0.69 (0.52 - 0.83)	2.66 (1.54 - 4.60)	0.26 (0.07 - 0.94)
Elizur[144]	2005	1	6	0	29	1.00 (0.03 - 1.00)	0.83 (0.66 - 0.93)	4.15 (1.44 - 11.99)	0.31 (0.03 - 3.38)
							Summary LR's	2.96 (2.02 – 4.33)	0.22 (0.08 – 0.64)
37 weeks									
Halle[146]	1999	22	11	6	54	0.79 (0.59 - 0.92)	0.83 (0.72 - 0.91)	4.64 (2.62 - 8.23)	0.26 (0.13 - 0.53)
Shine[136]	2001	8	5	2	17	0.80 (0.44 - 0.97)	0.77 (0.55 - 0.92)	3.52 (1.53 - 8.08)	0.26 (0.07 - 0.91)
Lembet[140]	2002	17	1	2	16	0.89 (0.67 - 0.99)	0.94 (0.71 - 1.00)	15.21 (2.26 - 102.48)	0.11 (0.03 - 0.42)
Choi[142]	2003	5	17	2	18	0.71 (0.29 - 0.96)	0.51 (0.34 - 0.69)	1.47 (0.82 - 2.62)	0.56 (0.16 - 1.87)
Park[143]	2003	17	1	5	24	0.77 (0.55 - 0.92)	0.96 (0.80 - 1.00)	19.32 (2.79 - 133.58)	0.24 (0.11 - 0.51)
Akercan[141;143]	2004	11	4	3	27	0.79 (0.49 - 0.95)	0.87 (0.70 - 0.96)	6.09 (2.34 - 15.82)	0.25 (0.09 - 0.68)
Kwek[139]	2004	14	4	5	17	0.74 (0.49 - 0.91)	0.81 (0.58 - 0.95)	3.87 (1.54 - 9.72)	0.33 (0.15 - 0.71)
Elizur[144]	2005	4	3	2	6	0.67 (0.22 - 0.96)	0.67 (0.30 - 0.93)	2.00 (0.68 - 5.91)	0.50 (0.15 - 1.70)
Paternoster[145]	2005	9	9	4	86	0.69 (0.39 - 0.91)	0.91 (0.83 - 0.96)	7.31 (3.56 - 15.0)1	0.34 (0.15 - 0.77)
							Summary LR's	4.26 (2.54 – 7.17)	0.28 (0.20 – 0.38)

Table 21 Characteristics of the included studies on accuracy of maternal serum α-fetoprotein (MSAFP) testing in predicting spontaneous preterm birth for asymptomatic pregnant women

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks')	Frequency of testing	Thresholds	Outcome (weeks' gestation)
Goldenberg[153]	2001	USA	2929	Cohort Prospective Blinded Test described	Singleton pregnancies	Pregnant women with cervical dilatation >2 cm (nulliparous) and >3 cm (multiparous), Placenta previa, Fetal anomaly	23-24	Single	90th centile	<32, <35
Tanaka[160]	1994	Japan	1097	Cohort Consecutive Prospective Test described	Singleton pregnancies	Fetal and chromosomal abnormalities	18-20	Single	2.0 MoM	<37
Simpson[158]	1995	USA	650	Cohort Prospective Blinded Test described	Singletons pregnant women who provided specimen on the two specified occasions	Congenital anomaly	15-20, 24-36	Single	2.0 MoM	<37
Dugoff[151]	2005	USA	33145	Cohort Prospective Test described	Singleton gestation, women >16 years	Fetal chromosomal or structural abnormalities	15-19	Single	2.0 MoM	<32
Morssink[156]	1995	Netherlands	7992	Cohort Prospective Test described	Singletons who underwent neural tube or Down's syndrome screening	Congenital anomaly, Delivery before 25 weeks' gestation, Insulin dependent diabetes mellitus	15-20	Single	2.5 MoM	<37
Davis*[150]	1992	USA	843	Cohort Prospective Test described	Singleton pregnancies	Non-viable pregnancy, Stillbirths, Fetal anomaly	14-22	Single	2.5 MoM	<37
Waller[162]	1996	USA	51008	Cohort Retrospective Test described	Singleton pregnancies	Fetal anomaly, Fetal death, Multiple gestations, (Non-lethal chromosomal abnormalities might have been included)	15-19	Single	2.0, 2.5 MoM	<28, <32, <34, <37
Spencer[159]	2000	UK	27129	Case-control Prospective Test described	Singleton pregnancies	Fetal anomaly, Chromosomal abnormality, Pregnancy termination, Loss before 24 weeks' gestation	14-18	Single	2.0 MoM	<35, <37
Yaron[165]	1999	USA	20982	Cohort Retrospective Test described	Singleton pregnancies	Fetal anomaly, Chromosomal abnormality	14-22	Single	2.5 MoM	<37
Hsieh[155]	1997	Taiwan	5885	Cohort Retrospective Test described	Singleton pregnancies	Multiple gestation, diabetes mellitus, fetal and chromosomal abnormalities	14-22	Single	2.0 MoM	<37
Davis*[150]	1992	USA	5555	Cohort Retrospective Test described	Singleton pregnancies	Non-viable pregnancy, Stillbirths, Fetal anomaly	14-22	Single	2.5 MoM	<37

Wenstorm[163]	1996	USA	4574	Cohort Retrospective Test described	Singleton pregnancies	Fetal and Chromosomal abnormality	14-20	Single	2.5 MoM	<37
Brazerol[148]	1994	USA	776	Cohort Retrospective Test described	Singleton pregnancies	Fetal anomaly, Oligohydramnios, Fetal death	15-20	Single	2.0 MoM	<28, <37
Duric[152]	2002	Croatia	672	Cohort Retrospective Test described	Singleton pregnancies	Fetal chromosomal or structural abnormalities	15-22	Single	2.02 MoM	37
Sharara[157]	1995	Qatar	360	Case-control Prospective Test described	Singleton pregnancies	Fetal anomaly, Chromosomal abnormality, Diabetes mellitus, Pre-existing hypertension, Threatened miscarriage, Molar pregnancy	16-18	Single	2.5 MoM	37
Akinbiyi[147]	1996	UK	300	Case-control Retrospective Test described	Singleton pregnancies	Fetal and chromosomal abnormality	16-18	Single	2.0 MoM	37
Cho[149]	1997	USA	255	Case-control Prospective Test described	Singleton pregnancies	Non-viable pregnancies, Fetal anomaly, Chromosomal abnormality	14-20	Single	2.5 MoM	37
Williams[164]	1992	USA	412	Case-control Retrospective Test described	Singleton pregnancies	Fetal anomaly, Chromosomal abnormality, Fetal death	14-20	Single	2.0 MoM	37
Hamilton[154]	1985	USA	286	Case-control Retrospective Test described	Singleton pregnancies	Congenital anomaly	16-20	Single, twice	2.5 MoM	<34, <37
Wald[161]	1977	UK	188	Case-control Retrospective Test described	Singleton pregnancies	Congenital abnormalities	14-22	Single	3.0 MoM	37

*Initial retrospective study consisted of 5555 pregnant women, followed by a prospective study on 843 women

Table 22 Individual accuracy results of maternal serum α-fetoprotein (MSAFP) testing in predicting spontaneous preterm birth among antenatal asymptomatic women

Authors	Threshold (MoM)*	Outcome (weeks' gestation)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Goldenberg[153]	90th centile	32	18	184	32	2695	0.36	0.23	0.51	0.94	0.93	0.94	5.63	3.79	8.36	0.68	0.56	0.84
Goldenberg[153]	90th centile	35	45	389	82	2490	0.35	0.27	0.44	0.86	0.85	0.88	2.62	2.04	3.38	0.75	0.66	0.85
Tanaka[160]	2.0	37	8	65	69	955	0.10	0.05	0.19	0.94	0.92	0.95	1.63	0.81	3.27	0.96	0.89	1.03
Simpson[+158]	2.0	37	8	119	34	489	0.19	0.09	0.34	0.80	0.77	0.84	0.97	0.51	1.85	1.01	0.86	1.17
Simpson[++158]	2.0	37	4	62	38	546	0.10	0.03	0.23	0.90	0.87	0.92	0.93	0.36	2.44	1.01	0.91	1.12
Dugoff[151]	2.0	32	28	531	229	32357	0.11	0.07	0.15	0.98	0.98	0.99	6.75	4.71	9.67	0.91	0.87	0.95
Morssink[156]	2.5	37	10	60	467	7455	0.02	0.01	0.04	0.99	0.99	0.99	2.63	1.35	5.10	0.99	0.97	1.00
Davis[150]	2.5	37	29	3	73	738	0.28	0.20	0.38	1.00	0.99	1.00	70.23	21.78	226.38	0.72	0.64	0.81
Waller[162]	2.0	28	48	2418	237	48305	0.17	0.13	0.22	0.95	0.95	0.95	3.53	2.72	4.59	0.87	0.83	0.92
Waller[162]	2.5	28	21	629	264	50094	0.07	0.05	0.11	0.99	0.99	0.99	5.94	3.91	9.03	0.94	0.91	0.97
Waller[162]	2.0	32	118	2348	576	47966	0.17	0.14	0.20	0.95	0.95	0.96	3.64	3.08	4.31	0.87	0.84	0.90
Waller[162]	2.5	32	47	603	647	49711	0.07	0.05	0.09	0.99	0.99	0.99	5.65	4.24	7.53	0.94	0.92	0.96
Waller[162]	2.0	34	227	2239	1149	47393	0.16	0.15	0.19	0.95	0.95	0.96	3.66	3.23	4.15	0.87	0.85	0.90
Waller[162]	2.5	34	79	571	1297	49061	0.06	0.05	0.07	0.99	0.99	0.99	4.99	3.97	6.28	0.95	0.94	0.97
Waller[162]	2.0	37	499	1967	3212	45330	0.13	0.12	0.15	0.96	0.96	0.96	3.23	2.95	3.55	0.90	0.89	0.91
Waller[162]	2.5	37	158	492	3553	46805	0.04	0.04	0.05	0.99	0.99	0.99	4.09	3.43	4.88	0.97	0.96	0.97
Spencer[159]	2.0	35	57	548	607	25917	0.09	0.07	0.11	0.98	0.98	0.98	4.15	3.19	5.39	0.93	0.91	0.96
Spencer[159]	2.0	37	123	482	1429	25095	0.08	0.07	0.09	0.98	0.98	0.98	4.21	3.47	5.09	0.94	0.92	0.95
Yaron[165]	2.5	37	9	75	757	20141	0.01	0.01	0.02	1.00	1.00	1.00	3.17	1.59	6.30	0.99	0.98	1.00
Hsieh[155]	2.0	37	23	153	329	5380	0.07	0.04	0.10	0.97	0.97	0.98	2.36	1.55	3.61	0.96	0.93	0.99
Davis[150]	2.5	37	87	19	393	5056	0.18	0.15	0.22	1.00	0.99	1.00	48.41	29.74	78.82	0.82	0.79	0.86
Wenstorm[163]	2.5	37	62	99	609	3804	0.09	0.07	0.12	0.97	0.97	0.98	3.64	2.68	4.95	0.93	0.91	0.95
Brazerol[148]	2.0	28	6	51	9	710	0.40	0.16	0.68	0.93	0.91	0.95	5.97	3.04	11.71	0.64	0.43	0.97
Brazerol[148;148]	2.0	37	4	53	37	682	0.10	0.03	0.23	0.93	0.91	0.95	1.35	0.51	3.56	0.97	0.88	1.08
Duric[152]	2.0	37	1	39	32	601	0.03	0.00	0.16	0.94	0.92	0.96	0.50	0.07	3.51	1.03	0.97	1.10
Sharara[157]	2.5	37	18	102	20	220	0.47	0.31	0.64	0.68	0.63	0.73	1.50	1.03	2.17	0.77	0.56	1.05
Akinbiyi[147]	2.0	37	9	91	4	196	0.69	0.39	0.91	0.68	0.63	0.74	2.18	1.46	3.26	0.45	0.20	1.02
Cho[149]	2.5	37	37	80	16	122	0.70	0.56	0.82	0.60	0.53	0.67	1.76	1.38	2.25	0.50	0.33	0.76

Williams[164]	2.0	37	43	158	23	188	0.65	0.52	0.76	0.54	0.49	0.60	1.43	1.16	1.76	0.64	0.45	0.90
Hamilton[**154]	2.5	34	19	81	1	185	0.95	0.75	1.00	0.70	0.64	0.75	3.12	2.53	3.84	0.07	0.01	0.49
Hamilton[**154]	2.5	37	26	74	6	180	0.81	0.64	0.93	0.71	0.65	0.76	2.79	2.16	3.60	0.26	0.13	0.55
Hamilton[154]	2.5	34	9	78	1	185	0.90	0.55	1.00	0.70	0.64	0.76	3.03	2.30	4.01	0.14	0.02	0.91
Hamilton[154]	2.5	37	18	68	6	180	0.75	0.53	0.90	0.73	0.67	0.78	2.74	2.01	3.72	0.34	0.17	0.69
Wald[161]	3.0	37	23	4	71	90	0.24	0.16	0.34	0.96	0.89	0.99	5.75	2.07	15.99	0.79	0.70	0.89

+ Tested at 15-20 weeks' gestation ++ Tested at 24-36 weeks' gestation * Unless otherwise stated ** Tested twice

Table 23 Characteristics of studies on test accuracy of maternal serum relaxin in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Asymptomatic										
Weiss[166]	1993	USA	76	Cohort Prospective Consecutive Test described	All 18 - 42 years old women who achieved singleton pregnancies from either ovulatory induction with or without IVF/ET	No previous history of preterm birth, uterine or fetal abnormalities, more than one major cervical surgery, no previous DES exposure, placenta previa, pre-eclampsia	6 - 12	Serial	+3SD*	<37
Vogel[168]	2006	USA	61	Cohort Prospective Consecutive Test described	Asymptomatic women with at least 1 previous late spontaneous miscarriage or early spontaneous preterm delivery between 16 - 30 weeks' gestation	Multiple gestation, PPROM, uterine or fetal abnormalities, threatened preterm labour	12 - 25	Single	406 mg/L	<37
Goldenberg[153]	2001	USA	2929	Case-control Retrospective Blinded Test described	Singleton pregnancy	Cervical dilatation >3cm in multiparous, >2cm in nulliparous, PPROM, bulging membrane at cervical os, placenta previa	24	Single	90th centile	<32, <35
Vogel[167]	2005	Denmark	483	Case-control Retrospective Test described	Singleton asymptomatic pregnancies	Multiple gestation, PPROM, fetal abnormalities, diabetes	18 - 24	Single	932 pg/ml	<37
Symptomatic										
Vogel[169]	2002	Denmark	34	Cohort Prospective Test described	Singleton pregnancy presenting with threatened preterm labour and intact membrane and without evidence of ripening cervix	Elevated blood pressure, women with major medical disease, vaginal bleeding	24 - 34	Single	300 pg/ml	<34, <37

*Standard deviation

Table 24 Individual accuracy results of maternal serum relaxin measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour

Authors	Outcome (weeks' gestation)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																	
Weiss[166]	37	6	37	3	30	0.67	0.30	0.93	0.45	0.33	0.57	1.21	0.73	2.01	0.74	0.28	1.95
Vogel[168]	37	9	33	11	8	0.45	0.23	0.68	0.20	0.09	0.35	0.56	0.34	0.93	2.82	1.35	5.89
Vogel[167]	37	18	50	66	350	0.21	0.13	0.32	0.88	0.84	0.91	1.71	1.06	2.78	0.90	0.80	1.01
Goldenberg[153]	32	11	628	39	2251	0.22	0.12	0.36	0.78	0.77	0.80	1.01	0.60	1.71	1.00	0.86	1.16
Goldenberg[153]	35	43	595	84	2214	0.34	0.26	0.43	0.79	0.77	0.80	1.60	1.24	2.06	0.84	0.74	0.95
Symptomatic																	
Vogel[169]	34	1	7	2	24	0.33	0.01	0.91	0.77	0.59	0.90	1.48	0.26	8.31	0.86	0.38	1.96
Vogel[167]	37	2	6	8	18	0.20	0.03	0.56	0.75	0.53	0.90	0.80	0.19	3.31	1.07	0.72	1.57

Table 25 Characteristics of studies on test accuracy of corticotrophin releasing hormone (CRH) in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour

Authors	Year	Country	Population	Quality of studies	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Frequency of testing	Thresholds	Outcome (weeks' gestation)
Asymptomatic										
Leung[173]	1999	Hong Kong	1014	Blinded Cohort Prospective Test described	Singleton pregnancies	Mid-trimester miscarriage	15-20	Single	1.9 MoM	<34
Berkowitz[170]	1996	USA	396	Cohort Prospective Test described	Asymptomatic Hispanic women	Multiple gestations, stillbirths, congenital malformation, iatrogenic preterm birth, women with chronic hypertension, pre-eclampsia	20-24 24-28 29-33 33-37	Serial	3.1, 41.3, 234, 665.7 pg/ml	<37
Inder[172]	2001	USA	297	Cohort Prospective Test described	Antenatal women from a local area medical practice	None stated	26	Single**	50, 70, 90, 110, 130, 150 pmol/l	<37
Goldenberg[153]	2001	USA	2929	Blinded Case-control Retrospective Test described	Singleton pregnancies	Fetal anomalies, chromosomal abnormalities, placenta previa, cervical dilatation >3 cm, or bulging membrane	23-24	Single	90th centile	<32 and <35
Holzman[171]	2001	USA	304 (White), 181(Black)	Blinded Case-control Retrospective Test described	Antenatal patients at tertiary referral centre	Other ethnic groups beside black or white, multiple gestations, diabetes before pregnancy, chromosomal abnormalities	15-19	Single	1.0, 1.5 MoM	<35
Symptomatic										
Coleman[174]	2000	New Zealand	94	Blinded Cohort Prospective Test described	Non-diabetic singleton pregnancies presenting with preterm labour, intact membrane, and cervical dilatation <3 cm	Fetal anomaly and chromosomal abnormality	24-36	Single	90th centile	<10 days of testing and <37

*(Sample was collected weekly from 17-30 weeks' gestation) but only the sample closest to 22nd weeks' gestation was used in the analysis)
**(Sample was collected weekly from 16-20 weeks' gestation) but only the sample closest to 26th weeks' gestation was used in the analysis)

Table 26 Individual accuracy results of maternal serum corticotrophin releasing hormone (CRH) measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour

Authors	Thresholds	Outcome	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																		
Leung[173]	1.9 MoM	34	8	217	3	786	0.73	0.39	0.94	0.78	0.76	0.81	3.36	2.30	4.92	0.35	0.13	0.91
Berkowitz[170]	3.1 pg/ml	37	4	25	41	326	0.09	0.02	0.21	0.93	0.90	0.95	1.25	0.46	3.42	0.98	0.89	1.08
Berkowitz[170]	41.3 pg/ml	37	11	71	34	280	0.24	0.13	0.40	0.80	0.75	0.84	1.21	0.69	2.10	0.95	0.80	1.13
Berkowitz[170]	234 pg/ml	37	13	71	32	280	0.29	0.16	0.44	0.80	0.75	0.84	1.43	0.86	2.36	0.89	0.73	1.08
Berkowitz[170]	665.7 pg/ml	37	9	74	36	277	0.20	0.10	0.35	0.79	0.74	0.83	0.95	0.51	1.76	1.01	0.87	1.18
Inder[172]	90 pmol/l	37	14	16	17	250	0.45	0.27	0.64	0.94	0.90	0.97	7.51	4.07	13.86	0.58	0.42	0.80
Inder[172]	70 pmol/l	37	17	29	14	237	0.55	0.36	0.73	0.89	0.85	0.93	5.03	3.15	8.04	0.51	0.34	0.75
Inder[172]	110 pmol/l	37	11	9	20	257	0.35	0.19	0.55	0.97	0.94	0.98	10.49	4.72	23.31	0.67	0.51	0.87
Inder[172]	130 pmol/l	37	8	6	23	260	0.26	0.12	0.45	0.98	0.95	0.99	11.44	4.25	30.82	0.76	0.62	0.93
Inder[172]	150 pmol/l	37	6	2	25	264	0.19	0.07	0.37	0.99	0.97	1.00	25.74	5.43	122.07	0.81	0.68	0.97
Inder[172]	50 pmol/l	37	21	60	10	206	0.68	0.49	0.83	0.77	0.72	0.82	3.00	2.16	4.18	0.42	0.25	0.70
Goldenberg[153]	90th centile	32	6	242	44	2637	0.12	0.05	0.24	0.92	0.91	0.93	1.43	0.67	3.05	0.96	0.87	1.06
Goldenberg[153]	90th centile	35	15	233	112	2569	0.12	0.07	0.19	0.92	0.91	0.93	1.42	0.87	2.32	0.96	0.90	1.03
Holzman[171]	1.0 MoM (Black)	35	33	78	8	62	0.80	0.65	0.91	0.44	0.36	0.53	1.44	1.17	1.78	0.44	0.23	0.84
Holzman[171]	1.0 MoM (White)	35	34	120	22	128	0.61	0.47	0.74	0.52	0.45	0.58	1.25	0.98	1.61	0.76	0.54	1.08
Holzman[171]	1.5 MoM (Black)	35	17	32	24	108	0.41	0.26	0.58	0.77	0.69	0.84	1.81	1.13	2.91	0.76	0.58	1.00
Holzman[171]	1.5 MoM (White)	35	16	48	40	200	0.29	0.17	0.42	0.81	0.75	0.85	1.48	0.91	2.40	0.89	0.74	1.06
Symptomatic																		
Coleman[174]	90th centile	10	6	12	7	69	0.46	0.19	0.75	0.85	0.76	0.92	3.12	1.42	6.84	0.63	0.38	1.05
Coleman[174]	90th centile	37	12	6	19	57	0.39	0.22	0.58	0.90	0.80	0.96	4.06	1.68	9.81	0.68	0.51	0.91

Table 27 Characteristics of the included studies on accuracy of β-human chorionic gonadotrophin (β-hcg) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and women who presented with threatened preterm labour

Authors	Year	Country	N	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold (MoM)+*	Outcome (weeks' gestation)*
Yaron[165]	2002	Israel	1,622	Cohort Consecutive Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	x	10 - 13	Single	≥1.0, ≥2.0, ≥3.0, ≥4.0, ≥5.0	<37
Dugoff[151]	2005	USA	33,145	Cohort Consecutive Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	x	15 - 19	Single	>2.0	<32
Ong[185]	2000	UK	5,297	Cohort Consecutive Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	x	10 - 14	Single	5th, 10th centile	<34, <37
Dugoff[179]	2004	USA	34,271	Cohort Prospective Test described	Singleton pregnancies without fetal and chromosomal abnormalities	x	10 - 14	Single	1st, 5th , and 10th centile	<32, <37
Morssink[156]	1995	Netherland	7,992	Cohort Prospective Test described	Singleton pregnancies	Unknown pregnancy outcome, a congenital anomaly, delivery before 25 weeks of amenorrhea, or known insulin-dependent diabetes	15 - 20	Single	≥2.5	<37
Chandra[178]	2003	Canada	8,585	Cohort Prospective Test described	< 35 years, low risk singleton pregnancies without fetal or chromosomal abnormalities	x	15 - 20	Single	≥2.0	<37
Tanaka[160]	1994	Japan	1,097	Cohort Consecutive Prospective Test described	Consecutive pregnant women in whom gestation was dated by ultrasonography, with singleton pregnancies	x	18 - 20	Single	≥2.0	<37
Haddad[188]	1999	France	169	Cohort Retrospective Test described	IVF singleton pregnancies	No fetal or chromosomal abnormalities	6 - 7	Serial	90th centile	<37

Duric[152]	2002	Croatia	672	Cohort Retrospective Test described	< 35 years women with singleton pregnancies without fetal or chromosomal abnormalities	x	15 - 22	Single	≥2.02	<37
Spencer[159]	2000	UK	26,918	Case-control Retrospective Test described	Control of singleton uncomplicated pregnancies outcome. Cases were those with spontaneous preterm delivery	x	14 - 18	Single	≥2.0	<35, <37
Lieppman[182]	1993	USA	460	Case-control Retrospective Test described	Non-diabetic women with singleton pregnancies between 15 and 18 weeks' gestation	Multiple gestations, diabetic pregnancies, fetal and chromosomal abnormalities	15 - 18	Single	≥2.0	<37
Onderoglu[184]	1997	Turkey	562	Case-control Retrospective Test described	Singleton non-diabetic pregnancies with know outcomes	Fetal and chromosomal abnormalities or maternal serum alpha feto-protein > 2.0 MoM	15 - 20	Single	≥2.0	<37
Hsieh[155]	1997	Taiwan	5,885	Cohort Retrospective Test described	Taiwanese women under 35 years of age with singleton pregnancies without fetal or chromosomal abnormalities	x	14 - 22	Single	≥2.0	<37
Wenstorm[186]	1994	USA	252	Case-control Retrospective Test described	Cases were singleton pregnancies without fetal or chromosomal abnormalities who underwent amniocentesis with matched control who did not have amniocentesis	x	15 - 20	Single	≥2.0	<37
Gonen[180]	1992	Israel	493	Case-control Retrospective Test described	Cases were singleton pregnancies with confirmed gestational age	Fetal or chromosomal abnormalities and maternal serum alpha feto-protein > 2.5 MoM	16 - 20	Single	≥2.5	<37
Yaron[165]	1999	Israel	45,565	Cohort Retrospective Test described	All singleton pregnancies screened for Down' syndrome risks	Fetal or chromosomal abnormalities	14 - 22	Single	>2.5	<37
Benn[176]	1996	USA	1,079	Case-control Retrospective Test described	<35 years, singleton pregnancies without diabetes mellitus, fetal and chromosomal abnormalities	x	15 - 22	Single	≥3.0	<37
Brajenovic[177]	2004	Croatia	1,507	Case-control Retrospective Test described	Singleton pregnancies without fetal or chromosomal abnormalities		15 - 20	Single	≥2.0	<37
Lepage[181]	2003	Canada	2,256	Case-control Retrospective Test described	Singleton pregnancies without fetal anomalies	x	15 - 20	Single	≥4.0	<37

Liu[183]	1999	USA	72	Case-control Retrospective Test described	Unexplained elevated maternal serum hcg levels compared with controls with normal ms-hcg levels delivering during the same period	x	15 - 20	Not stated	≥2.0	<36
Ramos[190]	2003	USA	86	Cohort Prospective Blinded Test described	Preterm labour, < 4cm cervical dilatation, intact membrane	PPROM, presence of gross blood in vagina, cervical cerclage, fetal anomaly, IUGR, pre-eclampsia	24 - 34	Single	25 mIU/ml	<37
Gurbuz[189]	2004	Turkey	102	Cohort Prospective Test described	Preterm labour, < 3cm cervical dilatation, intact membrane	Fetal compromise, placenta previa, abruption, fetal anomaly, PPROM, pre-eclampsia.	25 - 35	Single	32 mIU/ml 42 mIU/ml 30 mIU/ml 33 mIU/ml 27 mIU/ml	<100 hours <100 hours < 7 days <14 days of testing, <35 and <37
Guvenal[133]	2001	Turkey	60	Case-control Prospective Test described	Singleton pregnancies without fetal or chromosomal abnormalities, cervical dilatation <3cm	Placenta previa, vaginal bleeding, pre-eclampsia, hypertension, IUGR, fetal distress, rupture of membrane at presentation	24 - 36	Single	27.1 mIU/ml	<37

Table 28 Individual accuracy results of β-human chorionic gonadotrophin (β-hcg) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic women, threshold 2.0 MoM, <37 weeks gestation																
Yaron[165]	32	1246	12	332	0.73	0.57	0.85	0.21	0.19	0.23	0.92	0.77	1.11	1.30	0.79	2.12
Chandra[178]	203	637	1352	6393	0.13	0.11	0.15	0.91	0.90	0.92	1.44	1.24	1.67	0.96	0.94	0.98
Duric[152]	11	97	23	541	0.32	0.17	0.51	0.85	0.82	0.87	2.13	1.27	3.58	0.80	0.63	1.01
Tanaka[160]	8	65	69	955	0.10	0.05	0.19	0.94	0.92	0.95	1.63	0.81	3.27	0.96	0.89	1.03
Brajenovic[177]	5	116	44	1342	0.10	0.03	0.22	0.92	0.91	0.93	1.28	0.55	3.00	0.98	0.89	1.07
Lieppman[182]	25	200	9	226	0.74	0.56	0.87	0.53	0.48	0.58	1.57	1.25	1.96	0.50	0.28	0.88
Onderoglu[184]	27	54	39	442	0.41	0.29	0.54	0.89	0.86	0.92	3.76	2.56	5.52	0.66	0.54	0.81
Shieh[155]	33	383	329	5140	0.09	0.06	0.13	0.93	0.92	0.94	1.31	0.94	1.85	0.98	0.94	1.01
Spencer[159]	250	3713	1302	22541	0.16	0.14	0.18	0.86	0.85	0.86	1.14	1.01	1.28	0.98	0.96	1.00
Wenstorm[186]	4	18	37	193	0.10	0.03	0.23	0.91	0.87	0.95	1.14	0.41	3.20	0.99	0.88	1.10
Dugoff[1 179]	54	278	2137	30926	0.02	0.02	0.03	0.99	0.99	0.99	2.77	2.07	3.69	0.98	0.98	0.99
Dugoff[2 151]	187	1485	2004	29719	0.09	0.07	0.10	0.95	0.95	0.95	1.79	1.55	2.07	0.96	0.95	0.97
Dugoff[3 151]	329	2945	1862	28259	0.15	0.14	0.17	0.91	0.90	0.91	1.59	1.43	1.77	0.94	0.92	0.96
Symptomatic women, threshold 30 mIU/mL, within 7 days of testing																
Gurbuz[189]	56	7	2	37	0.97	0.88	1.00	0.84	0.70	0.93	6.07	3.07	11.99	0.04	0.01	0.16
Symptomatic women, threshold 30 mIU/mL, <37 weeks ' gestation																
Ramos[190]	18	17	10	41	0.64	0.44	0.81	0.71	0.57	0.82	2.19	1.35	3.56	0.51	0.30	0.85
Gurbuz[189]	61	10	19	12	0.76	0.65	0.85	0.55	0.32	0.76	1.68	1.04	2.69	0.44	0.25	0.75
Guvenal[133]	7	18	1	34	0.88	0.47	1.00	0.65	0.51	0.78	2.53	1.60	3.99	0.19	0.03	1.21

1. Threshold = 0.28 MoM (i.e. 1st centile), 2. Threshold = 0.42 MoM (5th centile) and 3. Threshold = 0.52 MoM (10th centile)

Table 29 Characteristics of studies on test accuracy of estriol in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and symptomatic women with threatened preterm labour

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks')	Frequency of testing	Threshold	Outcome (weeks' gestation)*
Asymptomatic										
Heine[192]	2000	USA	601	Cohort Prospective Blinded Test described	Singleton gestation, women >18 years	Placenta previa, cerclage, PPROM, pre-eclampsia, medications known to affect hormone levels, planned caesarean section, major congenital abnormalities, intra-uterine growth restriction, fetal chromosomal and structural abnormalities, erythroblastosis fetalis, oral conditions that interfere with saliva collections, maternal medical complications	21-25	Single and twice (7 days apart)	2.1 ng/ml	37
Dugoff[151]	2005	USA	33145	Cohort Prospective Test described	Singleton gestation, women >16 years	Fetal chromosomal or structural abnormalities	15-19	Single	0.5 MoM	32
Yaron[165]	1999	USA	24504	Cohort Retrospective Test described	All singleton pregnancies	Fetal chromosomal or structural abnormalities	14-22	Single	0.5 MoM	37
Kim[193]	2000	Korea	1096	Cohort Test described	All singletons <35 years old	Multiple pregnancies, diabetes mellitus, smoking abnormal alpha feto-protein and or human chorionic gonadotrophin	15-20	Single	0.75 MoM	37
Duric[152]	2003	Croatia	672	Cohort Retrospective Test described	Singleton pregnancies	Fetal chromosomal or structural abnormalities	15-22	Single	0.74 MoM	37
Kowalczyk[194]	1998	USA	399	Cohort Retrospective Test described	Singleton pregnancies, <35 years old	Elevated hcg and/or AFP	15-21	Single	0.75 MoM	37
Symptomatic										
Heine[192]	2000	USA	115	Cohort Prospective Blinded Test described	Symptomatic with threatened preterm labour	Placenta previa, tocolytics therapy, cerclage, PPROM, pre-eclampsia, medications known to affect hormone levels, planned caesarean section, major congenital abnormalities, intra-uterine growth restriction, fetal chromosomal and structural abnormalities, erythroblastosis fetalis, oral conditions that interfere with saliva collections, maternal medical complications	21-25	Single	1.4 ng/ml and 2.1 ng/ml	Within 14 days of testing
McGregor[191]	1995	USA	190	Cohort Prospective Test described	Singleton pregnancies presenting with threatened preterm labour	Fetal anomalies, IUGR,	22-26	Single	2.1 ng/ml	37

*Unless otherwise stated

Table 30 Individual accuracy results of maternal estriol measurement in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour[+]

Authors	Thresholds	Outcome (weeks)*	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																		
Heine[192]	2.1 ng/ml	37	10	46	13	532	0.43	0.23	0.66	0.92	0.90	0.94	5.46	3.18	9.40	0.61	0.43	0.88
Heine**[192]	2.1 ng/ml	37	13	128	10	450	0.57	0.34	0.77	0.78	0.74	0.81	2.55	1.73	3.77	0.56	0.35	0.89
Dugoff	0.5 MoM	32	5	369	252	32519	0.02	0.01	0.04	0.99	0.99	0.99	1.73	0.72	4.15	0.99	0.97	1.01
Yaron[165]	0.5 MoM	37	50	1688	865	21901	0.05	0.04	0.07	0.93	0.93	0.93	0.76	0.58	1.00	1.02	1.00	1.03
Kim[193]	0.75 MoM	37	7	100	54	935	0.11	0.05	0.22	0.90	0.88	0.92	1.19	0.58	2.44	0.98	0.89	1.07
Duric[152]	0.74 MoM	37	12	104	22	534	0.35	0.20	0.54	0.84	0.81	0.86	2.17	1.33	3.53	0.77	0.60	0.99
Kowalczyk[194]	0.75 MoM	37	12	69	38	190	0.24	0.13	0.38	0.73	0.68	0.79	0.90	0.53	1.54	1.04	0.87	1.23
Symptomatic																		
Heine[192]	1.4 ng/ml	<14 days of testing	14	22	9	70	0.61	0.39	0.80	0.76	0.66	0.84	2.55	1.56	4.16	0.51	0.31	0.87
Heine[192]	2.1 ng/ml	<14 days of testing	7	1	16	91	0.30	0.13	0.53	0.99	0.94	1.00	28.00	3.62	216.39	0.70	0.54	0.92
McGregor[191]	2.1 ng/ml	37	16	53	6	115	0.73	0.50	0.89	0.68	0.61	0.75	2.31	1.64	3.24	0.40	0.20	0.79

+Single testing unless otherwise stated
*Unless otherwise stated
**Serial testing 7 days apart

Table 31 Characteristic of studies on accuracy of maternal C-reactive protein (CRP) measurement in predicting spontaneous preterm birth

Author	Year	n	Study quality	Gestation at testing (weeks)	Cut-off [ng/mL]*	Reference Standard*
Amniotic fluid CRP in asymptomatic women						
Ghezzi[200]	2002	306	Cohort, blinding, test described	14-20	110	34 weeks' gestation
Ozer[205]	2005	141	Cohort, consecutive, prospective, test described	15-20	6.5	37 weeks' gestation
Blood serum CRP In asymptomatic women						
Hvilsom[202]	2002	484	Case-control, test described	14-18	7.6	37 weeks' gestation
Karinen[203]	2005	506	Case-control, test described	12-16	4.3	37 weeks' gestation
Rückhäberle[206]	1991	216	Cohort	Not reported	pos/neg	37 weeks' gestation
Blood serum CRP In symptomatic women						
Cammu[196]	1989	87	Cohort, consecutive, blinding, test described	22-35	12,5	7 days after testing, 37 weeks' gestation
Cylwik[197]	1997	35	Cohort, retrospective, test described	>24	10	37 weeks' gestation
Dodds[198]	1987	34	Cohort, retrospective, test described	24-35	8	7 days after testing
Foulon[199]	1995	44	Cohort, consecutive, retrospective, test described	20-34	15	34 weeks' gestation
Handwerker[201]	1984	50	Cohort, consecutive, blinding, test described	24-34	0,8-1,0	7 days after testing
Mazor[204]	1993	48	Cohort, consecutive, test described	24-36	8	37 weeks' gestation
Potkul[195]	1985	40	Cohort, consecutive, blinding, test described	24-36	7	37 weeks' gestation
Winkler[207]	1987	98	Cohort, consecutive	Not reported	10	7 days after testing

*unless otherwise stated

Table 32 Sensitivity and specificity (with corresponding 95% Confidence Intervals (CI)) of C-reactive protein (CRP) among individual studies in predicting spontaneous preterm birth according to type of tests, reference standards, and populations

Author	Year	Cut-off [ng/ml]	TP*	FP*	FN*	TN*	Sensitivity	95% CI lower limit	95% CI upper limit	Specificity	95% CI lower limit	95% CI upper limit
Amniotic fluid CRP for predicting birth before 34 weeks' gestation												
Asymptomatic women												
Ghezzi[200]	2002	110	8	90	2	206	0.80	0.44	0.97	0.70	0.64	0.75
Amniotic fluid CRP for predicting birth before 37 weeks' gestation												
Asymptomatic women												
Ozer[205]	2005	6.5	13	27	1	100	0.93	0.66	0.99	0.79	0.72	0.85
Blood Serum CRP for predicting birth within 7 days of testing												
Symptomatic women												
Cammu[196]	1989	12,5	9	1	2	41	0.82	0.48	0.98	0.98	0.87	1.00
Dodds[198]	1987	8	17	4	3	10	0.85	0.62	0.97	0.71	0.42	0.92
Handwerker[201]	1984	0,8-1,0	11	4	2	33	0.85	0.55	0.98	0.89	0.75	0.97
Winkler[207]	1987	10	13	14	27	44	0.33	0.19	0.49	0.76	0.63	0.86
Blood Serum CRP for predicting birth before 37 weeks' gestation												
Asymptomatic women												
Hvilsom[202]	2002	7.6	22	58	62	342	0.26	0.17	0.37	0.86	0.82	0.89
Karinen[203]	2005	4.3	36	90	68	312	0.35	0.26	0.46	0.78	0.73	0.82
Rückhäberle[206]	1991	pos/neg	39	20	66	91	0.37	0.28	0.47	0.82	0.74	0.89
Symptomatic women												
Cammu[196]	1989	12,5	14	19	7	47	0.67	0.43	0.85	0.71	0.59	0.82
Cylwik[197]	1997	10	2	4	3	26	0.40	0.05	0.85	0.87	0.69	0.96
Foulon**[199]	1995	15	3	2	5	34	0.38	0.09	0.76	0.94	0.81	0.99
Mazor[204]	1993	8	8	8	10	22	0.44	0.22	0.69	0.73	0.54	0.88
Potkul[195]	1985	7	14	2	11	13	0.56	0.35	0.76	0.87	0.60	0.98

*TP = true positive, FP = false positive, FN = false negative, TN = true negative.
**Reference standard births < 34 weeks' gestation

Table 33 Likelihood Ratios for positive (LR+) and negative (LR-) test results (with corresponding 95% Confidence Intervals (CI)) of C-reactive protein (CRP) in predicting spontaneous preterm birth among individual studies according to type of tests, reference standard and populations

Author	Year	Cut-off [ng/ml]	LR+	95% CI lower limit	95% CI upper limit	LR-	95% CI lower limit	95% CI upper limit
Amniotic fluid CRP for predicting birth before 34 weeks' gestation								
Asymptomatic women								
Ghezzi[200]	2002	110	2.63	1.85	3.75	0.29	0.08	0.99
Ozer[205]	2005	6.5	4.37	3.03	6.29	0.09	0.014	0.60
Blood Serum CRP for predicting birth within 7 days of testing								
Symptomatic women								
Cammu[196]	1989	12,5	34.36	4.86	243.09	0.19	0.05	0.65
Dodds[198]	1987	8	2.98	1.27	6.95	0.21	0.07	0.63
Handwerker[201]	1984	0,8-1,0	7.83	3.01	20.32	0.17	0.05	0.62
Winkler[207]	1987	10	1.35	0.71	2.55	0.89	0.69	1.15
		Summary	4.54	1.48	13.91	0.30	0.08	1.15
Blood Serum CRP for predicting birth before 37 weeks' gestation								
Asymptomatic women								
Hvilsom[202]	2002	7.6	1.81	1.17	2.78	0.86	0.76	0.98
Karinen[203]	2005	4.3	1.55	1.22	2.13	0.84	0.73	0.98
Rückhäberle[206]	1991	pos/neg	2.06	1.29	3.29	0.77	0.65	0.91
		Summary	1.72	1.38	2.16	0.83	0.76	0.91
Symptomatic women								
Cammu[196]	1989	12,5	2.32	1.43	3.76	0.47	0.25	0.87
Cylwik[197]	1997	10	3.00	0.73	12.27	0.69	0.33	1.44
Foulon[199]	1995	15	6.75	1.34	34.00	0.66	0.38	1.14
Mazor[204]	1993	8	1.67	0.76	3.66	0.76	0.48	1.21
Potkul[195]	1985	7	4.20	1.10	15.98	0.51	0.31	0.82
		Summary	2.29	1.57	3.35	0.60	0.46	0.79

**Reference standard births < 34 weeks' gestation
+ See table 1 for patient characteristics

Table 34 Characteristics of the included studies on accuracy of interleukin-6 (IL6) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and symptomatic women who presented with threatened preterm labour, stratified according to specimen source

Authors	Year	Country	n	Study designs	Inclusion criteria	Exclusion criteria	Testing gestations	Frequency of testing	Thresholds	Outcome (weeks' gestation)*
Asymptomatic										
Amniotic fluid										
Wenstorm[210]	1998	USA	482	Case-control Retrospective Test described	Singleton pregnancies that underwent amniocentesis for various reasons (e.g. prenatal diagnosis)	Aneuploidies, anomalies, pregnancy loss within 30 days of amniocentesis	14 - 18	Single	2.9 ng/ml	34, 37
Ghidini[212]	1997	USA	179	Case-control Retrospective Test described	Singleton uncomplicated pregnancy	Multiple gestations, uterine, fetal or neonatal abnormalities, cytogenetic evidence of karyotypical abnormalities.	15 - 20	Single	1740 pg/ml	34
Cervico-vaginal										
Lockwood[211]	1994	USA	161	Cohort Prospective Consecutive Blinding Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm	Unknown dates, placenta previa, hydatidiform mole, major congenital anomaly, serious maternal medical complications.	24 - 36	Serial 3 - 4 weekly	125 & 250 pg/ml	37
Inglis[96]	1994	USA	73	Cohort Prospective Consecutive Blinding Test described	All patients between 15 and 40 years old with singleton pregnancies.	Congenital anomalies, placenta previa, kwon genital or urinary tract infection, use of antibiotics within the past 7 days.	20 - 36	Single	50 pg/ml	37
Goepfert[221]	2001	USA	250	Case-control Retrospective Blinding Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm	Placenta previa, fetal abnormalities, maternal medical complications, uterine abnormalities.	22 - 24	Single	305 pg/ml	35, 37
Symptomatic										
Amniotic fluid										

Rizzo[217]	1996	Italy	92	Cohort Prospective Consecutive Blinding Test described	Singleton gestation in premature labour with intact membrane, cervical dilatation	Presence of other fetal or maternal complications, known genital or urinary infection, antibiotics use within the last 14 days.	24 - 36	Single	50 pg/ml	37
Romero[208]	1993	USA	146	Cohort Prospective Consecutive Test described	Singleton pregnant women with threatened preterm labour	x	20 - 34	Single	0.5, 2.0 & 11.30 ng/ml	36
Coultrip[214]	1994	USA	89	Cohort Prospective Blinding Test described	Symptomatic women singleton pregnancies with intact membrane.	x	20 - 36	Single	0.38, 0.617 & 1.13 ng/ml	Within 3 days of testing (0.38 ng/ml only), 37
Greig[229]	1993	USA	57	Cohort Prospective Blinding Test described	Singleton gestation in premature labour with intact membrane	Cervical dilatation >4 cm, antibiotic treatment in the past 7 days, any medical condition requiring antibiotic treatment.	24 - 34	Single	600 pg/ml	3
Greci[215]	1998	USA	53	Cohort Prospective Blinding Test described	Women who presented with threatened preterm labour and intact membrane	Vaginal bleeding, placenta previa, abruption, multiple gestations, polyhydramnios, pre-eclampsia, cervical cerclage, known uterine or fetal anomalies.	24 - 34	Single	7586 pg/ml	Within 2 & 7 days of testing
Burrus[114]	1995	USA	18	Cohort Prospective Blinding Test described	Symptomatic women in first pregnancy. Intact membrane. Cervical dilatation <3 cm	Chorioamnionitis, placental abruption.	24 - 34	Single	1500 pg/ml	48
Hillier[216]	1993	USA	50	Cohort Prospective Test described	Afebrile women who presented with threatened preterm labour with intact membrane	<16 or >40 years old, uterine or fetal abnormalities, multiple pregnancies, polyhydramnios, cervical cerclage, placenta previa, abruption, hypertension, diabetes or had received antibiotics the previous week.	23 - 34	Single	1500 pg/ml	Within 7 days of testing, 34

Silver[219]	1993	USA	29	Cohort Prospective Test described	Symptomatic women singleton pregnancies with intact membrane.	Additional medical or obstetrics problems e.g. diabetes, chronic hypertension, placental abruption	24 - 37	Single	400 & 500 ng/ml	37
Allbert[213]	1994	USA	23	Cohort Prospective Test described	Singleton gestation in premature labour with intact membrane	Fetal distress, IUGR, abruption, clinical amnionitis, substantial haemorrhage, fetal anomalies, or stillbirth.	20 - 32	Single	20 ng/ml	Within 2 & 7 days of testing
Romero[220]	1993	USA	120	Cohort Test described	Singleton pregnant women with threatened preterm labour	Patients who received antibiotics before amniocentesis, abnormal GTT or diabetes mellitus.	22 - 36	Single	11.30 ng/ml	37
Dudley[227]	1994	USA	75	Cohort Retrospective Test described	Women who presented with threatened preterm labour, intact membrane who delivered		x	Single	200 pg/ml	7
Romero[218]	1990	USA	56	Cohort Test described	Women admitted with threatened preterm labour and intact membrane		x	Single	46 ng/ml	35
Cervico-vaginal										
Inglis[96]	1994	USA	38	Cohort Prospective Consecutive Blinding Test described	All pregnant women between 15 and 40 years, singleton, less than 37 weeks and in	Fetal congenital anomalies, placenta previa, known genital or UTI, use of antibiotics within 7 days of testing.	24 - 37	Single	50 pg/ml	37
LaShay[83]	2000	USA	118	Cohort Prospective Blinding Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm	Coitus or digital vaginal examination within 24 hours. Vaginal bleeding. Placenta previa. Placental abruption. Polyhydramnios. Pre-eclampsia. Known uterine or fetal abnormalities.	24 - 34	Single	100 pg/ml	37

Kurkinen-Raty[223]	2001	Finland	77	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22 - 32 weeks' gestation who present	Coitus or digital vaginal examination within 24 hours. Vaginal bleeding. Placenta previa. Placental abruption. Polyhydramnios. Pre-eclampsia. Known uterine or fetal abnormalities.	22 - 32	Single	61 ng/L	37
Trebeden[226]	2001	France	142	Cohort Prospective Test described	Pregnant women with threatened preterm labour and intact membrane.	x	22 - 34	Single	20 pg/ml	Within 7 days of testing, 34
Holst[222]	2005	Sweden	91	Cohort Prospective Test described	Women with singleton pregnancy presenting with threatened preterm labour and intact membrane.	Uterine and fetal abnormalities, vaginal bleeding, imminent delivery and fetal distress.	22 - 34	Single	1.3 ng/ml	7
Sozmen[225]	2005	Turkey	40	Cohort Prospective Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm	Vaginal bleeding, placenta previa, abruption, intercourse within last 24 hours, signs of intra-uterine infection, polyhydramnios, IUGR, hypertension, diabetes, cervical cerclage, known uterine or fetal anomalies.	28 - 36	Single	172 pg/ml	37
Lange[224]	2003	Germany	27	Cohort Prospective Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm	Multiple gestations.	24 - 34	Single	20 pg/ml	Within 2 & 7 days of testing, 34
Serum										
Greig[229]	1997	USA	56	Cohort Prospective Blinded Test described	Pregnant women who presented to the clinic or hospital in suspected preterm labour	Refusal to participate, premature pre-labour rupture of membrane, multiple pregnancy, HIV infection, evidence of chorioamnionitis, UTI, pre-eclampsia, maternal age <17 or >40.	22 - 34	Single	6 pg/ml	Within 5 days of testing
Alvarez-de-la-Rosa[228]	2000	Spain	49	Cohort Prospective Blinded Test described	Pregnant women who presented to the clinic or hospital in suspected preterm labour	Refusal to participate, multiple pregnancies, HIV infection, evidence of chorioamnionitis or fetal distress.	26 - 37	Single	10 pg/ml	Within 2 days of testing, 34

Turhan[230]	2000	Turkey	82	Cohort Prospective Test described	Singleton pregnancies with threatened preterm labour. Intact membrane.	Fetal or uterine abnormalities, diabetes mellitus, placenta previa, bleeding consistent with placental abruption, cervical cerclage, pre-eclampsia, known or suspected maternal infectious disease, positive urine culture or known maternal medical condition leading to preterm delivery.	24 - 36	Single	8.3 pg/ml	Within 2 & 7 days of testing
vonMinckwitz[231]	2000	Germany	72	Cohort Prospective Test described	Singleton pregnancies with threatened preterm labour. Intact membrane.	Multiple gestation, diabetes mellitus, polyhydramnios, severe concomitant disease, clotting disorders, drug addictions.	25 - 37	Single	4 pg/ml	24
Sozmen[225]	2005	Turkey	40	Cohort Prospective Test described	Singleton pregnancies. Intact membrane. Cervical dilatation <3 cm	Vaginal bleeding, placenta previa, abruption, intercourse within last 24 hours, signs of intra-uterine infection, polyhydramnios, IUGR, hypertension, diabetes, cervical cerclage, known uterine or fetal anomalies.	28 - 36	Single	5 pg/ml	37

*Unless otherwise stated

Table 35 Individual accuracy results of interleukin-6 (IL6) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour, stratified according to outcome (weeks' gestation) and specimen source

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																
34 weeks																
Wenstorm[1] [210]	17	15	107	275	0.14	0.08	0.21	0.95	0.92	0.97	2.65	1.37	5.14	0.91	0.84	0.98
Ghidini[1] [212]	3	13	10	153	0.23	0.05	0.54	0.92	0.87	0.96	2.95	0.96	9.04	0.83	0.62	1.13
Goepfert[2] [221]	10	3	39	46	0.20	0.10	0.34	0.94	0.83	0.99	3.33	0.98	11.38	0.85	0.72	0.99
37 weeks	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Wenstorm[1] [210]	19	15	173	275	0.10	0.06	0.15	0.95	0.92	0.97	1.91	1.00	3.67	0.95	0.90	1.00
Lockwood[2] [211]	17	19	17	108	0.50	0.32	0.68	0.85	0.78	0.91	3.34	1.96	5.70	0.59	0.42	0.83
Lockwood[2] [211]	15	17	19	110	0.44	0.27	0.62	0.87	0.79	0.92	3.30	1.84	5.90	0.65	0.47	0.88
Inglis[2] [96]	1	10	10	52	0.09	0.00	0.41	0.84	0.72	0.92	0.56	0.08	3.97	1.08	0.87	1.35
Goepfert[2] [221]	25	12	100	113	0.20	0.13	0.28	0.90	0.84	0.95	2.08	1.10	3.96	0.88	0.80	0.98
Symptomatic																
7 - 10 days																
Greci[1] [215]	17	4	3	29	0.85	0.62	0.97	0.88	0.72	0.97	7.01	2.75	17.90	0.17	0.06	0.49
Hillier[1] [216]	22	8	4	15	0.85	0.65	0.96	0.65	0.43	0.84	2.43	1.36	4.36	0.24	0.09	0.61
Allbert[1] [213]	4	0	1	18	0.80	0.28	0.99	1.00	0.81	1.00	28.50	1.78	456.57	0.26	0.06	1.03
Dudley[1] [227]	26	9	14	26	0.65	0.48	0.79	0.74	0.57	0.88	2.53	1.38	4.64	0.47	0.30	0.75
Trebeden[2] [226]	18	10	26	88	0.41	0.26	0.57	0.90	0.82	0.95	4.01	2.02	7.96	0.66	0.51	0.85
Holst[2] [222]	22	13	7	51	0.76	0.56	0.90	0.80	0.68	0.89	3.73	2.21	6.33	0.30	0.16	0.58
Lange[2] [224]	6	8	0	13	1.00	0.54	1.00	0.62	0.38	0.82	2.40	1.37	4.23	0.12	0.01	1.72
Turhan[3] [230]	36	5	20	21	0.64	0.50	0.77	0.81	0.61	0.93	3.34	1.48	7.53	0.44	0.30	0.66
34 weeks																
Hillier[1] [216]	28	2	4	15	0.88	0.71	0.96	0.88	0.64	0.99	7.44	2.01	27.52	0.14	0.06	0.36
Trebeden[2] [226]	24	4	54	60	0.31	0.21	0.42	0.94	0.85	0.98	4.92	1.80	13.46	0.74	0.63	0.87
Lange[1] [224]	7	7	0	13	1.00	0.59	1.00	0.65	0.41	0.85	2.63	1.44	4.79	0.10	0.01	1.45
Alvarez-de-la-Rosa[3] [228]	7	19	3	20	0.70	0.35	0.93	0.51	0.35	0.68	1.44	0.86	2.41	0.59	0.22	1.58

34 weeks																
Rizzo[1] [217]	18	0	34	40	0.35	0.22	0.49	1.00	0.91	1.00	28.62	1.78	461.04	0.66	0.54	0.80
Coultrip[1] [214]	38	5	9	37	0.81	0.67	0.91	0.88	0.74	0.96	6.79	2.95	15.64	0.22	0.12	0.40
Silver[1] [219]	8	2	5	14	0.62	0.32	0.86	0.88	0.62	0.98	4.92	1.26	19.29	0.44	0.22	0.90
Romero[1] [208]	11	19	0	90	1.00	0.72	1.00	0.83	0.74	0.89	5.41	3.55	8.22	0.05	0.00	0.76
Inglis[2] [96]	1	10	10	52	0.09	0.00	0.41	0.84	0.72	0.92	0.56	0.08	3.97	1.08	0.87	1.35
LaShay[2] [83]	21	59	13	25	0.62	0.44	0.78	0.30	0.20	0.41	0.88	0.65	1.19	1.28	0.75	2.20
Kurkinen-Raty[2] [223]	8	26	3	40	0.73	0.39	0.94	0.61	0.48	0.72	1.85	1.15	2.95	0.45	0.17	1.20
Sozmen[2] [225]	14	1	6	19	0.70	0.46	0.88	0.95	0.75	1.00	14.00	2.03	96.62	0.32	0.16	0.62
Sozmen[3] [225]	9	8	11	12	0.45	0.23	0.68	0.60	0.36	0.81	1.13	0.55	2.32	0.92	0.54	1.56

1. Amniotic fluid specimen, 2. Cervico-vaginal specimen, 3. Maternal serum specimen

Table 36 Characteristics of the included studies on accuracy of interleukin-8 (IL8) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and symptomatic women who presented with threatened preterm labour

Authors	Year	Country	n	Study designs	Inclusion criteria	Exclusion criteria	Testing gestation (weeks)	Frequency of testing	Thresholds	Outcomes (weeks' gestation)*
Asymptomatic										
Sakai[235]	2004	Japan	4203	Cohort Prospective Blinding Test described	Asymptomatic women with singleton pregnancy and intact membrane	Preterm pre-labour rupture of membrane, threatened or impending miscarriage or preterm delivery, genital bleeding	20 - 28	Serial (2weekly)	360 ng/ml	32, 34, 37
Sakai[234]	2004	Japan	501	Cohort Prospective Test described	Asymptomatic women with singleton pregnancy	Iatrogenic prematurity, fetal asphyxia, abruption, placenta previa, pre-eclampsia	20 - 24	Single	377 ng/ml	37
Symptomatic										
Kurkinen[223]	2001	Finland	77	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22 - 32 weeks' gestation who presented with threatened preterm labour.	Preterm pre-labour rupture of membrane, impending preterm delivery	22 - 32	Single	3739 ng/L	37
Holst[222]	2005	Sweden	91	Cohort Prospective Test described	Women with singleton pregnancy presenting with threatened preterm labour and intact membrane	Uterine and fetal abnormalities, vaginal bleeding, imminent delivery and fetal distress	22 - 34	Single	7.7 ng/ml	Within 7 days of testing
Allbert** [213]	1994	USA	23	Cohort Prospective Test described	Singleton gestation in premature labour with intact membrane	Fetal distress, IUGR, abruption, clinical amnionitis, substantial haemorrhage, fetal anomalies, or stillbirth	20 - 32	Single	15 ng/ml	Within 2 & 7 days of testing

*Unless otherwise stated
**Amniotic fluid specimen

Table 37 Individual accuracy results of interleukin-8 (IL8) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour and stratified according to outcome (weeks' gestation)*

Authors	Outcome (weeks' gestation)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																	
Sakai[1 235]	32	7	838	11	3347	0.39	0.17	0.64	0.80	0.79	0.81	1.94	1.08	3.48	0.76	0.53	1.10
Sakai[1 235]	34	12	833	15	3343	0.44	0.25	0.65	0.80	0.79	0.81	2.23	1.46	3.41	0.69	0.50	0.97
Sakai[1 235]	37	38	807	101	3257	0.27	0.20	0.36	0.80	0.79	0.81	1.38	1.04	1.82	0.91	0.82	1.01
Sakai[234]	37	11	73	15	402	0.42	0.23	0.63	0.85	0.81	0.88	2.75	1.68	4.52	0.68	0.49	0.95
Symptomatic																	
Allbert[2 213]	2[3]	4	0	0	19	1.00	0.40	1.00	1.00	0.82	1.00	36.00	2.30	564.54	0.10	0.01	1.42
Holst[222]	7[3]	18	17	11	47	0.62	0.42	0.79	0.73	0.61	0.84	2.34	1.42	3.84	0.52	0.32	0.84
Allbert[2 213]	7[3]	4	0	1	18	0.80	0.28	0.99	1.00	0.81	1.00	28.50	1.78	456.57	0.26	0.06	1.03
Kurkinen[223]	37	7	30	4	36	0.64	0.31	0.89	0.55	0.42	0.67	1.40	0.83	2.35	0.67	0.30	1.50

*Unless otherwise stated, testing were done on a single occasion and cervico-vaginal samples of IL8 were used
1. Serial testing 2. Amniotic fluid 3. Birth within the stated number of days of testing

Table 38 Characteristics of the included studies on accuracy of matrix metalloprotease 9 (MMP-9) testing in predicting spontaneous preterm birth in symptomatic women who presented with threatened preterm labour

Authors	Year	Country	n	sample	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Makrakis[237]	2003	Greece	20	Urine, plasma	Cohort Prospective Test described	Symptomatic women who presented with threatened preterm labour, 20 - 35 years, no other pregnancy complication	Absence of cervical dilatation, no evidence of rupture membrane or chorioamnionitis	24 - 36	Single	7.71 ng/ml (urine), 68.43 ng/ml (plasma)	<37
Agrez[236]	1999	Australia	15	urine	Cohort Prospective Test described	Symptomatic women who presented with threatened preterm labour	x	27 - 34	Single	5 ng/ml	<37

Table 39 Individual accuracy results of matrix metalloprotease 9 (MMP-9) testing in predicting spontaneous preterm birth among asymptomatic and symptomatic women with threatened preterm labour

Authors	Thresholds	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Agrez[236]	5 ng/ml	4	1	2	8	0.67	0.22	0.96	0.89	0.52	1.00	6.00	0.87	41.44	0.38	0.12	1.19
Makrakis[237]	7.71 ng/ml	6	1	3	10	0.67	0.30	0.93	0.91	0.59	1.00	7.33	1.07	50.27	0.37	0.14	0.94
Makrakis[237]	68.43 ng/ml	6	1	3	10	0.67	0.30	0.93	0.91	0.59	1.00	7.33	1.07	50.27	0.37	0.14	0.94

Table 40 Characteristics of the included studies on accuracy of periodontal health assessment in predicting spontaneous preterm birth among asymptomatic pregnant women

Authors	Year	Country	N	Study designs	Inclusion	Exclusion	Testing gestation	Threshold	Outcome
Jeffcoat[244]	2001	USA	1313	Cohort Prospective Blinded Test described	All pregnant women being studied by the Perinatal Emphasis Research Center at UAB	Women who required antibiotic prophylaxis for dental examination or who is taking antibiotics	21 - 24	Periodontitis ≥3 sites with ≥3mm attachment loss (AL), severe periodontitis ≥90 sites, and healthy <3 sites <3mm AL	37
Offenbacher[238]	2001	USA	812	Cohort Prospective Blinded Test described	Pregnant women enrolled before 26 weeks' gestation		Before 26 weeks' gestation and within 48 hours of deliveries	Periodontitis: Periodontal health (absence of any probe depth (PD) >3mm and no sites with attachment loss (AL) >2mm), moderate severe disease (≥4 sites with PD ≥5mm & ≥2mm AL at ≥4 sites), and mild periodontitis i.e. less than the moderate to severe group but had more than the healthy group. Progression of periodontitis	37
Moore[246]	2004	UK	539	Cohort Prospective Blinded Test described	Women who attended for NT Down syndrome screening at 12 weeks' gestation	Pregnancy less than 10 or more than 15 weeks' gestation, multiple pregnancy and need for antibiotics before dental treatment	10 -15	Healthy: <10% sites with probe depth (PD) ≥3mm & <5% sites with loss of attachment (LA) ≥2mm, Severe: >5 sites with PD ≥5mm & >3 sites with LA ≥3mm	32, 37
Offenbacher[248]	1996	USA	124	Cohort Prospective Blinded Test described	Pregnant women under routine antenatal care in a University Hospital Prenatal Clinic	Concurrent genito-urinary tract infection, use of antibiotics and if at risk for bacterial endocarditis	Day 3 postnatal	Probe depth and loss of attachment ≥3mm affecting >60% (Extent 3:60) in all women and in primiparous	37
Holbrook[242]	2004	Iceland	96	Cohort Consecutive Prospective Test described	Healthy otherwise unselected pregnant women. Bacterial vaginosis testing using Amsel's criteria was also performed on enrolled women		28 - 30	>4 pockets >4mm probe depth	37
Rajapakse[250]	2005	Sri Lanka	227	Cohort Prospective Test described	Nulliparous, 18 - 34 years, singleton pregnancy	Hypertension, diabetes, smoking, betel chewing, alcohol and drug abuse	24 - 37	Mean pocket depth, plaque scores, and bleeding scores composite that are greater than the median value in the total cohort.	37

Moore[247]	2005	UK	154	Case-control Prospective Blinded Test described	Cases were women who had spontaneous preterm birth before 37 weeks' gestation. Controls were uncomplicated term vaginal or elective caesarean section delivery.	Multiple pregnancy, medical history that require antibiotic cover, iatrogenic preterm delivery, hypertension, pre-eclampsia, diabetes mellitus.	Day 5 postnatal	Probe depth (≥4mm, ≥5mm) and loss of attachment (≥2mm, ≥3mm)	37
Goepfert[241]	2004	USA	103	Case-control Prospective Blinded Test described	Cases were women who delivered between 24 and 32 weeks' gestation.		Day 3 postnatal	>3mm and >5mm loss of attachment	32
Dasanayake[239]	2001	USA	80	Case-control Prospective Blinded Test described	Cases were women who had spontaneous preterm birth before 37 weeks' gestation. Controls were term delivery.	Missing second trimester samples and elective preterm deliveries	14 - 24	Median and >75% Ig Prophyromonas gingivalis presence in serology.	37
Dortbudak[240]	2005	Austria	36	Cohort Prospective Test described	Pregnant women undergoing amniocentesis for medical conditions	x	15 - 20	Probe depth ≥5mm	37
Radnai[249]	2004	Hungary	85	Case-control Retrospective Blinded Test described	Systematically healthy women, cases were spontaneous premature birth before 37 weeks' gestation.	Diabetes, asthma, cardiac or renal problems, thyroid problems, chronic infectious disease or multiple pregnancies, patients who needed prophylaxis antibiotics.	Day 3 postnatal	Probe depth ≥4mm, bleeding on probing, and combination of probe depth, bleeding on probing	37
Jarjoura[243]	2005	USA	203	Case-control Retrospective Test described	Singleton pregnancies	Fetal or uterine anomalies, cervical incompetence, iatrogenic premature delivery, women who required antibiotics prophylaxis before dental assessment	Day 3 postnatal	Clinical attachment loss (CAL) ≥3mm in ≥5 sites	37
Konopka[245]	2003	Poland	128	Case-control Retrospective Test described	Cases were women who had spontaneous preterm birth before 37 weeks' gestation of infant who weighed <2500g	Multiple pregnancy, developmental defects, treated infertility patients, IVF, iatrogenic preterm births and systemic infection (apart from UTI)	Day 3 postnatal	Periodontal index >4	37

Table 41 Individual accuracy results of periodontal health assessment in predicting spontaneous preterm birth among asymptomatic women

Authors	Thresholds	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Offenbacher[238]	Mild periodontitis	132	434	38	163	0.78	0.71	0.84	0.27	0.24	0.31	1.07	0.97	1.17	0.82	0.60	1.12
Offenbacher[238]	Moderate-severe periodontitis	18	27	38	163	0.32	0.20	0.46	0.86	0.80	0.90	2.26	1.35	3.79	0.79	0.65	0.96
Offenbacher[238]	Progressive periodontitis	75	180	113	444	0.40	0.33	0.47	0.71	0.67	0.75	1.38	1.12	1.71	0.84	0.74	0.96
Moore[* 246]	Severe periodontitis	9	254	4	272	0.69	0.39	0.91	0.52	0.47	0.56	1.43	0.99	2.08	0.60	0.26	1.35
Moore[246]	Severe periodontitis	24	239	20	256	0.55	0.39	0.70	0.52	0.47	0.56	1.13	0.85	1.50	0.88	0.63	1.23
Offenbacher[248]	All women with periodontitis	87	22	6	9	0.94	0.86	0.98	0.29	0.14	0.48	1.32	1.05	1.66	0.22	0.09	0.57
Offenbacher[248]	Primiparous with periodontitis	41	11	5	9	0.89	0.76	0.96	0.45	0.23	0.68	1.62	1.08	2.44	0.24	0.09	0.63
Holbrook[242]	PD≥4mm in > pockets	0	16	6	74	0.00	0.00	0.46	0.82	0.73	0.89	0.39	0.03	5.90	1.13	0.90	1.42
Rajapakse[250]	PD≥ cohort median value	27	39	12	149	0.69	0.52	0.83	0.79	0.73	0.85	3.34	2.35	4.73	0.39	0.24	0.63
Moore[247]	PD≥4mm	5	10	56	83	0.08	0.03	0.18	0.89	0.81	0.95	0.76	0.27	2.12	1.03	0.93	1.14
Moore[247]	LA≥3mm	1	2	60	91	0.02	0.00	0.09	0.98	0.92	1.00	0.76	0.07	8.23	1.01	0.96	1.05
Moore[247]	LA≥2mm	3	7	58	86	0.05	0.01	0.14	0.92	0.85	0.97	0.65	0.18	2.43	1.03	0.95	1.12
Moore[247]	PD≥5mm	1	4	60	89	0.02	0.00	0.09	0.96	0.89	0.99	0.38	0.04	3.33	1.03	0.97	1.08
Goepfert[*241]	Extent 5	11	4	48	40	0.19	0.10	0.31	0.91	0.78	0.97	2.05	0.70	6.01	0.89	0.77	1.04
Goepfert[* 241]	Extent 3	28	13	31	31	0.47	0.34	0.61	0.70	0.55	0.83	1.61	0.95	2.73	0.75	0.55	1.02
Dortbudak[240]	PD≥5mm	5	6	1	30	0.83	0.36	1.00	0.83	0.67	0.94	5.00	2.22	11.28	0.20	0.03	1.20
Radnai[249]	PD≥4mm	22	18	19	26	0.54	0.37	0.69	0.59	0.43	0.74	1.31	0.83	2.07	0.78	0.52	1.18
Radnai[249]	Bleeding on probing (BOP)	20	9	21	35	0.49	0.33	0.65	0.80	0.65	0.90	2.38	1.23	4.62	0.64	0.46	0.90
Radnai[249]	PD≥4mm + BOP	19	5	22	39	0.46	0.31	0.63	0.89	0.75	0.96	4.08	1.68	9.92	0.61	0.45	0.82
Jarjoura[243]	Periodontitis	21	25	62	95	0.25	0.16	0.36	0.79	0.71	0.86	1.21	0.73	2.02	0.94	0.81	1.10
Konopka[245]	Periodontal index greater than 4	27	12	57	32	0.32	0.22	0.43	0.73	0.57	0.85	1.18	0.66	2.09	0.93	0.74	1.18

Spontaneous preterm birth before 32 weeks' gestation

Table 42 Characteristics of the included studies on accuracy of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation for asymptomatic pregnant women

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Outcome (weeks' gestation)
MSU									
Wren[278]	1969	Australia	3099	Cohort Consecutive Prospective Test described	All pregnant patient booking at their first antenatal visit	Twin pregnancies and women who moved hospital	Antenatal	Repeat if positive	<37
Robertson[269]	1968	UK	2184	Cohort Consecutive Prospective Test described	Singleton pregnancies	Miscarriages, treated women, delivered elsewhere	Booking	Single	<37
Uncu[274]	2002	Turkey	186	Cohort Consecutive Prospective Test described	Singleton pregnancies	Patient with renal disease, recent or current antibiotic treatment, current or recent asymptomatic bacteriuria	<32	Repeat if positive	<37
Layton[262]	1964	UK	176	Cohort Consecutive Prospective Test described	Antenatal asymptomatic women		<32	Single	<37
Versi[275]	1997	UK	6864	Cohort Prospective Test described	Singleton pregnancies (Caucasian & Bangladeshi populations only)		11 - 14	Single	<37
Patrick[268]	1967	UK	575	Cohort Prospective Test described	Antenatal asymptomatic women		Booking	Single	<37
Schieve[271]	1994	USA	25663	Cohort Retrospective Test described	Singleton pregnancies		Antenatal	Single	<37
LeBlanc[263]	1964	USA	1248	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Gold[256]	1966	USA	1246	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Kass[259]	1962	USA	1095	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Hoja[258]	1964	USA	879	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37

Stuart[273]	1965	UK	817	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Henderson[257]	1965	USA	808	Case-control Retrospective Test described	Singleton pregnancies	Placenta previa, pre-eclampsia, abruption, induced labour, erythroblastosis fetalis	<22	Single	<36
Low[264]	1964	USA	771	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Forkman[255]	1964	Sweden	595	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Schamadan[270]	1965	USA	556	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Kincaid[260]	1964	USA	556	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Whalley[276]	1965	USA	283	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Sleigh[272]	1964	UK	200	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Norden[267]	1965	USA	197	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Kubicki[261]	1976	Poland	192	Case-control Retrospective Test described	Singleton pregnancies		18 - 23	Single	<37
Bryant[254]	1964	USA	66	Case-control Retrospective Test described	Singleton pregnancies		<20	Single	<37
Abdul-Jabbar[253]	1991	Saudi		Case-control Retrospective Test described	Pregnant women without apparent ailments		Booking	Single	<37
GBS									
Moller[266]	1984	Denmark	2745	Cohort Consecutive Prospective Test described	Singleton pregnancies		Antenatal	Single	<37
McDonald[265]	1989	Australia	692	Cohort Consecutive Prospective Test described	Singleton pregnancies		20 - 24	Single	<37

White[277]	1984	UK	8083	Cohort Retrospective Test described	Singleton pregnancies			Antenatal	Single	<37

Table 43 Individual accuracy results of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth before 37 weeks' gestation among asymptomatic antenatal women

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
MSU																
Wren[278]	15	75	204	2805	0.07	0.04	0.11	0.97	0.97	0.98	2.63	1.54	4.50	0.96	0.92	0.99
Robertson[269]	13	191	62	1918	0.17	0.10	0.28	0.91	0.90	0.92	1.91	1.15	3.19	0.91	0.82	1.01
Uncu[274]	6	17	16	147	0.27	0.11	0.50	0.90	0.84	0.94	2.63	1.16	5.96	0.81	0.62	1.05
Layton[262]	4	59	9	104	0.31	0.09	0.61	0.64	0.56	0.71	0.85	0.37	1.97	1.09	0.74	1.59
Versi[a] [275]	13	139	624	6694	0.02	0.01	0.03	0.98	0.98	0.98	1.00	0.57	1.76	1.00	0.99	1.01
Versi[b] [275]	39	393	512	5920	0.07	0.05	0.10	0.94	0.93	0.94	1.14	0.83	1.56	0.99	0.97	1.01
Patrick[268]	7	68	21	479	0.25	0.11	0.45	0.88	0.85	0.90	2.01	1.02	3.97	0.86	0.69	1.06
Schieve[271]	293	1687	2546	21137	0.10	0.09	0.11	0.93	0.92	0.93	1.40	1.24	1.57	0.97	0.96	0.98
LeBlanc[263]	6	21	133	1088	0.04	0.02	0.09	0.98	0.97	0.99	2.28	0.94	5.55	0.98	0.94	1.01
Gold[256]	0	30	168	1048	0.00	0.00	0.02	0.97	0.96	0.98	0.10	0.01	1.70	1.03	1.01	1.04
Kass[259]	26	69	88	912	0.23	0.15	0.32	0.93	0.91	0.94	3.24	2.16	4.87	0.83	0.75	0.92
Hoja[258]	1	21	54	803	0.02	0.00	0.10	0.97	0.96	0.98	0.71	0.10	5.21	1.01	0.97	1.05
Stuart[273]	20	68	83	646	0.19	0.12	0.28	0.90	0.88	0.93	2.04	1.30	3.21	0.89	0.81	0.98
Henderson[257]	33	15	371	389	0.08	0.06	0.11	0.96	0.94	0.98	2.20	1.21	3.99	0.95	0.92	0.99
Low[264]	5	75	49	642	0.09	0.03	0.20	0.90	0.87	0.92	0.89	0.37	2.10	1.01	0.93	1.11
Forkman[255]	1	33	19	542	0.05	0.00	0.25	0.94	0.92	0.96	0.87	0.13	6.06	1.01	0.91	1.12
Schamadan[270]	8	48	25	475	0.24	0.11	0.42	0.91	0.88	0.93	2.64	1.36	5.11	0.83	0.69	1.01
Kincaid[260]	12	44	25	475	0.32	0.18	0.50	0.92	0.89	0.94	3.83	2.22	6.59	0.74	0.59	0.92
Whalley[276]	11	96	21	155	0.34	0.19	0.53	0.62	0.55	0.68	0.90	0.54	1.49	1.06	0.81	1.39
Sleigh[272]	7	93	7	93	0.50	0.23	0.77	0.50	0.43	0.57	1.00	0.58	1.72	1.00	0.58	1.72
Norden[267]	11	77	14	95	0.44	0.24	0.65	0.55	0.47	0.63	0.98	0.61	1.58	1.01	0.70	1.47
Kubicki[261]	18	83	5	86	0.78	0.56	0.93	0.51	0.43	0.59	1.59	1.22	2.08	0.43	0.19	0.94
Bryant[254]	2	30	4	40	0.33	0.04	0.78	0.57	0.45	0.69	0.78	0.24	2.49	1.17	0.64	2.13
Abdul-Jabbar[253]	18	180	16	184	0.53	0.35	0.70	0.51	0.45	0.56	1.07	0.77	1.49	0.93	0.64	1.35
GBS																
Moller[266]	14	54	228	2449	0.06	0.03	0.10	0.98	0.97	0.98	2.68	1.51	4.76	0.96	0.93	0.99
McDonald[265]	4	24	46	618	0.08	0.02	0.19	0.96	0.94	0.98	2.14	0.77	5.93	0.96	0.88	1.04
White[277]	10	127	389	7557	0.03	0.01	0.05	0.98	0.98	0.99	1.52	0.80	2.86	0.99	0.98	1.01

a. Caucasian population, b. Bangladeshi population

Table 44 Characteristics of the included studies on accuracy of bacterial vaginosis (BV) testing in predicting spontaneous preterm birth for asymptomatic pregnant women and women who presented with threatened preterm labour

Study				Population		Test			Reference standards
Population Author, publication year	Country	Study quality*	n	Inclusion criteria	Exclusion criteria	Gestational age at testing	Site and frequency of testing	Criteria for diagnosis of BV	Gestational age at birth (weeks' gestation)
Asymptomatic pregnant women									
Oakeshott, 2004[285]	USA	Cohort Consecutive Prospective Test described	887	All consecutive <10 weeks' gestation.	Miscarriages, terminations, multiple gestations, antibiotics treatment, missing specimen slides.	<10	Vaginal swab Single	Gram's staining (Nugent's criteria)	<37
Klebanoff, 2005[284]	USA	Cohort Prospective Blinded Test described	12937	Did not report genital itching, burning, malodour to questioning, no major medical or obstetrics complications in current pregnancy, not received or expected to receive antibiotics, could be followed after delivery.		<13, 13-14, 15-16, 17-18, 19-20, 21-22	Vaginal swab Single	Gram's staining (Nugent's criteria)	<37 (data was collected for 23-26 weeks' gestation births but this was not published)
DeSeta, 2005[286]	Italy	Cohort Consecutive Prospective Test described	598	Singleton, negative urine culture the past two weeks, no other genito-urinary tract infection	Diabetes, hypertension, cardiac or chronic renal disease, Rh iso-immunization, cervical cerclage, antibiotics treatment, un-protected intercourse or vaginal washing in the last 48 hours.	13-18	Vaginal swab Single	Gram's staining (Nugent's criteria)	<37
Purwar, 2001[295]	India	Cohort Blind Prospective Test described	938	Arbitrary selection of singleton pregnancies	Multiple pregnancy Placenta previa Symptomatic vaginal discharge History suggestive of cervical incompetence Vaginal bleeding Leaking membrane Antibiotic use in the preceding 15 days Suspected uterine malformation	16-28	Vaginal swab Single	Gram's staining (Nugent's criteria)	<37

Hillier, 1995[294]	USA	Cohort Blind Prospective Test described	8197	Women with singleton pregnancies who has completed 23-26 weeks' gestation and attending routine antenatal clinic	<16 years old Rhesus iso-immunisation disease Preceding 2 weeks or current use of antibiotics Chronic renal disease Organic heart disease Insulin dependent diabetes mellitus Multiple gestation Cervical cerclage Hypertension requiring treatment	23-26	Posterior fornix Single	Gram's staining (Nugent's criteria) Or Vaginal pH >4.5	<37
Govender, 1996[293]	S Africa	Cohort Blind Prospective Test described	168	Singleton pregnancies less than 30 weeks' gestation	Previous spontaneous premature birth Antibiotics in the current pregnancy Symptomatic discharge Urinary tract infection Multiple pregnancy	<30 weeks	Vaginal swab Single	Gram's staining (Nugent's criteria)	<37
Kurki, 1992[296]	Finland	Cohort Blind Prospective Test described	733	Singletons First pregnancy	Antibiotics in current pregnancy Multiple pregnancy Induction prior to 37 weeks	8-17	Posterior fornix Single	Gram's staining (Spiegel's criteria)	<37
Crane, 1999[92]	Canada	Cohort Blind Prospective Test described	140	Singletons	Multiple pregnancy Pre-labour rupture of membranes Placenta previa Previously treated for BV in current pregnancy Cerclage Major fetal anomalies	20-24	Posterior fornix Single	Gram staining (Nugent's criteria) Or Clinical criteria	<37
Hay, 1994[297]	England	Cohort Blind Prospective Test described	706	Singletons First antenatal visit between 9-24 weeks' gestation	Multiple pregnancy Lethal congenital malformations Antibiotics in the current pregnancy	9-24	Posterior fornix Single	Gram's staining (Spiegel's criteria)	<37
McGregor, 1990[298]	USA	Cohort Blind Prospective Test described	194	Singletons Women receiving care at 2 prenatal clinics	Multiple pregnancy Cerclage Placenta previa Vaginal bleeding Preterm labour. Preceding 2 weeks antibiotics course Douching within 24 hours of examination	24	Mid-vaginal swab Single	Gram's staining (Spiegel's criteria)	<37
Gratacos, 1998[291]	Spain	Cohort Blind Prospective Test described	635	Singletons	Multiple pregnancy Abortion or termination Congenital malformation Lost to follow-up	<24 and <35	Posterior fornix Single	Gram's staining (Nugent's criteria)	<37

Helou, 1996[292]	Israel	Cohort Blind Prospective Test described	400	Singletons	Iatrogenic preterm delivery	15-20 and 27-32	Vaginal swab Serial (twice)	Gram's staining (Nugent's criteria)	<37
Balu, 2003[287]	USA	Cohort Prospective Test described	646	Singleton pregnancy, access to telephone, >16 years old, planned to continue care in the same hospital		24-29		Gram's staining (Nugent's criteria)	<32, <34, and <37
Riduan, 1993[289]	Indonesia	Cohort Prospective Test described	490	Singletons	Medical conditions associated with preterm delivery Previous tocolysis or steroids treatment Antibiotics within 2 weeks of enrolment Incompetent cervix	16-20 and 28-32	Vaginal swab Serial (twice)	Gram's staining (Nugent's criteria)	<37
Meis, 1995[288]	USA	Cohort Prospective Test described	2929	Singletons	Cerclage Major congenital anomaly Placenta previa, Polyhydramnios Oligohydramnios Cervix >2cm dilated in nulliparous and >3cm multiparous women	24 and 28	Posterior fornix Serial (twice)	Gram's staining (Nugent's criteria)	<35
Cauci, 2003[283]	USA	Cohort Retrospective Test described	417	Singletons	Major congenital anomaly	8-24	Posterior fornix (Single)	Clinical criteria	<37
Thorsen, 1996[290]	USA	Cohort Test described	2927	Singletons	Congenital malformations Placenta previa, pre-eclampsia Cerclage, placental abruption Serious medical disease Rhesus iso-immunisation	7-24	Posterior fornix Single	Clinical criteria	<37
Mascagni, 2004[282]	USA	Retrospective Case-control	103	Singleton pregnancy, 18 - 34 years old, asymptomatic from vaginal infection	Medical or obstetrics problem requiring elective preterm delivery, cigarette smoking, diabetes, hypertension, STD.	15-16	Vaginal swab Single	Gram's staining (Nugent's criteria)	<37
Women with threatened preterm labour									
Goffinet, 2003[300]	France	Cohort Prospective Blind Test described	212	Singleton with threatened preterm labour and intact membrane.	Rupture of membrane, chorioamnionitis, suspected fetal distress, fetal malformation, maternal disorder requiring delivery, > 3cm dilatation.	24 - 34	Vaginal swab Single	Gram staining (Nugent's criteria)	<7 days of testing, <33, and <35

Martius, 1988[305]	USA	Blind Prospective Case-control Test described	212	Singletons	<16 years Antibiotics within 2 weeks Insulin dependent diabetes mellitus Congenital heart disease Pre-eclampsia Renal disease Essential hypertension Placental abruption Placenta previa Multiple gestation Congenital malformation	20-36	Vaginal swab Single	Gram's staining (Spiegel's criteria)	<37
Holst, 1994[232]	Sweden	Prospective Case-control Consecutive Test described	87	Women with singleton pregnancies admitted for preterm labour Control were women admitted in labour at term	Diabetics Pre-eclampsia Placental abruption Placenta previa Multiple gestation Cervical cerclage Pre-labour preterm rupture of membrane	24-36	Vaginal swab Single	Gram's staining (Spiegel's criteria)	< 34 and <37
Eschenbach, 1984[304]	USA	Blind Prospective Case-control Test described	171	Women admitted in labour and had vaginal exam 2 controls, women who delivered at term, were selected for each case enrolled	Vaginal swab was not obtained Iatrogenic preterm birth Congenital malformation Placental abruption Placenta previa Vaginal bleeding of indeterminate origin	24-36	Vaginal swab Single	Gas liquid chromatography	<37
Elliott, 1990[301]	Kenya	Retrospective Case-control Test described	276	Preterm singleton pregnancies who presented with preterm labour Control were women who delivered >36 weeks' gestation	None stated	24-36	Vaginal swab Single	Gram's staining (Spiegel's criteria)	<36
Subtil, 2002[303]	France	Prospective Case-control Test described	102	Women presented with preterm labour with either cervical dilatation >2 cm or history of previous preterm labour. Control matched for gestation and admitted preterm for reasons unrelated to preterm labour (e.g. pre-eclampsia, diabetes, intra-uterine growth restriction, and cholestasis).	Gestational age less than 20 or more than 34 weeks' gestation, local or general antibiotic therapy within the past 8 days, premature rupture of membrane, bleeding, or presence of a clear cause for preterm labour (e.g. multiple pregnancy, hydramnios).	20-34	Vaginal swab Single	Clinical criteria	<37

Krohn, 1991[302]	USA	Prospective Test described	211	Women who presented with preterm labour	Less than 16 or more than 40 years old Uterine or fetal anomaly Hypertension Diabetics Cervical cerclage Placenta previa Placenta abruption	22-34	Vaginal swab Single	Gram's staining (Nugent's criteria)	<35
Carlini, 2003[299]	USA	Case-control Prospective Test described	753	Singleton with threatened preterm labour and intact membrane	Elective preterm delivery	20 – 37	Vaginal swab Single	Gram's staining (Nugent's criteria)	<37

Table 45 Individual accuracy results of bacterial vaginosis (BV) testing in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																
Single testing (Nugent)																
Oakeshott[285]	6	143	38	700	0.14	0.05	0.27	0.83	0.80	0.86	0.80	0.38	1.72	1.04	0.92	1.17
Crane[92]	1	30	8	101	0.11	0.00	0.48	0.77	0.69	0.84	0.49	0.07	3.16	1.15	0.90	1.48
DeSeta[286]	14	90	35	459	0.29	0.17	0.43	0.84	0.80	0.87	1.74	1.08	2.82	0.85	0.71	1.02
Govender[293]	24	64	11	69	0.69	0.51	0.83	0.52	0.43	0.61	1.43	1.07	1.90	0.61	0.36	1.01
Gratacos[291]	20	105	26	484	0.43	0.29	0.59	0.82	0.79	0.85	2.44	1.68	3.54	0.69	0.53	0.89
Helou[292]	7	53	31	309	0.18	0.08	0.34	0.85	0.81	0.89	1.26	0.62	2.57	0.96	0.82	1.12
Hillier[294]	77	1141	29	6949	0.73	0.63	0.81	0.86	0.85	0.87	5.15	4.53	5.86	0.32	0.23	0.43
Klebanoff[284]	74	121	423	1156	0.15	0.12	0.18	0.91	0.89	0.92	1.57	1.20	2.06	0.94	0.90	0.98
Purwar[295]	30	83	29	783	0.51	0.37	0.64	0.90	0.88	0.92	5.31	3.84	7.33	0.54	0.42	0.71
Balu[287]	71	157	171	350	0.29	0.24	0.36	0.69	0.65	0.73	0.95	0.75	1.20	1.02	0.93	1.13
Riduan[289]	17	67	48	358	0.26	0.16	0.39	0.84	0.80	0.88	1.66	1.04	2.64	0.88	0.75	1.02
Mascagni[282]	6	22	6	69	0.50	0.21	0.79	0.76	0.66	0.84	2.07	1.06	4.05	0.66	0.37	1.17
Single testing (Amsel)																
Crane[92]	2	18	7	113	0.22	0.03	0.60	0.86	0.79	0.92	1.62	0.44	5.91	0.90	0.63	1.29
Thorsen[290]	14	438	91	2434	0.13	0.07	0.21	0.85	0.83	0.86	0.87	0.53	1.43	1.02	0.95	1.10
Cauci[283]	11	61	75	356	0.13	0.07	0.22	0.85	0.82	0.89	0.87	0.48	1.59	1.02	0.93	1.12
Serial testing (Nugent)																
Gratacos[291]	8	33	7	38	0.53	0.27	0.79	0.54	0.41	0.65	1.15	0.67	1.96	0.87	0.49	1.56
Helou[292]	3	24	20	330	0.13	0.03	0.34	0.93	0.90	0.96	1.92	0.63	5.92	0.93	0.79	1.10
Riduan[289]	8	31	53	370	0.13	0.06	0.24	0.92	0.89	0.95	1.70	0.82	3.52	0.94	0.85	1.04
Symptomatic																
Subtil[303] Amsel	6	8	38	50	0.14	0.05	0.27	0.86	0.75	0.94	0.99	0.37	2.64	1.00	0.86	1.17
Goffinet[300] Nugent	4	19	33	156	0.11	0.03	0.25	0.89	0.84	0.93	1.00	0.36	2.76	1.00	0.88	1.13
Carlini[299] Nugent	85	39	321	308	0.21	0.17	0.25	0.89	0.85	0.92	1.86	1.31	2.65	0.89	0.84	0.95
Krohn[302] Nugent	35	20	104	52	0.25	0.18	0.33	0.72	0.60	0.82	0.91	0.57	1.45	1.04	0.87	1.23

Holst[232] Spiegel	9	3	13	24	0.41	0.21	0.64	0.89	0.71	0.98	3.68	1.13	11.97	0.66	0.46	0.96
Martius[305] Spiegel	21	34	40	117	0.34	0.23	0.48	0.77	0.70	0.84	1.53	0.97	2.41	0.85	0.69	1.03
Elliot[301] Spiegel	30	115	27	104	0.53	0.39	0.66	0.47	0.41	0.54	1.00	0.76	1.32	1.00	0.73	1.36

Table 46 Characteristic of studies on test accuracy of mammary stimulation test in predicting spontaneous preterm birth among asymptomatic women

Authors	Year	Country	Population	Quality of studies	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Frequency of testing	Outcome (weeks' gestation)
Eden[306]	1991	USA	94	Cohort Blinded Prospective Test described	Inner city pregnant women	None stated	24-32	Single	<5 days of testing, <34 <37
Guinn[307]	1994	USA	247	Cohort Blinded Prospective Test described	Nulliparous women receiving private ante-natal care with singleton pregnancies	Placenta previa Multiple gestations Preterm pre-labour rupture of membrane	26-28	Single	<34 and <37

Table 47 Individual accuracy results of mammary stimulation test in predicting spontaneous preterm birth among asymptomatic women stratified according testing gestation and outcome gestations

Authors	Outcome (weeks' gestation)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Guinn[307]	34	7	40	2	198	0.78	0.40	0.97	0.83	0.78	0.88	4.63	2.95	7.25	0.27	0.08	0.91
Guinn[307]	37	3	44	2	198	0.60	0.15	0.95	0.82	0.76	0.86	3.30	1.54	7.08	0.49	0.17	1.43
Eden[306]	37	16	31	3	44	0.84	0.60	0.97	0.59	0.47	0.70	2.04	1.46	2.84	0.27	0.09	0.77
Eden[* 306]	37	11	8	2	16	0.85	0.55	0.98	0.67	0.45	0.84	2.54	1.38	4.68	0.23	0.06	0.85
Eden[306]	5[**]	12	35	0	47	1.00	0.74	1.00	0.57	0.46	0.68	2.25	1.71	2.95	0.07	0.00	1.02

*High risk women according to Creasy risk scoring system **Within 5 days of testing

Table 48 Characteristics of test accuracy studies of uterine activities monitoring in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and women symptomatic with threatened preterm labour

Authors	Year	Country	n	Test	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of testing	Threshold	Outcome (weeks' gestation)
Asymptomatic											
Iams[69]	2002	USA	270	Tocograph	Cohort Prospective Blinded Test described	Singleton pregnancies	Women who had received or were scheduled to receive an ambulatory monitor or tocolytic medication or to undergo cerclage were complicated by placenta previa or a major fetal anomaly detected by ultrasonography. Women who did not have telephones were not enrolled, because the transmission of data collected by the monitoring system required a telephone.	22 - 30	Four times – two sessions of at least two hours apart (one at night, one at day time) before 28 week and two more sessions between 28 – 30 weeks	Max night-time and day time contraction of ≥4/h	<35
Iams[309]	1988	USA	100	Tocograph	Cohort Prospective Test described	Asymptomatic singleton pregnancies data only	x	20 - 34	Single	≥4contractions/hour	<37
Symptomatic											
Bell[308]	1983	UK	15	Tocograph	Cohort Test described	Singleton pregnancy presenting with threatened preterm labour		20 - 28	Single	Pmax ≥15mmHg	<37
Maner[310]	2003	USA	99	Electromyography	Case-control Retrospective Test described	Singleton pregnancies presenting with threatened preterm labour leading to vaginal deliveries, intact membrane, dilatation <2cm, no evidence of systemic infection or fetal distress	To ensure optimal recording, patient over 230 lb was excluded	24 - 42	Single	0.463	<37

Table 49 Individual accuracy results of uterine activities monitoring in predicting spontaneous preterm birth stratified according to population of asymptomatic antenatal women and symptomatic women with threatened preterm labour

Authors	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																
Iams[a 69]	4	8	42	214	0.09	0.02	0.21	0.96	0.93	0.98	2.41	0.76	7.68	0.95	0.86	1.04
Iams[b 69]	0	4	48	218	0.00	0.00	0.07	0.98	0.95	1.00	0.51	0.03	9.24	1.01	0.98	1.05
Iams[309]	14	15	2	69	0.88	0.62	0.98	0.82	0.72	0.90	4.90	2.99	8.04	0.15	0.04	0.56
Symptomatic																
Bell[308]	3	2	1	9	0.75	0.19	0.99	0.82	0.48	0.98	4.13	1.04	16.32	0.31	0.05	1.71
Maner[310]	23	3	19	54	0.55	0.39	0.70	0.95	0.85	0.99	10.40	3.34	32.38	0.48	0.34	0.67

a. night-time contraction, b. day time contraction

Table 50 Characteristic of studies on test accuracy of rheobase measurement in predicting spontaneous preterm birth among symptomatic women

Authors	Year	Country	n	Quality of studies	Inclusion criteria	Exclusion criteria	Testing gestation (weeks' gestation)	Frequency of testing	Thresholds	Outcome (weeks' gestation)
Arabin[311]	1985	Germany	176	Cohort Prospective Test described	Singleton pregnancies presenting with threatened preterm labour from 20 weeks' gestation onwards	Iatrogenic preterm delivery, suspected chorioamnionitis, fetal distress, placental bleeding, polyhydramnios	20 - 36	Serial	>2.8, >3.4 mA	37

Table 51 Individual accuracy results of rheobase measurement in predicting spontaneous preterm birth among asymptomatic women stratified according testing gestation and outcome gestations

Authors	Threshold (mA)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Arabin[311]	2.8	18	34	15	109	0.55	0.36	0.72	0.76	0.68	0.83	2.29	1.50	3.52	0.60	0.41	0.88
Arabin[311]	3.4	25	46	8	97	0.76	0.58	0.89	0.68	0.60	0.75	2.36	1.73	3.20	0.36	0.19	0.66

Table 52 Characteristic of studies on test accuracy of absence of fetal breathing movement (FBM) in predicting spontaneous preterm birth in symptomatic women

Study	Year	Language	Study quality	Population	Inclusion criteria	Exclusion criteria	Frequency of testing	Testing gestation (weeks' gestation)	Definitions of thresholds for abnormality	Outcome
Senden[85]	1996	English	Cohort Prospective Consecutive Blinding Test described	25	Singletons presenting with threatened preterm labour	PPROM Vaginal bleeding Chorioamnionitis Diabetes mellitus Cervical dilatation >4cm History suggestive of cervical incompetence	Single	25-35	Absence of sustained FBM in a 30s period during a 30 minutes observations	<7 days
Schreyer[318]	1988	English	Cohort Prospective Consecutive Test described	70	Uncomplicated singleton pregnancies presenting with threatened preterm labour	Multiple pregnancies PPROM Vaginal bleeding Pyrexia Non-recordable uterine contractions on tocodynamometer Non-reassuring fetal heart rate recording	Single	32-36	No sustained FBM (lasting >20s) in a 45 minutes observation period	<24 hours <48 hours <7 days
Agustsson[313]	1987	English	Cohort Retrospective Test described	64	Women suspected of preterm labour	Advanced cervical dilatation Regular contraction not detectable	Single	26-36	No sustained FBM (lasting >20s) in a 45 minutes observation period	<56 hours <7 days
Besinger[314]	1987	English	Cohort Prospective Test described	50	Women suspected of threatened preterm labour	None stated	Single	26-34	No sustained FBM (lasting >20s) in a 20 minutes observation period	<48 hours
Kanaan[316]	1991	English	Cohort Prospective Test described	34	Singletons Healthy volunteers Regular preterm uterine contractions	Vaginal bleeding PPROM	Single	24-36	Absence of FBM in a 20s period or decreased FBM in a 15 minutes observation	<48 hours
Markwitz[317]	2001	Polish	Cohort Retrospective Test described	36	Singleton pregnancies with suspected preterm labour	None stated	Single	28-36	No sustained FBM (lasting >20s) in a 30 minutes observation period	<7 days
Devoe[315]	1994	English	Cohort Prospective Test described	25	Regular uterine contractions No clinical signs of chorioamnionitis No significant vaginal bleeding Singletons	Congenital abnormalities Maternal medical or obstetrical complications	Single	28-36	Absence of FBM within 6s period in a 45 minutes observation	<7 days

Castle[312]	1983	English	Cohort Prospective Test described	24	Women suspected of preterm labour	None stated		Single	25-34	No sustained FBM (lasting >20s) in a 45 minutes observation period	<7 days

Table 53 Individual accuracy results of absence of fetal breathing movement in predicting spontaneous preterm birth among symptomatic women with threatened preterm labour

Study	Intact membrane (Intact) or Pre-labour premature rupture of membrane (PPROM)	Reference standards *(hours to delivery or within days of testing)*	FP	FP	FN	TN	Likelihood ratios for positive test (LR+) (95% confidence interval)	Likelihood ratios for negative test (LR-) (95% confidence interval)
Agustsson[313]	Intact	<56 hours	17	0	5	42	65.43 (4.12 - 1039.20)	0.23 (0.11 - 0.49)
Agustsson[313]	Intact	<7 days	17	0	14	33	37.19 (2.33 - 93.09)	0.45 (0.31 - 0.67)
Besinger[314]	Intact	<48 hours	9	1	4	26	18.69 (2.64 - 132.33)	0.32 (0.14 - 0.72)
Besinger[314]	PPROM	<48 hours	7	0	0	3	7.50 (0.56 - 100.87)	0.07 (0.00 - 1.07)
Castle[312]	Intact	<7 days	5	0	2	17	24.75 (1.55 - 396.04)	0.29 (0.09 - 0.92)
Castle[312]	PPROM	<7 days	10	0	6	1	2.47 (0.22 - 28.05)	0.38 (0.20 - 0.71)
Devoe[315]	Intact	<7 days	2	0	10	38	15.00 (0.77 - 292.61)	0.83 (0.65 - 1.07)
Devoe[315]	Intact	<72 hours	2	0	8	40	18.64 (0.96 - 360.56)	0.80 (0.59 - 1.09)
Devoe[315]	PPROM	<7 days	9	0	14	2	2.38 (0.18 - 31.28)	0.61 (0.44 - 0.84)
Devoe[315]	PPROM	<72 hours	11	0	9	5	6.57 (0.45 - 96.05)	0.45 (0.28 - 0.73)
Kanaan[316]	Intact	<48 hours	4	11	1	18	2.11 (1.11 - 4.00)	0.32 (0.05 - 1.90)
Markwitz[317]	Intact	<7 days	8	0	4	24	32.69 (2.04 - 522.93)	0.33 (0.15 - 0.74)
Markwitz[317]	PPROM	<7 days	16	0	6	2	4.30 (0.34 - 54.76)	0.27 (0.14 - 0.54)
Schreyer[318]	Intact	<24 hours	7	7	1	55	7.75 (3.68 - 16.33)	0.14 (0.02 - 0.88)
Schreyer[318]	Intact	<48 hours	11	3	2	54	16.08 (5.22 - 49.55)	0.16 (0.05 - 0.58)
Schreyer[318]	Intact	<7 days	12	2	4	52	20.25 (5.05 - 81.23)	0.26 (0.11 - 0.61)
Senden[85]	Intact	<7 days	2	2	3	18	4.00 (0.73 - 21.84)	0.67 (0.32 - 1.38)

Table 54 Characteristics of test accuracy studies of cervical length measurement in predicting spontaneous preterm birth in antenatal asymptomatic women

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Test gestation	Frequency of testing	Threshold (mm)	Outcome (weeks' gestation)
Leung[326]	2005	HK	2952	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancy of ethnic Chinese women only	Fetal abnormalities, non-viable pregnancies, lack of outcome information, outside test gestation	18 - 22	Single	<15, <20, <25, <27, <30, <35	<34
Yazici[332]	2004	Turkey	357	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies in the absence of history of cervical incompetence, PPROM or previous preterm delivery	Uterine or fetal anomalies, pregnancy related complications, maternal systemic disease	24	Single	<32.5	<36
Owen[328]	2001	USA	183	Cohort Prospective Consecutive Blinded Test described	Singletons with at least one previous spontaneous preterm birth.	Cervical cerclage, uterine anomaly, chronic medical problem which may cause iatrogenic preterm delivery.	16 - 18	Single	<15, <20, <25, <30	<35
Berghella[323]	1997	USA	96	Cohort Prospective Consecutive Blinded Test described	Singletons, previous spontaneous preterm birth, >2 previous abortions, previous cone biopsy, Ehler-Danlos syndrome.	Cervical cerclage, placenta previa, major fetal anomaly.	14 - 22	Single	<16, <25	<35
Andrews[322]	2000	USA	69	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies with previous history of spontaneous preterm birth between 16 - 30 weeks' gestation	Medical or obstetrics complication. History of incompetent cervix that required cerclage. Presented for antenatal care after 28 weeks	<20	Thrice	<22, <25	<35
To[331]	2001	UK	6334	Cohort Prospective Consecutive Test described	Singleton pregnancies	x	22 - 24	Single	<15	33
Sakai[235]	2004	Japan	4203	Cohort Prospective Blinding Test described	Asymptomatic women with singleton pregnancy and intact membrane	Preterm pre-labour rupture of membrane, threatened or impending miscarriage or preterm delivery, genital bleeding	20 - 28	Single	25	<32, <34, <37
Taipale[330]	1998	Finland	3694	Cohort Prospective Consecutive Test described	Singleton pregnancies	Inadequate imaging, iatrogenic preterm delivery, fetal death or malformation	18 - 22	Single	<25, <29, <35, <40, <45, <50	<35, <37
Hibbard[325]	2000	USA	760	Cohort Prospective Consecutive Test described	Singleton pregnancies	x	16 - 22	Single	<22, <27, <30	<35

Dilek[324]	2006	Turkey	250	Cohort Prospective Consecutive Test described	Singleton pregnancies in the absence of history of cervical incompetence, PPROM or previous preterm delivery	Uterine or fetal anomalies, pregnancy related complications, maternal systemic disease	22	Single	<33.15	<37
Andersen[321]	1990	USA	113	Cohort Prospective Blinded Test described	Singletons	Placenta previa, patient thought to be at risk from cervical incompetence.	7 - 30	Single	<39	<37
deCarvalho[59]	2005	Brazil	1958	Cohort Retrospective Test described	Singleton pregnancy attending routine antenatal care at 21 - 24 weeks' gestation	Iatrogenic preterm delivery, missing outcomes	21 - 24	Single	<10, <15, <20, <25, <30	<34
Pires[329]	2005	Brazil	338	Cohort Prospective Test described	Singleton uncomplicated pregnancy	Previous history of preterm delivery, uterine or fetal abnormalities, miscarriage, fetal death, alteration in amniotic fluid, placenta previa, previous uterine or cervical surgery, surgical procedures during gestation and conditions requiring iatrogenic preterm delivery	21 - 24	Single	<20	<35, <37
Mara[327]	2002	Czech	247	Case-control Prospective Test described	Singleton viable pregnancy, delivering at investigating institution	Congenital or chromosomal abnormalities, history of uterine or cervix surgery, greater than 3 previous vaginal deliveries	18 - 20	Single	<20	<34

Table 55 Characteristics of test accuracy studies of cervical length measurement in predicting spontaneous preterm birth in women symptomatic with threatened preterm labour

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of Testing	Threshold (mm)	Outcome (weeks' gestation)*
Crane[333]	1997	USA	136	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies whose contraction has been arrested by tocolysis	Cervical dilatation > 3cm, placenta previa, PPROM	24 - 34	Single	<30	<34
Gomez[337]	1994	USA	59	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies	PPROM, cervix dilatation >3 cm	21 - 35	Single	<18	<37
Tsoi[346]	2005	UK	510	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	x	24 - 34	Single	<5, <10, <15, <20	<48 hours, <7 days of testing, <37
Schmitz[342]	2006	France	359	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	Cervical manipulation, PPROM, fetal or uterine anomalies, vaginal bleeding, placenta previa, abruption, IUGR, pre-eclampsia, iatrogenic preterm delivery	18 - 34	Single	<15, <25, <30	<7 days of testing, <35
Fuchs[335]	2004	Germany	253	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	PPROM, cervical cerclage, requirement for iatrogenic preterm delivery, abruption, placenta previa, suspected fetal distress	24 - 36	Single	<15	<7 days of testing
Tsoi[344]	2003	UK	216	Cohort Prospective Blinded Test described	Singleton viable pregnancies presenting with threatened preterm labour	Cervical dilatation >3 cm or PPROM	24 - 36	Single	<15	<7 days of testing
Onderoglu[75]	1997	Turkey	90	Cohort Prospective Blinded Test described	Singletons, intact membrane, cervical dilatation <3cm, absence of fetal and maternal complication	x	25 - 36	Single	<28	<37
Tekesin[343]	2005	Germany	85	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	Fetal abnormalities, PPROM, cervical cerclage, requirement for iatrogenic preterm delivery, abruption, placenta previa, suspected fetal distress	24 - 36	Single	<25	<37
Kurkinen[223]	2001	Finland	76	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22 - 32 weeks' gestation who presented with threatened preterm labour.	Preterm pre-labour rupture of membrane, impending preterm delivery	22 - 32	Single	<29.3	<37

Tsoi[345]	2004	UK	63	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	PPROM	24 - 36	Single	<15	<7 days of testing
Rozenberg[341]	2003	France	28	Cohort Prospective Blinded Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	History of cervical incompetence with cerclage, suspected chorioamnionitis, PPROM, polyhydramnios, placenta previa, abruption, IUGR, pre-eclampsia, feta distress, other maternal or fetal distress requiring preterm delivery	24 - 34	Single	<26	<37
Gomez[106]	2005	Chile	215	Cohort Prospective Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	x	22 - 35	Single	<15, <30	<48 hours, <7, <14 days of testing, <32, <35
Venditelli[347]	2001	France	174	Cohort Prospective Test described	Singleton pregnancies	Cervical dilatation >3 cm, PPROM, cervical cerclage, active vaginal bleeding, known fetal malformation or death, placenta previa	18 - 36	Single	<30	<37
Daskalakis[334]	2005	Greece	172	Cohort Prospective Test described	Singleton pregnancy presenting with threatened preterm labour, intact membrane, cervical dilatation <3cm	PPROM, cervical cerclage, requirement for iatrogenic preterm delivery, abruption, placenta previa, suspected fetal distress	24 - 34	Single	<20, <25, <30, <35	<34
Goffinet[336]	1997	France	108	Cohort Prospective Test described	Singleton pregnancies	Cervical cerclage, PPROM, cervical dilatation >2cm, iatrogenic preterm delivery	24 - 34	Single	<26	<37
Rizzo[340]	1996	Italy	108	Cohort Prospective Test described	Singletons pregnancies, intact membrane, cervical dilatation <3cm, absence of maternal or fetal complication		24 - 36	Single	<20	<37
Botsis[57]	2005	Greece	104	Cohort Prospective Test described	Singleton viable pregnancy presenting with threatened preterm labour between 24 - 36 weeks' gestation with intact fetal membrane and cervical dilatation <2cm		24 - 36	Single	<15	<7 days of testing
Murakawa[338]	1993	Japan	32	Cohort Prospective Test described	Singleton pregnancies	Suspicion of cervical incompetence	25 - 35	Single	<30, <35	<37
Rageth[339]	1997	Switzerland	61	Cohort Retrospective Test described	Singleton pregnancies whose contraction has been arrested by tocolysis	IUGR, pre-eclampsia, diabetes	25 - 35	Single	<30	<34

*Unless otherwise stated

Table 56 Characteristics of test accuracy studies of cervical funnelling assessment in predicting spontaneous preterm birth stratified according to population of antenatal asymptomatic women and women symptomatic with threatened preterm labour

Authors	Year	Country	n	Study designs	Inclusion	Exclusion	Testing gestation (weeks)	Frequency of Testing	Threshold	Outcome (weeks' gestation)*
Asymptomatic										
Leung[326]	2005	HK	2952	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancy of ethnic Chinese women only	Fetal abnormalities, non-viable pregnancies, lack of outcome information, outside test gestation	18 - 22	Single	5mm length	34
Iams[319]	1996	USA	2915	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies	Multiple gestations, cervical cerclage, placenta previa, fetal anomaly	at 28	Twice	3mm length	35
Andrews[322]	2000	USA	69	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies with previous history of spontaneous preterm birth between 16 - 30 weeks' gestation	Medical or obstetrics complication. History of incompetent cervix that required cerclage. Presented for antenatal care after 28 weeks	25 - 29	Twice	any	35
To[331]	2001	UK	6334	Cohort Prospective Consecutive Test described	Singleton pregnancies	x	22 - 24	Single	5mm width	33
Pires[329]	2005	Brazil	338	Cohort Prospective Test described	Singleton uncomplicated pregnancy	Previous history of preterm delivery, uterine or fetal abnormalities, miscarriage, fetal death, alteration in amniotic fluid, placenta previa, previous uterine or cervical surgery, surgical procedures during gestation and conditions requiring iatrogenic preterm delivery	21 - 24	Single	any	35
Mara[327]	2002	Czech	247	Case-control Prospective	Singleton viable pregnancy, delivery at investigating institutions	Congenital or chromosomal abnormalities, history of uterine or cervix surgery, greater than 3 previous vaginal deliveries	18 - 20	Single	any	34
Symptomatic										
Crane[333]	1997	USA	136	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies whose contraction has been arrested by tocolysis	Cervical dilatation > 3cm, placenta previa, PPROM	24 - 34	Single	V-shaped	37

Gomez[337]	1994	USA	59	Cohort Prospective Consecutive Blinded Test described	Singleton pregnancies	PPROM, cervix dilatation >3 cm	21 - 35	Single	6mm width	36
Kurkinen[223]	2001	Finland	76	Cohort Prospective Consecutive Test described	Consecutive singleton pregnant women between 22 - 32 weeks' gestation who presented with threatened preterm labour.	Preterm pre-labour rupture of membrane, impending preterm delivery	22 - 32	Single	5mm width	37
Okitsu[320]	1992	Japan	130	Cohort Prospective Test described	Singleton pregnancies	Placenta previa	25 - 36	Single	5mm width	36
Rizzo[340]	1996	Italy	108	Cohort Prospective Test described	Singletons pregnancies, intact membrane, cervical dilatation <3cm, absence of maternal or fetal complication	x	24 - 36	Single	5mm width	37

*Unless otherwise stated

Table 57 Individual accuracy results of cervical length measurement in predicting spontaneous preterm birth among asymptomatic antenatal women stratified according to outcome (weeks' gestation) and testing gestation (weeks')

Authors	Thresholds (mm)	Outcome (weeks' gestation)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
<20 weeks' gestation																		
Andrews[* 322]	25	35	5	0	10	38	0.33	0.12	0.62	1.00	0.91	1.00	26.81	1.57	457.07	0.66	0.47	0.95
Andrews[* 322]	22	35	4	0	11	38	0.27	0.08	0.55	1.00	0.91	1.00	21.94	1.25	384.29	0.73	0.53	0.99
Leung[326]	25	34	5	48	15	2884	0.25	0.09	0.49	0.98	0.98	0.99	15.27	6.80	34.30	0.76	0.59	0.98
Leung[326]	15	34	2	0	18	2932	0.10	0.01	0.32	1.00	1.00	1.00	698.33	34.56	14109.00	0.88	0.75	1.03
Leung[326]	30	34	7	288	13	2644	0.35	0.15	0.59	0.90	0.89	0.91	3.56	1.94	6.54	0.72	0.52	0.99
Leung[326]	35	34	12	1021	8	1911	0.60	0.36	0.81	0.65	0.63	0.67	1.72	1.20	2.47	0.61	0.36	1.05
Leung[326]	27	34	7	111	13	2821	0.35	0.15	0.59	0.96	0.95	0.97	9.25	4.95	17.26	0.68	0.49	0.93
Leung[326]	20	34	2	4	18	2928	0.10	0.01	0.32	1.00	1.00	1.00	73.30	14.23	377.66	0.90	0.78	1.04
Owen[328]	20	35	5	1	42	135	0.11	0.04	0.23	0.99	0.96	1.00	14.47	1.73	120.69	0.90	0.81	0.99
Owen[328]	25	35	9	3	39	132	0.19	0.09	0.33	0.98	0.94	1.00	8.44	2.38	29.88	0.83	0.72	0.95
Owen[328]	30	35	12	24	29	118	0.29	0.16	0.46	0.83	0.76	0.89	1.73	0.95	3.15	0.85	0.69	1.05
Owen[328]	15	35	5	0	43	135	0.10	0.03	0.23	1.00	0.97	1.00	30.53	1.72	542.02	0.89	0.81	0.98
Hibbard[325]	27	35	15	25	36	684	0.29	0.17	0.44	0.96	0.95	0.98	8.34	4.70	14.80	0.73	0.61	0.87
Hibbard[325]	22	35	11	16	40	693	0.22	0.11	0.35	0.98	0.96	0.99	9.56	4.68	19.50	0.80	0.69	0.93
Hibbard[325]	30	35	21	66	30	643	0.41	0.28	0.56	0.91	0.88	0.93	4.42	2.96	6.60	0.65	0.51	0.82
Mara[327]	20	34	3	0	6	238	0.33	0.07	0.70	1.00	0.98	1.00	167.30	9.25	3024.97	0.65	0.41	1.03
20 – 24 week' gestation																		
Iams[* 322]	20	35	29	84	97	2705	0.23	0.16	0.31	0.97	0.96	0.98	7.64	5.21	11.20	0.79	0.72	0.87
Andrews[* 322]	22	35	4	3	9	41	0.31	0.09	0.61	0.93	0.81	0.99	4.51	1.15	17.64	0.74	0.51	1.08
Iams[* 322]	25	35	47	218	79	2571	0.37	0.29	0.46	0.92	0.91	0.93	4.77	3.68	6.19	0.68	0.59	0.78
Andrews[* 322]	25	35	5	5	8	39	0.38	0.14	0.68	0.89	0.75	0.96	3.38	1.16	9.91	0.69	0.45	1.08
Iams[* 322]	30	35	68	661	58	2128	0.54	0.45	0.63	0.76	0.75	0.78	2.28	1.91	2.71	0.60	0.50	0.73
To[331]	15	33	21	80	38	6195	0.36	0.24	0.49	0.99	0.98	0.99	27.92	18.59	41.92	0.65	0.54	0.79
deCarvalho[59]	10	34	3	3	38	1734	0.07	0.02	0.20	1.00	0.99	1.00	42.37	8.81	203.65	0.93	0.85	1.01
deCarvalho[59]	10	34	5	5	61	1887	0.08	0.03	0.17	1.00	0.99	1.00	28.67	8.51	96.62	0.93	0.86	0.99
deCarvalho[59]	10	34	2	2	23	153	0.08	0.01	0.26	0.99	0.95	1.00	6.20	0.91	42.03	0.93	0.83	1.05
deCarvalho[59]	15	34	23	16	43	1876	0.35	0.24	0.48	0.99	0.99	1.00	41.21	22.87	74.26	0.66	0.55	0.78

deCarvalho[59]	15	34	11	6	14	149	0.44	0.24	0.65	0.96	0.92	0.99	11.37	4.62	27.97	0.58	0.41	0.83
deCarvalho[59]	15	34	12	10	29	1727	0.29	0.16	0.46	0.99	0.99	1.00	50.84	23.31	110.90	0.71	0.58	0.87
Pires[329]	20	37	4	10	17	307	0.19	0.05	0.42	0.97	0.94	0.98	6.04	2.07	17.64	0.84	0.68	1.03
deCarvalho[59]	20	34	34	47	32	1845	0.52	0.39	0.64	0.98	0.97	0.98	20.74	14.37	29.92	0.50	0.39	0.64
deCarvalho[59]	20	34	18	17	7	138	0.72	0.51	0.88	0.89	0.83	0.93	6.56	3.94	10.94	0.31	0.17	0.59
deCarvalho[59]	20	34	16	30	25	1707	0.39	0.24	0.55	0.98	0.98	0.99	22.60	13.41	38.07	0.62	0.49	0.79
Pires[329]	20	35	3	7	8	320	0.27	0.06	0.61	0.98	0.96	0.99	12.74	3.79	42.80	0.74	0.52	1.07
deCarvalho[59]	25	34	38	171	28	1721	0.58	0.45	0.70	0.91	0.90	0.92	6.37	4.95	8.19	0.47	0.35	0.62
deCarvalho[59]	25	34	19	38	6	117	0.76	0.55	0.91	0.75	0.68	0.82	3.10	2.18	4.41	0.32	0.16	0.64
deCarvalho[59]	25	34	19	134	22	1603	0.46	0.31	0.63	0.92	0.91	0.93	6.01	4.16	8.67	0.58	0.44	0.77
deCarvalho[59]	30	34	42	442	24	1450	0.64	0.51	0.75	0.77	0.75	0.79	2.72	2.23	3.33	0.47	0.34	0.65
deCarvalho[59]	30	34	22	372	19	1365	0.54	0.37	0.69	0.79	0.77	0.80	2.51	1.86	3.38	0.59	0.42	0.82
deCarvalho[59]	30	34	20	71	5	84	0.80	0.59	0.93	0.54	0.46	0.62	1.75	1.35	2.27	0.37	0.17	0.82
<20 weeks' gestation																		
Hibbard[325]	22	37	11	10	74	665	0.13	0.07	0.22	0.99	0.97	0.99	8.74	3.82	19.96	0.88	0.81	0.96
Taipale[330]	25	37	5	8	83	3598	0.06	0.02	0.13	1.00	1.00	1.00	25.61	8.55	76.72	0.95	0.90	1.00
Hibbard[325]	27	37	17	23	68	652	0.20	0.12	0.30	0.97	0.95	0.98	5.87	3.27	10.53	0.83	0.74	0.92
Taipale[330]	29	37	14	96	74	3510	0.16	0.09	0.25	0.97	0.97	0.98	5.98	3.56	10.04	0.86	0.79	0.95
Hibbard[325]	30	37	28	59	57	616	0.33	0.23	0.44	0.91	0.89	0.93	3.77	2.55	5.56	0.73	0.63	0.85
Taipale[330]	35	37	31	962	57	2644	0.35	0.25	0.46	0.73	0.72	0.75	1.32	0.99	1.76	0.88	0.76	1.03
Andersen[321]	39	37	13	39	4	56	0.76	0.50	0.93	0.59	0.48	0.69	1.86	1.30	2.66	0.40	0.17	0.96
Taipale[330]	40	37	53	1875	35	1731	0.60	0.49	0.71	0.48	0.46	0.50	1.16	0.97	1.38	0.83	0.64	1.07
Taipale[330]	45	37	78	2731	10	875	0.89	0.80	0.94	0.24	0.23	0.26	1.17	1.08	1.26	0.47	0.26	0.84
Taipale[330]	50	37	87	3261	1	345	0.99	0.94	1.00	0.10	0.09	0.11	1.09	1.07	1.12	0.12	0.02	0.84
20 – 24 week' gestation																		
Yazici[332]	32.5	36	16	61	6	274	0.73	0.50	0.89	0.82	0.77	0.86	3.99	2.84	5.62	0.33	0.17	0.66
Dilek[324]	33.15	37	14	29	4	203	0.78	0.52	0.94	0.88	0.83	0.91	6.22	4.09	9.48	0.25	0.11	0.60

*Women were scanned twice, a few weeks apart within the testing gestation

Table 58 Individual accuracy results of cervical length measurement in predicting spontaneous preterm birth among women symptomatic with threatened preterm labour stratified according to outcome (within days of testing and according to weeks' gestation)

Authors	Thresholds (mm)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
<48 hours of testing																	
Tsoi[346]	5	9	11	12	478	0.43	0.22	0.66	0.98	0.96	0.99	19.05	8.87	40.94	0.58	0.40	0.85
Tsoi[346]	10	17	31	4	458	0.81	0.58	0.95	0.94	0.91	0.96	12.77	8.57	19.03	0.20	0.08	0.49
Tsoi[346]	15	21	74	0	415	1.00	0.84	1.00	0.85	0.81	0.88	6.43	5.17	8.00	0.03	0.00	0.42
Tsoi[346]	20	21	150	0	339	1.00	0.84	1.00	0.69	0.65	0.73	3.18	2.75	3.69	0.03	0.00	0.51
Gomez[106]	15	11	19	6	179	0.65	0.38	0.86	0.90	0.85	0.94	6.74	3.88	11.72	0.39	0.20	0.74
Gomez[106]	30	15	93	2	105	0.88	0.64	0.99	0.53	0.46	0.60	1.88	1.50	2.36	0.22	0.06	0.82
<7 days of testing																	
Tsoi[346]	5	16	4	27	463	0.37	0.23	0.53	0.99	0.98	1.00	43.44	15.20	124.17	0.63	0.50	0.80
Tsoi[346]	10	28	20	15	447	0.65	0.49	0.79	0.96	0.93	0.97	15.20	9.40	24.61	0.36	0.24	0.55
Tsoi[346]	15	42	53	1	414	0.98	0.88	1.00	0.89	0.85	0.91	8.61	6.65	11.14	0.03	0.00	0.18
Tsoi[346]	20	42	129	1	338	0.98	0.88	1.00	0.72	0.68	0.76	3.54	3.03	4.12	0.03	0.00	0.22
Schmitz[342]	15	12	45	11	291	0.52	0.31	0.73	0.87	0.82	0.90	3.90	2.42	6.27	0.55	0.36	0.85
Schmitz[342]	25	20	131	3	205	0.87	0.66	0.97	0.61	0.56	0.66	2.23	1.81	2.74	0.21	0.07	0.62
Schmitz[342]	30	23	193	0	143	1.00	0.85	1.00	0.43	0.37	0.48	1.71	1.53	1.90	0.05	0.00	0.76
Fuchs[335]	15	17	19	4	213	0.81	0.58	0.95	0.92	0.88	0.95	9.88	6.13	15.95	0.21	0.09	0.50
Tsoi[345]	15	16	27	1	172	0.94	0.71	1.00	0.86	0.81	0.91	6.94	4.79	10.05	0.07	0.01	0.46
Tsoi[345]	15	20	10	0	33	1.00	0.83	1.00	0.77	0.61	0.88	4.09	2.40	6.96	0.03	0.00	0.49
Gomez[106]	15	17	13	11	174	0.61	0.41	0.78	0.93	0.88	0.96	8.73	4.78	15.96	0.42	0.27	0.67
Gomez[106]	30	25	83	3	104	0.89	0.72	0.98	0.56	0.48	0.63	2.01	1.64	2.47	0.19	0.07	0.57
Botsis[57]	15	10	9	1	84	0.91	0.59	1.00	0.90	0.82	0.95	9.39	4.91	17.97	0.10	0.02	0.65
Gomez[106]	15	17	13	17	168	0.50	0.32	0.68	0.93	0.88	0.96	6.96	3.74	12.97	0.54	0.38	0.76
Gomez[106]	30	29	79	5	102	0.85	0.69	0.95	0.56	0.49	0.64	1.95	1.57	2.43	0.26	0.11	0.59
<34 weeks' gestation																	
Gomez[106]	15	7	5	2	87	0.78	0.40	0.97	0.95	0.88	0.98	14.31	5.70	35.95	0.23	0.07	0.80
Gomez[106]	30	9	40	0	52	1.00	0.66	1.00	0.57	0.46	0.67	2.18	1.66	2.86	0.09	0.01	1.33
Crane[333]	30	30	35	7	64	0.81	0.65	0.92	0.65	0.54	0.74	2.29	1.68	3.12	0.29	0.15	0.58
Daskalakis[334]	20	21	3	18	60	0.54	0.37	0.70	0.95	0.87	0.99	11.31	3.61	35.42	0.48	0.34	0.68

Daskalakis[334]	25	28	13	11	50	0.72	0.55	0.85	0.79	0.67	0.89	3.48	2.06	5.87	0.36	0.21	0.60
Daskalakis[334]	30	39	21	0	42	1.00	0.91	1.00	0.67	0.54	0.78	2.94	2.08	4.16	0.02	0.00	0.30
Daskalakis[334]	35	39	47	0	16	1.00	0.91	1.00	0.25	0.15	0.38	1.33	1.15	1.54	0.05	0.00	0.79
Daskalakis[334]	20	15	1	10	44	0.60	0.39	0.79	0.98	0.88	1.00	27.00	3.79	192.51	0.41	0.25	0.66
Daskalakis[334]	25	16	9	9	36	0.64	0.43	0.82	0.80	0.65	0.90	3.20	1.66	6.16	0.45	0.26	0.77
Daskalakis[334]	30	25	15	0	30	1.00	0.86	1.00	0.67	0.51	0.80	2.91	1.93	4.38	0.03	0.00	0.45
Daskalakis[334]	35	25	33	0	12	1.00	0.86	1.00	0.27	0.15	0.42	1.35	1.12	1.62	0.07	0.00	1.15
Rageth[339]	30	4	25	0	32	1.00	0.40	1.00	0.56	0.42	0.69	2.05	1.36	3.09	0.18	0.01	2.50
Tsoi[346]	5	17	3	59	431	0.22	0.14	0.33	0.99	0.98	1.00	32.36	9.72	107.75	0.78	0.69	0.88
Tsoi[346]	10	33	15	43	419	0.43	0.32	0.55	0.97	0.94	0.98	12.56	7.18	21.98	0.59	0.48	0.71
Tsoi[346]	15	54	41	22	393	0.71	0.60	0.81	0.91	0.87	0.93	7.52	5.44	10.41	0.32	0.22	0.46
Tsoi[346]	20	59	112	17	322	0.78	0.67	0.86	0.74	0.70	0.78	3.01	2.46	3.67	0.30	0.20	0.46
Schmitz[342]	15	22	35	26	276	0.46	0.31	0.61	0.89	0.85	0.92	4.07	2.63	6.31	0.61	0.47	0.79
Schmitz[342]	25	36	115	12	196	0.75	0.60	0.86	0.63	0.57	0.68	2.03	1.63	2.52	0.40	0.24	0.65
Schmitz[342]	30	43	173	5	138	0.90	0.77	0.97	0.44	0.39	0.50	1.61	1.40	1.85	0.23	0.10	0.54
Gomez[106]	15	19	11	15	170	0.56	0.38	0.73	0.94	0.89	0.97	9.20	4.82	17.54	0.47	0.32	0.69
Gomez[106]	30	30	78	4	103	0.88	0.73	0.97	0.57	0.49	0.64	2.05	1.66	2.52	0.21	0.08	0.52
<37 weeks' gestation																	
Crane[333]	30	30	35	7	64	0.81	0.65	0.92	0.65	0.54	0.74	2.29	1.68	3.12	0.29	0.15	0.58
Gomez[106]	18	16	8	6	29	0.73	0.50	0.89	0.78	0.62	0.90	3.36	1.73	6.54	0.35	0.17	0.70
Onderoglu[75]	28	25	10	7	48	0.78	0.60	0.91	0.83	0.71	0.91	4.53	2.50	8.20	0.26	0.14	0.51
Tekesin[343]	25	17	22	6	40	0.74	0.52	0.90	0.65	0.51	0.76	2.08	1.38	3.15	0.40	0.20	0.82
Rozenberg[128]	26	14	6	2	6	0.88	0.62	0.98	0.50	0.21	0.79	1.75	0.96	3.17	0.25	0.06	1.03
Venditelli[347]	30	55	53	12	54	0.82	0.71	0.90	0.50	0.41	0.60	1.66	1.33	2.07	0.35	0.21	0.61
Rizzo[340]	20	32	13	15	48	0.68	0.53	0.81	0.79	0.66	0.88	3.19	1.90	5.38	0.41	0.26	0.63
Goffinet[336]	26	19	28	5	56	0.79	0.58	0.93	0.67	0.56	0.77	2.38	1.65	3.42	0.31	0.14	0.69
Murakawa[338]	25	7	3	4	18	0.64	0.31	0.89	0.86	0.64	0.97	4.45	1.43	13.91	0.42	0.19	0.95
Murakawa[338]	30	11	6	0	15	1.00	0.72	1.00	0.71	0.48	0.89	3.24	1.68	6.25	0.06	0.00	0.90
Murakawa[338]	35	11	14	0	7	1.00	0.72	1.00	0.33	0.15	0.57	1.45	1.05	2.01	0.12	0.01	1.96

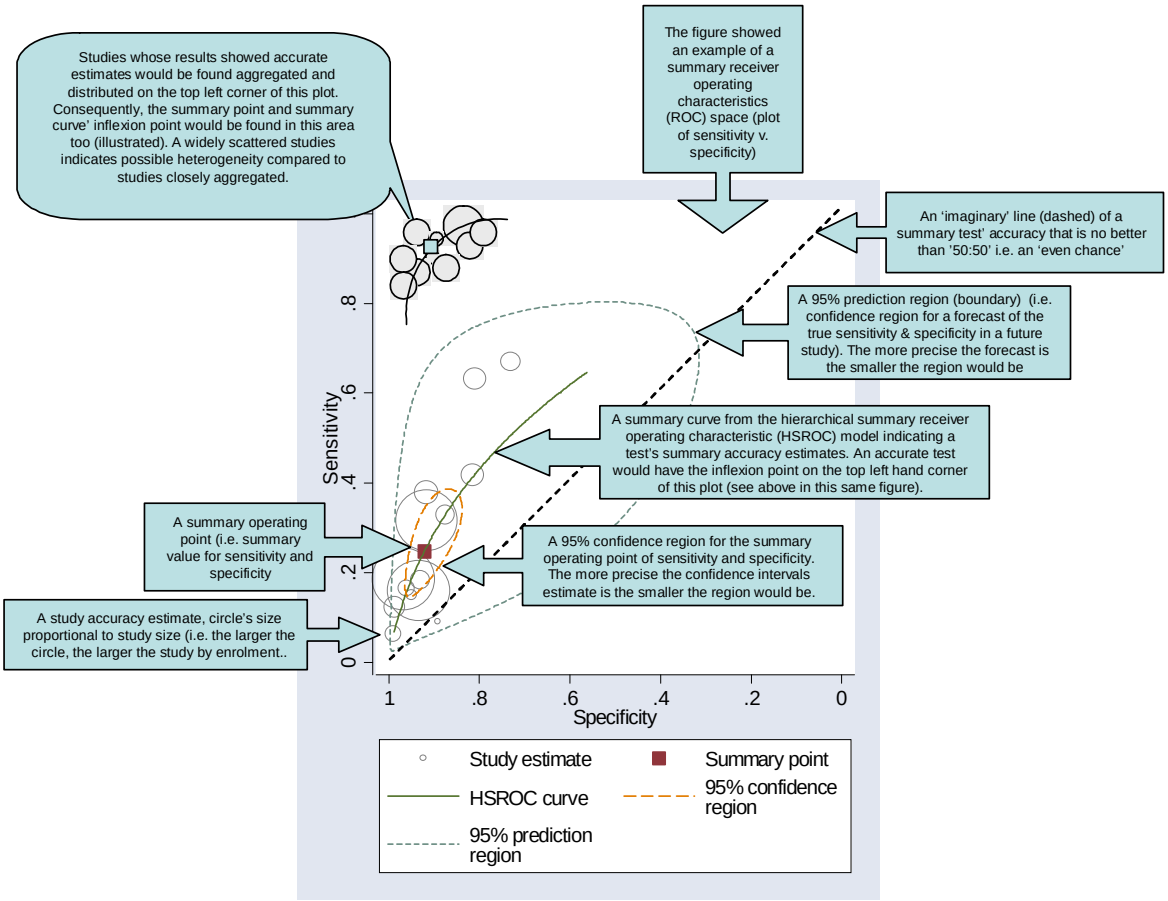
Table 59 Individual accuracy results of cervical funnelling assessment in predicting spontaneous preterm birth among women symptomatic with threatened preterm labour stratified according to outcome (weeks' gestation)

Authors	Thresholds	Outcome (weeks' gestation)	TP	FP	FN	TN	SENS	SENS_LB	SENS_UB	SPECS	SPEC_LB	SPEC_UB	LR+	LR+_LB	LR+_UB	LR-	LR-_LB	LR-_UB
Asymptomatic																		
Leung*[326]	any	34	6	175	14	2757	0.30	0.12	0.54	0.94	0.93	0.95	5.03	2.53	9.97	0.74	0.56	0.99
Andrews**+ [322]	any	35	4	5	9	39	0.31	0.09	0.61	0.89	0.75	0.96	2.71	0.85	8.64	0.78	0.54	1.14
Andrews**+ [322]	any	35	5	0	10	38	0.33	0.12	0.62	1.00	0.91	1.00	26.81	1.57	457.07	0.66	0.47	0.95
Andrews**+ [322]	any	35	7	8	2	24	0.78	0.40	0.97	0.75	0.57	0.89	3.11	1.55	6.23	0.30	0.09	1.02
To**[331]	5mm width	33	16	215	43	6103	0.27	0.16	0.40	0.97	0.96	0.97	7.97	5.14	12.35	0.75	0.65	0.88
Pires*[329]	any	37	3	11	18	324	0.14	0.03	0.36	0.97	0.94	0.98	4.35	1.31	14.42	0.89	0.74	1.06
Pires*[329]	any	35	3	11	8	316	0.27	0.06	0.61	0.97	0.94	0.98	8.11	2.63	25.01	0.75	0.52	1.08
Mara*[327]	any	34	7	33	2	205	0.78	0.40	0.97	0.86	0.81	0.90	5.61	3.50	8.99	0.26	0.08	0.88
Mara*[327]	any	37	22	18	11	196	0.67	0.48	0.82	0.92	0.87	0.95	7.93	4.79	13.12	0.36	0.22	0.59
Symptomatic																		
Crane[333]	V-shaped	37	7	9	25	95	0.22	0.09	0.40	0.91	0.84	0.96	2.53	1.02	6.25	0.86	0.71	1.04
Crane[333]	V-shaped	34	4	12	5	115	0.44	0.14	0.79	0.91	0.84	0.95	4.70	1.90	11.66	0.61	0.34	1.10
Gomez[337]	any	36	17	17	5	20	0.77	0.55	0.92	0.54	0.37	0.71	1.68	1.11	2.55	0.42	0.18	0.96
Gomez[337]	6mm width	36	14	8	7	25	0.67	0.43	0.85	0.76	0.58	0.89	2.75	1.40	5.40	0.44	0.23	0.83
Gomez[337]	9mm length	36	15	3	6	30	0.71	0.48	0.89	0.91	0.76	0.98	7.86	2.58	23.90	0.31	0.16	0.62
Rizzo[340]	5mm width	37	34	20	13	41	0.72	0.57	0.84	0.67	0.54	0.79	2.21	1.48	3.29	0.41	0.25	0.67
Okitsu[320]	5mm width	36	9	18	4	46	0.69	0.39	0.91	0.72	0.59	0.82	2.46	1.44	4.20	0.43	0.19	0.98

*Testing <20 weeks' gestation **Testing between 20 – 24 weeks' gestation + Tested twice within a two weeks apart

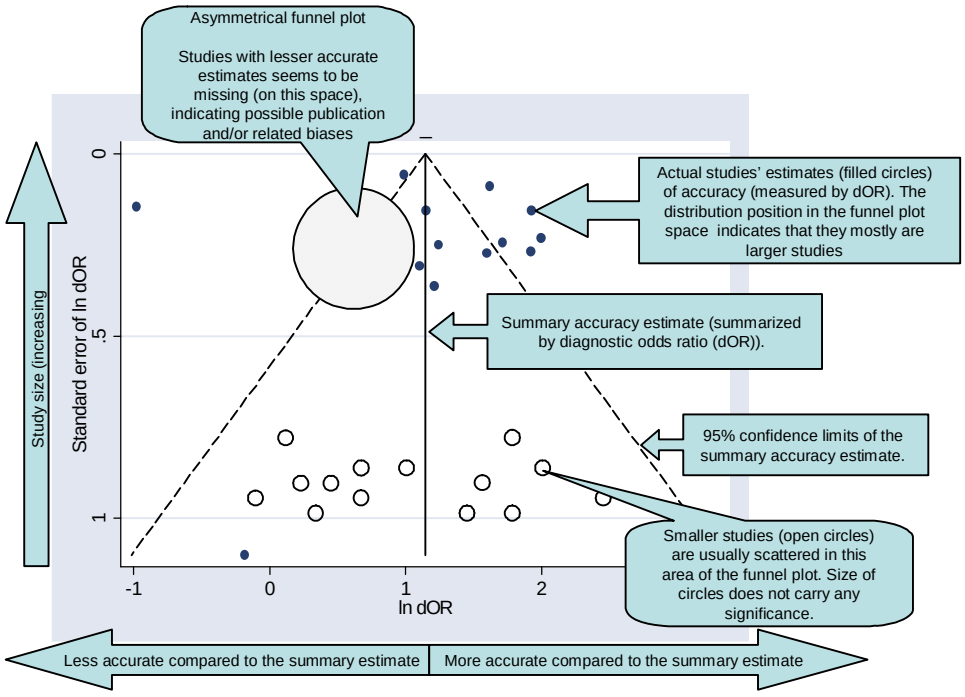
Appendix V – Guide to summary ROC & funnel plots interpretations

A graphical method for assessment of heterogeneity is to plot sensitivity and specificity of the various studies in a summary receiver operating characteristics (ROC) space. A summary ROC space plot will show, as a minimum, distribution of studies along with the summary point the accuracy estimate and summary curve for estimates of the test's accuracy from the various studies but it is usually accompanied by the 95% confidence region. A representation is shown below with key explanations.

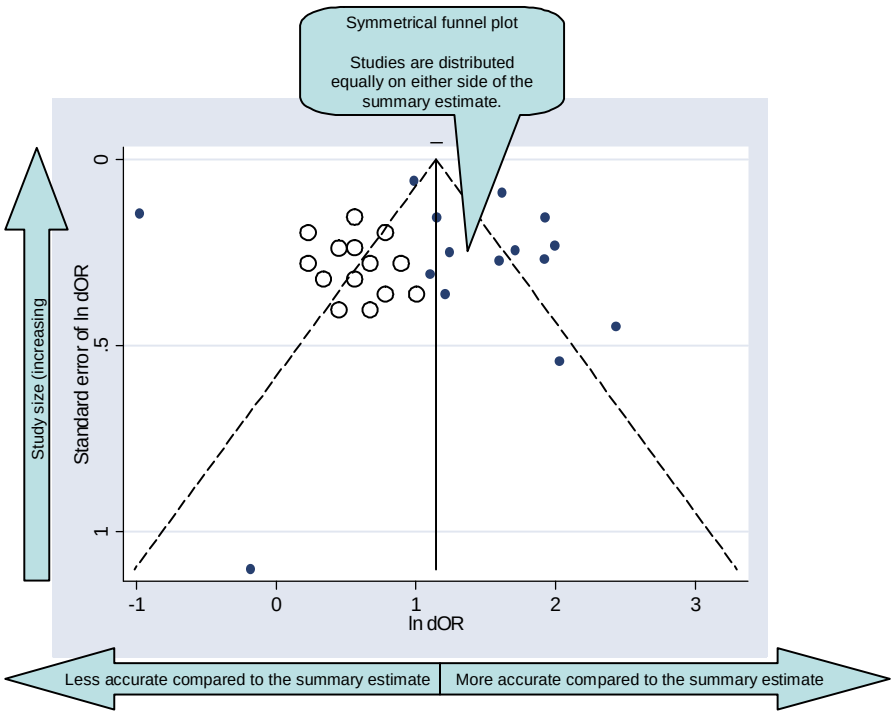


Another method for assessing heterogeneity (esp. publication and related biases) is to perform a simple, but commonly used method, funnel plot. To make a meaningful analysis and interpretation of a funnel plot requires inclusion of numerous studies (≥10 studies), preferably larger studies. The result is interpreted as either an asymmetrical (indicative of a possible presence of publication and related biases) or a symmetrical funnel plot (indicative of a possible absence of publication and related biases). Their representations are shown below with key explanations.

An asymmetrical funnel plot analysis



A symmetrical funnel plot analysis



Neither summary ROC nor funnel plot individually or jointly provides a conclusive evidence of heterogeneity or the presence of publication and related biases. Instead both are complementary and should be used as adjunct to studies' methods and quality assessments, and forest plots to draw an inference regarding presence of heterogeneity, publication and related biases.

Publications directly contributing to and from the work of thesis

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