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# Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling

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# Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/03/01. The contractual start date was in October 2005. The draft report began editorial review in September 2006 and was accepted for publication in March 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

## Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling

H Honest,[1]* CA Forbes,[2] KH Durée,[2] G Norman,[2] SB Duffy,[2] A Tsourapas,[3] TE Roberts,[3] PM Barton,[3] SM Jowett,[3] CJ Hyde[4] and KS Khan[1]

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**Objectives:** To identify combinations of tests and treatments to predict and prevent spontaneous preterm birth.

**Data sources:** Searches were run on the following databases up to September 2005 inclusive: MEDLINE, EMBASE, DARE, the Cochrane Library (CENTRAL and Cochrane Pregnancy and Childbirth Group trials register) and MEDION. We also contacted experts including the Cochrane Pregnancy and Childbirth Group and checked reference lists of review articles and papers that were eligible for inclusion.

**Review methods:** Two series of systematic reviews were performed: (1) accuracy of tests for the prediction of spontaneous preterm birth in asymptomatic women in early pregnancy and in women symptomatic with threatened preterm labour in later pregnancy; (2) effectiveness of interventions with potential to reduce cases of spontaneous preterm birth in asymptomatic women in early pregnancy and to reduce spontaneous preterm birth or improve neonatal outcome in women with a viable pregnancy symptomatic of threatened preterm labour. For the health economic evaluation, a model-based analysis incorporated the combined effect of tests and treatments and their cost-effectiveness.

**Results:** Of the 22 tests reviewed for accuracy, the quality of studies and accuracy of tests was generally poor. Only a few tests had LR+ > 5. In asymptomatic women these were ultrasonographic cervical length measurement and cervicovaginal prolactin and fetal fibronectin screening for predicting spontaneous preterm birth before 34 weeks. In this group, tests with LR– < 0.2 were detection of uterine contraction by home uterine monitoring and amniotic fluid C-reactive protein (CRP) measurement. In symptomatic women with threatened preterm labour, tests with LR+ > 5 were absence of fetal breathing movements, cervical length and funnelling, amniotic fluid interleukin-6 (IL-6), serum CRP for predicting birth within 2–7 days of testing, and matrix metalloprotease-9, amniotic fluid IL-6, cervicovaginal fetal fibronectin and cervicovaginal human chorionic gonadotrophin (hCG) for predicting birth before 34 or 37 weeks. In this group, tests with LR– < 0.2 included measurement of cervicovaginal IL-8, cervicovaginal hCG, cervical length measurement, absence of fetal breathing movement, amniotic fluid IL-6 and serum CRP, for predicting birth within 2–7 days of testing, and cervicovaginal fetal fibronectin and amniotic fluid IL-6 for predicting birth before 34 or 37 weeks. The overall quality of the trials included in the 40 interventional topics reviewed for effectiveness was also poor. Antibiotic treatment was generally not beneficial but when used to treat bacterial vaginosis in women with intermediate flora it significantly reduced the incidence of spontaneous preterm birth. Smoking cessation programmes, progesterone, periodontal therapy and fish oil appeared promising as preventative interventions in asymptomatic women. Non-steroidal anti-inflammatory agents were the most effective tocolytic agent for reducing spontaneous preterm birth and prolonging pregnancy in symptomatic women.

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Antenatal corticosteroids had a beneficial effect on the incidence of respiratory distress syndrome and the risk of intraventricular haemorrhage (28–34 weeks), but the effects of repeat courses were unclear. For asymptomatic women, costs ranged from £1.08 for vitamin C to £1219 for cervical cerclage, whereas costs for symptomatic women were more significant and varied little, ranging from £1645 for nitric oxide donors to £2555 for terbutaline; this was because the cost of hospitalisation was included. The best estimate of additional average cost associated with a case of spontaneous preterm birth was approximately £15,688 for up to 34 weeks and £12,104 for up to 37 weeks. Among symptomatic women there was insufficient evidence to draw firm conclusions for preventing birth at 34 weeks. Hydration given to women testing positive for amniotic fluid IL-6 was the most cost-effective test–treatment combination. Indomethacin given to all women without any initial testing was the most cost-effective option for preventing birth before 37 weeks among symptomatic women. For a symptomatic woman, the most cost-effective test–treatment combination for postponing delivery by at least 48 h was the cervical length (15 mm) measurement test with treatment with indomethacin for all those testing positive. This combination was also the most cost-effective option for postponing delivery by at least 7 days. Antibiotic treatment for asymptomatic bacteriuria of all women without any initial testing was the most cost-effective option for preventing birth before 37 weeks among asymptomatic women but this does not take into account the potential side effects of antibiotics or issues such as increased resistance.

**Conclusions:** For primary prevention, an effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective approach in asymptomatic women in early pregnancy. For secondary prevention among women at risk of preterm labour in later pregnancy, a management strategy based on the results of testing is likely to be more cost-effective. Implementation of a treat-all strategy with simple interventions, such as fish oils, would be premature for asymptomatic women. Universal provision of high-quality ultrasound machines in labour wards is more strongly indicated for predicting spontaneous preterm birth among symptomatic women than direct management, although staffing issues and the feasibility and acceptability to mothers and health providers of such strategies need to be explored. Further research should include investigations of low-cost and effective tests and treatments to reduce and delay spontaneous preterm birth and reduce the risk of perinatal mortality arising from preterm birth.

# Contents





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# List of abbreviations

| | |
|---|---|
| AIDS | acquired immune deficiency syndrome |
| BMI | body mass index |
| BNF | *British National Formulary* |
| BV | bacterial vaginosis |
| BWH | Birmingham Women's Hospital |
| CDE | cervical digital examination |
| CDSR | Cochrane Database of Systematic Reviews |
| CEAC | cost-effectiveness acceptability curve |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CI | confidence interval |
| CRD | Centre for Reviews and Dissemination |
| CRH | corticotrophin-releasing hormone |
| CTG | cardiotocography |
| CRP | C-reactive protein |
| DARE | Database of Abstracts of Reviews of Effect |
| ELISA | enzyme-linked immunosorbent assay |
| fFN | fetal fibronectin |
| GTN | glyceryl trinitride |
| hCG | human chorionic gonadotrophin |
| HEED | Health Economic Evaluations Database |
| β-hCG | beta-human chorionic gonadotrophin |
| HCHS | hospital and community health services |
| HIV | human immunodeficiency virus |
| HRG | health resources groups |
| HTA | health technology assessment |
| ICER | incremental cost-effectiveness ratios |
| IL-6 | interleukin-6 |
| IL-8 | interleukin-8 |
| IPD | individual patient data (meta-analysis) |
| ITT | intention to treat |
| LBW | low birthweight |
| LR | likelihood ratio (LR+, LR for positive test result; LR–, LR for negative test result) |
| MeSH | medical subject heading (indexing) |
| MMP-9 | matrix metalloprotease-9 |
| MSAFP | maternal serum α-fetoprotein |
| NHS EED | NHS Economic Evaluation Database |
| NNT | number needed to treat |



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| | |
|---|---|
| NRR | National Research Register |
| NSAID | non-steroidal anti-inflammatory drug |
| NSC | National Screening Committee |
| NTIS | National Technical Information Service |
| OMNI | Organising Medical Networked Information |
| OR | odds ratio |
| phIGFBP-1 | phosphorylated insulin-like growth factor binding protein 1 |
| PROM | pre-labour rupture of membrane |
| PPROM | premature pre-labour rupture of membrane |
| PSA | probabilistic sensitivity analysis |
| PSSRU | Personal Social Services Research Unit |
| PTB | preterm birth |
| PTL | threatened preterm labour |
| QALY | quality-adjusted life-year |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| RCT | randomised controlled trial |
| RD | risk difference |
| 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 |
| SQT | subcutaneous terbutaline |
| TNELIP | non-elective inpatient HRG data |
| TNELIPXS | elective inpatient excess bed day HRG data |
| WMD | weighted mean difference |

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

# Executive 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 30–40% of all cases of preterm births are the result of elective delivery for a maternal or a fetal complication. The remaining 60–70% of preterm births occur spontaneously, and these are the focus of this report. Preterm birth complicates about 3% of pregnancies before 34 weeks' gestation and between 7 and 12% before 37 weeks' gestation. The former particularly has serious effects on mother, child and society, making 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 a spontaneous preterm birth can be determined, interventions can be deployed to prevent or delay birth and to improve subsequent neonatal mortality/morbidity.

## Objectives

The aim of this health technology assessment project was to identify combinations of tests and treatments that would predict and prevent spontaneous preterm birth. It completed three distinct pieces of work to contribute to this goal:

1. A series of systematic reviews of accuracy of tests for the prediction of spontaneous preterm birth in asymptomatic antenatal women in early pregnancy and in women symptomatic with threatened preterm labour in later pregnancy.
2. A series of systematic reviews of effectiveness of interventions with potential to reduce cases of spontaneous preterm birth in asymptomatic antenatal women in early pregnancy and to reduce spontaneous preterm birth and/or improve neonatal outcome in women with a viable pregnancy symptomatic of threatened preterm labour.
3. Health economic evaluation, including an economic model, of the combined effect of tests and treatments and their cost-effectiveness.

## Methods

Protocols were developed for systematic reviews of test accuracy and effectiveness 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.

For test accuracy reviews, literature was identified from several sources (up to September 2005 inclusive), including databases: MEDLINE, EMBASE, 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 report. 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 $2 \times 2$ table could be calculated. Quality assessment was based on modified QUADAS criteria. Meta-analyses of likelihood ratios (LRs) were performed using random effects model. In general, the higher the LR+ (i.e. the likelihood ratio for a positive test) was above 1 the more accurate was the test in ruling in the condition while the lower the LR– (i.e. the likelihood ratio for a negative test) was below 1 the more accurate was the test in ruling out the condition.

Effectiveness reviews were identified (up to September 2005 inclusive) from a number of databases including the Cochrane Library (CENTRAL and Cochrane Pregnancy and Childbirth Group trials register), MEDLINE, EMBASE and reference lists of trial reports. Included were randomised or quasi-randomised controlled trials of the relevant intervention compared to placebo, no treatment or usual care in



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any pregnant women that measured spontaneous preterm birth and neonatal complications as outcomes. Quality assessment was as described in the Cochrane Handbook. Meta-analyses were conducted in Review Manager Software, using fixed effect models.

For the economic evaluation, the structure used a decision tree constructed in DATA Treeage software. Four options (test no one and treat all, test all and treat no one, test all and treat only with positive test and test all and treat all) were compared to test no one and treat no one. Inputs to the model were test accuracy and effectiveness systematic review results, test and intervention costs, cost of spontaneous preterm birth as an outcome and the prevalence of spontaneous preterm birth. The primary analysis used point estimates of key parameters of all tests and the most effective interventions. Extensive threshold, deterministic and probabilistic sensitivity analyses were conducted. The outputs were incremental cost-effectiveness ratios for test and treatment combinations.

# Results

## Main findings of test accuracy reviews

For the 22 tests reviewed, the quality of studies and accuracy of tests was generally poor. 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 length measurement and cervicovaginal fetal fibronectin screening for predicting spontaneous preterm birth before 34 weeks' gestation. In this group, tests with LR– point estimates <0.2 were detection of uterine contraction (by home uterine monitoring device) and amniotic fluid C-reactive protein measurement. In symptomatic women with threatened preterm labour tests with LR+ point estimate >5 were absence of fetal breathing movements, cervical length and funnelling, amniotic fluid interleukin-6 (IL-6), serum C-reactive protein (for predicting birth within 2–7 days of testing); and matrix metalloprotease-9, amniotic fluid interleukin-6, cervicovaginal fetal fibronectin and cervicovaginal human chorionic gonadotrophin (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation). In this group, tests with LR– point estimate <0.2 were measurement of cervicovaginal interleukin-8, cervicovaginal human chorionic gonadotrophin, cervical length measurement, absence of fetal breathing movement, amniotic fluid interleukin-6, and serum C-reactive protein (for predicting birth within 2–7 days of testing); and cervicovaginal fetal fibronectin and amniotic fluid interleukin-6 (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation).

## Main findings of effectiveness review

The overall quality of many of the trials included in the 40 interventional topics reviewed was often poor or unclear because of poor reporting. However, a number of interventions did demonstrate some benefit towards preventing spontaneous preterm birth. Although antibiotic treatment was generally not beneficial, those used to treat bacterial vaginosis in women with intermediate flora did significantly reduce the incidence of spontaneous preterm birth. Smoking cessation programmes, progesterone, periodontal therapy and fish oil appeared promising as preventative interventions in asymptomatic women. Non-steroidal anti-inflammatory agents were found to be the most effective tocolytic agent in terms of reducing spontaneous preterm birth and prolongation of pregnancy in symptomatic women, although evidence to support their safety or a reduction in perinatal mortality and morbidity was less convincing. There was insufficient good-quality evidence to assess the use of tocolytic maintenance therapy. Antenatal corticosteroids were found to have a beneficial effect on the incidence of respiratory distress syndrome and the risk of intraventricular haemorrhage (28–34 weeks' gestation), but the effects of repeat courses were unclear because of insufficient data.

## Main findings of economic evaluations

The cost of the tests for both asymptomatic and symptomatic women varied, ranging from £9.50 for venous blood tests like serum interleukin-6 to approximately £216 for an amniocentesis. Similarly the cost of the interventions for asymptomatic women varied, ranging from £1.08 for vitamin C to £1219 for cervical cerclage. In contrast, the cost of all interventions for symptomatic women was significant enough and varied little, ranging from £1645 for nitric oxide donors to £2555 for terbutaline; this was because the cost of hospitalisation was included in the estimate. The

best estimate of additional average cost associated with a case of spontaneous preterm birth was high, at approximately £15,688 for up to 34 weeks' gestation and £12,104 for up to 37 weeks' gestation.

Among women symptomatic of threatened preterm labour, there was insufficient evidence on which to base any firm conclusions for preventing spontaneous preterm birth at 34 weeks' gestation. The deterministic analysis suggested that hydration given to the positive cases tested with amniotic fluid interleukin-6 was the most cost-effective test–treatment combination. Indomethacin to all women without any initial testing was the most cost-effective option for preventing spontaneous preterm birth before 37 weeks' gestation among symptomatic women, delivering the greatest reduction in number of cases of spontaneous preterm birth and this result was produced in both the deterministic and probabilistic sensitivity analysis.

For a woman with symptoms of threatened preterm labour, the most cost-effective test and treatment combination for postponing delivery by at least 48 h, was shown to be the cervical length (15 mm) measurement test with treatment with indomethacin for all those testing positive. Other considered combinations, including treatments using atosiban and nifedipine, were however dominated by indomethacin. Separate data and a separate analysis showed the same test and treatment combination, cervical length (15 mm) measurement test with treatment for all those tested positive with indomethacin, was also the most cost-effective option for postponing delivery by at least 7 days after the test and treatment. These results did not take into account the potential side effects of indomethacin, nifedipine or atosiban on the fetus or mother.

For preventing preterm birth at 34 weeks' gestation among asymptomatic women, the most cost-effective option was to treat all with fish oils without the requirement for any preceding test. This finding was supported by the probabilistic sensitivity analysis but the effectiveness of fish oils requires further investigation because the underlying evidence was based on two relatively small trials. Antibiotic treatment for asymptomatic bacteriuria to all women without any initial testing was the most cost-effective option for preventing spontaneous preterm birth before 37 weeks' gestation among asymptomatic women, delivering the greatest reduction in number of cases of spontaneous preterm birth but this result does not take into account the potential side effects of antibiotics or issues such as resistance if antibiotics were to be provided to all asymptomatic women.

The recommended option for the models in asymptomatic women was to provide treatment to all without a preceding test, but this was because of relatively poor information on inexpensive tests like mammary stimulation and previous history. These and other tests with negligible cost require further investigation. Treatments that require further investigation as a result of our analysis include hydration for symptomatic women, and fish oils, antibiotics for asymptomatic bacteriuria and periodontal therapy for asymptomatic women. Further research is also required for effective tests and treatments to reduce the risk of perinatal mortality as the result of spontaneous preterm birth.

## Conclusions

An effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective approach to reducing spontaneous preterm births among asymptomatic antenatal women in early pregnancy for primary prevention. For secondary prevention among women symptomatic of threatened preterm labour in later pregnancy, a management strategy based on the results of testing is likely to be more cost-effective. It is premature to suggest implementation of a treat-all strategy of simple interventions such as fish oil for asymptomatic women. On the other hand, the case for a universal provision for high-quality ultrasound machine (e.g. for cervical length measurement and/or assessment for the absence of fetal breathing movement) in labour wards is stronger for predicting spontaneous preterm birth among women with a viable pregnancy who present with threatened preterm labour, in order to direct management (involving tocolysis and corticosteroids). Nevertheless, provision for round-the-clock trained personnel to perform such a scan in the interim is lacking. Additionally, the feasibility and acceptability to mothers and health providers of such 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 randomised controlled trials to investigate whether interventions are indeed effective in reducing



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(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 1
# Background

## 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.[1]

## Aetiology of preterm birth

Preterm birth is a heterogeneous condition; up to 30–40% of all cases of preterm birth are the result of 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, intrauterine growth restriction.[2] The remaining 60–70% of preterm births are probably the result of covert or subclinical infective/inflammatory processes, cervical dysfunction, idiopathic (unknown causes), multiple gestations and possible social, nutritional and environmental interactions.[3] This report focuses on this latter group of so-called 'spontaneous' preterm births.

## Consequences of preterm birth

Preterm delivery, particularly that before 34 weeks' gestation, accounts for three-quarters of neonatal mortality and one-half of long-term neurological impairment in children.[4–6] Many of the surviving infants also suffer from other serious short-term and long-term morbidity,[5,7,8] such as respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, retrolental fibroplasia and developmental problems. Even those premature infants that are classified as developmentally 'normal' or as having 'mild' developmental problems, in the longer term have higher rates of multiple problems that affect their lives.[9] Although complications of prematurity are significantly reduced after 32–34 weeks' gestation, minor morbidities, which often lengthen hospitalisation, remain for neonates born between 34 and 37 weeks' gestation.[10–14]

## Clinical burden of preterm birth

Spontaneous preterm birth before 37 weeks' gestation occurs in 7–12% of pregnancies[1,15,16] and it occurs in about 4% of pregnancies before 34 weeks' gestation.[17] Advances in perinatal health care have not reduced the rate of spontaneous preterm birth.[16] Extrapolation from live births data in England and Wales (2004),[18] shows that an estimated 76,000 and 26,000 spontaneous preterm births occur before 37 weeks' and 34 weeks' gestation, respectively.

## Economic burden of preterm birth

Preterm birth has a major and significant direct and indirect cost. There is a direct cost in terms of clinical resource use, e.g. intensive and often prolonged neonatal care as inpatient followed by higher rate of rehospitalisation following discharge,[19,20] and emotional, psychological and financial burdens on the parents who are usually the main carers. There are also indirect costs to society where scarce public resources are used for long-term care of the handicapped premature child and 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. Once information on accuracy and effectiveness become available through systematic reviews, economic modelling will allow the benefit in terms of both human and financial costs to be estimated.



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## Current service provision

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 as at risk, they may be targeted for more intensive antenatal surveillance and prophylactic measures, either 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 by injection or ensuring and maintaining healthy maternal genitourinary tract and periodontal status. Secondary prevention involves 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 those measures aimed at preventing neonatal complications associated with prematurity, e.g. maternal administration of antenatal corticosteroids to accelerate fetal lung maturity. This project is focused on primary prevention but it models the effect on outcomes of primary prevention taking into account secondary and tertiary prevention strategies.

## 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 the institution of timely antenatal interventions. Wrong or delayed diagnosis can put mother and baby at risk of an adverse outcome whereas correct prediction of preterm birth will provide an opportunity to institute effective interventions. This Health Technology Assessment report will address these issues using systematic reviews to estimate the accuracy of tests for predicting spontaneous preterm birth and the effectiveness of interventions in preventing or delaying it. The report will incorporate the output of systematic reviews into decision analyses to determine the optimal management strategies.

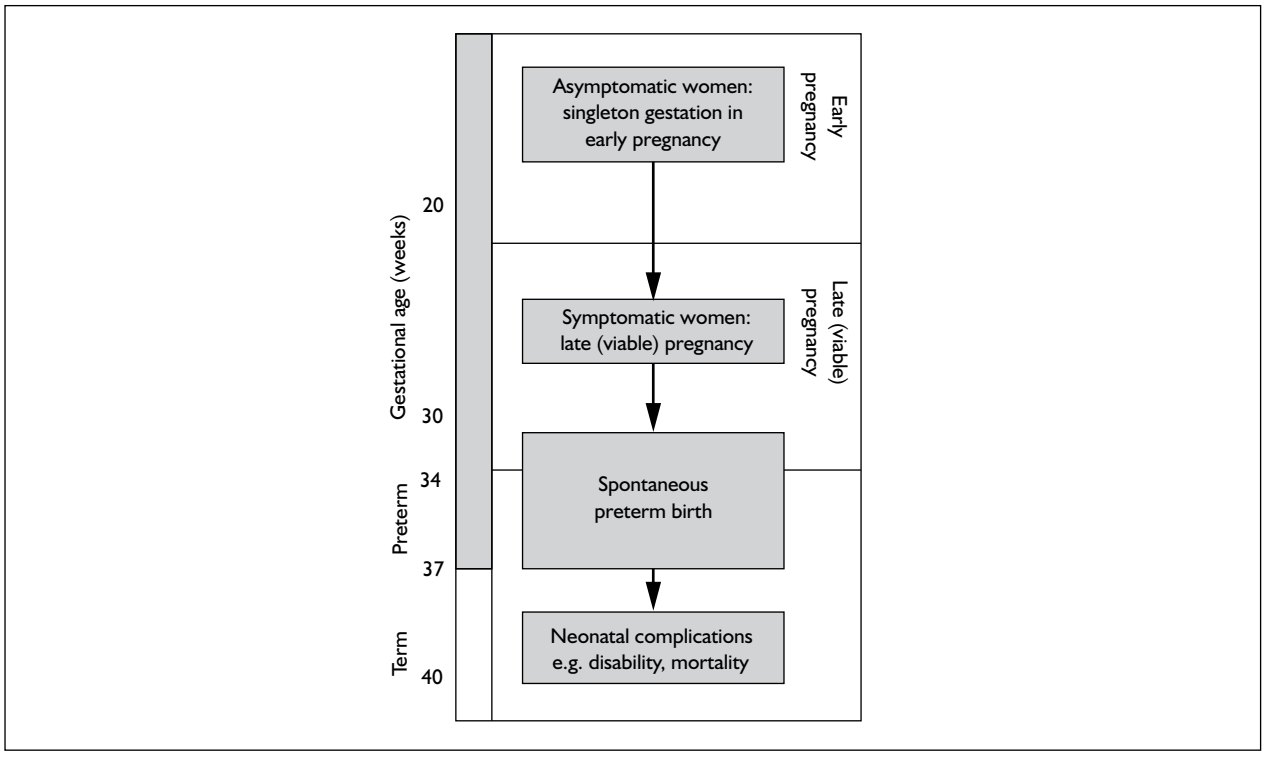


***FIGURE 1*** *Target populations and outcomes in the course of pregnancy.*

Two target populations of pregnant women need to be tested for the risk of spontaneous preterm birth (*Figure 1*). The first is the population of antenatal asymptomatic women carrying a singleton gestation and receiving routine care. In this important, and by far the largest, epidemiological target 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 factors 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 measures 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.

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 because the key clinical decisions following testing relate to immediate management and outcome. For example, if cervicovaginal fetal fibronectin testing could predict spontaneous preterm birth among these women before advanced cervical dilatation,[23] then 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 because it would risk delivery en-route. In such cases, knowledge of a higher likelihood of imminent birth may allow rational use of tocolytic agents, which aim to suppress or diminish contractions allowing time for the administration of antenatal corticosteroids to exert its beneficial effects.[27] Antenatal corticosteroids have maximal effectiveness in preventing neonatal complications of prematurity when delivery is 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.



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# Chapter 2
# Aims and objectives

## Aim

This Health Technology Assessment (HTA) project was undertaken for the National Screening Committee (NSC) to systematically review evidence on tests that identify women with singleton pregnancy who are at risk of spontaneous preterm birth and interventions that prevent or delay birth to allow the institution of treatments to improve neonatal outcome. The output from these reviews was used in economic modelling to determine the most efficient management strategies.

## Objectives

Considering the background and aim, this HTA project 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):
   i. the accuracy of various tests (history, examination and investigations) for predicting the risk of spontaneous preterm birth
   ii. the effectiveness of various interventions for preventing spontaneous preterm birth.
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):
   i. the accuracy of various tests (history, examination and investigations) for predicting the risk of imminent preterm birth
   ii. the effectiveness of various antenatal interventions to delay preterm birth to allow the institution of interventions for improving outcome of the premature neonate.
3. To determine the cost-effectiveness of testing (in antenatal asymptomatic women and symptomatic women) and of the consequent prevention and treatment strategies in terms of both human and financial costs using decision-analytic modelling.

From this work, this HTA project aims to identify areas where evidence is strong enough to generate recommendations for clinical practice. Additionally, it aims to identify key areas and research questions requiring further primary research.



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# Chapter 3
# Methods

## Protocol development

This report 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 project followed key steps involved in diagnostic Health Technology Assessment (HTA).[29–31] Systematic reviews of accuracy and effectiveness of tests and interventions were carried out using contemporaneous methodology,[32–34] which is in line with the recommendations of the Centre for Reviews and Dissemination,[35] and the Cochrane Collaboration including the recommendations of the Cochrane Methods Working Group on Screening and Diagnostic tests.[36]

The strategy for undertaking this HTA review was based on a prospective protocol, which included reviews of existing test accuracy and effectiveness reviews, updating those that were out of date, and performing rapid reviews of topics not reviewed in the literature. A literature search was performed first to identify potentially relevant citations. The search strategy can be found in Appendix 1. The systematic reviews of accuracy, effectiveness and economic literature were then executed initially simultaneously, followed by economic modelling and cost-effectiveness analysis integrating the accuracy and effectiveness data.

Once tests and interventions were identified, and clinically relevant tests and treatment combinations were generated; we sought clinical experts' input for their comments concerning alternative management strategies (see list of experts in the Acknowledgements). We supplied them with a list of tests and interventions and their clinically relevant combinations, and asked whether the list was exhaustive. We also asked them to rank the importance of these tests, interventions and combinations. We provided spaces for comments and opinions if they wished to add these to their replies.

## Research question

We addressed the following structured questions.

### *Populations*

Asymptomatic low-risk pregnant women with singleton gestation in early pregnancy and low-risk women symptomatic for threatened preterm labour with a viable singleton pregnancy. We focussed on singleton pregnancies because multiples fall in a high-risk category that represents a different disease spectrum.

### *Tests*

Options 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 for threatened preterm labour (Appendix 2).

### *Interventions*

Options available to prevent preterm birth in asymptomatic pregnant women and those available to delay delivery in women symptomatic for threatened preterm labour and to improve neonatal outcome for prematurely born infants (Appendix 3).

### *Outcomes*

Spontaneous preterm birth < 37 weeks' gestation and < 34 weeks' gestation in asymptomatic pregnant women, and birth within 24 hours, 48 hours and up to 7–10 days of testing or presentation in women symptomatic for threatened preterm labour. Information on maternal morbidity, neonatal mortality and morbidity, and resource use including admission to neonatal intensive care unit was also sought.

### *Study designs*

1. 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 standard) to generate $2 \times 2$ tables to compute indices of test accuracy.



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2. Randomised controlled trials to assess effectiveness of tests (in combination with interventions) or interventions.
3. Economic evaluations providing cost-effectiveness analyses of tests and interventions outlined above.

## Systematic reviews of accuracy of tests

We first identified existing reviews, assessed them 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, we carried out rapid systematic reviews and updated non-current existing reviews where appropriate.

### Study identification and selection

We undertook a formal search to identify existing reviews of accuracy of tests for preterm birth. The Cochrane Library, the National Research Register (NRR), the 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, 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, ClinicalTrials.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 citations 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 that met the predefined criteria. These criteria were pilot tested using a sample of papers. Disagreements were resolved by consensus 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). Most of the identified reviews were updated, where the experts surveyed for this project 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.

1. *Population* Asymptomatic antenatal women and women symptomatic for threatened preterm labour with singleton gestation to allow interventions that delay delivery and improve neonatal outcome for prematurely born infants.
2. *Index tests* Tests that purported to predict spontaneous preterm birth as described in Appendix 2.
3. *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 report: 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.
4. *Study design* Systematic reviews of test accuracy studies were included; all reviews were of a standard quality accepted by DARE produced by the Centre for Reviews and Dissemination (CRD). For primary studies, we looked for observational cohort studies or, if unavailable, 'case–control' studies of test accuracy.

### 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.[39–42] In addition to using study quality as a possible explanation for differences in results (heterogeneity), the extent to which primary research met methodological standards is important *per se* for assessing the strength of any conclusions that are reached. In the main text of our report, we provide graphical summaries of the five most important quality items while others can be extracted from tables of study characteristics for the individual test (Appendix 5).

Any randomised trials of effectiveness of test–treatment combinations were assessed for validity separate from the diagnostic accuracy studies. Study findings were extracted in duplicate for 10% of randomly selected studies, while the remainder were carried out by one investigator, using predesigned 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. Data extraction was carried out in the context of rapid reviews, where because of the time constraints, missing information was obtained from investigators only if it was crucial to the subsequent analysis and modelling. To avoid introducing bias, unpublished information was coded in the same fashion as the published information.

### Data synthesis

A brief narrative review of findings and quality was undertaken for each test considered. We explored causes of variation in results from study to study (heterogeneity), synthesised results from individual studies (meta-analysis) if appropriate and assessed for funnel asymmetry for publication and related biases. 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 (LRs) and distribution of sensitivity and specificity was assessed in summary receiver operating characteristics (ROC) space (for the latter only those 'more accurate tests' included in the threshold analysis with the relevant clinical outcomes are shown in this report, the remainder are not shown). The latter show the trade-off between sensitivity and specificity across different studies with explicit or implicit variation in thresholds. A general guide for interpreting summary LRs can be found in Chapter 4, *Table 1*.

Subgroup analyses were planned a priori to explore the 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 ten studies in a review to determine their unique contribution, allowing for other factors. Conclusions regarding the typical estimate of accuracy were interpreted cautiously if there was significant heterogeneity.[46]

In addition to meta-analyses that generated summary estimates primarily of LRs; we also estimated sensitivity, specificity and summary ROC curves where in our judgement, they would add to the interpretation of the results.[47] LRs are considered more clinically meaningful as measures of test accuracy[48–50] and would allow estimation of probabilities for use in the decision-analytic modelling. These post-test probabilities can be used to calculate the absolute effects of interventions according to test results.[51] Publication and related biases were assessed using funnel plots of diagnostic odds ratios against corresponding variances among reviews with more than ten studies.[35] 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*.

## Systematic reviews of effectiveness of interventions

Once accurate tests have been identified, women deemed to be at high risk of developing preterm labour may benefit from interventions that are effective in preventing or delaying progression to preterm birth and associated complications of prematurity. When conducting or updating effectiveness reviews we followed existing guidelines[35,52] so that our output would comply with the QUOROM statement.[53]

### Study identification and selection

As part of the study identification process a detailed search of the relevant literatures was conducted. The Cochrane Library, NRR, the HTA database, the National Guideline Clearinghouse and a range of other guideline and effectiveness collections were searched for systematic reviews, guidelines and ongoing research. This included a MEDLINE search using a systematic review methodological filter for the period 2000–2005. The search strategy used can be found in Appendix 1. Update searches were performed for the DARE and the CDSR in August 2005.



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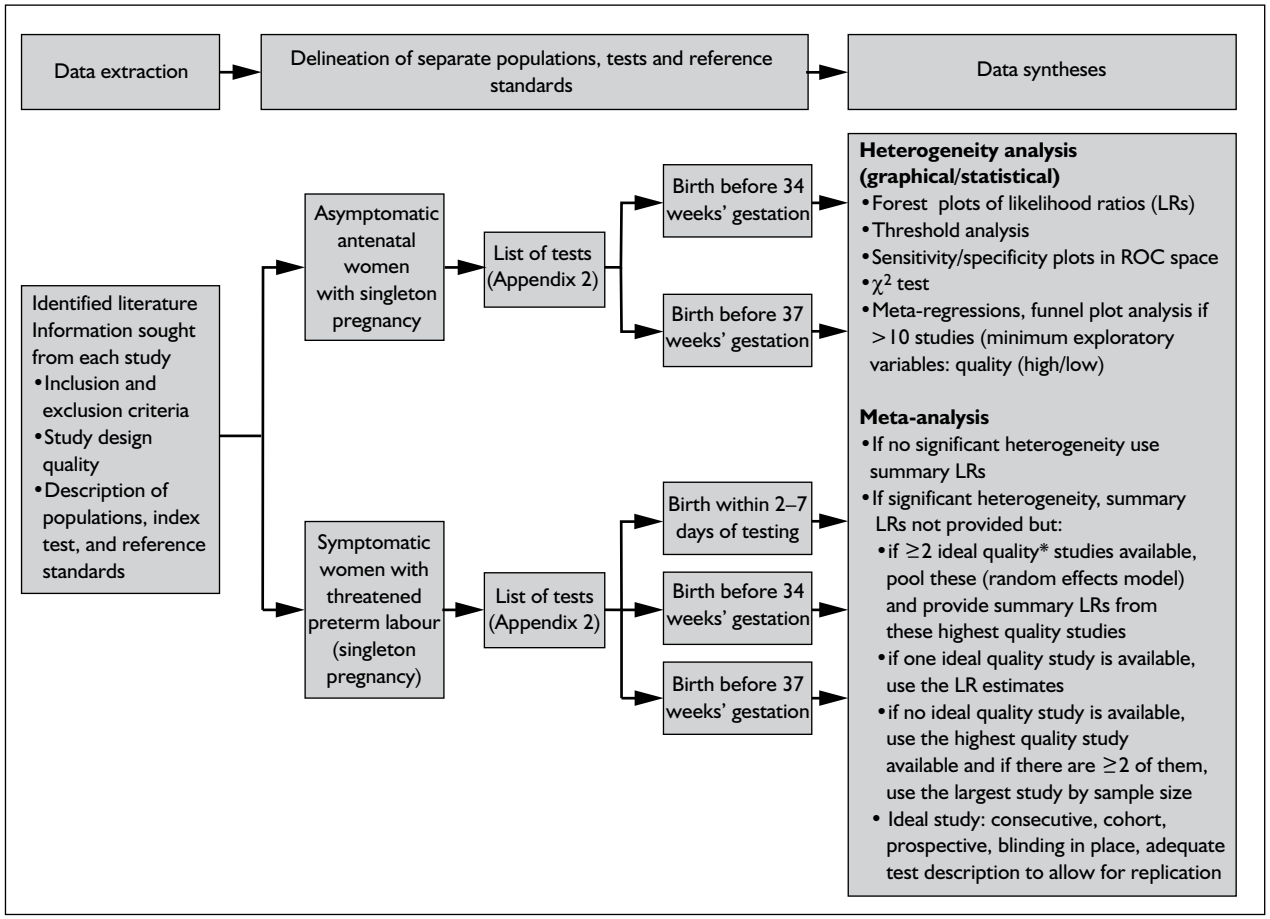


***FIGURE 2*** *Flow chart of procedures for reviews of test accuracy studies. *Ideal study: consecutive cohort, prospective, blinding in place, and adequate test description to allow for replication.*

A search was then undertaken to identify potentially relevant trials. This search was restricted by including a methodological search filter to help identify randomised controlled trials The following databases were searched: MEDLINE, EMBASE, BIOSIS, Pascal, Science Citation Index, CDSR, CENTRAL, DARE and HTA database. 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, SIGLE, Dissertation Abstracts, the NRR, National Technical Information Service (NTIS) and ClinicalTrials.gov.

The search revealed a number of reviews at various levels of currency. Most of the identified reviews were updated, where experts commissioned for this project decided the priority on clinical grounds, and a small number of new rapid reviews were carried out to fill the identified gaps. Two reviewers independently selected studies for inclusion in the review in a two-stage process using predefined and explicit criteria regarding populations, interventions and outcomes using the procedures outlined below. Disagreements were resolved by consensus or arbitration involving a third reviewer.

To be included in updated systematic reviews, primary studies had to fulfil the individual criteria as stated in the original reviews, including the following criteria:

1. *Population* Asymptomatic antenatal women and women symptomatic for threatened preterm labour with singleton gestation to allow interventions, which delay delivery and improve neonatal outcome for prematurely born infants.
2. *Interventions* Interventions and comparators were as described in Appendix 3.
3. *Outcomes* Any outcomes as reported in the individual reviews. However, only data relating to the following outcome measures were used in the report: spontaneous preterm birth <37 weeks' gestation, <34 weeks' gestation; within 24 hours, 48 hours, up to 7–10 days of

presentation; maternal and neonatal mortality and morbidity (adverse event data); and resource use including admission to neonatal intensive care unit. If relevant outcomes were not reported in the original reviews this was noted.

4. *Study design* Systematic reviews of randomised controlled trials (RCTs), quasi-RCTs and controlled trials were included; all reviews were of a standard quality accepted by the DARE. When updating systematic reviews the inclusion criteria for the original review were applied to additional trials. Where new rapid reviews were conducted only RCTs were eligible for inclusion.

### Study quality assessment and data extraction

Quality of evidence was assessed on two levels: (1) at the level of systematic reviews and (2) at the level of the primary studies included in the reviews. All of the included systematic reviews were of a given standard quality accepted by DARE. The DARE approach to assessing the validity of the individual review considers various factors important to the method of conducting systematic reviews, such as: a well-defined research question, clear inclusion and exclusion criteria, a detailed search strategy, assessment of validity, and provision of sufficient details of the primary studies included in the review. Validity assessment considered factors associated with bias in such trials, e.g. concealment of randomisation, sequence generation, follow-up and blinding. The extent to which primary research met methodological standards is important *per se* for assessing the strength of any conclusions that are reached.

Two reviewers independently assessed the quality of each study; disagreements were resolved by consensus or arbitration involving a third reviewer. Findings of studies were independently extracted by one reviewer and checked by a second reviewer using predesigned and piloted data extraction forms for effectiveness studies (Appendix 4). The structure for the extraction form for existing systematic reviews was taken from DARE abstract guidelines, and covered the following areas: review details, methodology, including search, inclusion/exclusion criteria, procedures for study selection and data extraction, validity assessment and synthesis, results and conclusions. Summary variables were entered onto Microsoft Word tables. The presentation and content of the extraction table was consistent across intervention topics. The economic extraction form included the following data for input into the economic model: summary estimates [relative risk (RRs)] of effectiveness, variation in outcome (e.g. as the result of specific risk factors), adverse effects and resource use. Procedures for obtaining missing information and resolving disagreements were similar to the ones outlined above.

### Data synthesis

A brief narrative of review findings and quality was generated for each intervention considered. For the existing reviews, summary estimates (RRs) of the treatment effects were extracted in relation to the primary outcomes of spontaneous preterm birth, together with 95% confidence intervals (95% CI) if these were reported. Data were re-analysed and any anomalies were corrected; where appropriate, subgroups were analysed. If a narrative synthesis had been carried out a concise summary of the main results has been presented. Where additional relevant trials were found, numerical estimates for each identified trial were extracted and the summary estimates of the existing review were recalculated, incorporating the new data. Where singleton and multiple gestations were pooled, data from singletons were extracted separately if possible, or studies were excluded. Heterogeneity of results between studies was statistically assessed where appropriate. Conclusions regarding the typical estimate of an effect of intervention were interpreted cautiously if there was significant heterogeneity. Where no previous reviews exist, numerical estimates from all identified trials were extracted and, if appropriate, summarised by meta-analysis. Revman version 4.1 and Stata version 8.2 software were used in the statistical analyses. The former allows uniformity with Cochrane reviews and the latter allows the data analytic flexibility that was not included in the Revman software.

## Economic evaluation

This consisted of a systematic review of existing economic evaluation and a model-based analysis incorporating information extracted from the accuracy and effectiveness reviews. The search strategy was adapted to focus on economic evaluations using terms adapted from the strategies used to identify studies for inclusion in National Health Service Economic Evaluation Database (NHS EED; see http://nhscrd.york.ac.uk/nfaq2.htm). In addition, the two predominant economic evaluation databases were searched: NHS EED



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and Health Economic Evaluations Database (HEED). Searches for economic working papers were undertaken using the Internet Documents in Economics Access Service (IDEAS) database. Additional searches were undertaken to provide a range of evidence to help populate the decision model. Information to answer these questions was provided by focused searching of appropriate databases, statistical sources and other sources of relevant information.[54]

The objective of searching the economic literature was to identify studies reporting costs and consequences associated with preterm birth, which provided estimates for a comparison with a 'do nothing' option. Cost information associated with the consequences of preterm birth was identified in the literature.[55–61] The review of economic studies aided the identification of quality of life information that could be used to estimate the proposed secondary outcome of cost per Quality Adjusted Life Year (QALY). Cost data were collected from two principal sources. First from the clinical evidence synthesised into the main strategies of diagnosis and treatment, where relevant studies were examined for their data on costs and resource use. These data were subject to relevant quality criteria. Second, additional cost data were obtained from sources such as the National Schedule for Reference Costs. Primary cost and resource data were collected from Birmingham Women's Hospital, when there were gaps in the information required for the modelling process, to enable estimations of relative cost-effectiveness of different strategies. Appropriate sensitivity analysis, such as probabilistic sensitivity analysis, was carried out where required. The modelling framework allowed simple decision strategies associated with one screening test and one possible intervention to be evaluated. Where information on the correlation between packages of tests and correlation between packages of treatments was available from the reviews, the framework allowed these more complex strategies to be evaluated, as well as strategies that allow alteration in the form of repeated testing.

The economic evaluation took the form of a cost-effectiveness analysis within a decision-analytic framework based on a primary outcome of cost per case of spontaneous preterm birth avoided. Where possible, and depending on the information available in the reviews, this principal outcome was desegregated into two further outcomes of cost per case of spontaneous preterm birth before 34 weeks' and before 37 weeks' gestation avoided. There is a significant cost and consequence impact associated with births at these different times.[4] Combining the results from the model with additional information from the reviews on neonatal morbidity in cases of spontaneous preterm birth allowed prediction of outcomes in terms of cost per neonatal mortality avoided. The comparator was a policy of no screening/testing and no interventions. If suitable data on neonatal morbidity became available from the reviews then a secondary outcome of cost per QALY associated with each alternative combination of screening/testing and intervention was estimated. The economic evaluation adopts the perspective of the NHS and so private costs to patients associated with the proposed screening and intervention were not included.

The evidence found in the clinical accuracy and effectiveness reviews provided the majority of the parameters required to perform the economic evaluations of alternative tests and interventions. The data were synthesised to construct a decision-analytic model. The model allows comparisons of various strategies of screening tests for risk of spontaneous preterm birth, e.g. bedside cervicovaginal fetal fibronectin testing and interventions to prevent spontaneous preterm birth, e.g. progestational agents, in terms of their relative effectiveness and cost. Alternative combinations of screening or diagnostic tests were paired with appropriate alternative interventions and explored by the decision modelling, to calculate the costs and consequences for each combination. A decision tree was the chosen modelling approach for this evaluation because the time horizons available for both the screening or diagnostic tests and the interventions, being within the duration of the pregnancy, are relatively short.

The number of possible combinations assessed in the modelling framework depended on the results of the reviews. In the event that the reviews reveal a large number of relevant studies on accurate screening tests and effective interventions, the group intended to attempt to prioritise the number of modelling scenarios having sought approval of the National Screening Committee (NSC).

## Modifications to the protocol and original grant proposal

Following approval of this HTA project, a systematic review (periodontal assessment in pregnant women) appeared in the literature that impacted on our plans (i.e. it needed to

be included in our reviews), having not been considered at bid-proposal stage. Its inclusion was crucial because within the NHS periodontal care is free at the point of delivery to pregnant women, so our assessment may have an impact on the delivery of the service. A review of interventions to promote smoking cessation in pregnant women was also included as a protocol amendment. The clinical experts we consulted suggested reviews that we may consider abandoning either for historical reasons or because of their irrelevance to UK clinical practice. They also suggested additional reviews. However, in view of the deadline imposed by the HTA and the fact that we have included two additional effectiveness reviews (periodontal assessment and smoking cessation), we were unable to fulfil the additional requests. Otherwise, there were no other protocol modifications to the submitted proposal.

## Report structure

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



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# Chapter 4

# Results of reviews of accuracy of tests

A list of tests reviewed can be found in Appendix 2. We divided the reviews of test accuracy into history, examination and investigations. *Figure 3* shows the process of identification of literature reviews for test accuracy studies.

## Identification of accuracy literature

### 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 scans, this history can be accurately assessed at the antenatal booking consultation.

#### *Study characteristics and quality*

There were ten studies evaluating the accuracy of previous history of spontaneous preterm birth among asymptomatic antenatal women in predicting spontaneous preterm birth in the subsequent pregnancy ($n = 55{,}885$).[62–71] One study[72] was excluded on closer inspection because it used the same population as another included study.[68] Appendix 5, *Table 68* summarises 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 multiple episodes of spontaneous preterm birth. Two studies evaluated the accuracy of previous history of two versus one spontaneous preterm birth,[65,71] while one study evaluated the accuracy of gestation at which the previous spontaneous preterm birth occurred in predicting spontaneous preterm birth in a subsequent pregnancy.[69]

None of the studies fulfilled our criteria for an ideal quality study (consecutive, cohort, prospective, blinding in place, and adequate test description to allow for replication). None of the studies reported blinding and consecutive enrolment. The quality features are summarised in *Figure 4*. Aside from three studies,[64,66,68] 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 a likelihood ratio for a positive test result (LR+) of 4.62 [with 95% confidence interval (95% CI) 3.28–6.52] and a likelihood ratio for a negative test result (LR–) of 0.68 (95% CI 0.56–0.82),[66] which was used in the decision-analytic modelling. 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)[65] with one previous spontaneous preterm birth to 10.12 (95% CI 4.54–22.59)[65] with two previous spontaneous preterm births, and a range of LR– from 0.45 (95% CI 0.33–0.61)[69] with previous history of spontaneous preterm birth before 26 weeks' gestation to LR– of 1.38 (95% CI 1.27–1.49)[65] with one previous spontaneous preterm birth. However, LR+ of 2.26 (95% CI 1.86–2.74) and LR– of 0.72 (95% CI 0.64–0.81) from Goldenberg *et al.*[68] were used in the decision-analytic modelling as it represented the largest higher-quality study. The accuracy of previous history of spontaneous preterm birth in predicting subsequent spontaneous preterm birth is shown in *Figure 5* while individual accuracy data are summarised in Appendix 5, *Table 69*.

## 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 women with threatened preterm labour to predict spontaneous preterm birth has not been evaluated.

### Study characteristics and quality

There were ten studies that evaluated the accuracy of cervical digital examination in predicting spontaneous preterm birth, nine in asymptomatic antenatal women ($n = 12{,}325$)[73–81] and one in symptomatic women ($n = 90$) with threatened preterm labour.[82] There were variations in testing



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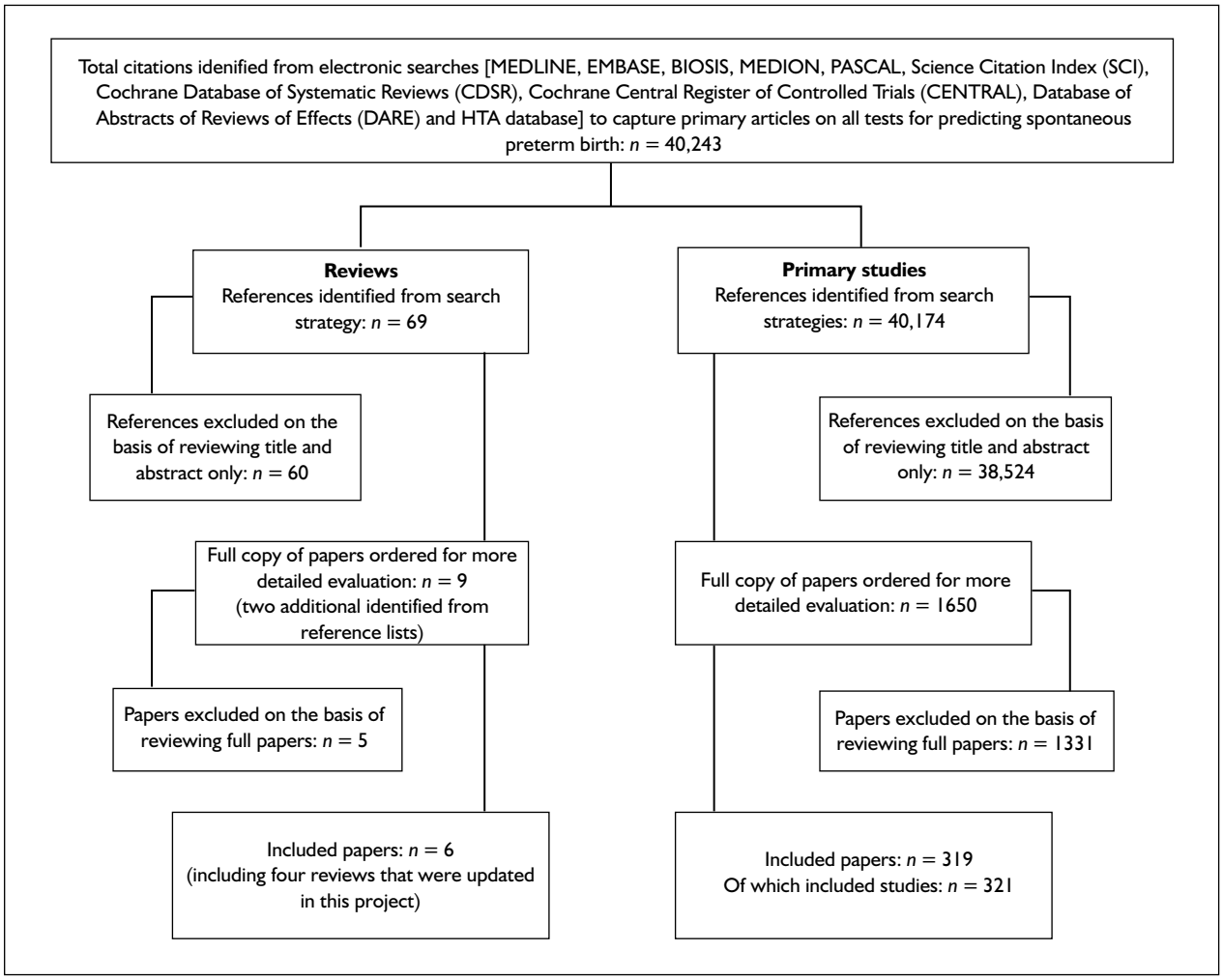


***FIGURE 3*** *Identification of accuracy literature – systematic review.*

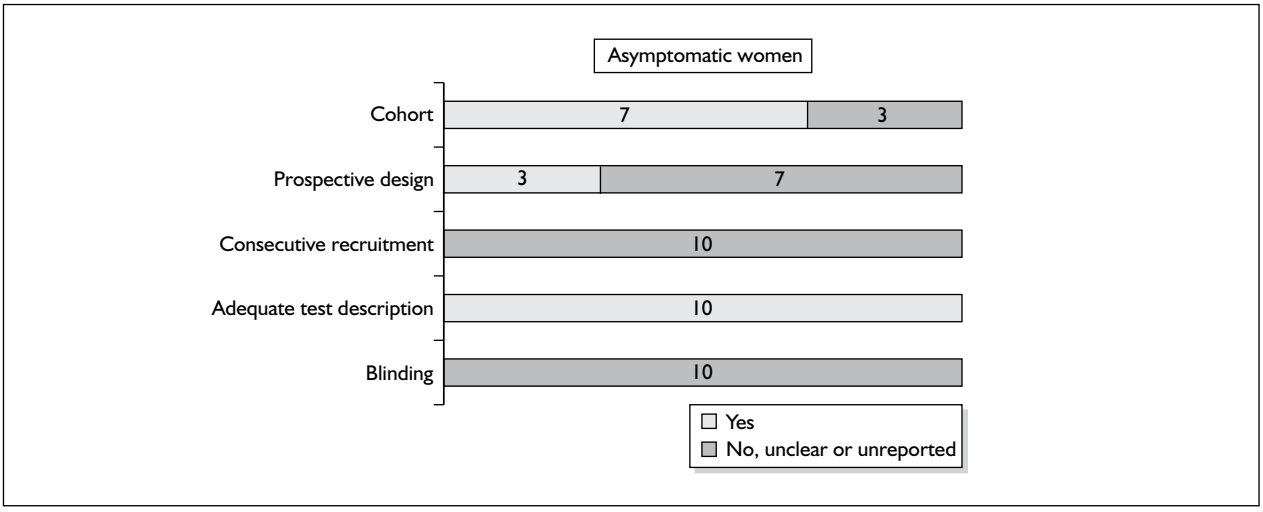


***FIGURE 4*** *Methodological quality of studies of previous history of spontaneous preterm birth in predicting subsequent spontaneous preterm birth included in the systematic review. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

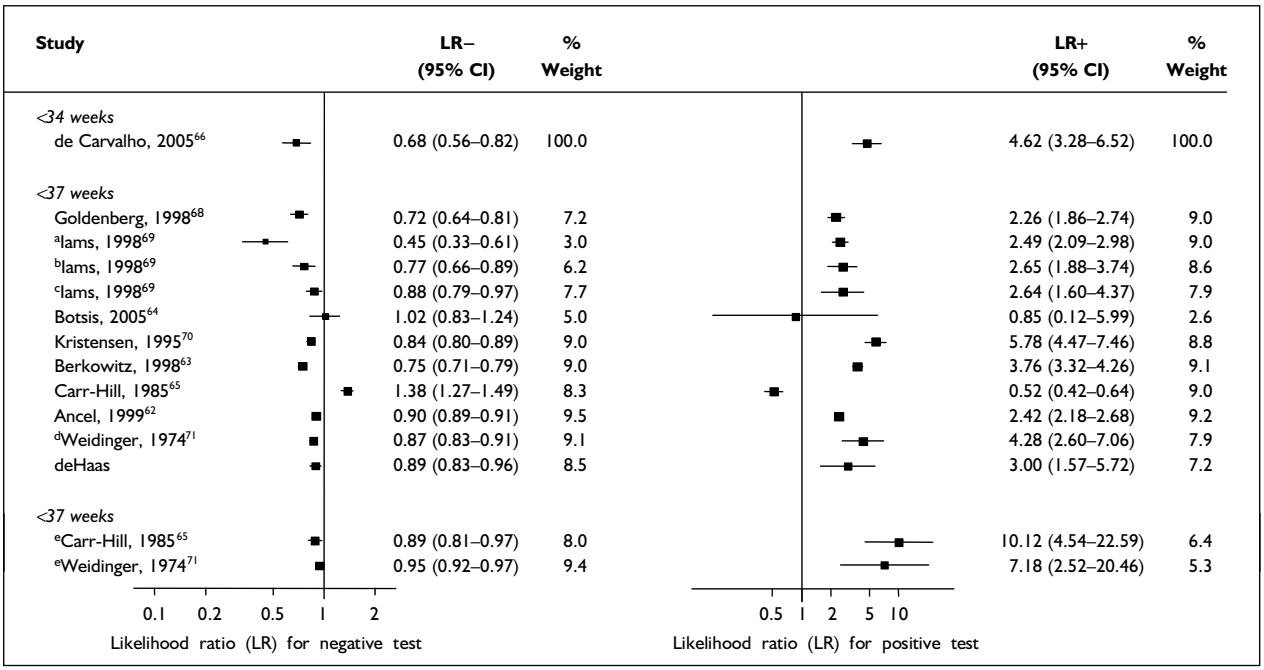


***FIGURE 5*** *Forest plots of likelihood ratios (LRs) of the accuracy of previous history of spontaneous preterm birth in asymptomatic women for predicting spontaneous preterm birth stratified according to outcome gestation. $\chi^2$ heterogeneity test $p = 0.000$ for LR+ and LR– of spontaneous preterm birth before 37 weeks' gestation. Studies are listed in descending order of quality. a, Previous spontaneous preterm birth before 26 weeks' gestation. b, Previous spontaneous preterm birth before 31 weeks' gestation. c, Previous spontaneous preterm birth before 36 weeks' gestation. d, One previous spontaneous preterm birth. e, Two previous spontaneous preterm births.*

gestation, frequency of testing and threshold selection among the included studies. Noticeably, for all of the studies, testing gestation commenced after 24 weeks' gestation, currently accepted as the lower limit of neonatal viability. Aside from three studies, which used birth before 34 and 35 weeks' gestation[76–78] as their outcome measurement, the studies used 37 weeks' gestation. Individual study characteristics are summarised in Appendix 5, *Table 70*.

One study fulfilled our criteria for an ideal quality study;[77] the remaining studies lacked one or more criteria for an ideal quality study with consecutive enrolment being the most commonly absent feature. Blinding was only reported by four studies in asymptomatic women. The methodological quality of the included studies is summarised in *Figure 6*.

## 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 7*). For predicting spontaneous preterm birth before 34 weeks' gestation, digital examination showed an LR+ of 9.25 (95% CI 3.91–21.85) and LR– of 0.46 (95% CI 0.19–1.08) in a mixed population of nulliparous/multiparous antenatal asymptomatic women and a threshold of >2 cm cervical dilatation.[77] These LRs were used in the decision-analytic modelling. 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[80] to 9.17 (95% CI 0.52–160.08) in a mixed population of nulliparous/multiparous antenatal asymptomatic women with a centrally positioned cervix and >1.5 cm dilatation,[75] and LR– ranged from 0.42 (95% CI 0.26–0.68) in nulliparous antenatal women with a soft cervix[73] 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.[75] However, an LR+ of 1.15 (0.86–1.53) and LR– of 0.89 (0.68–1.16) from Parikh *et al.*,[79] who evaluated digital examination in a mixed population of nulliparous/multiparous women using the threshold of admitting a finger at the cervical internal os, was used in the decision-



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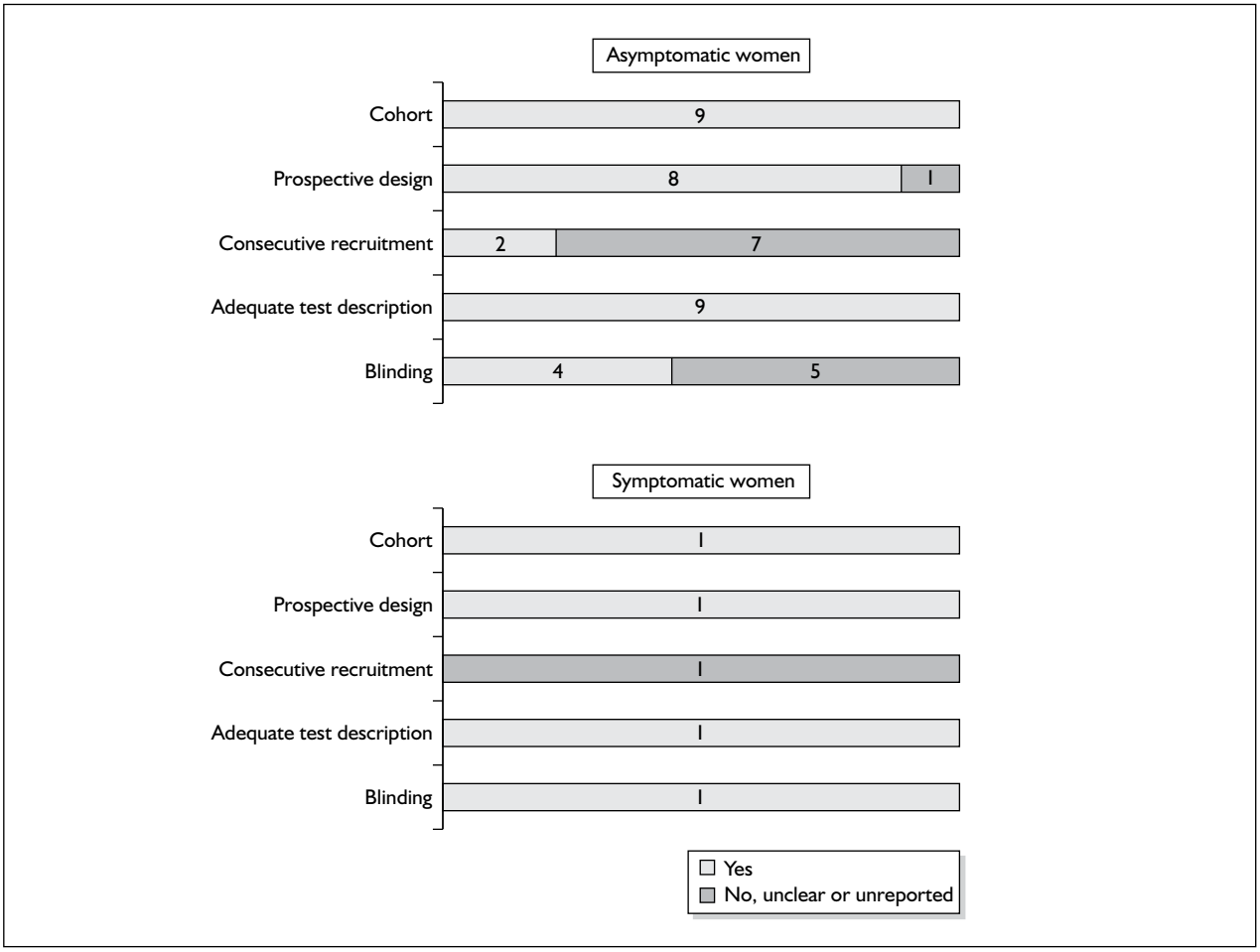



***FIGURE 6*** *Methodological quality of studies included in the systematic review of accuracy of digital examination in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

analytic modelling because it represented a higher-quality methodological study. Individual accuracy results are summarised in Appendix 5, *Table 71*.

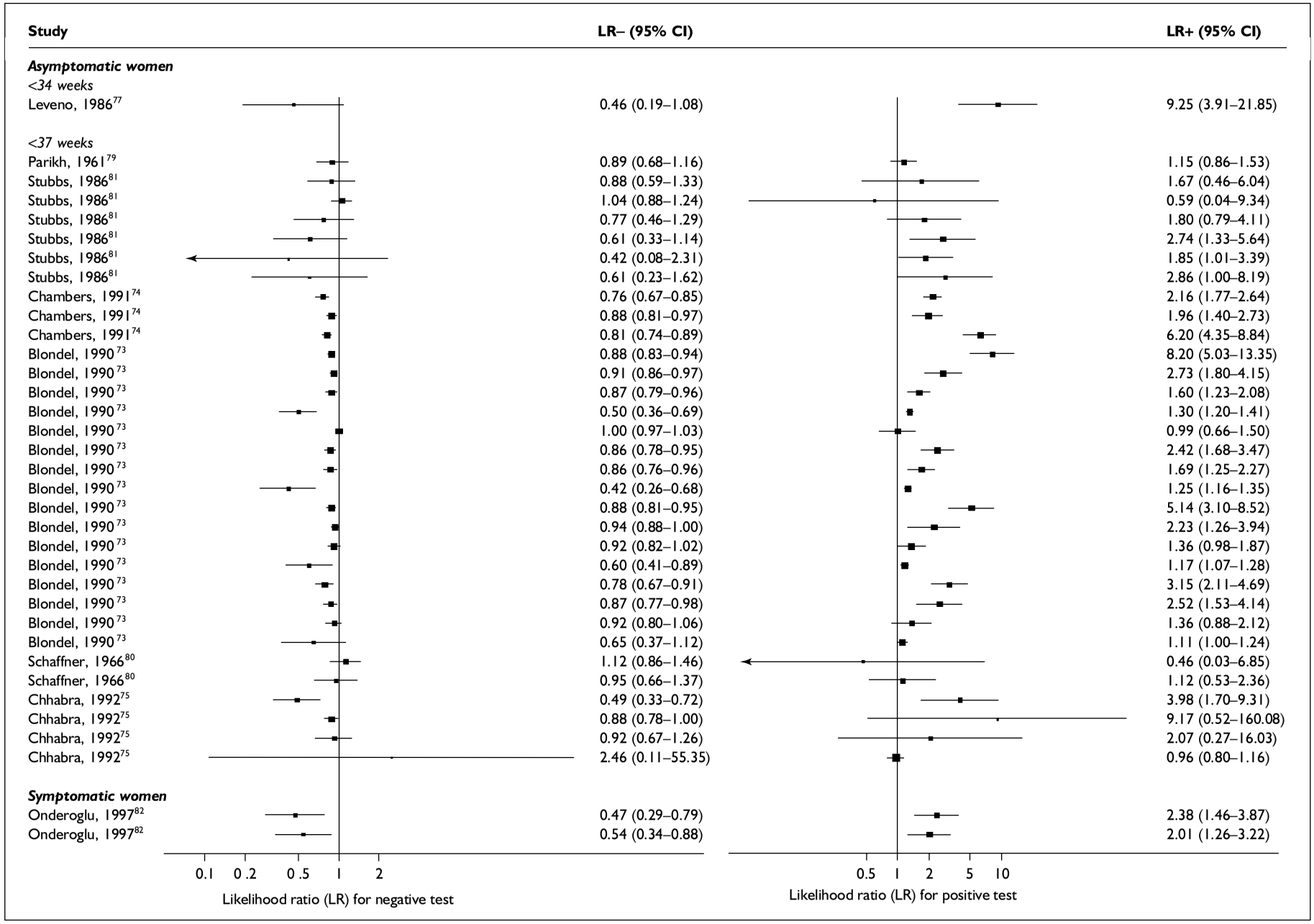
## Accuracy of digital examination in symptomatic women

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 of >2 cm cervical dilatation or >40% effacement (the latter threshold corresponded to the less accurate results).[82] These values were used for the decision-analytic modelling. Individual accuracy results are summarised in Appendix 5, *Table 71*.

## Cervicovaginal fetal fibronectin

Cervicovaginal fetal fibronectin (fFN) is a glycoprotein, present in trace quantities, that is usually undetectable in the cervicovaginal secretion. A higher quantity has been purported to be an indication of imminent labour onset. The test is readily available in the form of a commercial rapid test kit. A cotton swab is used to collect samples of cervicovaginal 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

***FIGURE 7*** *(opposite) Forest plots of likelihood ratios (LRs) of digital examination in predicting spontaneous preterm birth as a predictor of spontaneous preterm birth. No weights attached because of multiple contributions of subjects within a particular study evaluating different thresholds.*

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the test. These commercial preparations used a positivity threshold of 50 ng/ml.

## Study characteristics and quality

There were 58 primary studies ($n = 22,905$ women) on the accuracy of bedside cervicovaginal fFN testing, comprising 18 studies on asymptomatic antenatal women ($n = 18,696$) and 40 studies on symptomatic women presenting with threatened preterm labour ($n = 4209$). Appendix 5, *Table 72* 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. The enrolment for the studies ranged from 20 to 6508 women[83,84] with a median of 147 women in asymptomatic populations, and from 26 to 725 women[85,86] with a median of 86 women for the symptomatic women. All the studies had used cervicovaginal fFN specimens taken from either the posterior fornix or the cervix.

There were three studies in asymptomatic women[87–89] and five studies in symptomatic women that fulfilled our definition of high-quality test accuracy studies.[85,90–93] The methodological quality of the included primary studies is summarised in *Figure 8*. There were 7 and 15 studies that reported the accuracy of the test for predicting spontaneous preterm birth before 34 weeks'[83,88,94–98] and 37 weeks' gestation[83,84,87,89,94,95,97,99–106] respectively in asymptomatic women. For symptomatic women presenting with threatened preterm labour, 17 studies[86,90,92,93,107–119] reported the accuracy of the test in predicting spontaneous preterm birth within 7–10 days of testing in addition to eight studies that reported birth before 34 weeks'[93,114,120–125] and 31 studies [85,86,90,91,93,103,104,106–109,111,113–115,117,119,122–124,126–136] that reported birth before 37 weeks' gestation.

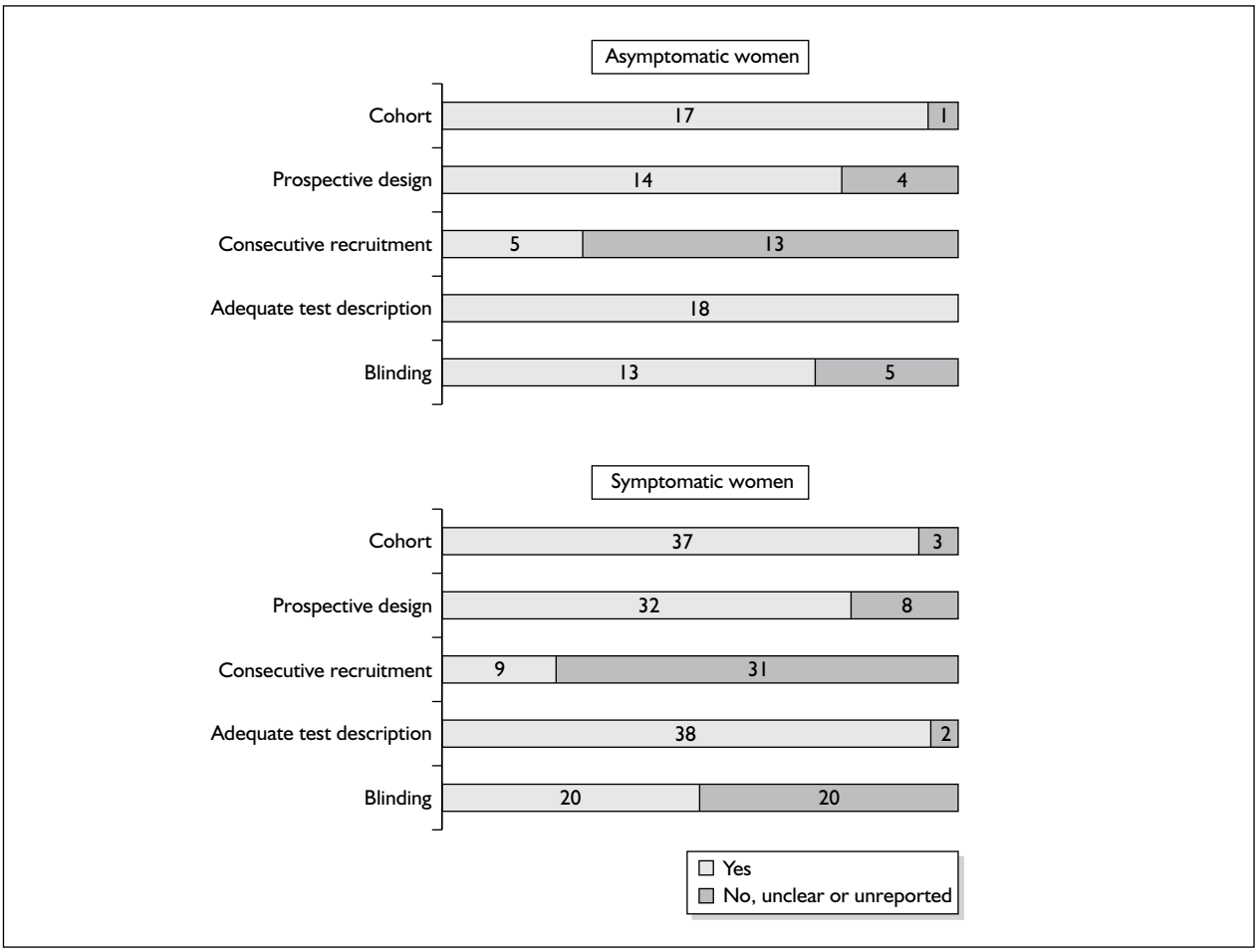


***FIGURE 8*** *Methodological quality of studies included in the systematic review of accuracy of bedside test for cervicovaginal fetal fibronectin in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

### 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 3.93–14.86) ($\chi^2$ heterogeneity test $p = 0.00$) 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) ($\chi^2$ heterogeneity test $p = 0.08$) (*Figure 9*). For predicting spontaneous preterm birth before 37 weeks' gestation, the range of LR+ was from 0.43 (95% 0.07–2.78) to 26.38 (95% 1.73–402.99) with a summary LR+ of 3.17 (95% 2.00–5.02) ($\chi^2$ heterogeneity test $p = 0.00$) and the range of LR– was from 0.28 (95% 0.03–3.07) to 1.20 (95% 0.93–1.54) with a summary LR– of 0.87 (95% 0.77–0.97) ($\chi^2$ heterogeneity test $p = 0.00$) (*Figure 10*). Individual test accuracy results from the included studies for asymptomatic women can be found in Appendix 5, *Table 74*.

### Accuracy of fFN in symptomatic women

For predicting spontaneous preterm birth within 7–10 days of testing, the range of LR+ was from 2.12 (95% 1.05–4.28) to 9.29 (95% 5.06–17.06) with a summary LR+ of 4.10 (95% 3.37–4.98) ($\chi^2$ heterogeneity test $p = 0.00$) and the range of LR– from 0.09 (95% 0.01–0.58) to 0.59 (95% 0.25–1.39) with a summary LR– of 0.35 (95% 0.27–0.46) ($\chi^2$ heterogeneity test $p = 0.322$) (*Figure 11*). For predicting spontaneous preterm birth before 34 weeks' gestation, the range of LR+ was from 1.57 (95% 0.53–4.60) to 5.70 (95% 2.88–11.28) with a summary LR+ of 3.58 (95% 2.56–5.00) ($\chi^2$ heterogeneity test $p = 0.05$), and the range of LR– from 0.12 (95% 0.02–0.79) to 0.91 (95% 0.69–1.20) with summary LR– of 0.34 (95% 0.17–0.68) ($\chi^2$ heterogeneity test $p = 0.00$) (*Figure 12*). For predicting spontaneous preterm birth before 37 weeks' gestation, the range of LR+ was from 1.00 (95% 0.44–2.30)[85] to 14.36 (95% 5.81–35.47)[117] with summary LR+ of 3.62 (95% 3.02–4.33) ($\chi^2$ heterogeneity test $p = 0.00$), and the range of LR– from 0.08 (95% CI 0.01–0.54)[124] to 1.00 (95% 0.44–2.30)[85] with a summary LR– of 0.50 (95% 0.43–0.59) ($\chi^2$ heterogeneity test $p = 0.00$) (*Figure 13*). A receiver operating characteristics (ROC) plot of sensitivity versus specificity for cervicovaginal fFN in symptomatic women is shown in *Figure 14* and *Figure 15*. Individual test accuracy results from the included studies for symptomatic women can be found in Appendix 5, *Table 73*.

## Cervicovaginal 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 cervicovaginal prolactin is a reliable predictor of the onset of spontaneous preterm labour and hence of spontaneous preterm birth.[137] A cotton swab is used to collect samples

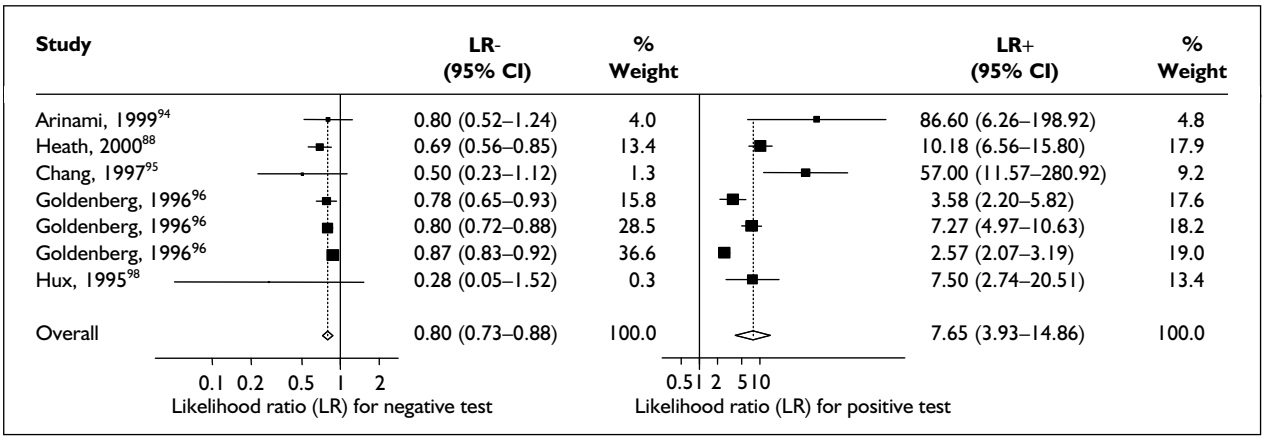


***FIGURE 9*** *Forest plots of likelihood ratios (LRs) for cervicovaginal fetal fibronectin bedside testing on asymptomatic antenatal women as a predictor of spontaneous preterm birth before 34 weeks' gestation. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test p = 0.00 for LR+ and p = 0.08 for LR–.*



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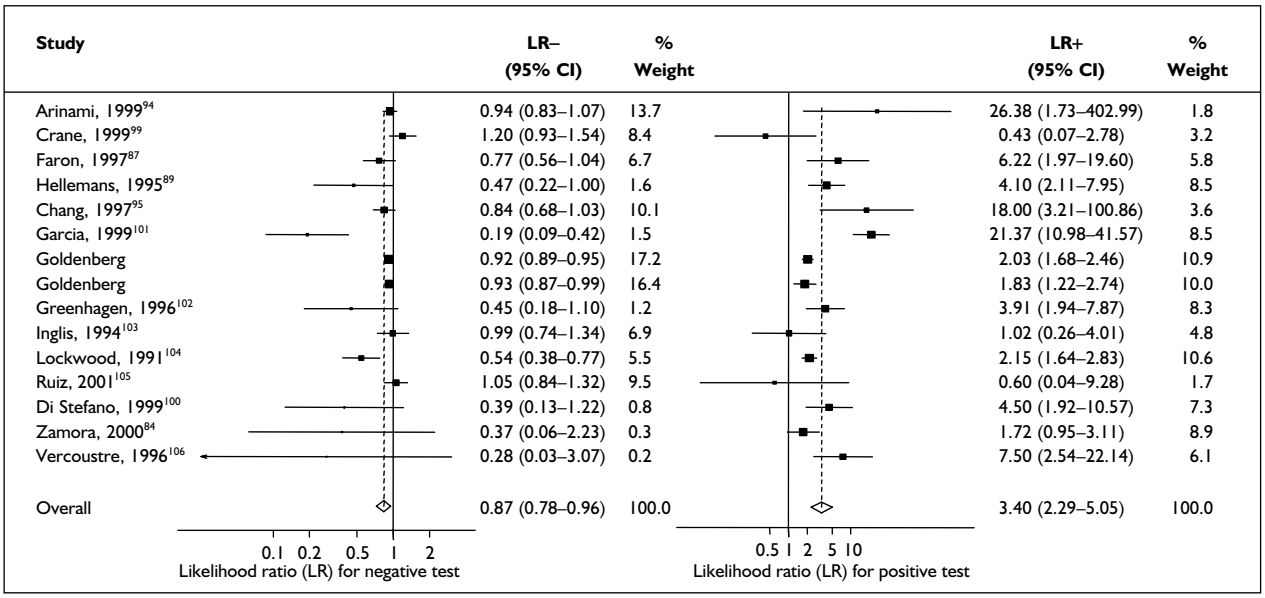


***FIGURE 10*** *Forest plots of likelihood ratios (LRs) for cervicovaginal fetal fibronectin bedside testing on asymptomatic antenatal women as a predictor of spontaneous preterm birth before 37 weeks' gestation. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test $p = 0.000$ for LR+ and $p = 0.000$ for LR–.*

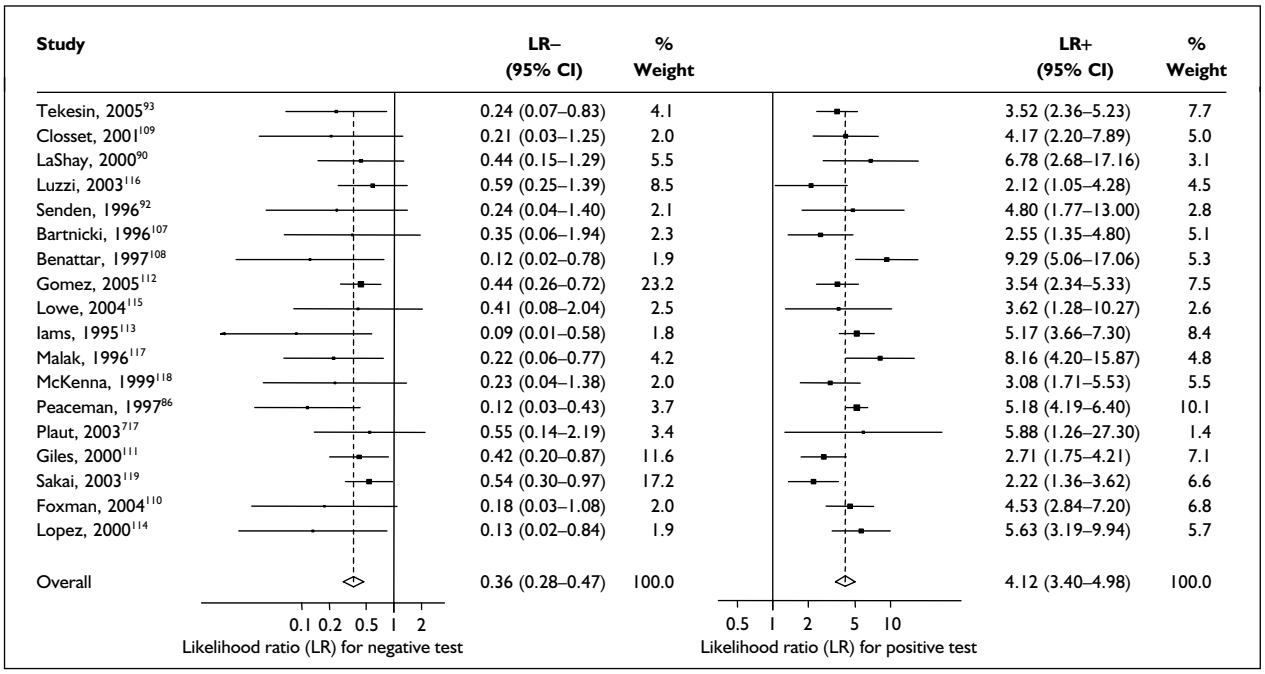


***FIGURE 11*** *Forest plots of likelihood ratios (LRs) for cervicovaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth within 7–10 days of testing. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test $p = 0.002$ for LR+ and $p = 0.424$ for LR–.*

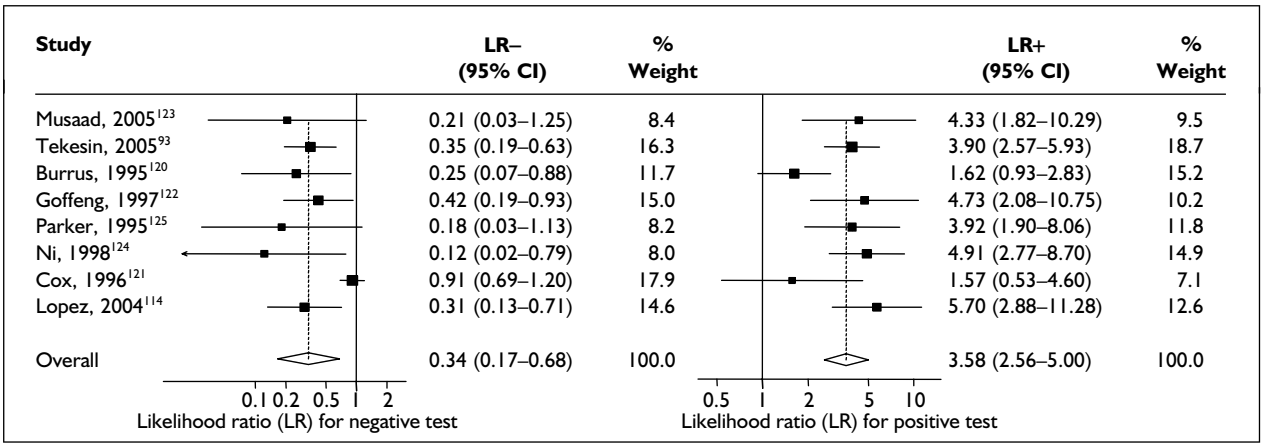


***FIGURE 12*** *Forest plots of likelihood ratios (LRs) for cervicovaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 34 weeks' gestation. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test $p = 0.052$ for LR+ and $p = 0.000$ for LR–.*

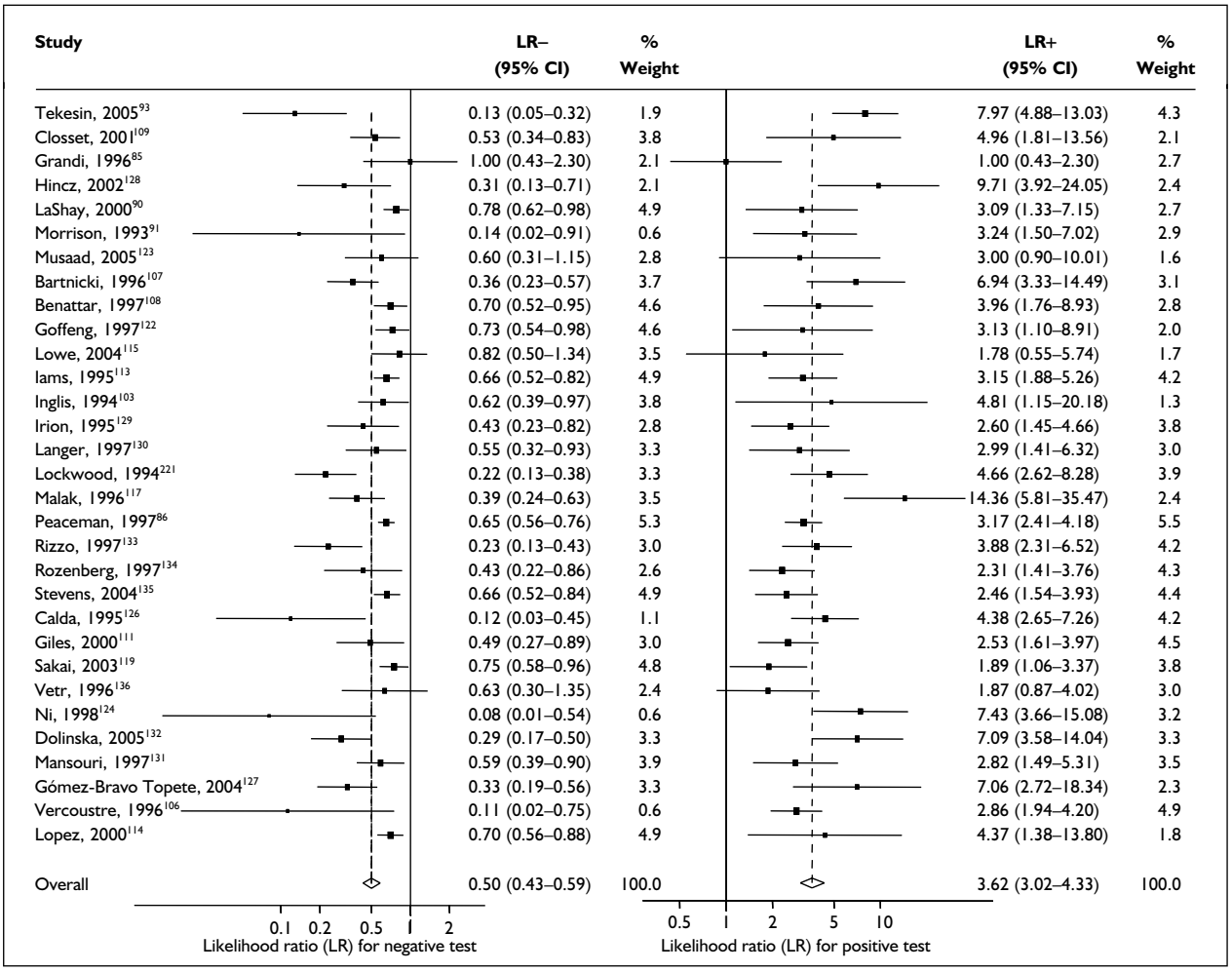


***FIGURE 13*** *Forest plots of likelihood ratios (LRs) for cervicovaginal fetal fibronectin bedside testing on women presenting with symptoms of threatened preterm labour as a predictor of spontaneous preterm birth before 37 weeks' gestation. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test $p = 0.000$ for LR+ and $p = 0.000$ for LR–.*



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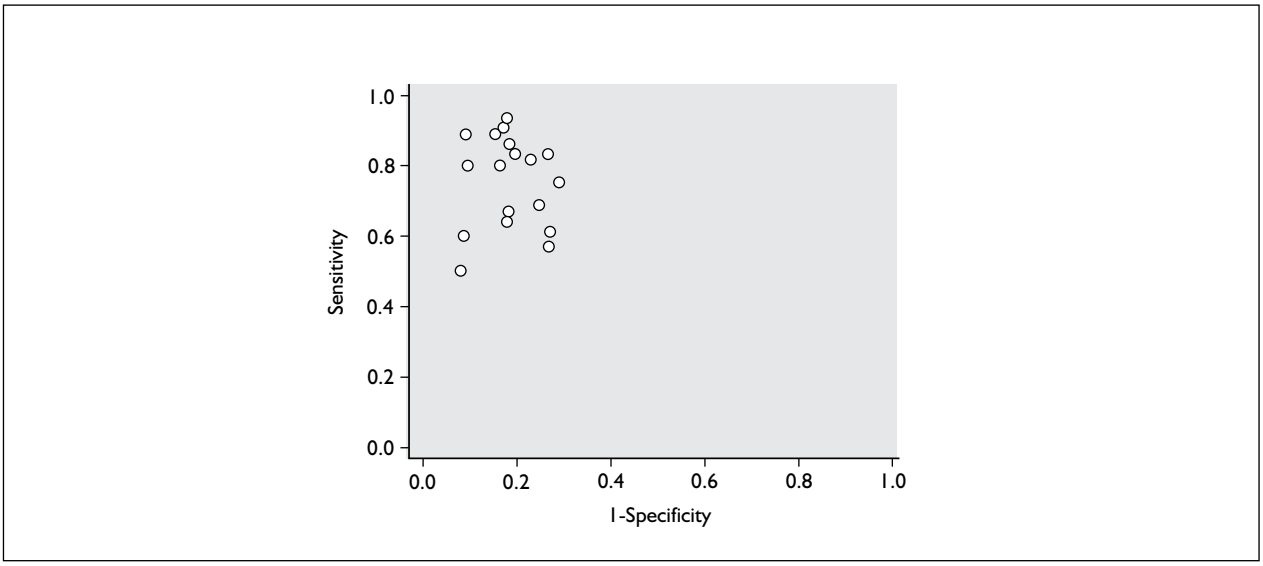


***FIGURE 14*** *Plot of sensitivity versus 1-specificity in ROC space for cervicovaginal fibronectin studies in symptomatic women with threatened preterm labour for predicting spontaneous preterm birth within 7 days of testing.*

of cervicovaginal secretions during a speculum examination, which was then sent for laboratory assay.

## Study characteristics and quality

There were five primary studies, two evaluating the test in a population of asymptomatic women ($n = 80$)[137,138] and five evaluating the test in symptomatic women ($n = 265$),[137–141] presenting with threatened preterm labour, including two studies that evaluated the test in both populations.[137,138] The study enrolment ranged from 35 women[138] to 66 women.[141] In asymptomatic women, the test was performed between 24 and 32 weeks' gestation. The study enrolment for asymptomatic women ranged from 35 to 66 women[138,141] with a median of 40 women.[137] Only two studies, both in symptomatic women, used the same threshold of abnormality of 2.0 ng/ml.[137,140] The remaining studies used 1.5 ng/ml,[138] 1.8 ng/ml[139] and 50 ng/ml thresholds.[141] All the studies evaluated cervicovaginal prolactin test on a single occasion rather than as a serial test.

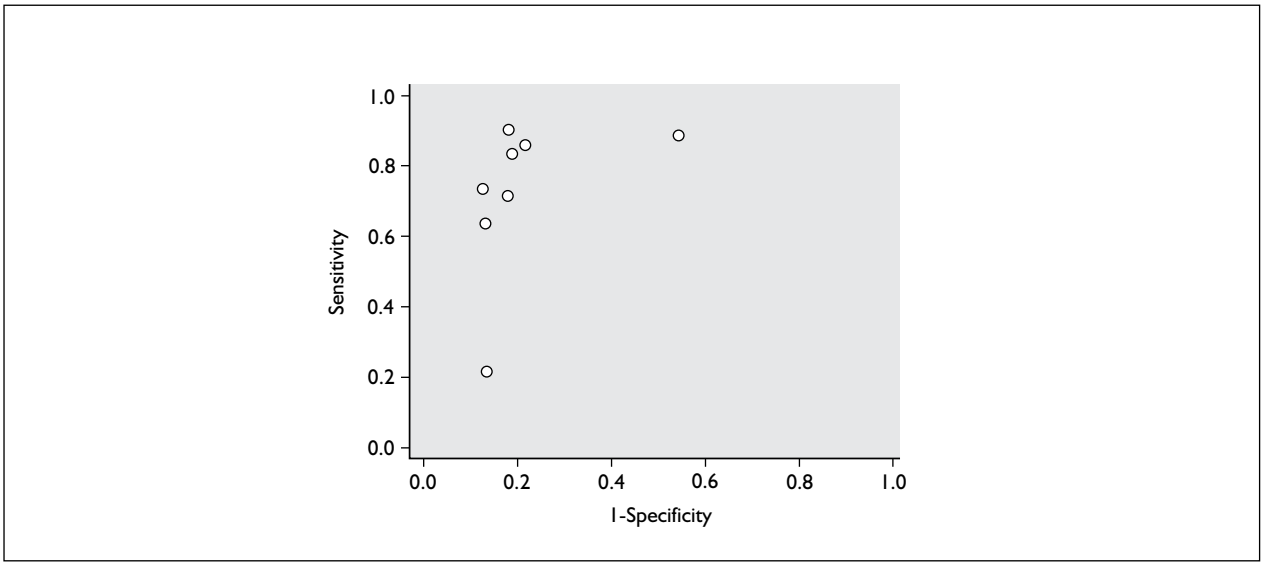


***FIGURE 15*** *Plot of sensitivity versus 1-specificity in ROC space for cervicovaginal fibronectin studies in symptomatic women with threatened preterm labour for predicting spontaneous preterm birth before 34 weeks' gestation.*

None of the studies reported consecutive enrolment and only three studies, one in the asymptomatic population[137] and two in the symptomatic population[137,140] reported blinding. The methodological quality of the included primary studies is summarised in *Figure 16*. None of the studies fulfilled our definition of ideal quality test accuracy study design. One study each reported outcome of spontaneous preterm birth before 34 weeks'[137] and 37 weeks' gestation.[138] One study reported outcome within 7 days of testing,[137] three studies reported outcome before 34 weeks' gestation[137,138,140] and all studies reported outcome before 37 weeks' gestation in symptomatic women.[137–141] Information on individual study characteristics can be found in Appendix 5, *Table 75*, which summarises each study's salient features, stratified according to the population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour.

## Accuracy of cervicovaginal 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),[137] 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)[138] (*Figure 17*). These LR values were used in the decision-analytic modelling. The accuracy measures of the test in predicting spontaneous preterm births in asymptomatic women are summarised in Appendix 5, *Table 76*.

## Accuracy of cervicovaginal prolactin in symptomatic women

For predicting spontaneous preterm birth within 7 days of testing, LR+ was 1.48 (95% CI 0.81–2.70) and LR– was 0.61 (95% CI 0.23–1.62)

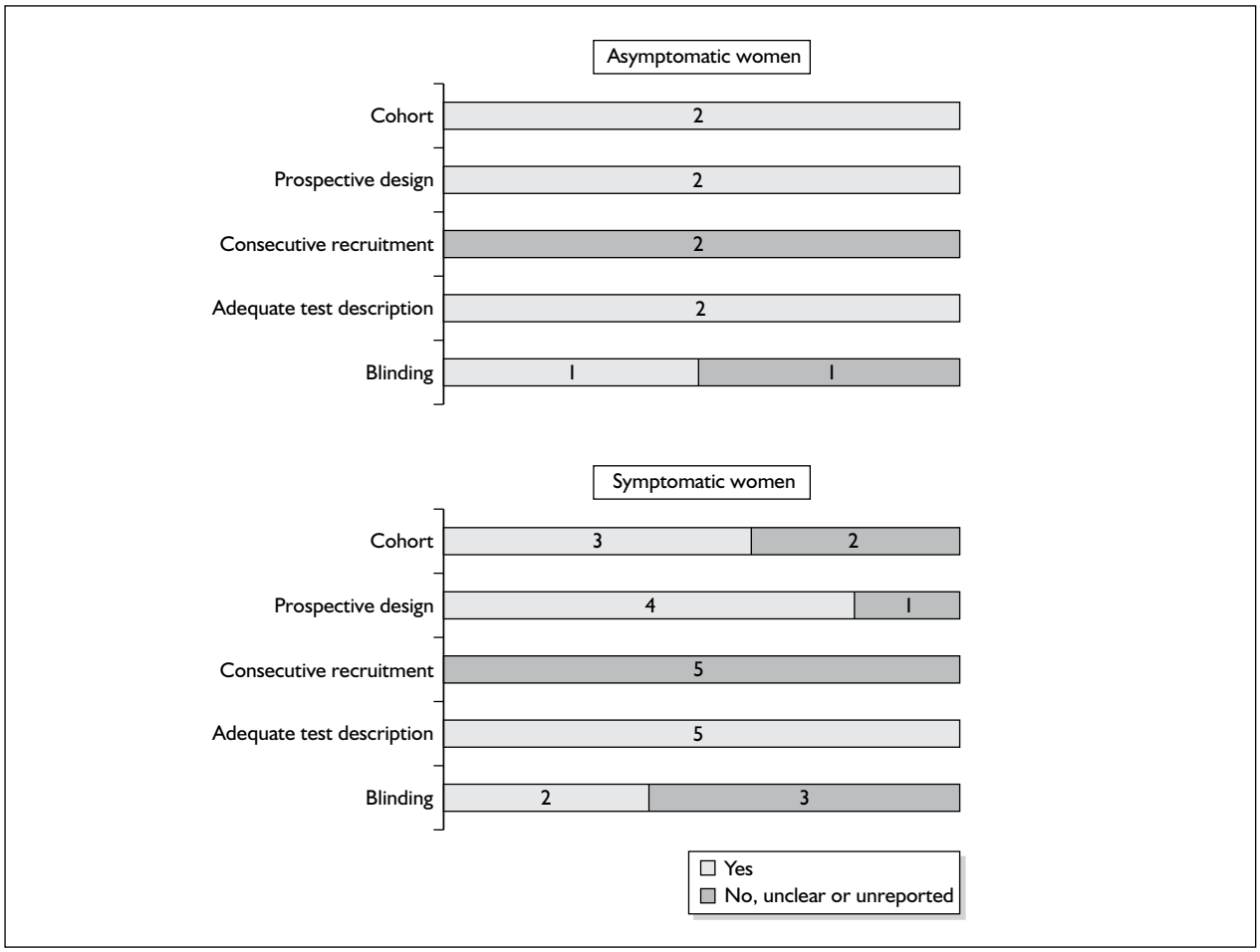


***FIGURE 16*** *Methodological quality of studies included in the systematic review of accuracy of cervicovaginal prolactin in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*



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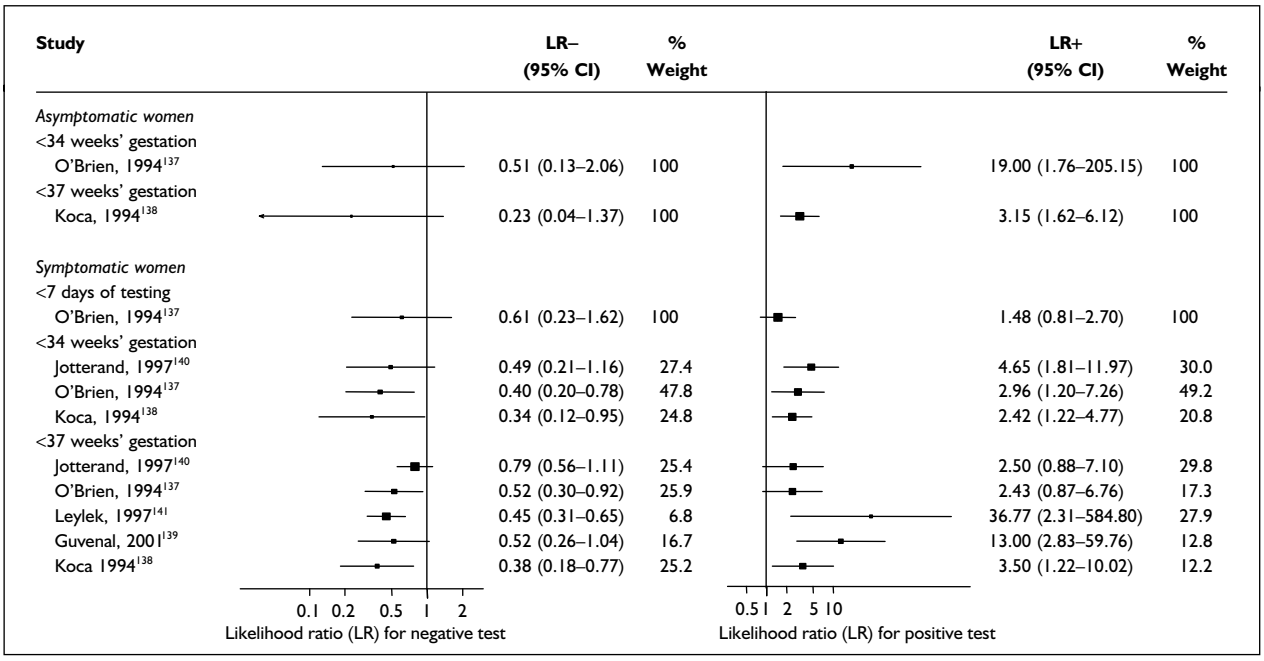


***FIGURE 17*** *Forest plots of likelihood ratios (LRs) of rapid test for cervicovaginal prolactin as a predictor of spontaneous preterm birth according to population and outcome gestations. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test for 34 weeks' 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 17*). These LRs were used in the decision-analytic modelling. The accuracy for predicting spontaneous preterm birth before 34 weeks' gestation ranged from LR+ of 2.42 (95% CI 1.22–4.77) and LR– of 0.34 (95% CI 0.12–0.95)[138] to LR+ of 4.65 (95% CI 1.81–11.97) and LR– of 0.49 (95% CI 0.21–1.16).[140] LRs from Jotterand *et al.*[140] were used in the decision-analytic modelling because this represented the best higher-quality study available. The accuracy for predicting spontaneous preterm birth before 37 weeks' gestation ranged from LR+ of 2.43 (95% CI 0.87–6.76) and LR– of 0.52 (95% CI 0.30–0.92)[137] to LR+ of 36.77 (95% CI 2.31–584.80) and LR– of 0.45 (95% CI 0.31–0.65)[141] (*Figure 17*). However, only the LR+ of 2.50 (95% CI 0.88–7.10) and LR– of 0.79 (95% CI 0.56–1.11) from Jotterand *et al.*[140] was used in decision-analytic modelling because it represented the best higher-quality study. Heterogeneity assessment of the LRs did not reveal significant graphical or statistical differences in the accuracy of 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 summarised in Appendix 5, *Table 76*.

## Cervicovaginal phosphorylated form of insulin-like growth factor binding protein 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 so has been put forward as a reliable predictor of the onset of preterm labour and hence of spontaneous preterm birth. The novel test is an immune-chromatographic dipstick test based on monoclonal antibodies that detects the presence of the phosphorylated form of IGFBP-1 release from decidual cells. The test is readily available in the form of a commercial rapid test kit.[142] A cotton swab is used to collect samples of cervicovaginal secretions during a speculum examination. The result is either positive (phIGFBP-1 is present; threshold exceeded 30 µg/l), or negative (phIGFBP-1 less than 30 µg/l) obtained within 10–15 minutes of performing the test.

## Study characteristics and quality

There were ten primary studies, involving a total of 568 women. One potentially eligible study for inclusion was excluded because data were unobtainable.[143] Appendix 5, *Table 77* summarises each study's salient features, stratified according to the population of women tested, i.e. asymptomatic antenatal women (one study)[144] and women with symptoms of threatened preterm labour (nine studies).[142–152] The single study which included an asymptomatic antenatal population had targeted the test, which was performed 3-weekly between 24 and 34 weeks' gestation, at women who had a previous spontaneous preterm birth. Enrolment in the studies ranged from 32 to 135 women, with a median of 46 women.

Only one study reported consecutive enrolment[145] and only two studies reported blinding to test results and/or reference standards.[146,150] Otherwise all studies used cohorts of pregnant women; all except two[151,152] reported prospective data collection design and, with one exception,[151] had provided adequate test description. The methodological quality of the included primary studies is summarised in *Figure 18*. The only study on asymptomatic women 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, three studies also reported birth within 48 hours of testing,[145,146,150] four studies reported birth within 7 days of testing,[145,146,149,150] and three studies reported birth before 34 weeks' gestation.[142,149,150]

## Accuracy of phIGFBP-1 in asymptomatic women

In the single study evaluating the test on asymptomatic women for predicting spontaneous

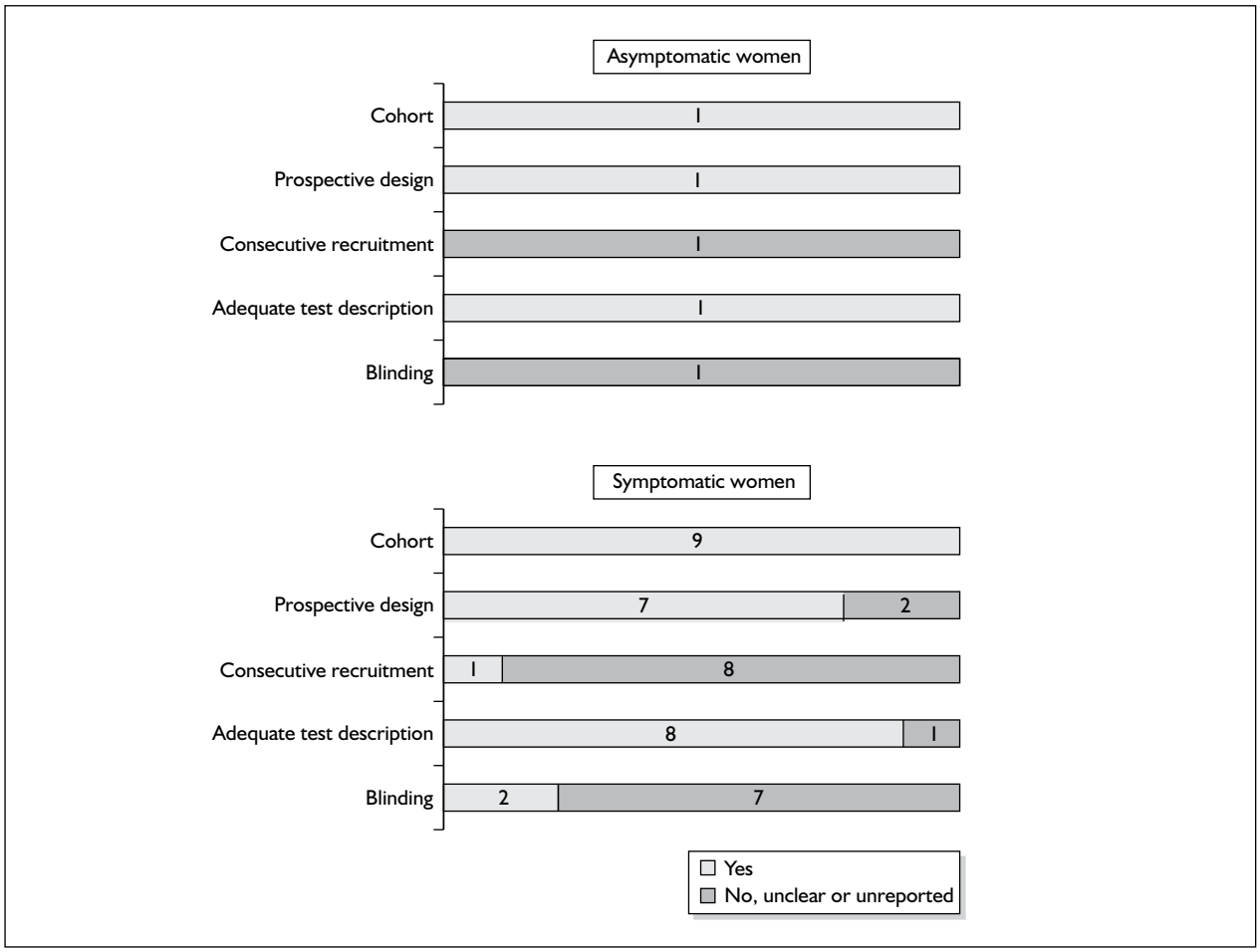


***FIGURE 18*** *Methodological quality of studies included in the systematic review of accuracy of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*



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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).[144] These values were used in the decision-analytic modelling.

### 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 19*). However, summary LR+ of 1.73 (95% CI 0.92–3.25) and summary LR– of 0.59 (95% CI 0.24–1.45) from two studies of equal size and representing higher-quality studies[145,150] were used for the decision-analytic modelling. The accuracy for predicting spontaneous preterm birth within 7 days of testing was shown in *Figure 20*, 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). Summary LR+ of 2.83 (95% CI 1.57–5.09) and summary LR– of 0.371 (95% CI 0.13–1.04) from the higher-quality studies of equal size[145,150] were used in the decision-analytic modelling. The accuracy for predicting spontaneous preterm birth before 34 weeks' gestation was shown in *Figure 21*, 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). However, LR+ of 4.15 (95% CI 1.43–11.99) and LR– of 0.31 (95% CI 0.03–3.38) from the largest higher-quality study[150] were used in the decision-analytic modelling. 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 22*). LRs from the largest higher-quality study[145] of LR+ of 3.87 (95% CI 1.54–9.72) and LR– of 0.33 (95% CI 0.15–0.71) for this outcome were used for the decision-analytic modelling. Heterogeneity assessment of the LRs did not reveal significant graphical or statistical differences 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. ROC plots of sensitivity versus specificity for cervicovaginal phIGFBP-1 in symptomatic women predicting spontaneous preterm birth within 7 days of testing as well as before 34 weeks' gestation are shown in *Figure 23* and *Figure 24*, respectively. The accuracy measures of the test in predicting spontaneous preterm births in symptomatic women are summarised in Appendix 5, *Table 78*.

## Serum α-fetoprotein

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 defects and as an integral part of screening for trisomy 21.

### Study characteristics and quality

There were 20 primary accuracy studies that met the selection criteria, all in asymptomatic women. Appendix 5, *Table 79* summarises each study's salient features.[153–171] One citation contributed to two separate studies and results.[156] The most common gestation tested was the mid-trimester (14–28 weeks). The threshold at which studies

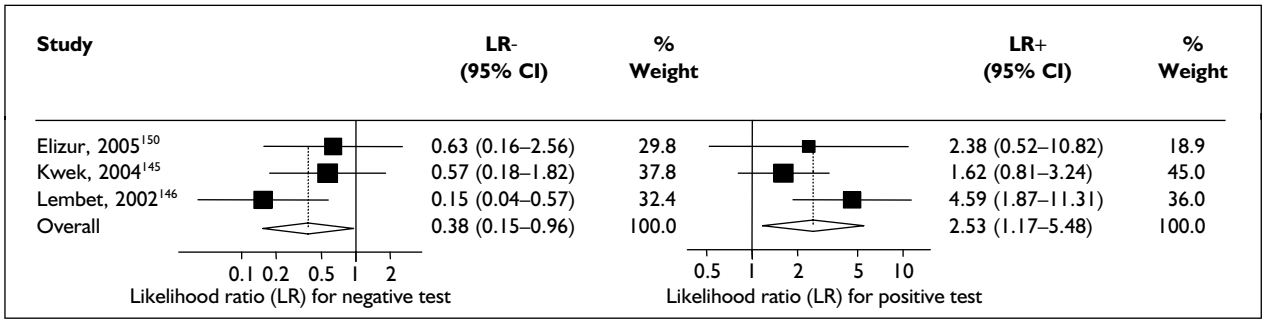


***FIGURE 19*** *Forest plots of likelihood ratios (LRs) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth within 48 hours of testing. Studies are arranged in descending order of methodological quality.* $\chi^2$ *heterogeneity test* $p = 0.150$ *for LR+ and* $p = 0.22$ *for LR–.*

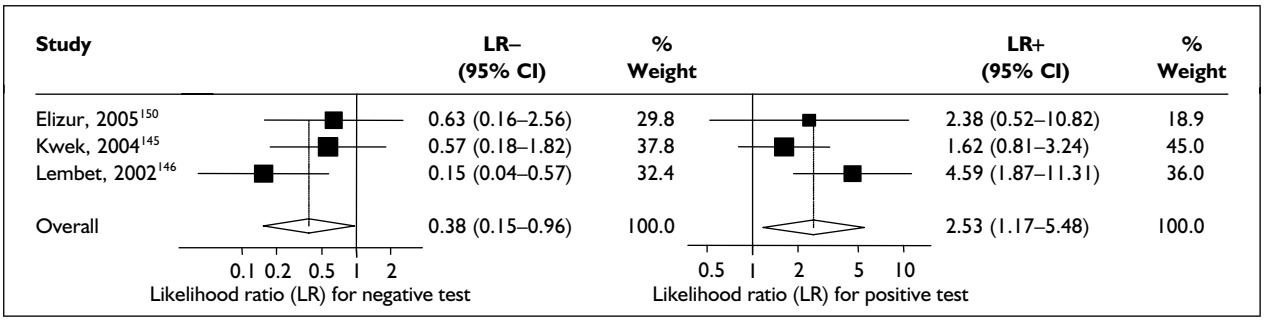


***FIGURE 20*** *Forest plots of likelihood ratios (LRs) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth within 7 days of testing. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test $p = 0.57$ for LR+ and $p = 0.29$ for LR–.*

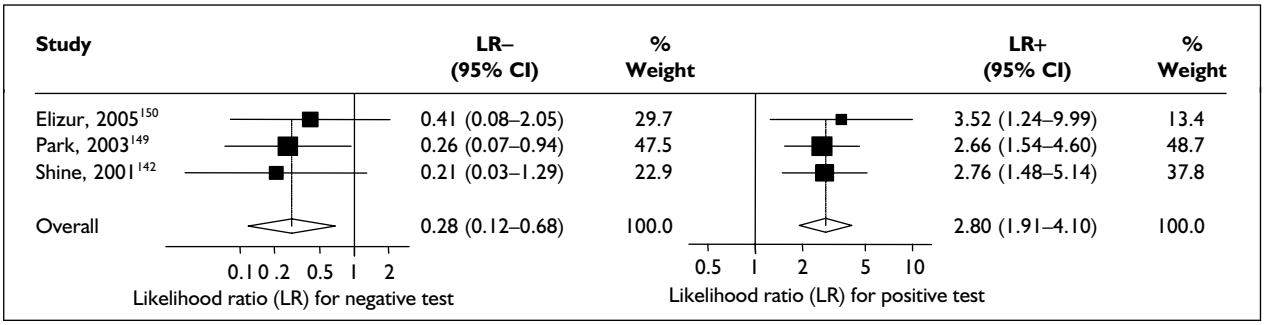


***FIGURE 21*** *Forest plots of likelihood ratios (LRs) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth before 34 weeks' gestation. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test $p = 0.76$ for LR+ and $p = 0.85$ for LR–.*

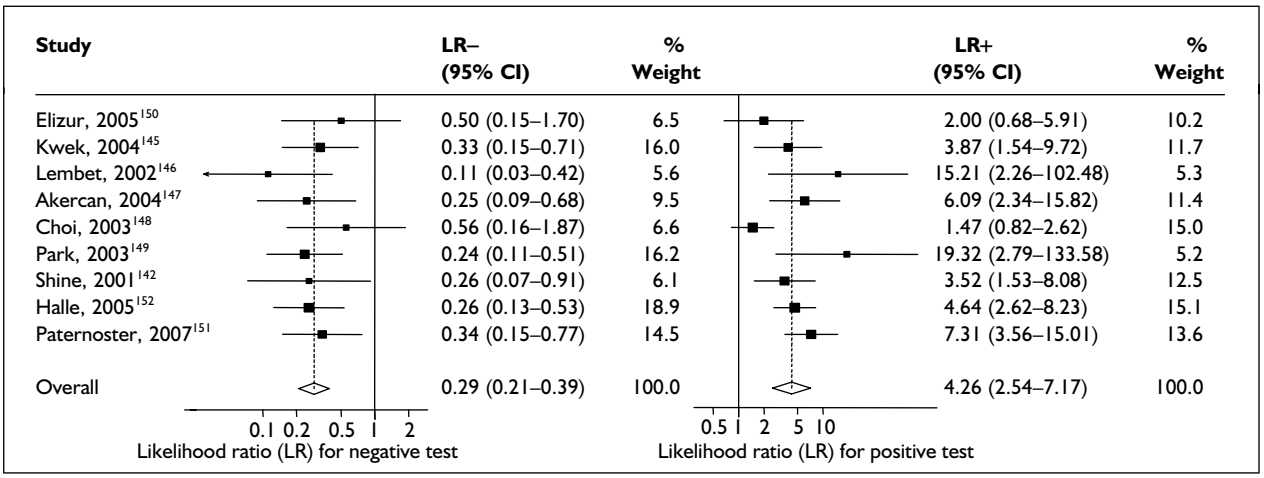


***FIGURE 22*** *Forest plots of likelihood ratios (LRs) of rapid test for phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) in cervical secretion as a predictor of spontaneous preterm birth before 37 weeks' gestation. Studies are arranged in descending order of methodological quality. $\chi^2$ heterogeneity test $p = 0.00$ for LR+ and $p = 0.79$ for LR–.*



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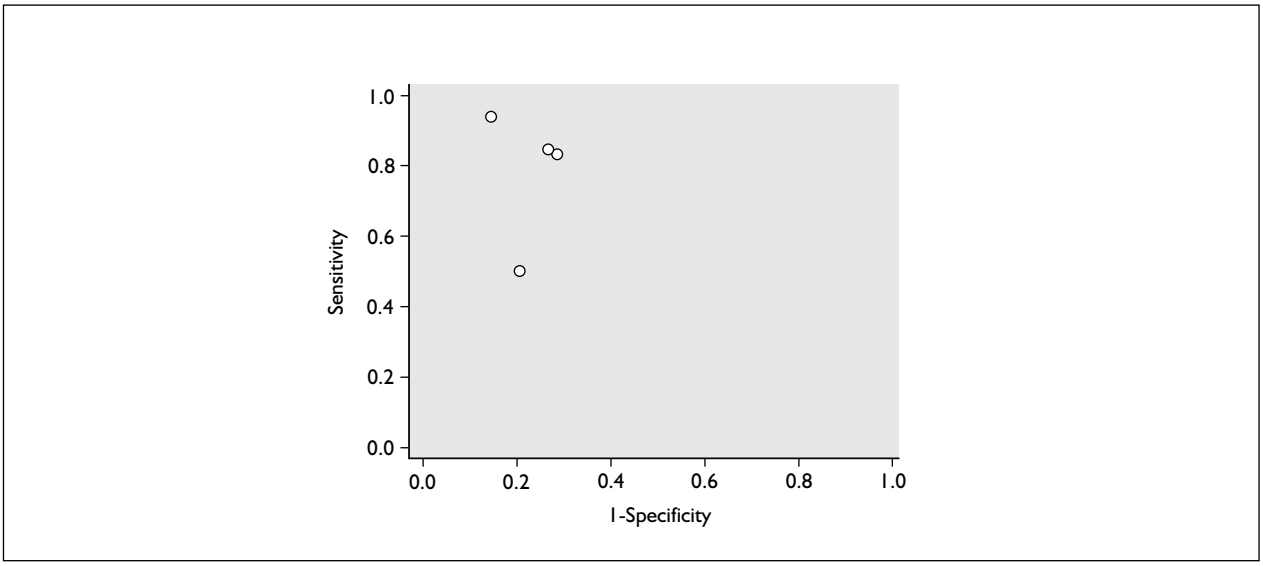


***FIGURE 23*** *Plot of sensitivity versus 1-specificity in ROC space for cervicovaginal phIGFBP-1 studies in symptomatic women with threatened preterm labour for predicting spontaneous preterm birth within 7 days of testing.*

commonly reported their results were 2.0 and 2.5 multiples of the median (MoMs). The commonest reference standard was spontaneous preterm birth before 37 weeks' gestation with only five studies reporting spontaneous preterm birth before 34 weeks' gestation.[154,157,160,168,172] The methodological quality of the included primary studies is summarised in *Figure 25* where it is shown that all the included studies were missing one or more ideal quality features.

## Accuracy of 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)[160] to 4.99 (95% CI 3.97–6.28)[168] and a range of LR– from 0.14 (95% CI 0.02–0.91)[160] to 0.95 (95% CI 0.94–0.97).[168] LRs from Waller *et al.*[168] were used in the decision analyses because it represented the best available higher-quality study.

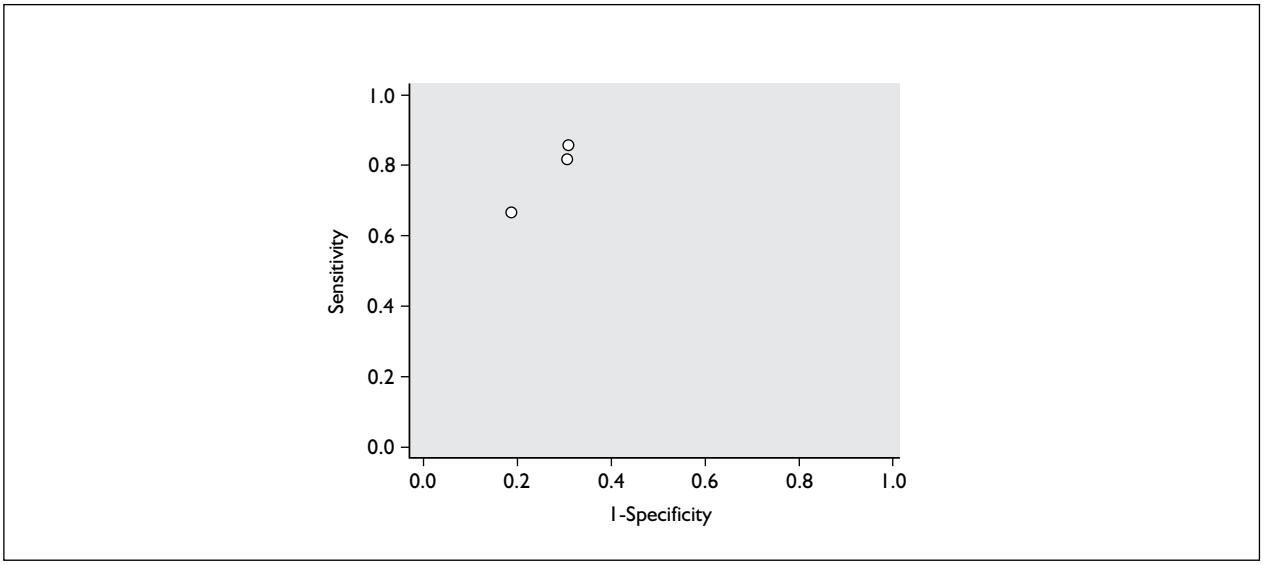


***FIGURE 24*** *Plot of sensitivity versus 1-specificity in ROC space for cervicovaginal phIGFBP-1 studies in symptomatic women with threatened preterm labour for predicting spontaneous preterm birth before 34 weeks' gestation.*

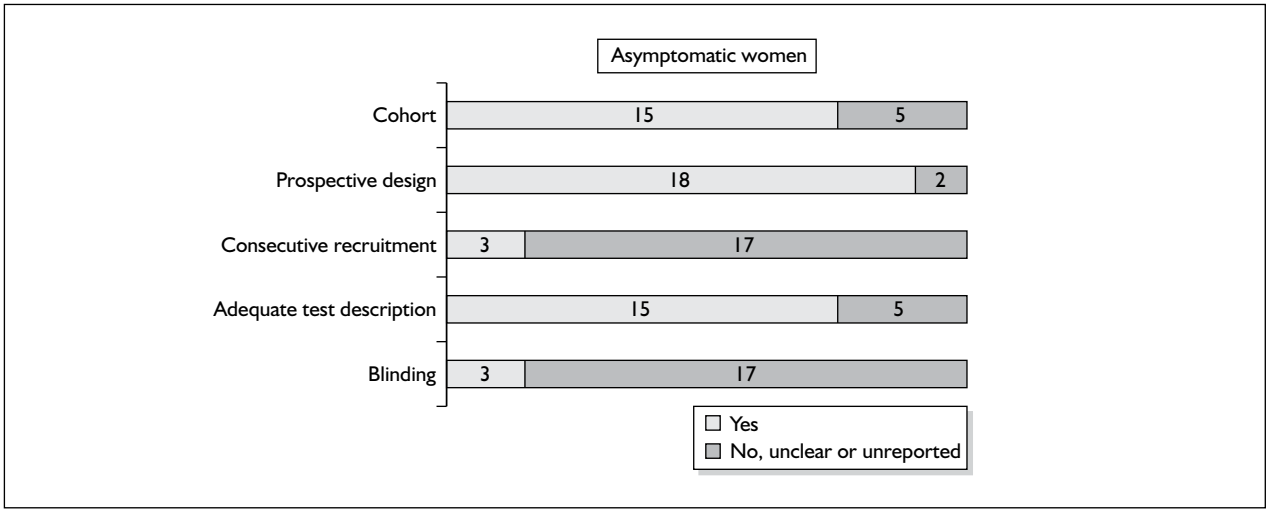


***FIGURE 25*** *Methodological quality of studies included in the systematic review of accuracy of maternal serum α-fetoprotein in predicting spontaneous preterm birth among asymptomatic antenatal women. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

For predicting spontaneous preterm birth before 37 weeks' gestation with MSAFP, two thresholds were used more commonly than others: 2.0 MoM and 2.5 MoM. With the threshold of 2.0 MoM, there was a range of LR+ from 0.97 (95% CI 0.51–1.85)[164] to 4.21 (95% CI 3.47–5.09)[165] and a range of LR– from 0.45 (95% CI 0.20–1.02)[153] to 1.01 (95% CI 0.86–1.17).[164] The LR+ of 1.63 (95% CI 0.81–3.27) and LR– of 0.96 (95% CI 0.89–1.03) from Tanaka *et al.*[166] were used in the decision analyses because this represented the best available higher-quality study. With a threshold of 2.5 MoM, there was a range of LR+ from 1.50 (95% CI 1.03–2.17)[163] to 70.23 (95% CI 21.78–226.38) and LR– from 0.34 (95% CI 0.17–0.69)[160] to 0.99 (95% CI 0.97–1.00).[162] The LRs from Morssink *et al.*[162] were used in the decision analyses because it represented the best higher-quality study available. *Figure 26* and *Figure 27* summarise the accuracy of each threshold in predicting spontaneous preterm birth. Individual accuracy results are summarised in Appendix 5, *Table 80*.

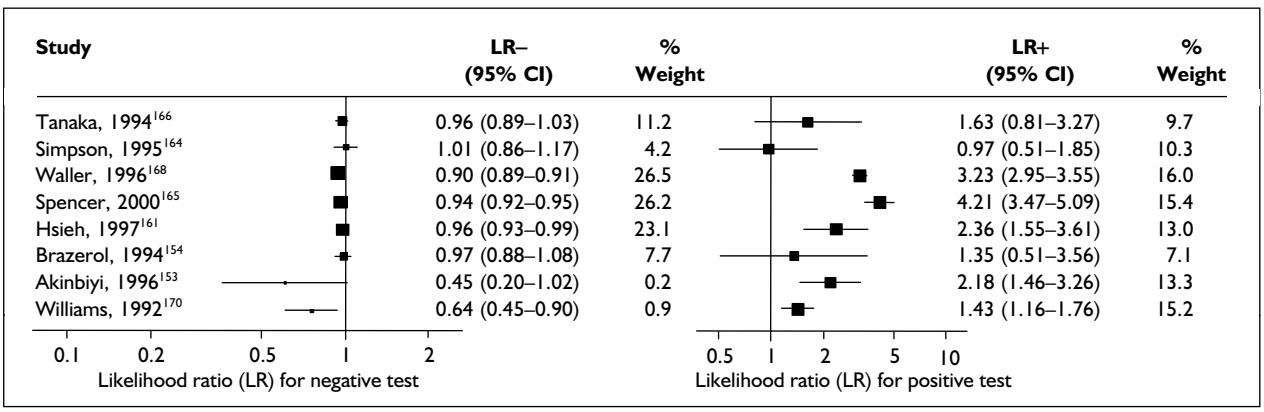


***FIGURE 26*** *Forest plots of likelihood ratios of maternal serum α-fetoprotein in asymptomatic women (threshold of 2.0 MoM) as a predictor of spontaneous preterm birth before 37 weeks' gestation. Studies are arranged in descending order of methodological quality.*



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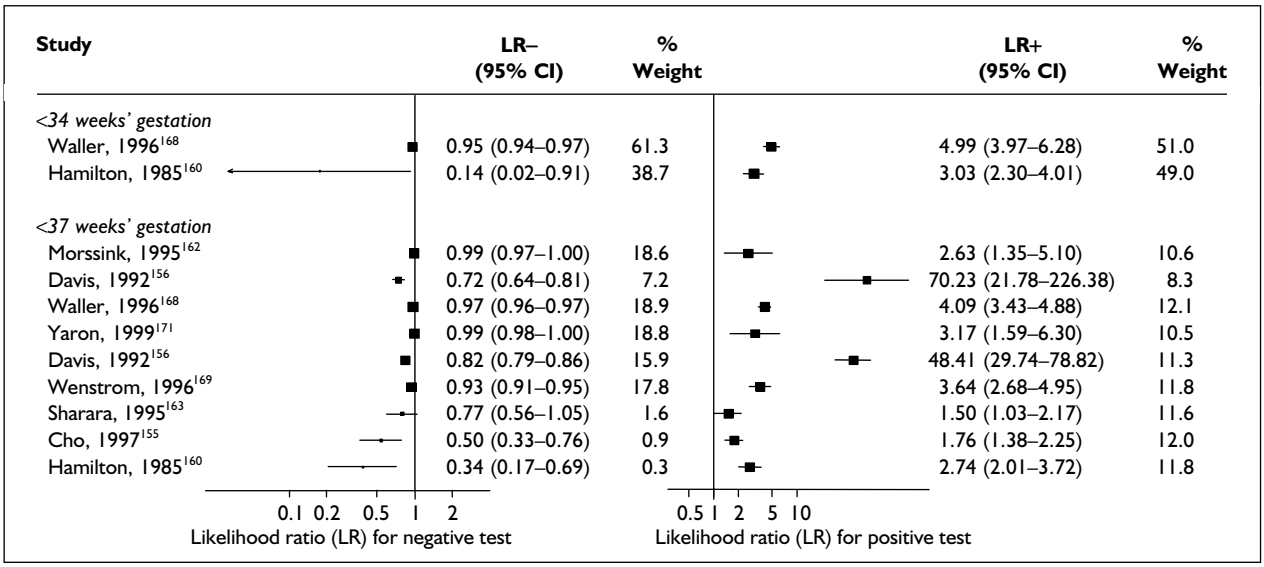


***FIGURE 27*** *Forest plots of likelihood ratios of maternal serum α-fetoprotein in asymptomatic women (threshold of 2.5 MoM) as a predictor of spontaneous preterm birth before34 and 37 weeks' gestation. Studies are arranged in descending order of methodological quality.*

# Serum relaxin

Relaxin is a peptide hormone produced by the corpus luteum and is known to soften and ripen the human cervix. Hyper-relaxinaemia has been associated with prematurity.[173] 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 performed on asymptomatic women ($n = 3549$)[173–176] while one involved symptomatic women with threatened preterm labour ($n = 34$).[177] One study evaluated the test's serial testing accuracy in predicting spontaneous preterm birth in asymptomatic women.[173] Appendix 5, *Table 81* summarises 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 our ideal definition of high-quality test accuracy studies either in asymptomatic or symptomatic women. Blinding was absent in all but one study.[176] However, all studies have an adequate test description report. The methodological quality of the included primary studies is summarised in *Figure 28*.

## Accuracy of maternal serum relaxin in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, serum relaxin had an LR+ of 1.60 (95% CI 1.24–2.06) and LR– of 0.84 (95% CI 0.74–0.95).[174] For predicting spontaneous preterm birth before 37 weeks' gestation serum relaxin had an LR+ of 1.21 (95% CI 0.73–2.10) and LR– of 0.74 (95% CI 0.29–1.95).[173] LRs from these studies were used in the decision-analytic modelling because they represented the largest higher-quality studies for the respective outcomes. The accuracy results are summarised in *Figure 29*. Individual accuracy results are summarised in Appendix 5, *Table 82*.

## Accuracy of maternal serum relaxin in symptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, maternal serum relaxin had an LR+ of 1.48 (95% CI 0.26–8.31) and LR– of 0.861 (95% CI 0.38–1.96) and before 37 weeks' gestation it had LR+ of 0.80 (95% CI 0.19–3.31) and LR– of 1.07 (95% CI 0.72–1.57) *Figure 29*.[177] These LRs were used in decision-analytic modelling because they represented the largest higher-quality study for this reference standard. Individual accuracy results for symptomatic women can be found in Appendix 5, *Table 82*.

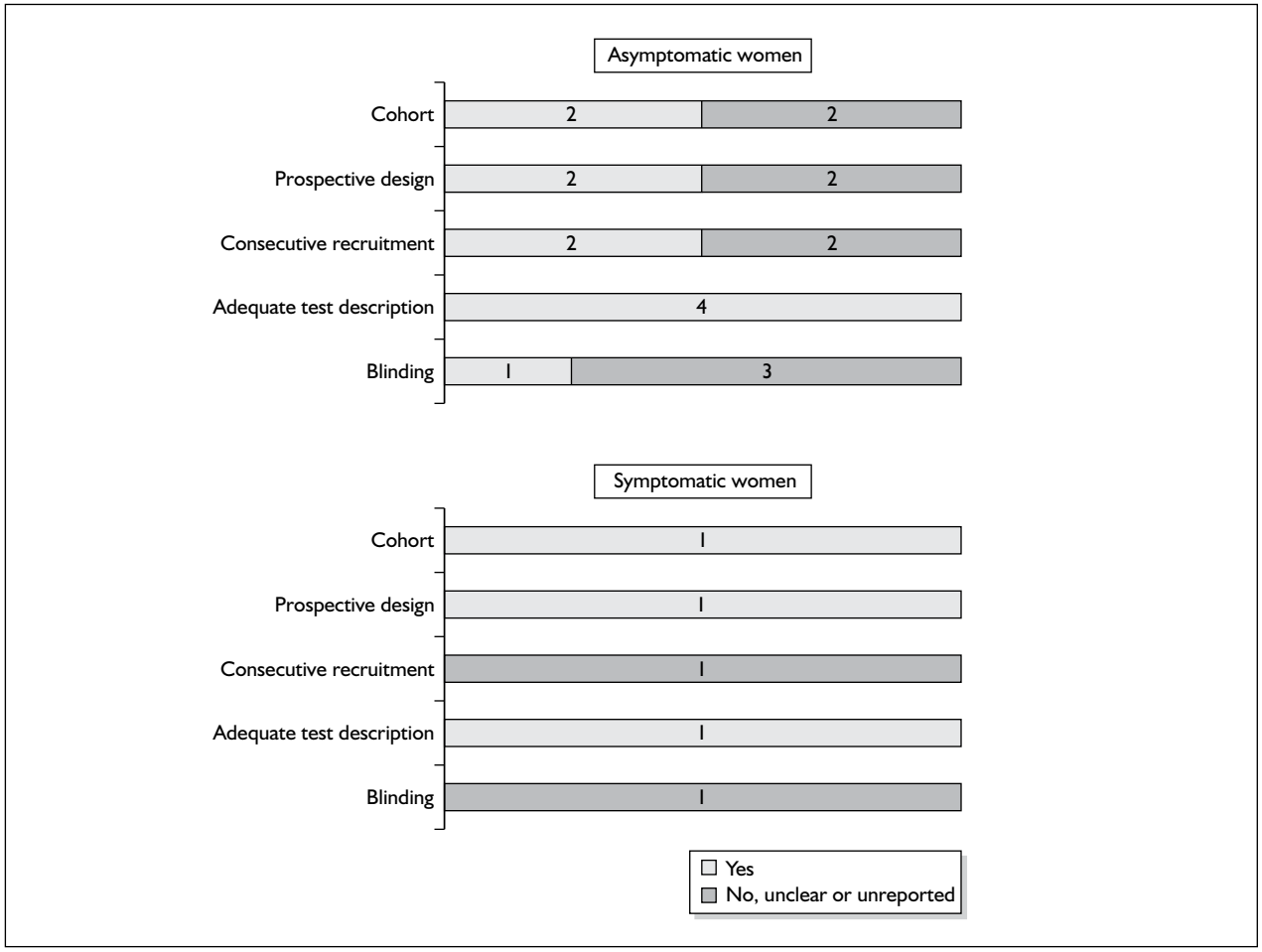


***FIGURE 28*** *Methodological quality of studies included in the systematic review of accuracy of maternal serum relaxin in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

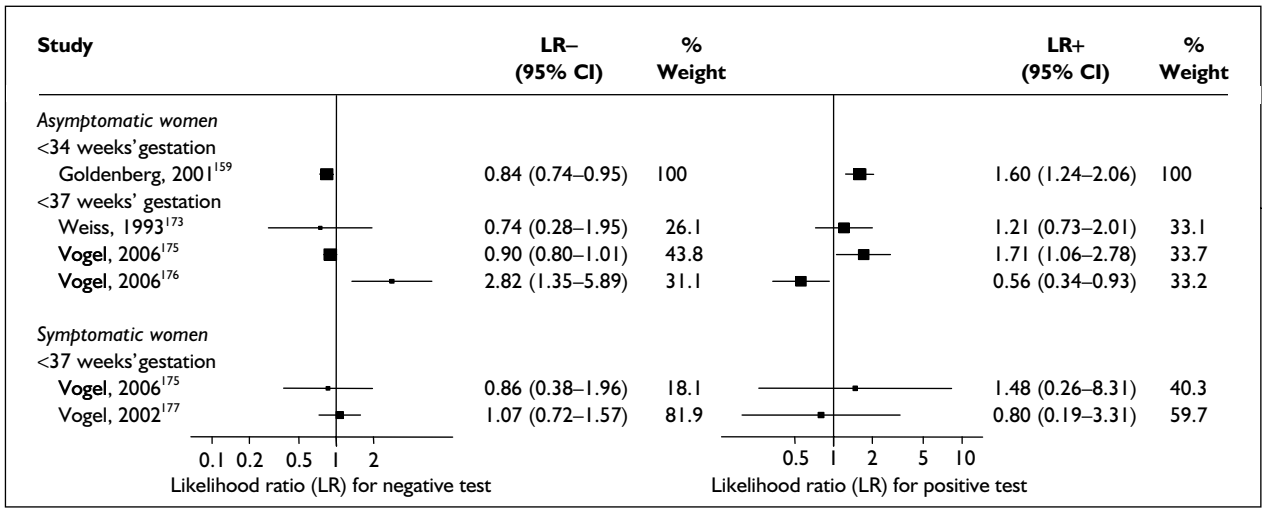


***FIGURE 29*** *Forest plots of likelihood ratios (LRs) of maternal serum relaxin measurement in predicting spontaneous preterm birth stratified according to population and outcomes. Studies are arranged in descending order of methodological quality.*



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## Serum corticotrophin-releasing hormone

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 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 six primary studies ($n = 5034$ women) on the accuracy of CRH testing, comprising five studies on asymptomatic antenatal women ($n = 4940$)[174,178–181] and one study on symptomatic women who presented with threatened preterm labour ($n = 94$).[182] Appendix 5, *Table 83* 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. One study was not included because it included multiple gestations in its population and iatrogenic preterm birth in its outcome.[183] The studies' enrolment for asymptomatic women ranged from 181 to 2929 women[174,179] with a median of 396 women.[178]

There were no studies included within the systematic review of the accuracy of CRH testing in predicting spontaneous preterm births that fulfil our ideal definition of high-quality test accuracy studies either in asymptomatic or symptomatic women. None of the studies in either 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.[174,179] Blinding of carers to the results of CRH tests was absent from two studies on asymptomatic women.[178,180] The methodological quality of the included primary studies is summarised in *Figure 30*.

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,[179–182] while the remainder used it as a serial test. For asymptomatic women, one study used spontaneous preterm birth before 32 weeks' gestation,[174] one 34 weeks' gestation,[181] and two each used 35 weeks' gestation,[174,179] and 37 weeks' gestation[178,180] as the reference standard.

### 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),[181] estimates used in the decision-analytic modelling. For predicting spontaneous preterm birth before 37 weeks' gestation, CRH had a range of LR+ from 1.43

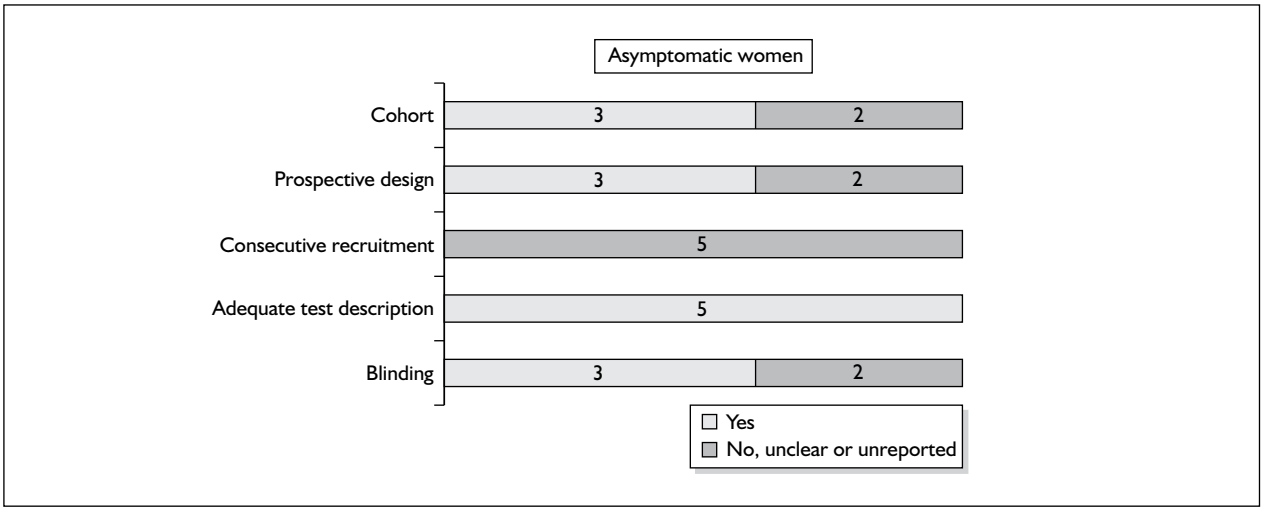


***FIGURE 30*** *Methodological quality of studies included in the systematic review of accuracy of CRH in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

(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 31*).[178,180] Estimates from Berkowitz *et al.*[178] were used in the decision-analytic modelling because it represented the largest higher quality study of the reference standard. Individual accuracy results can be found in Appendix 5, *Table 84*.

### 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 3.12 (95% CI 1.42–6.84) and LR– of 0.68 (95% CI 0.51–0.91) (*Figure 31*). Individual accuracy results can be found in Appendix 5, *Table 84*.

## β-Human chorionic gonadotrophin

The hormone β-human chorionic gonadotrophin (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 is imminent, has been postulated as the rationale for testing for the presence of β-hCG in the cervicovaginal secretions,[139] in addition to its presence in the maternal serum.[184] Measurements of β-hCG can be made either by taking a maternal blood serum sample during the asymptomatic antenatal period, usually as part of the 'triple test' to screen for Down syndrome, or by taking a cotton-tipped swab of cervicovaginal secretions obtained from speculum examination.

### Study characteristics and quality

There were 23 primary articles, of which 19 evaluated the use of mid-trimester maternal serum hCG as a predictor of spontaneous preterm birth ($n = 177,730$ women)[157,158,162,165,166,184–197] while one article evaluated it in early first trimester ($n = 169$),[198] and three articles evaluated cervicovaginal hCG as a predictor of spontaneous preterm birth in women who presented with symptoms of threatened preterm labour ($n = 248$).[139,199,200] Appendix 5, *Table 85* summarises each study's salient features, stratified according to the population of women tested, i.e. asymptomatic antenatal women and symptomatic women with threatened preterm labour.

None of the studies fulfilled the ideal quality study design. There were nine case–control studies in asymptomatic women[165,185,186,189–193,195] and one in symptomatic women.[139] Four studies in asymptomatic women reported consecutive enrolments,[157,166,194,197] while none was reported in symptomatic women. There were 13 retrospective studies in asymptomatic women[158,165,184–186,189–193,195,196,198] while all the studies in symptomatic women were prospective. None of the studies on asymptomatic women reported

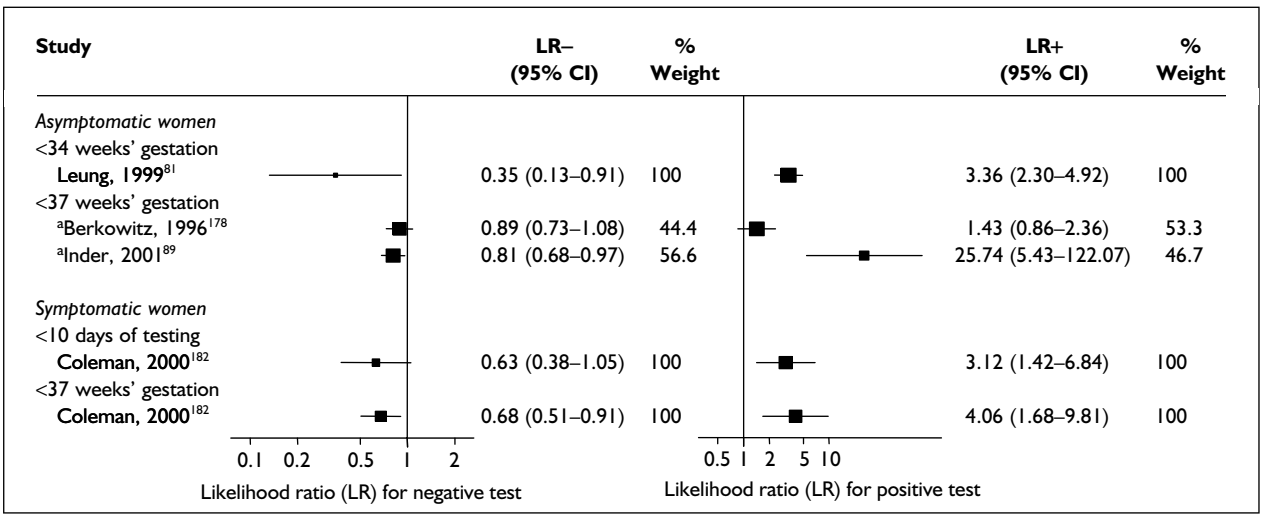


***FIGURE 31*** *Forest plots of likelihood ratios (LRs) of CRH in predicting spontaneous preterm birth within 7–10 days of testing and 37 weeks' gestation in symptomatic women and before 34 and 37 weeks' gestation strain asymptomatic women. Studies are arranged in descending order of methodological quality. a, Serial testing.*



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blinding and only one study in symptomatic women reported it.[200] The methodological quality of the included primary studies is summarised in *Figure 32*.

Most of the study in asymptomatic women reported their thresholds in terms of MoM, except for three studies,[188,194,198] which used percentiles. The commonest threshold used was 2.0 MoM, values above this were defined as abnormal. The three studies that evaluated cervicovaginal 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' gestation[157,188] and 34 weeks' gestation,[194] the studies used birth before 37 weeks' gestation as their reference standard. One study reported birth within 7 days of testing in symptomatic women,[199] while the remainder reported before 37 weeks' gestation as their reference standard. There was graphical (*Figure 33*) and statistical evidence of heterogeneity in the accuracy results ($\chi^2$ heterogeneity test $p = 0.00$ for LR+ and $\chi^2$ heterogeneity test $p = 0.00$ 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 a threshold of 2.0 MoM, showed variable accuracy in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic women. The LR+ ranged from 0.92 (95% CI 0.77–1.11)[197] to 3.76 (95% CI 2.56–5.52)[193] and LR– ranged from 0.50 (95% CI 0.28–0.88)[191] to 1.30 (95% CI 0.79–2.12)[197] (*Figure 33*). The largest better quality study reported LR+ of 2.77 (95% CI 2.07–3.69) and LR– of 0.984 (95% CI 0.98–0.99) when the

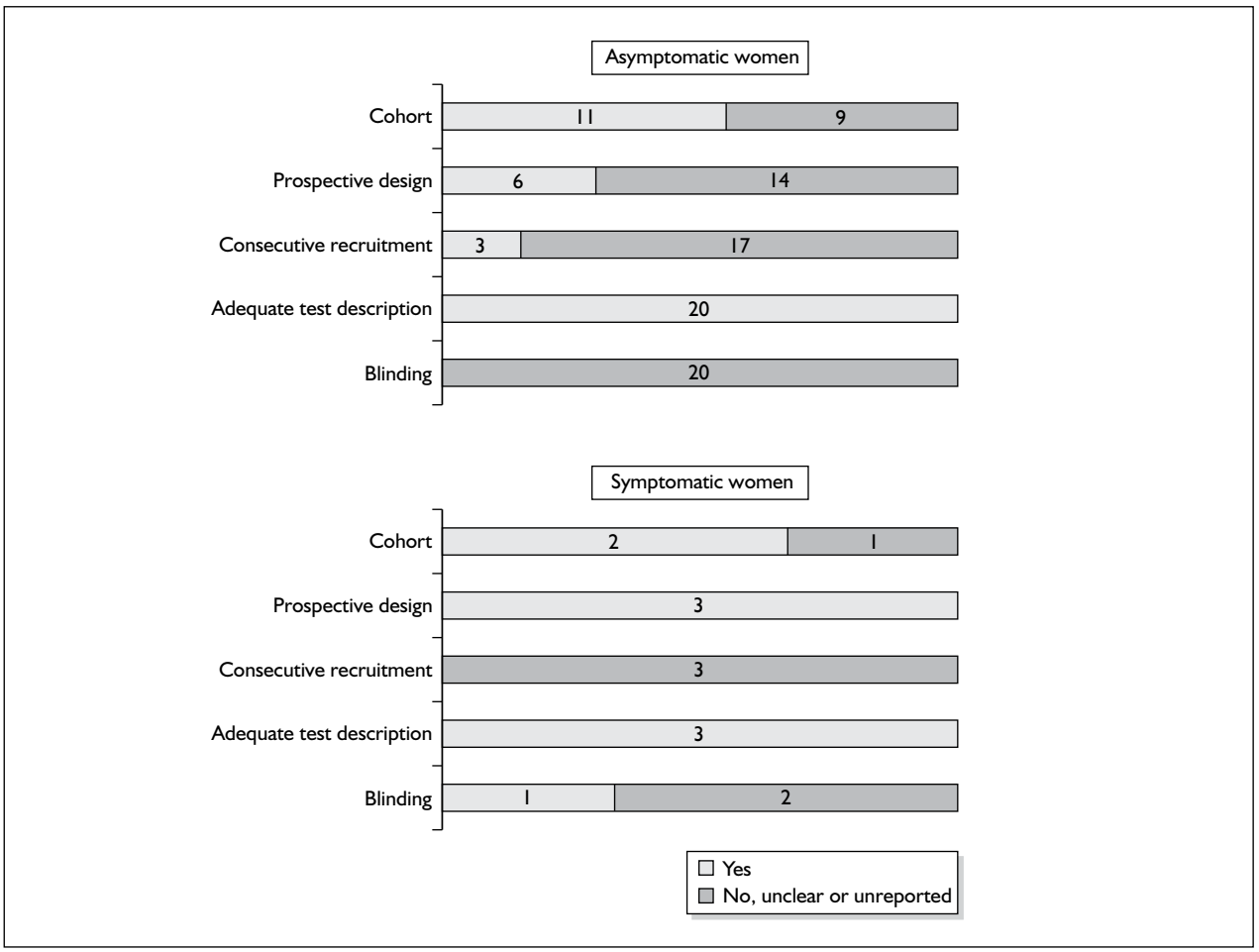


***FIGURE 32*** *Methodological quality of studies included in the systematic review of accuracy of human chorionic gonadotrophin in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

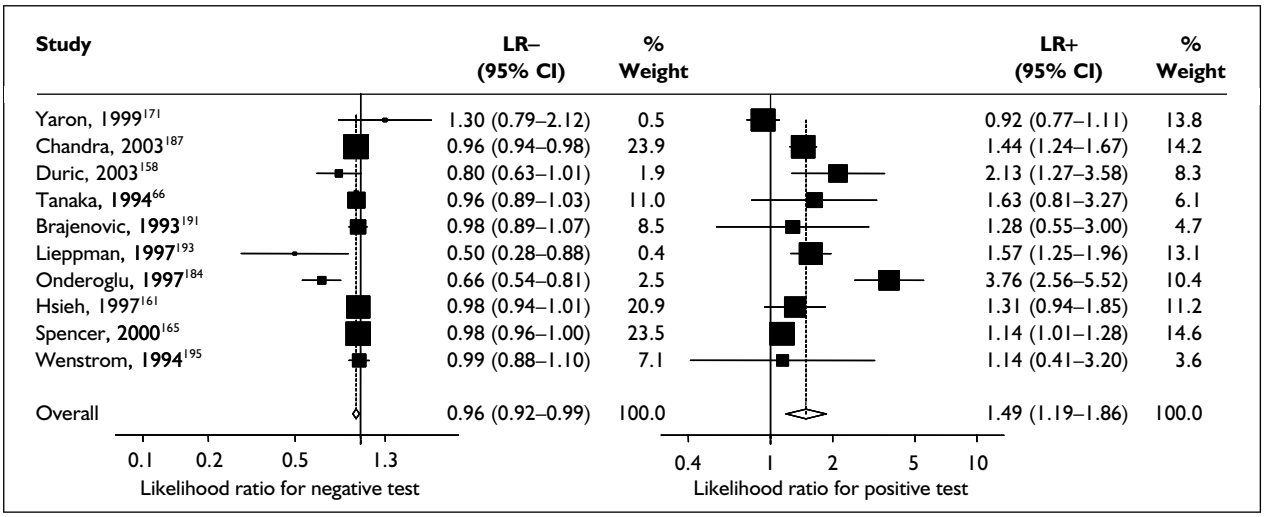


***FIGURE 33*** *Forest plots of likelihood ratios (LRs) of serum β-human chorionic gonadotrophin (β-hCG) testing in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test $p = 0.00$ for LR+ and $\chi^2$ heterogeneity test $p = 0.00$ for LR–.*

first percentile was used as threshold to define abnormality.[188] LRs from Dugoff *et al.*[188] were used in the decision-analytic modelling because it represents the largest higher-quality study. The accuracy results for asymptomatic women are summarised in Appendix 5, *Table 86*.

## Accuracy of β-hCG in symptomatic women

In a study that reported birth within 7 days of testing, the LR+ was 6.07 (95% CI 3.07–11.99) and LR– was 0.04 (95% CI 0.01–0.16), values which were used for the decision-analytic modelling.[199] 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 34*). However, LR+ of 2.19 (95% CI 1.35–3.57) and LR– of 0.51 (95% CI 0.30–0.85) from the largest higher-quality study was used in the decision-analytic modelling.[200] The accuracy results for symptomatic women are summarised in Appendix 5, *Table 86*.

## Estriol

Estriol is produced by both mother and fetus during pregnancy. There is a surge in the maternal levels of estriol which occurs several weeks before the onset of spontaneous labour. Measurement of either salivary or serum estriol was therefore purported to be a predictor of spontaneous preterm birth.[201]

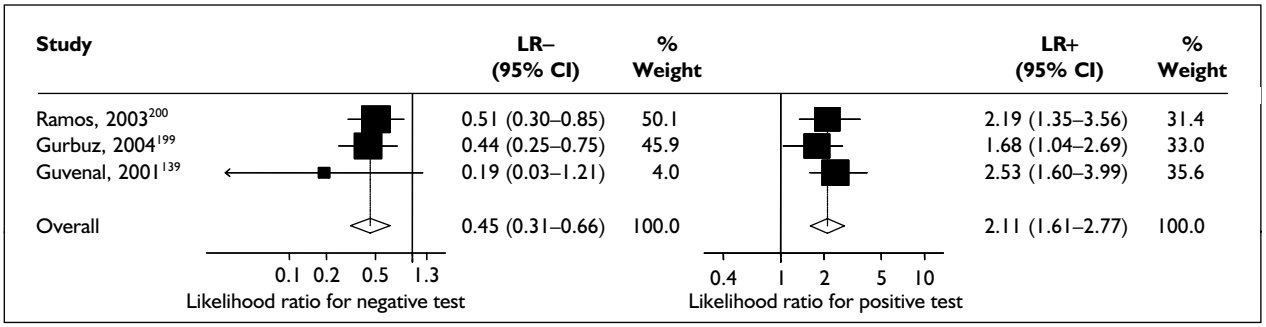


***FIGURE 34*** *Forest plots of likelihood ratios (LRs) of serum β-human chorionic gonadotrophin (β-hCG) testing in symptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test $p = 0.42$ for LR+ and $\chi^2$ heterogeneity test $p = 0.57$ for LR–.*



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### Study characteristics and quality

There were seven primary studies ($n = 60,722$ women) on the accuracy of estriol testing as predictor of spontaneous preterm birth, comprising six studies on asymptomatic antenatal women ($n = 60,417$)[157,158,196,202–204] and two studies on symptomatic women presenting with threatened preterm labour ($n = 305$).[201,202] Appendix 5, *Table 87* summarises each study's salient features, stratified according to the 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[157,204] with a median of 601 women,[202] while that of symptomatic women ranged from 115 to 190 women.[201,202] Two studies evaluated salivary estriol[201,202] while the remainder evaluated maternal serum estriol.[157,158,196,203,204] One study contributed to both asymptomatic and symptomatic populations.[202]

There were no studies included within the systematic review of the accuracy of estriol testing in predicting spontaneous preterm births that fulfil our ideal definition of high-quality test accuracy studies either in asymptomatic or symptomatic women. None of the studies in either 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.[158,196,204] Blinding of carers to the results of estriol tests was absent from five studies on asymptomatic women[157,158,196,203,204] and one study on symptomatic women.[201] The methodological quality of the included primary studies is summarised in *Figure 35*.

Three studies used the same threshold of abnormality of 0.75 MoM in asymptomatic women[158,203,204] while the two studies in symptomatic women used 2.1 ng/ml as their threshold.[201,202] Two studies in asymptomatic women used 0.5 MoM as their thresholds[157,196] and one study in symptomatic women explored the accuracy of 1.4 ng/ml as the threshold cut-off in predicting spontaneous preterm birth.[202] One study in asymptomatic women evaluated the accuracy of repeat tests in predicting spontaneous preterm birth.[202] For asymptomatic women, one study used spontaneous preterm birth before 32 weeks' gestation,[157] while the remaining studies 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.

### Accuracy of estriol in asymptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, a single salivary estriol testing had an LR+ of 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 36*).[202] These estimates were used in the decision-analytic modelling. For predicting spontaneous preterm birth before 37 weeks' gestation, the 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 36*).[158,196] Estimates from Yaron *et al.*[196] and Kim *et al.*[203] [LR+ of 1.19 (95% CI 0.58–2.44) and LR– of 0.98 (95% CI 0.89–1.08)] were used in the decision-analytic modelling because they represented the largest higher-quality studies of the reference standard, with commonly used thresholds of 0.75 MoM and 0.5 MoM respectively. No study reported spontaneous preterm birth before 34 weeks' gestation. Individual accuracy results can be found in Appendix 5, *Table 88*.

### 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 36*).[201] No study evaluated serum estriol in predicting spontaneous preterm birth in symptomatic women. Individual accuracy results can be found in Appendix 5, *Table 88*.

## C-reactive protein

C-reactive protein (CRP) is an acute-phase reactant associated with the 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 of amniotic fluid from amniocentesis. It is produced by the hepatocytes in response to the circulating inflammatory cytokines released by the presence of infections.[205]

### Study characteristics and quality

There were 13 primary articles, involving a total of 2142 women.[205–217] *Table 89*, Appendix 5,

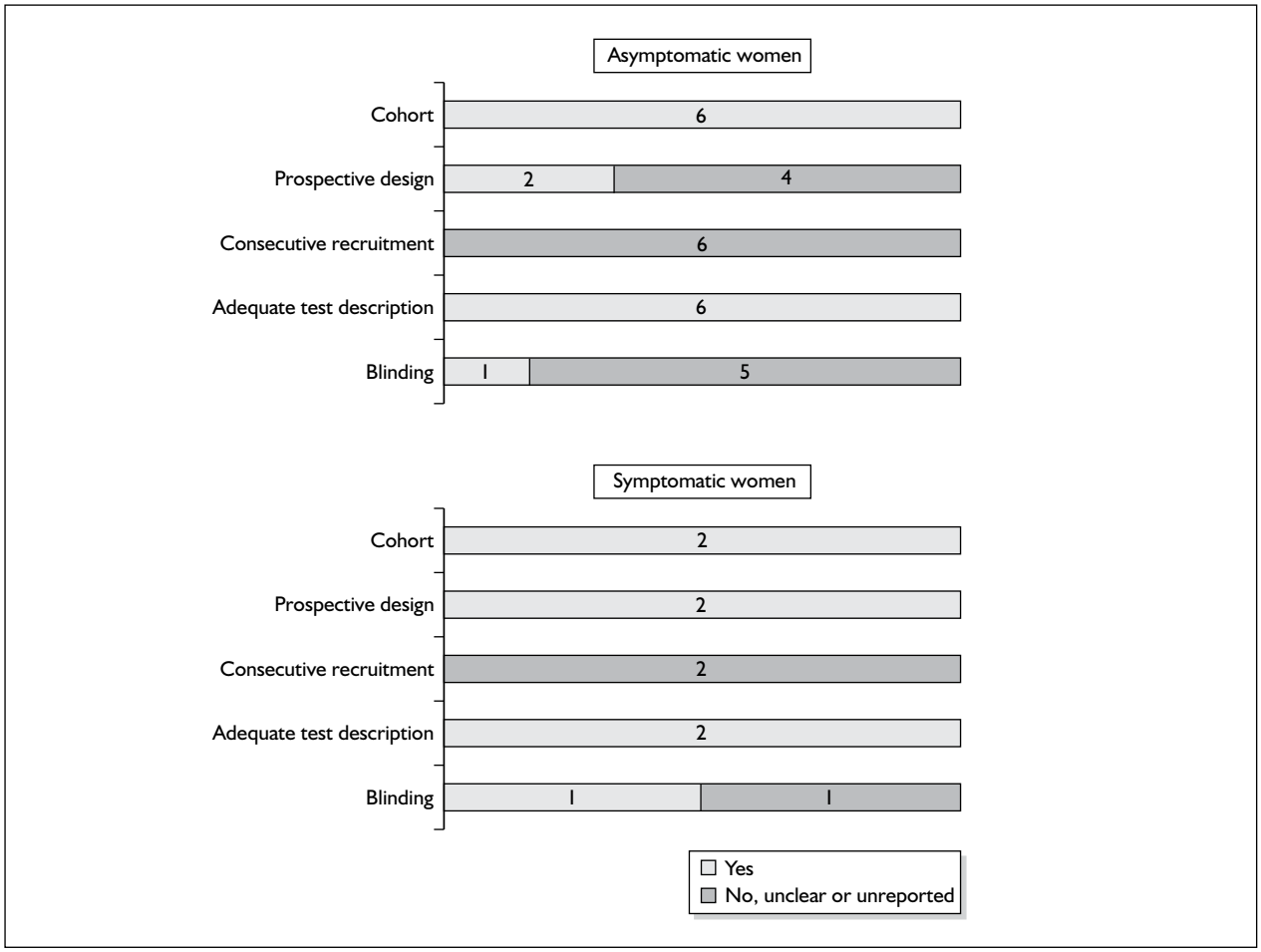


***FIGURE 35*** *Methodological quality of studies included in the systematic review of accuracy of estriol in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

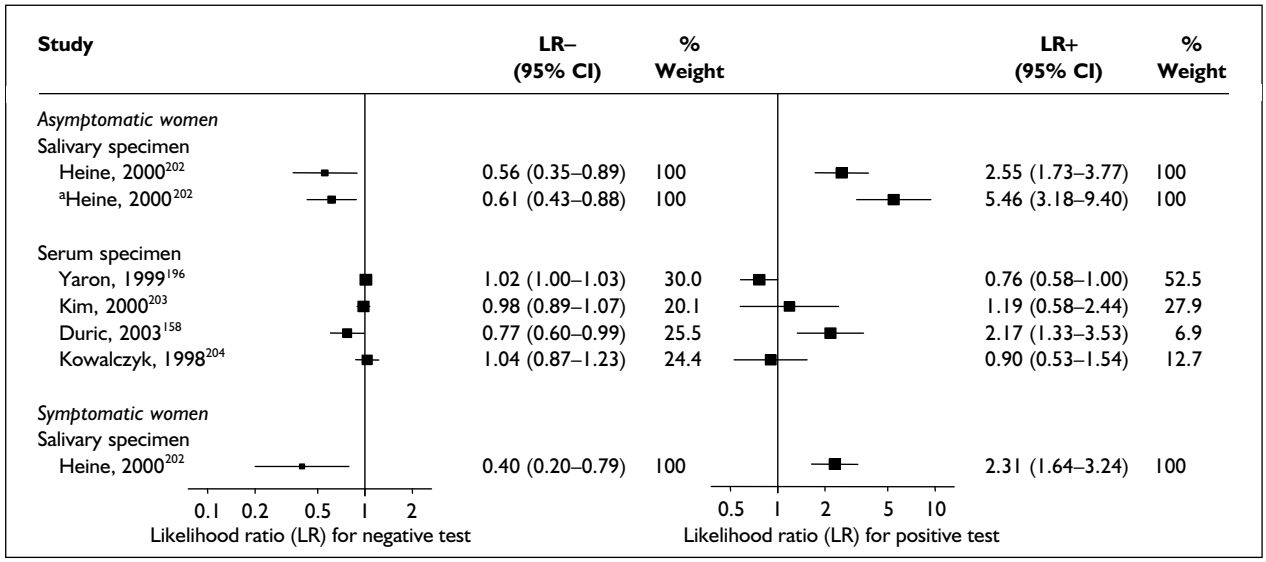


***FIGURE 36*** *Forest plots of likelihood ratios (LRs) of salivary and serum estriol in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic and symptomatic women. Studies are arranged in descending order of methodological quality. a, Repeat testing within 7 days of the first test.*



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summarises each study's salient features, stratified according to the population of women tested, i.e. asymptomatic antenatal women and women with symptoms of threatened preterm labour, and the 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 obtained at mid-trimester gestation among asymptomatic women,[210,215] while the remaining studies used maternal blood plasma serum levels of CRP obtained either at mid-trimester gestation for asymptomatic women or at presentation for women who presented with symptoms of threatened preterm labour. The study population ranged from 34 to 506 women, with a median of 69 women. Appendix 5, *Table 89* summarises the individual study characteristics.

Only one study reported prospective data collection design[215] and only seven of the 13 studies included reported consecutive enrolment.[205,206,209,211,214,215,217] Most of the studies had provided adequate test description but blinding was evident in only four studies.[205,206,210,211] The methodological quality of the primary studies included is summarised in *Figure 37*. There was no uniform test threshold used; they 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,[210] while for symptomatic women with threatened preterm labour, they were birth within 7 days of testing,[206,208,211,217] 34 weeks' gestation 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% CI 1.85–3.75) and LR– was 0.29 (95% CI 0.08–0.99).[210] In another study, for predicting

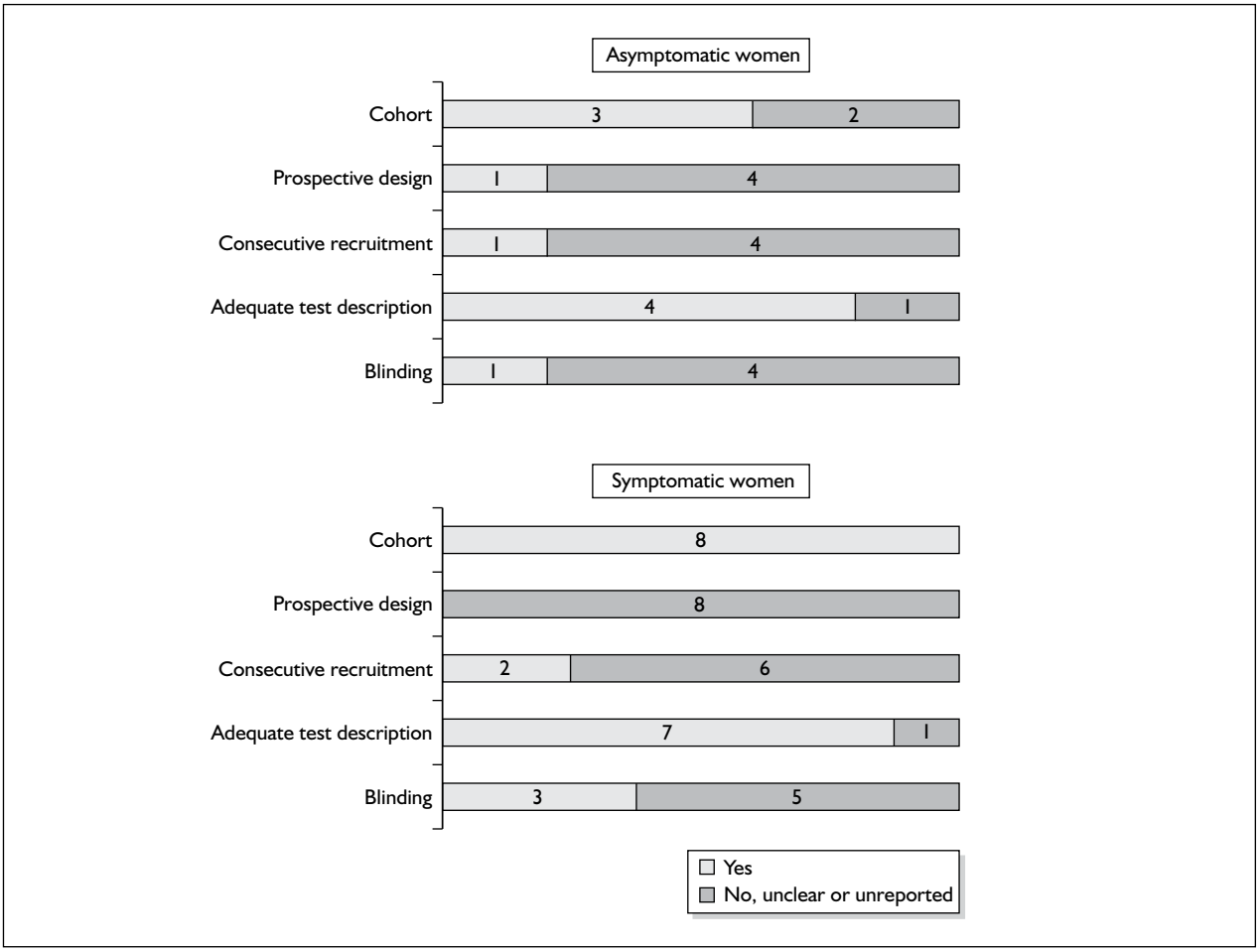


***FIGURE 37*** *Methodological quality of studies of C-reactive protein in predicting spontaneous preterm birth included in the systematic review. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

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).[215] In three studies of maternal plasma CRP measurements in 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).[212,213,216] 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 38*). The accuracy of the CRP test in predicting spontaneous preterm births in asymptomatic women is summarised in Appendix 5, *Tables 90* and *91*.

### Accuracy of CRP in symptomatic women

In four studies of maternal plasma CRP level measurements in 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).[206,208,211,217] 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 $p = 0.00$) and summary LR– was 0.296 (95% CI 0.08–1.15) ($\chi^2$ heterogeneity test $p = 0.00$) (*Figure 39*). Cammu *et al.*[206] represented the largest higher-quality study and was therefore used for the decision-analytic modelling. A study on maternal plasma CRP levels in women symptomatic with threatened preterm labour that 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).[209] This result was used in our decision-analytic modelling. In four studies of maternal plasma CRP measurements in 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).[205–207,214] 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 40*). The result of Cammu *et al.*[206] represented the largest higher-quality study and was therefore used for the decision-analytic modelling. A ROC plot of sensitivity versus specificity for serum CRP in symptomatic women predicting spontaneous preterm birth within 7 days of testing is shown in *Figure 41*. The accuracy of the CRP test in predicting spontaneous preterm births in symptomatic women who presented with threatened preterm labour is summarised in Appendix 5, *Table 90* and *Table 91*.

## Interleukin-6

Interleukin 6 (IL-6) is a protein compound produced in response to the presence of inflammation, usually in response to the presence of an infection. It can be found in amniotic fluid, cervical secretions and in maternal blood serum. Its presence or increasing values have

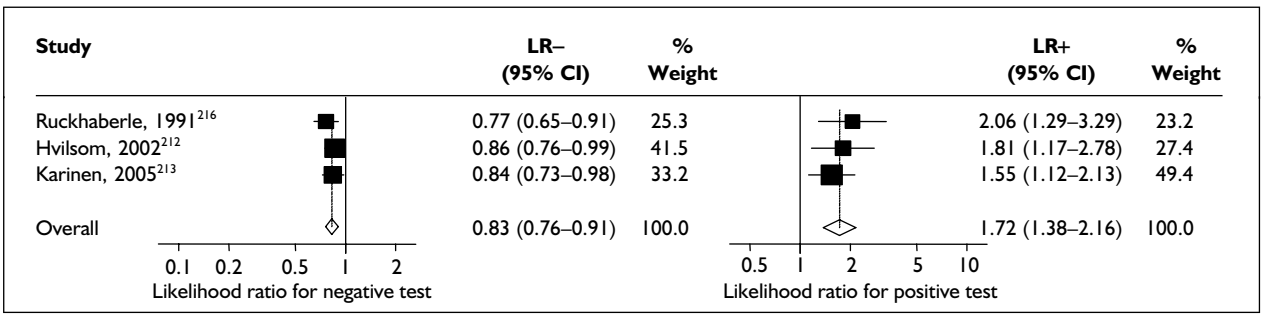


***FIGURE 38*** *Forest plots of likelihood ratios (LRs) of the accuracy of mid-trimester maternal serum C-reactive protein level measurement in asymptomatic women for predicting spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test $p = 0.59$ for LR+ and $p = 0.55$ for LR–. +Studies are arranged in descending order of methodological quality.*



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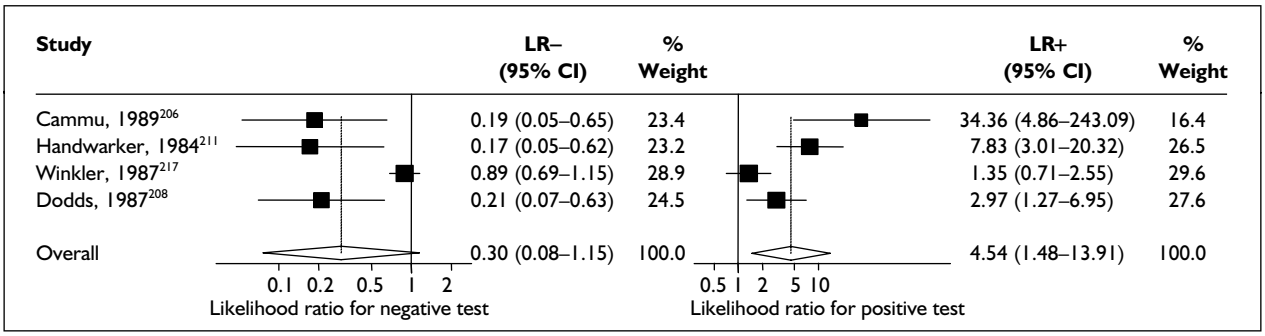


***FIGURE 39*** *Forest plots of likelihood ratios (LRs) of the accuracy of maternal serum C-reactive protein level measurement in symptomatic women with threatened labour for predicting spontaneous preterm birth within 7 days of testing. $\chi^2$ heterogeneity test $p = 0.001$ for LR+ and $p = 0.000$ for LR–. Studies are arranged in descending order of methodological quality.*

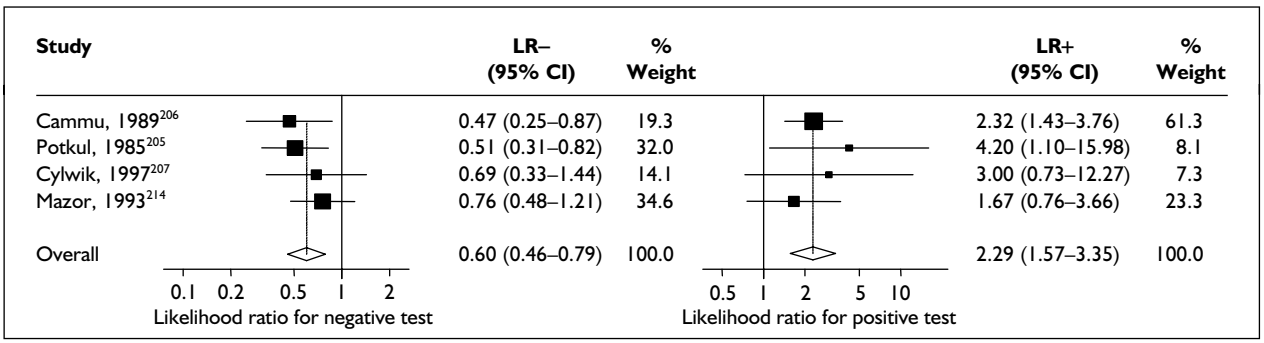


***FIGURE 40*** *Forest plots of likelihood ratios (LRs) for maternal serum C-reactive protein level measurement in symptomatic women with threatened labour for predicting spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test $p = 0.66$ for LR+ and $p = 0.53$ for LR–. Studies are arranged in descending order of methodological quality.*

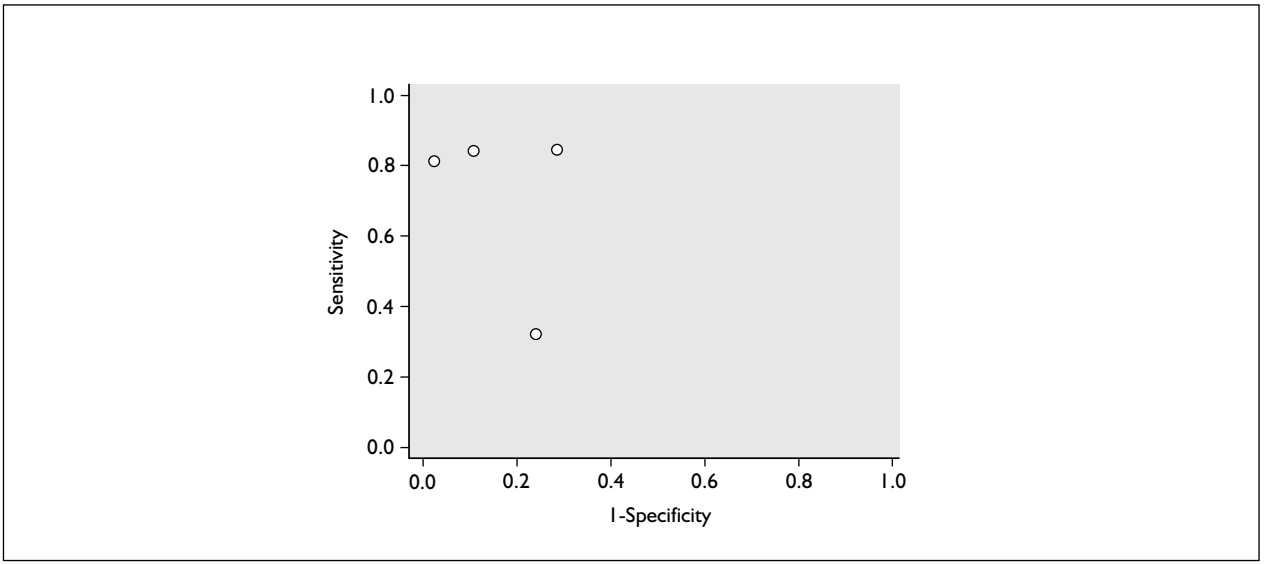


***FIGURE 41*** *Plot of sensitivity versus 1-specificity in ROC space for maternal serum measurement of C-reactive protein studies in symptomatic women with threatened preterm labour for predicting spontaneous preterm birth within 7 days of testing.*

been purported to predict spontaneous preterm birth in symptomatic women who presented with threatened preterm labour.[218]

## Study characteristics and quality

There were 26 primary studies ($n = 2594$ women) on the accuracy of IL-6 testing in predicting spontaneous preterm birth. However, one study,[219] which evaluated cervical IL-6 as predictor of spontaneous preterm birth in women who presented with symptoms of threatened preterm labour, was excluded because the author was not able to provide the data within the time constraint of the project. The number of women enrolled ranged from 73[103] to 290[220] with a median of 161 in asymptomatic women[221] and from 18[120] to 146[218] with a median of 73 in symptomatic women.[103] There were 12 studies evaluating the amniotic level of IL-6, two in asymptomatic women[220,222] and ten in symptomatic women,[120,218,223–230] as a predictor for spontaneous preterm birth. There were ten studies evaluating cervical IL-6, three in asymptomatic women[103,221,231] and seven in symptomatic women[90,103,232–236] as a predictor of spontaneous preterm birth in women. One study evaluated serial testing of cervical IL-6 in asymptomatic women.[221] There were five studies, all in symptomatic women who presented with threatened preterm labour, which evaluated serum IL-6 as a predictor for spontaneous preterm birth.[235,237–240] Two studies provided information for more than one category of either population[103] or type of IL-6 specimen.[235] Appendix 5, *Table 92* summarises individual study characteristics.

Three studies fulfilled our ideal definition of high-quality test accuracy studies.[103,221,227] 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 reporting consecutive enrolment[103,227,233] and blinding of test results, where only eight studies reported it.[90,103,120,224,225,227,237,238] The methodological quality of the primary studies included is summarised in *Figure 42*. No two studies had reported using the same threshold. Three studies on asymptomatic women reported birth before 37 weeks' gestation as their reference standard[103,220,221] and one each for birth before 34 weeks'[222] and 35 weeks' gestation.[231] For symptomatic women, one study reported spontaneous preterm birth within 24 hours,[240] five studies within 48 hours[120,223,225,237,239] and four studies reported birth within 5–7 days of testing,[226,236,238,241] while the remainder reported birth before 35–37 weeks' gestation.[90,103,218,224,227–230,233,235]

## Accuracy of IL-6 in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, a single amniotic fluid IL-6 measurement had a range of LR+ of 2.65 (95% CI 1.37–5.14)[220] to 2.95 (95% CI 0.96–9.04)[222] ($\chi^2$ heterogeneity test $p = 0.87$) and LR– of 0.84 (95% CI 0.62–1.13)[222] to 0.91 (95% CI 0.84–0.98)[220] ($\chi^2$ heterogeneity test $p = 0.57$) (*Figure 43*). For predicting spontaneous preterm birth before 37 weeks' gestation, a single amniotic fluid IL-6 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 43*).[220] LR estimates from one study were used for decision-analytic modelling because it represented the largest higher-quality study available for amniotic fluid IL-6 in asymptomatic women for predicting spontaneous preterm birth before 34 and 37 weeks' gestation.[220] Serial testing of cervical IL-6 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.[221] Single testing of cervical IL-6 in asymptomatic women had a range of LR+ from 0.564 (95% CI 0.08–3.97)[103] to 2.08 (95% CI 1.10–3.96)[231] and a range of LR– from 0.88 (95% CI 0.80–0.98)[231] to 1.08 (95% CI 0.87–1.35)[103] for predicting spontaneous preterm birth before 37 weeks' gestation ($\chi^2$ heterogeneity test $p = 0.14$ for LR+ and $p = 0.003$ for LR–). *Figure 43* summarises the accuracy results for amniotic fluid IL-6 in predicting spontaneous preterm birth in asymptomatic women. LR estimates from two studies were used for decision-analytic modelling because they represented the largest higher-quality study available for cervical IL-6 in asymptomatic women for preterm birth before 37 weeks' gestation for single and serial testings.[103,221] There is no information on birth before 34 weeks' gestation using cervical IL-6 testing. Individual accuracy results can be found in Appendix 5, *Table 93*.

## Accuracy of IL-6 in symptomatic women

For predicting spontaneous preterm birth within 7–10 days of testing, cervical IL-6 had a range of LR+ from 2.40 (95% CI 1.37–4.23)[234] to 4.01 (95% CI 2.02–7.96)[236] and a range of LR– from 0.12 (95% CI 0.01–1.72)[234] to 0.66 (95% CI 0.51–0.85).[236] LR estimates from one study were used for decision-analytic modelling because it represented



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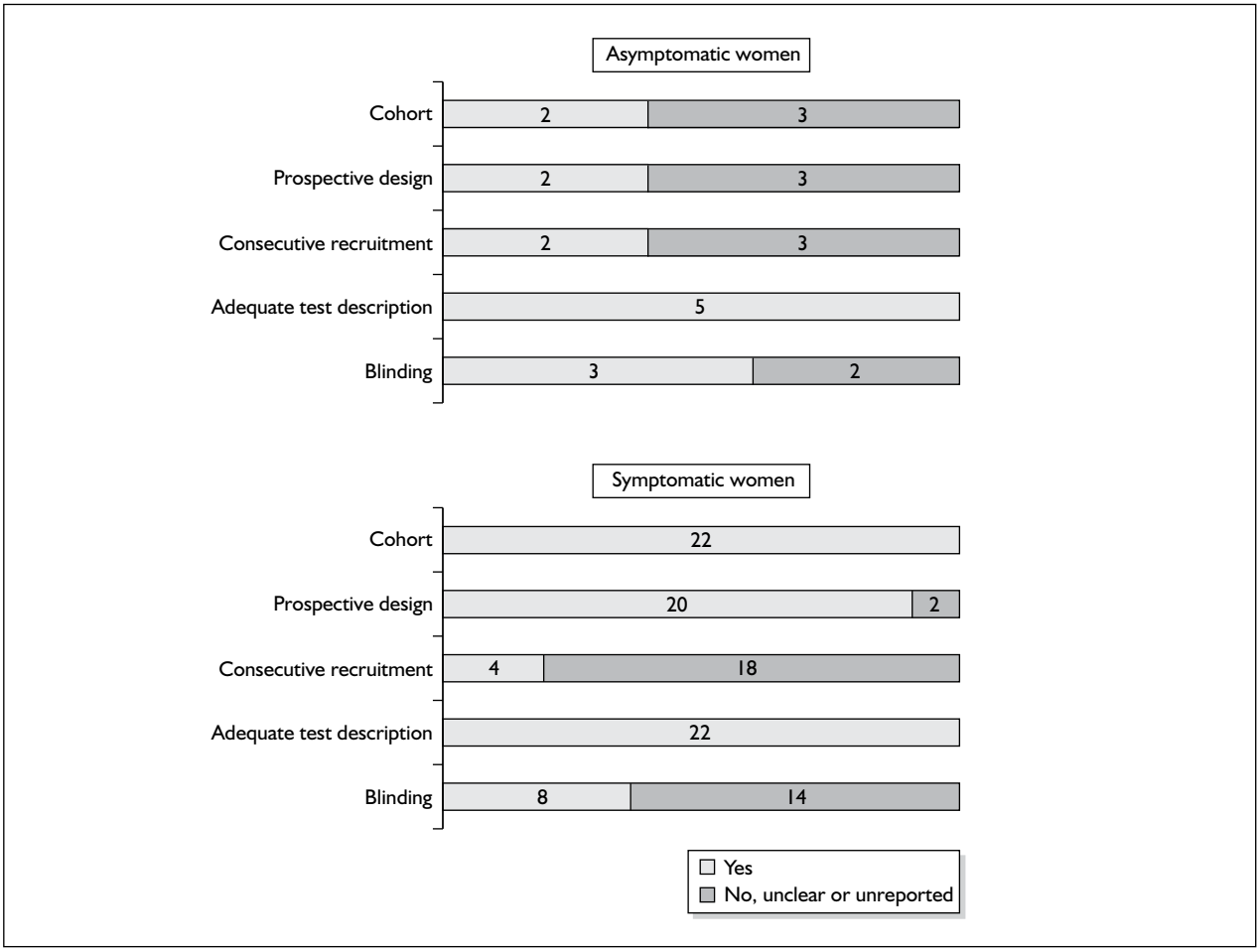


***FIGURE 42*** *Methodological quality of studies included in the systematic review of accuracy of interleukin-6 in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

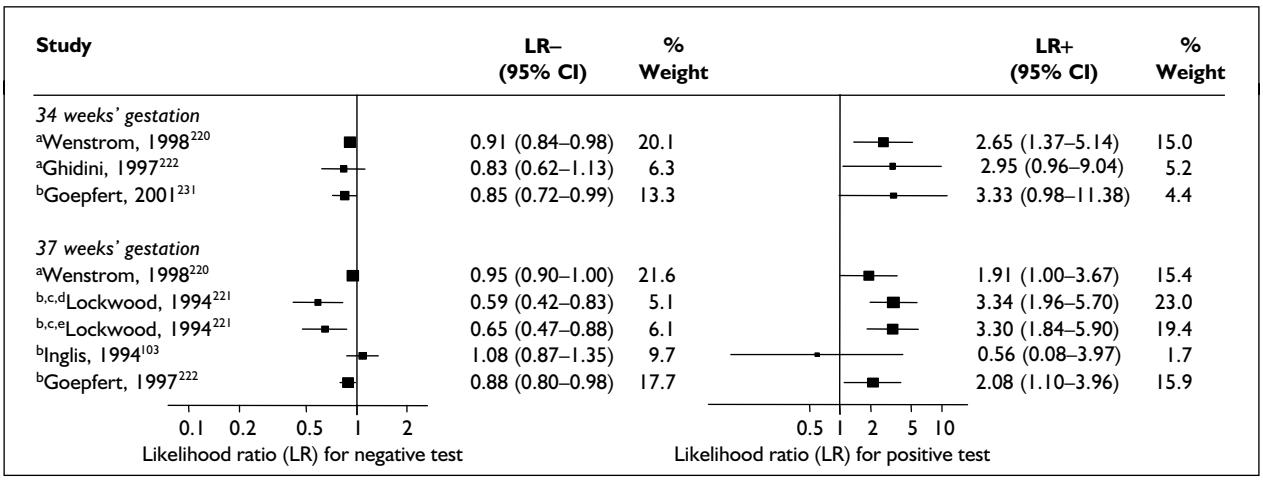


***FIGURE 43*** *Forest plots of likelihood ratios (LRs) of amniotic fluid interleukin-6 (IL-6)measurement as a predictor of spontaneous preterm birth. Studies are arranged in descending order of methodological quality for each type of test. For individual thresholds see Table 92, Appendix 5. a, Amniotic fluid measurement of IL-6. b, Cervicovaginal measurements of IL-6. c, Serial measurement (repeated after a 3- to 4-week interval). d, Threshold 250 pg/ml. e, Threshold 125 pg/ml.*

the largest higher-quality cervical IL-6 study available in symptomatic women for predicting spontaneous preterm birth within 7–10 days of testing.[236] Amniotic fluid measurement of IL-6 had a range of LR+ from 2.43 (95% CI 1.36–4.36)[226] to 7.01 (95% CI 2.75–17.90)[225] and a range of LR– from 0.17 (95% CI 0.06–0.49)[225] to 0.24 (0.09–0.61)[226] LR estimates from Greci *et al.*,[225] the largest higher-quality study for this reference standard, were used in the decision-analytic modelling. Serum measurement of IL-6 had an LR+ of 3.34 (95% CI 1.48–7.53) and LR– of 0.44 (95% CI 0.30–0.66).[239] The accuracy results for the different types of IL-6 sources are shown in *Figure 44*.

For predicting spontaneous preterm birth before 34 weeks' gestation (*Figure 45*), amniotic fluid IL-6 had an LR+ of 7.44 (95% CI 2.01–27.52) and LR– of 0.14 (95% CI 0.06–0.36).[226] For predicting spontaneous preterm birth before 34 weeks' gestation, cervical IL-6 had a range of LR+ from 2.63 (95% CI 1.44–4.79)[234] to 4.92 (95% CI 1.80–13.46)[236] and LR– from 0.097 (95% CI 0.01–1.45)[234] to 0.74 (95% CI 0.63–0.87);[236] the latter estimates were used in the decision-analytic modelling because the study represented the largest higher-quality study of cervical IL-6 in this reference standard. Serum IL-6 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.[237]

For predicting spontaneous preterm birth before 37 weeks' gestation, amniotic fluid IL-6 had a range of LR+ from 4.92 (95% CI 1.26–19.29)[229] to 28.62 (95% CI 1.78–461.04)[227] and LR– from 0.05 (95% CI 0.003–0.76)[230] to 0.66 (95% CI 0.54–0.80).[227] Estimates from Rizzo *et al.*[227] were used for the decision-analytic modelling because their study represented the largest higher-quality study for this reference standard. For the same reference standard, cervical IL-6 had a range of LR+ from 1.83 (95% CI 0.79–4.25)[103] to 14.0 (95% CI 2.03–96.62)[235] and LR– from 0.10 (95% CI 0.01–1.45)[234] to 1.29 (95% CI 0.75–2.20) (*Figure 45*).[90] Estimates from Inglis *et al.*[103] were used for the decision-analytic modelling because their study represented the sole ideal-quality study within this subgroup of reference standards of spontaneous preterm birth before 37 weeks' gestation. Serum IL-6 had an LR+ of 1.13 (95% CI 0.55–2.32) and LR– of 0.92 (95% CI 0.54–1.56).[235] A ROC plot of sensitivity versus specificity for amniotic and cervical fluid in symptomatic women is shown in *Figure 46*. The accuracy of IL-6 in predicting spontaneous preterm birth in asymptomatic and symptomatic women is summarised in Appendix 5, *Table 93*.

## Interleukin-8

Similar to IL-6, interleukin-8 (IL-8) is a protein compound produced in response to the presence of inflammation usually in response to the presence of an infection. It can be found in amniotic fluid, cervical secretions and in maternal blood serum. Its presence in cervicovaginal secretions[219] or in increasing values in maternal serum[223] have been purported to predict spontaneous preterm birth in symptomatic women who presented with threatened preterm labour.

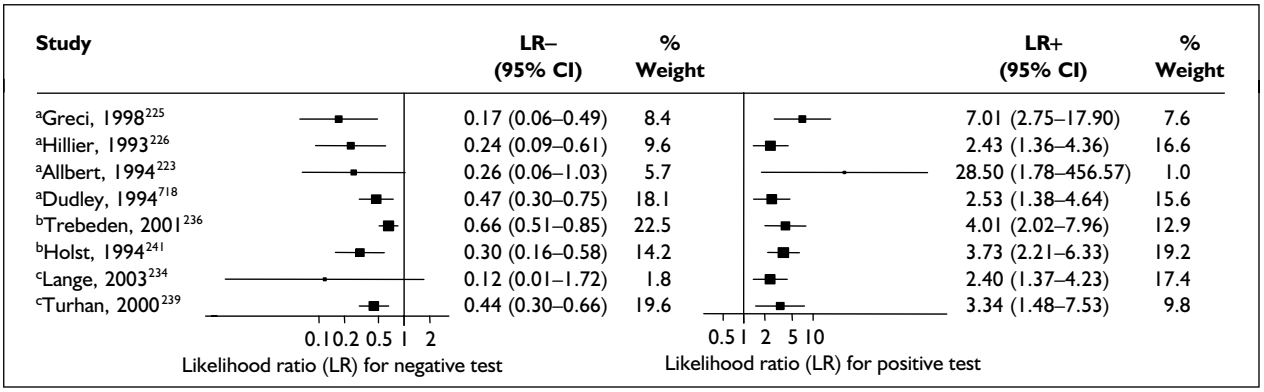


***FIGURE 44*** *Forest plots of likelihood ratios (LRs) of interleukin-6 measurement from amniotic fluid and cervical specimen as a predictor of spontaneous preterm birth within 7–10 days of testing in symptomatic women. Studies are arranged in descending order of methodological quality for each type of test. a, Amniotic fluid measurement of IL-6. b, Cervicovaginal measurements of IL-6. c, Serum measurement of IL-6.*



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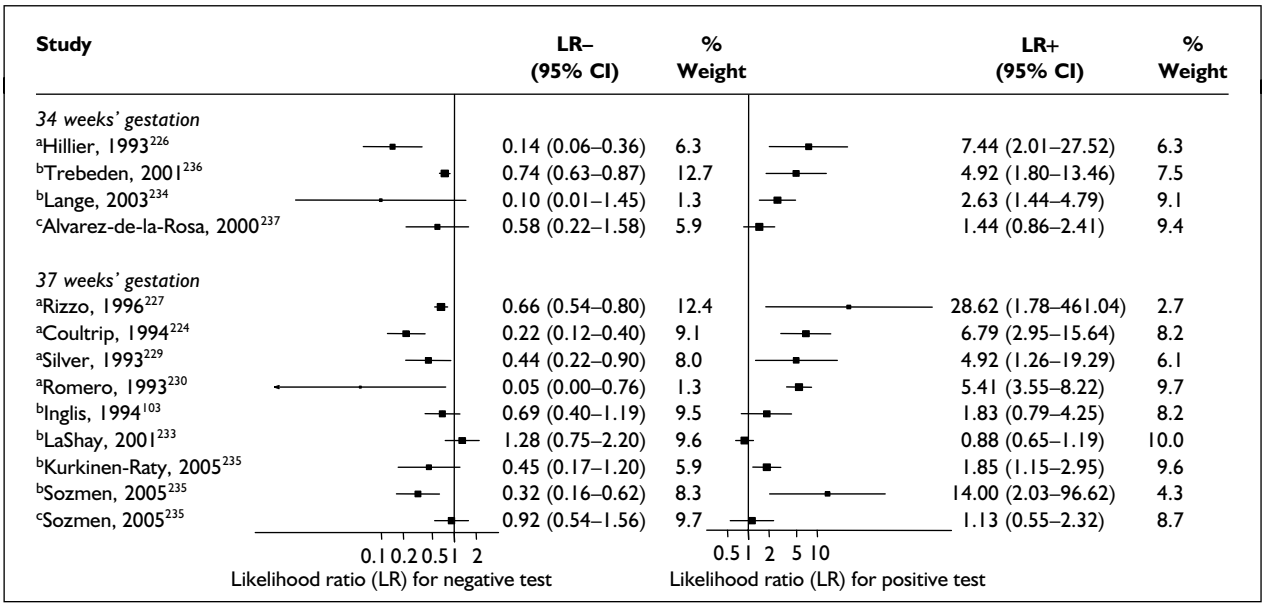


***FIGURE 45*** *Forest plots of likelihood ratios (LRs) of interleukin-6 (IL-6) measurement from amniotic fluid, cervical swab and serum specimen as a predictor of spontaneous preterm birth before 34 and 37 weeks' gestation. Studies are arranged in descending order of methodological quality for each type of test. a, Amniotic fluid measurement of IL-6. b, Cervicovaginal measurements of IL-6. c, Serum measurement of IL-6.*

## Study characteristics and quality

There were five primary studies, involving altogether, a total of 568 women. Three potentially eligible studies for inclusion were excluded because data were unobtainable.[219,240,242] Appendix 5, *Table 94* summarises each study's salient features, stratified according to the population of women tested, i.e. asymptomatic antenatal women (two studies)[243,244] and women with symptoms of threatened preterm labour (three studies).[223,232,233] One of the included studies, on the asymptomatic antenatal population, had the test performed two-weekly between 24 and 28 weeks' gestation.[244] Except for one study,[223] the studies evaluated IL-8 in cervicovaginal specimens.

None of the studies fulfilled our 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[223,232,233] and only one study, in symptomatic women, reported consecutive enrolment.[233] All studies in both asymptomatic and symptomatic women provided adequate test descriptions. The methodological quality of the included primary studies is summarised in *Figure 47*. 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[244] additionally reported birth before 32 and 34 weeks' gestation and had performed their test serially with a two-weekly interval. For symptomatic women, one study reported spontaneous preterm birth within 24 hours,[240] five studies within 48 hours[120,223,225,237,239] and four studies reported birth within 5–7 days of testing,[226,236,238,241] while the remainder reported birth before 35–37 weeks' gestation.[90,103,218,224,227–230,233,235] There was an insufficient number of studies for statistical heterogeneity analysis to be conducted in the case of IL-8.

## Accuracy of IL-8 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 involved serial testing of cervical IL-8, LR+ was 2.23 (95% CI 1.46–3.41) and LR– was 0.69 (0.50–0.97).[244] These values were used for the decision-analytic modelling. For predicting spontaneous preterm birth before 37 weeks' gestation, the LR+ ranged from 1.38 (95% CI 1.04–1.81)[244] to LR+ 2.75 (95% CI 1.68–4.52)[243] while LR– ranged from 0.68 (95% CI 0.49–0.95)[243] to 0.91 (95% CI 0.82–1.01).[244] LRs from Sakai *et al.*[244] were used in the decision-analytic modelling because it represented the largest higher-quality

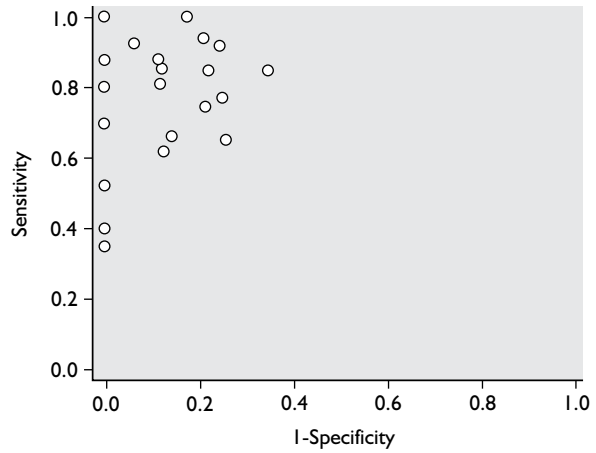


***FIGURE 46*** *Plot of sensitivity versus 1-specificity in ROC space for amniotic fluid and cervicovaginal interleukin-6 (IL-6) studies in symptomatic women with threatened preterm labour in predicting spontaneous preterm birth within 48 hours and 7 days of testing, and before 34 weeks' gestation.*

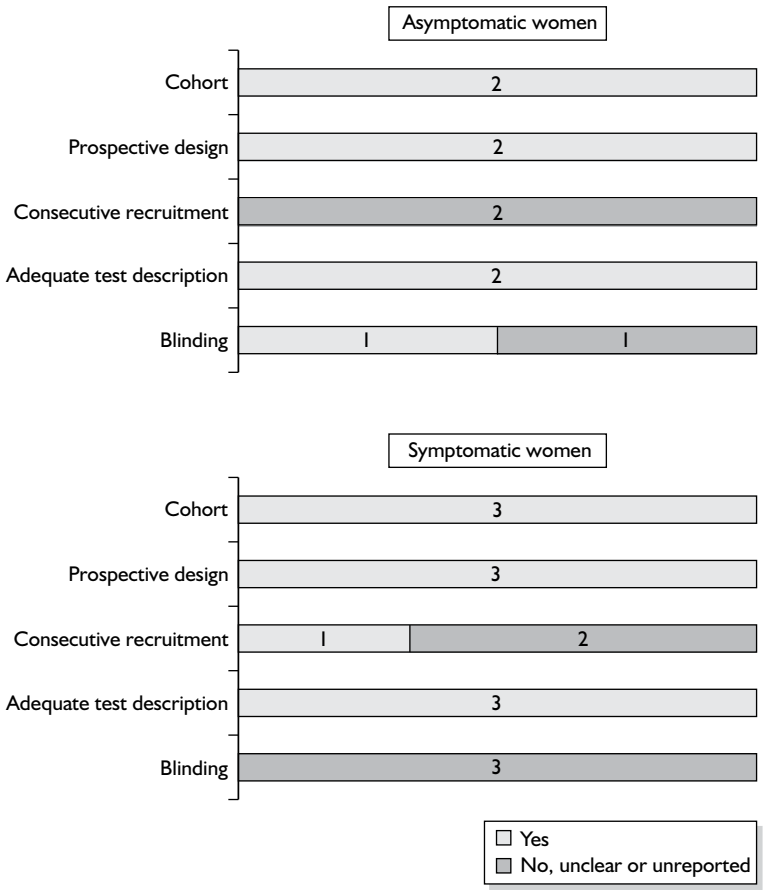


***FIGURE 47*** *Methodological quality of studies included in the systematic review of accuracy of test for interleukin-8 (IL-8) in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*



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study available for the population. *Figure 48* shows the forest plots of the accuracy of the IL-8 test in predicting spontaneous preterm birth. Individual accuracy measures of the test are summarised in Appendix 5, *Table 95*.

### Accuracy of IL-8 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– was 0.10 (95% CI 0.007–1.42); these LRs were used in the decision-analytic modelling.[223] The accuracy for predicting spontaneous preterm birth within 7 days of testing was shown in *Figure 48* where the LR+ ranged from 2.34 (95% CI 1.42–3.84) (cervical IL-8)[241] to 28.5 (95% CI 1.78–456.57) (amniotic fluid IL-8)[223] and LR– ranged from 0.26 (95% CI 0.06–1.03) (amniotic fluid IL-8)[223] to 0.52 (95% CI 0.32–0.84) (cervical IL-8).[241] The LR+ from Holst *et al.*[241] was used in the decision-analytic modelling because it 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– was 0.67 (95% CI 0.30–1.50); these LRs were used in the decision-analytic modelling.[233] *Figure 48* shows the forest plots of the accuracy of the IL-8 test in predicting spontaneous preterm birth. A ROC plot of sensitivity versus specificity for amniotic fluid IL-8 in symptomatic women is shown in *Figure 49*. Individual accuracy measures of the test are summarised in Appendix 5, *Table 95*.

## Matrix metalloprotease-9

During pregnancy, matrix metalloprotease-9 (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 involves the disruption of decidua–membrane interface, measurement of MMP-9 may served as a marker for impending preterm labour that leads to spontaneous preterm birth.[245]

### Study characteristics and quality

There were two 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 ($n = 15$)[245] while the other ($n = 20$) evaluated it in maternal plasma and urine specimens.[246] There were no studies on asymptomatic women.

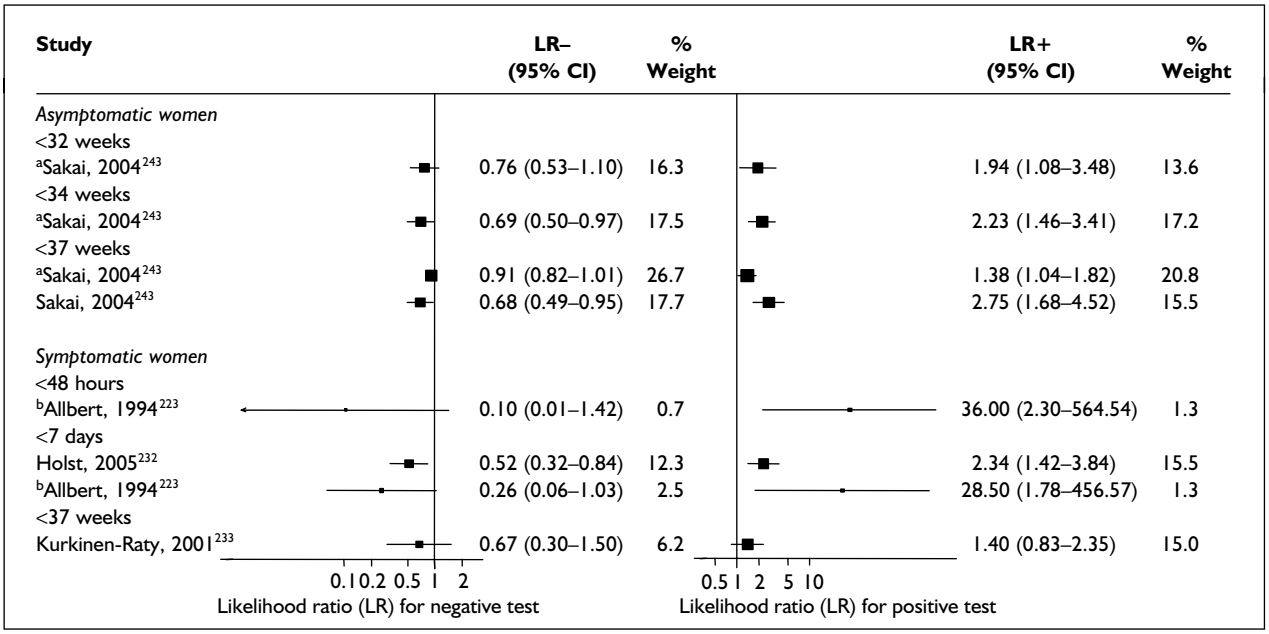


***FIGURE 48*** *Forest plots of likelihood ratios (LRs) of interleukin-8 (IL-8) measurement from amniotic fluid and cervical specimen as a predictor of spontaneous preterm birth stratified according to population and outcome. Studies are arranged in descending order of methodological quality and unless otherwise stated, were single testing, using samples obtained from cervicovaginal swabs. a, Serial testing. b, Amniotic fluid specimens.*

Appendix 5, *Table 96* summarises 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 our ideal definition of high-quality test accuracy studies either in asymptomatic or symptomatic women. Neither of the studies reported using consecutive enrolment of women into the study or blinding of carers or assessors to test results. However, both studies have an adequate test description report. The methodological quality of the included primary studies is summarised in *Figure 50*.

### 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)[245] and an LR– of 0.37 (95% CI 0.14–0.94)[246] 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)[246] and LR– from 0.37 (95% CI 0.14–0.94)[246] to 0.38 (95% CI 0.12–1.19) (*Figure 51*).[245] Estimates from Makrakis *et al.*[246] were used in decision-analytic modelling because their study represented the largest higher-quality study for this reference standard. Individual accuracy results for symptomatic women can be found in Appendix 5, *Table 97*.

## Periodontal assessment

Periodontal health care is provided 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.[247]

### 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 ($n = 3900$ women).[247–259] The number of women enrolled ranged from 36[249] to 1313[247] with a median of 128. Two studies published their preliminary results ($n = 176$ women), but their full results were not available at the time of writing.[251,258] The accuracy of one study was not evaluated further because data were not extractable from the publication and the corresponding author was not able to provide it within the time scale of this project.[253] 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. Appendix 5, *Table 98* 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.

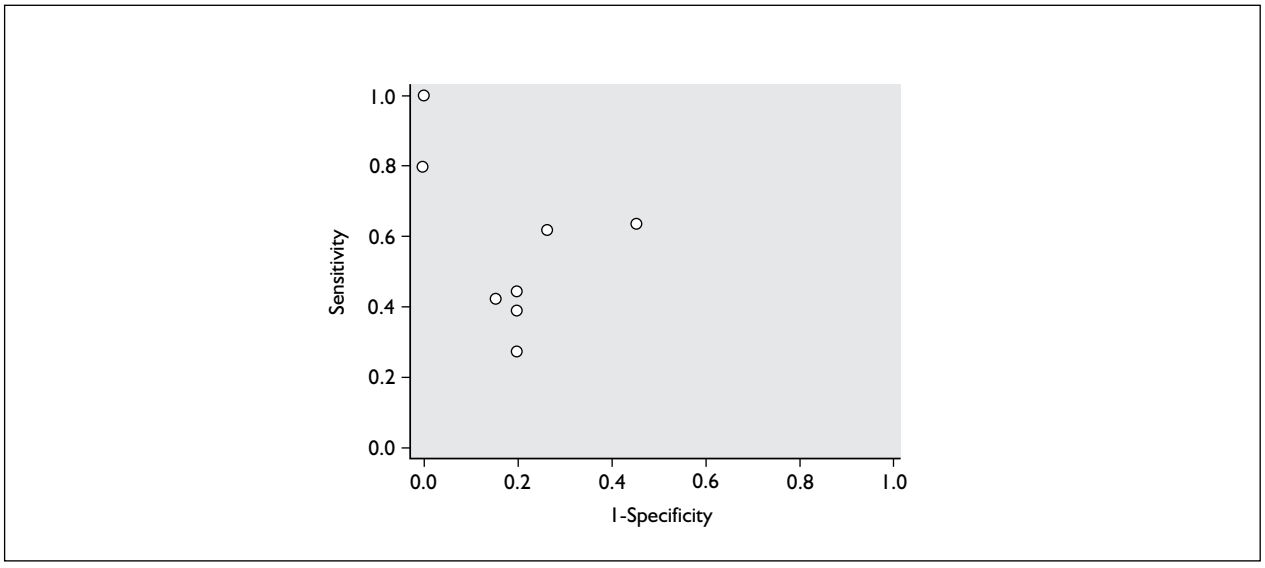


***FIGURE 49*** *Plot of sensitivity versus 1-specificity in ROC space for amniotic fluid interleukin-8 (IL-8) studies in symptomatic women with threatened preterm labour in predicting spontaneous preterm birth within 48 hours or 7 days of testing.*



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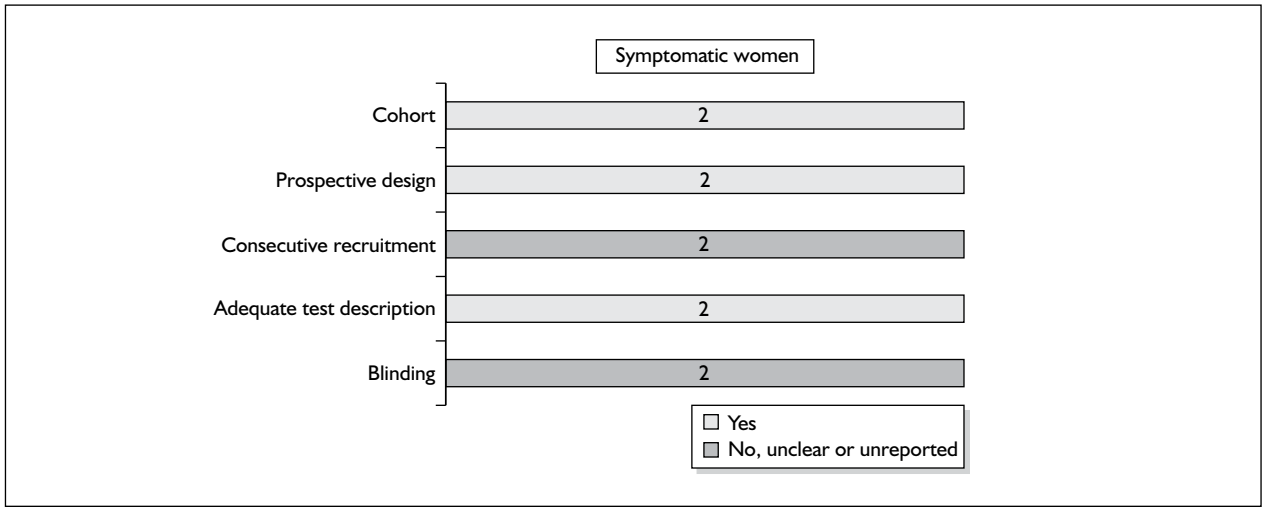


***FIGURE 50*** *Methodological quality of studies included in the systematic review of accuracy of matrix metalloprotease-9 in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

None of the studies fulfilled ideal quality study designs. There were ten studies that reported prospective data collection[247–251,253,255–257,259] and six that reported case–control design.[248,250,252,254,256,258] Consecutive enrolment was only evident in one study.[247] Blinding was reported in eight studies.[247,248,250,253,255–258] Overall, there were adequate reports of test description from the studies. The methodological quality of the included primary studies is summarised in *Figure 52*.

All but one study assessed women's periodontal status for the presence of periodontitis. The remaining study assessed women's antibody serology for *Porphyromonas gingivalis,* the predominant organism implicated in periodontitis in the general population.[248] Seven studies performed their periodontal assessment in the second trimester[247–249,251,253,255,259] while six studies performed theirs within 2–5 days of delivery.[250,252,254,256–258] 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,[250 255] most studies had used 37 weeks' gestation as their reference standard.

## Accuracy of periodontal assessment in asymptomatic women

The presence of periodontal disease showed variable accuracy in predicting spontaneous preterm birth (*Figure 53*). The LR+ ranged from 0.38 (95% CI 0.04–3.33)[256] to 5.00 (95% CI 2.22–11.28)[249] and the LR– ranged from 0.22 (95% CI 0.09–0.57)[257] to 1.13 (95% CI 0.90–1.42).[251]

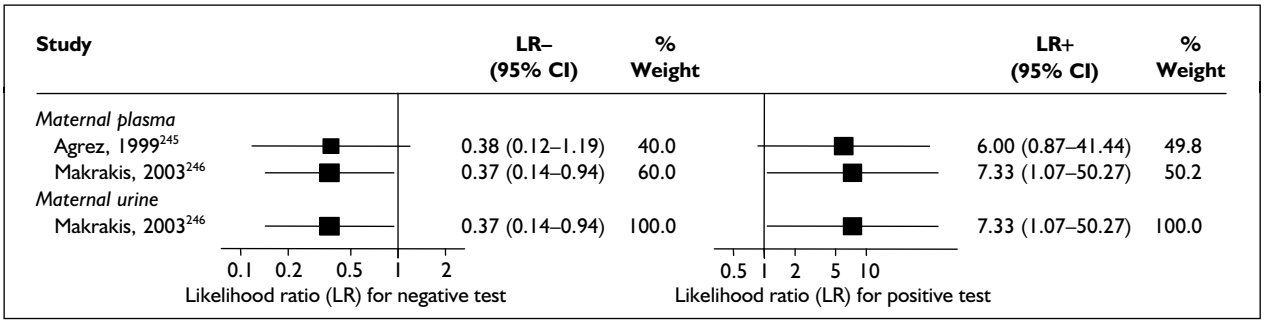


***FIGURE 51*** *Forest plots of likelihood ratios of MMP-9 in predicting spontaneous preterm birth before 37 weeks' gestation in symptomatic women. Studies are arranged in descending order of methodological quality.*

The largest higher-quality study reported LR+ of 2.26 (95% CI 1.35–3.79) and LR– of 0.79 (95% CI 0.65–0.96).[247] These estimates were used for the decision-analytic modelling. The individual accuracy result of the state of periodontal health in predicting spontaneous preterm birth in asymptomatic women is summarised in Appendix 5, *Table 99*. Meta-analysis was not performed because of the clinical heterogeneity in the criteria defining periodontal disease.

## Asymptomatic bacteriuria assessment

Screening for asymptomatic bacteriuria has been a routine component of antenatal care. When present, it 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 the recognised contribution of vaginal colonisation to the development of spontaneous preterm labour, there is even a call to re-evaluate the usefulness of screening for asymptomatic bacteriuria.[260] One systematic review had been performed.[261]

### Study characteristics and quality

There were 26 studies ($n = 66,824$) evaluating the accuracy of screening for asymptomatic bacteriuria in predicting spontaneous preterm birth.[262–287] Three of the included studies ($n = 11,520$) evaluated the accuracy of asymptomatic group B streptococcal bacteriuria exclusively.[274,275,286] All the studies used birth before 37 weeks' gestation as their outcome measurement. Appendix 5, *Table 100* summarises the characteristics of the included studies.

None of the studies fulfilled our criteria for an ideal quality study. Specifically, blinding was absent from all the studies. Only six and nine studies used consecutive enrolment[271,274,275,278,283,287] and prospective data collection,[271,274,275,277,278,283,284,287] respectively. *Figure 54* summarises 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 55*). LR+ ranged from 0.10 (95% CI 0.01–1.70)[265] to 3.83 (95% 2.22–6.59)[269] while LR– ranged from 0.43 (95% CI 0.19–0.94) to 1.17 (95% CI 0.64–2.13)[263] for asymptomatic bacteriuria. For asymptomatic group B streptococcal bacteriuria, LR+ ranged from 1.52 (95% CI 0.80–2.86)[286] to 2.69 (95% CI 1.51–4.76)[275] and LR– ranged from 0.96 (95% CI 0.88–1.04)[274] to 0.99 (95% CI 0.98–1.01).[286] The LR+ of 2.63 (95% CI 1.54–4.50) and LR– of 0.96 (95% CI 0.92–0.99) from Wren[287] was used in the decision-analytic modelling because it represented the best higher-quality study available. Individual accuracy data are summarised in Appendix 5, *Table 101*.

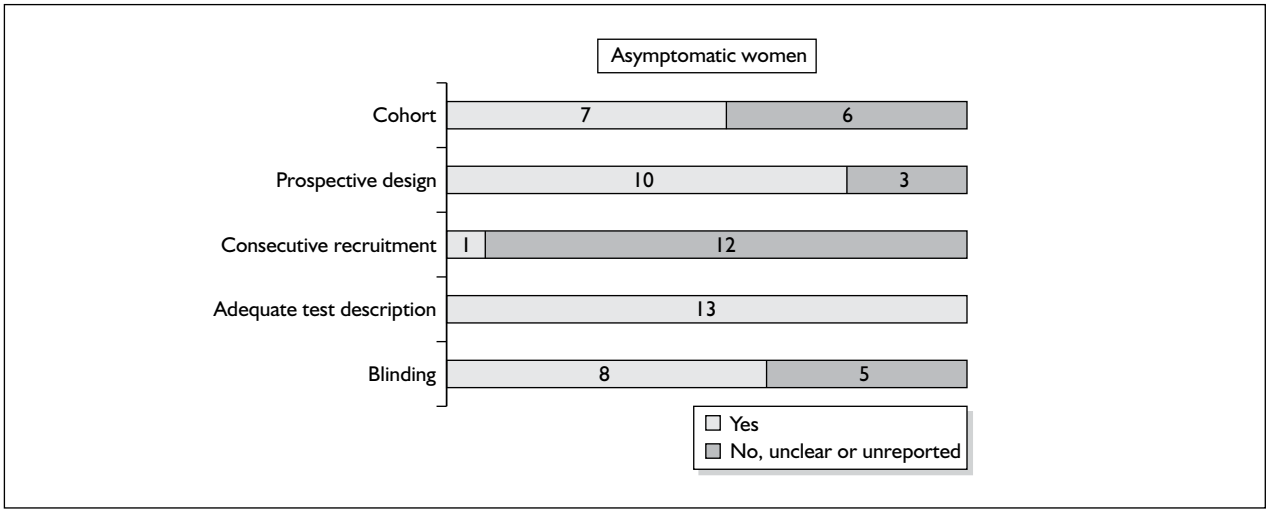


***FIGURE 52*** *Methodological quality of studies included in the systematic review of accuracy of periodontal health assessment in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*



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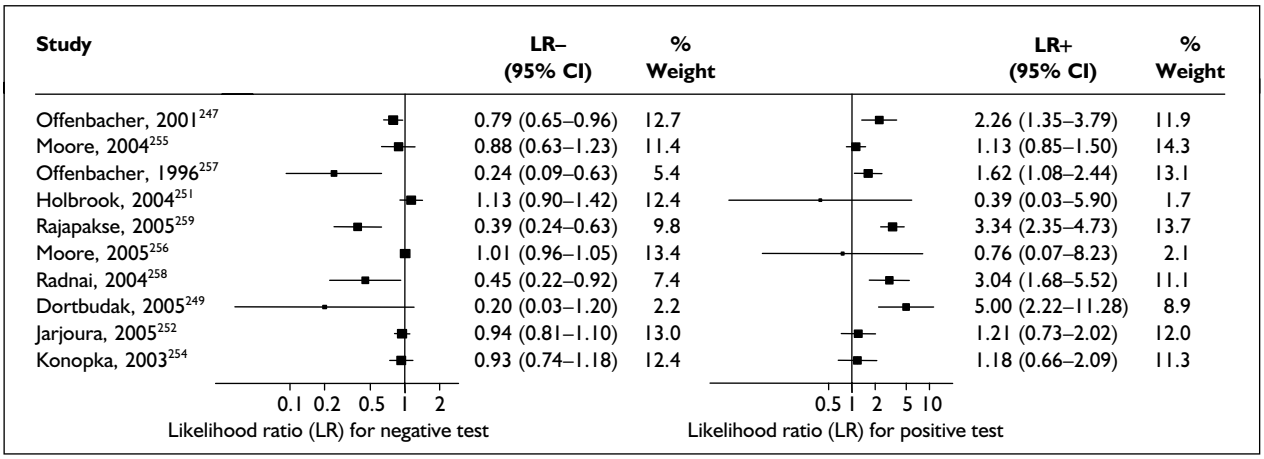


***FIGURE 53*** *Forest plots of likelihood ratios of periodontal health status in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic women. Studies using the same source of IL-6 are arranged in descending order of methodological quality.*

## Bacterial vaginosis

Bacterial vaginosis (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 a high vaginal swab specimen during speculum examination for clinical evaluation (Amsel criteria), Gram staining (Nugent or Spiegel 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 17 studies on asymptomatic antenatal women ($n = 33{,}628$) and eight studies on symptomatic women who presented with threatened preterm labour ($n = 2024$). Appendix 5, *Table 102* summarises each study's salient features, stratified according to the 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[288,289] with a median of 646 women in the asymptomatic population and from 87 to 753 women[241,290] with a median of 211 women for the symptomatic population.

No studies included within the systematic review of the accuracy of BV testing in predicting spontaneous preterm births fulfilled our ideal definition of high-quality test accuracy studies. Blinding of carers to the results of BV tests was often absent from studies on asymptomatic[289,291–296] and symptomatic[241,290,297–299] women. For symptomatic women, six studies had used a case–control design to assess the accuracy of BV testing in predicting spontaneous preterm births in symptomatic women.[241,290,297,299–301] The methodological quality of the included primary studies is summarised in *Figure 56*.

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 were Gram staining using Spiegel's[241,297,301] and bedside diagnosis using Amsel's clinical criteria.[99,296,299,302] Three studies evaluated the accuracy of serial BV testing in asymptomatic pregnant women for predicting spontaneous preterm births[295,303,304] while the remainder evaluated a single BV testing, usually performed at mid-trimester.[99,288,289,291–293,295,303–307]

One study in asymptomatic antenatal women collected data for the prediction of spontaneous preterm births at 23–26 weeks' gestation but was not published.[288] Otherwise, most studies reported births before 37 weeks' gestation as their reference standards with two exceptions; one study used birth before 32 and 34 weeks' gestation as its reference standard[291] while another study used 35 weeks' gestation as its reference standard.[294] Similarly, for symptomatic women, the most commonly used reference standard was births before 37 weeks' gestation, except for three studies that reported births within 7 days of testing and before 33 weeks'

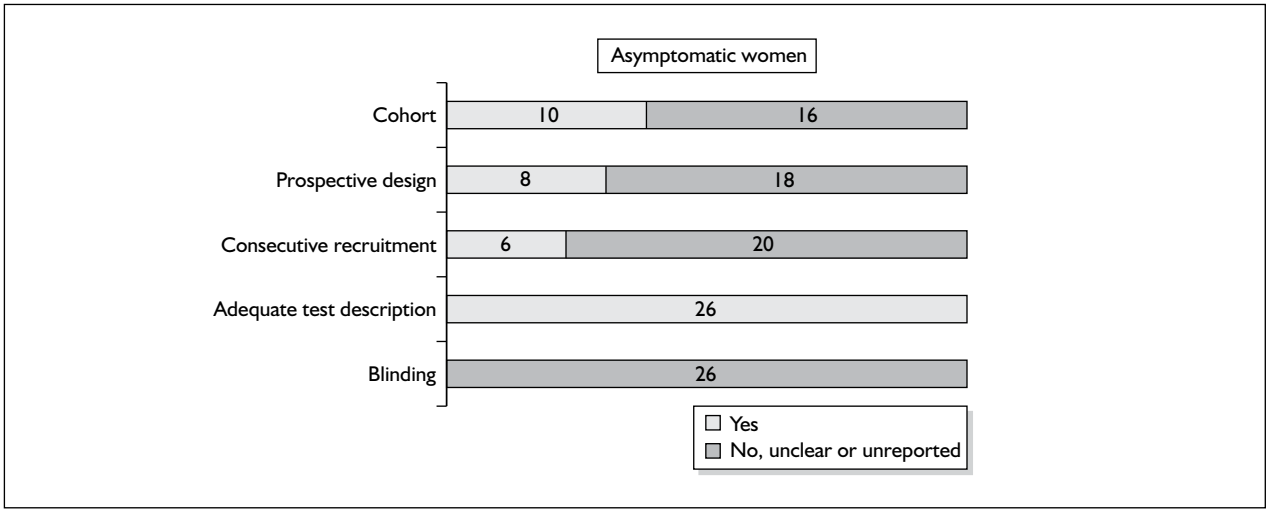


***FIGURE 54*** *Methodological quality of studies included in the systematic review of accuracy of asymptomatic bacteriuria assessment in predicting spontaneous preterm birth among asymptomatic antenatal women. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

gestation,[308] birth before 34 weeks' gestation[241] and births before 35 weeks' gestation.[298] One study reported birth within 7 days of testing.[308]

### 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) ($\chi^2$ heterogeneity test $p = 0.00$) 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) ($\chi^2$ heterogeneity test $p = 0.00$) (*Figure 57*). LR+ of 0.80 (95% CI 0.38–1.72) and LR– of 1.04 (95% CI 0.92–1.17) from the sole ideal quality study were used in the decision-analytic modelling.[293] 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) ($\chi^2$ 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) ($\chi^2$ heterogeneity test $p = 0.96$) (*Figure 58*). LR+ 1.92 (95% CI 0.63–5.92) and LR– 0.93 (95% CI 0.79–1.10) from the largest higher-quality study[304] was used in the decision-analytic modelling. 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)[302] to 1.62 (95% CI 0.44–5.91)[99] ($\chi^2$ heterogeneity test $p = 0.67$) and LR– from 0.90 (95% CI 0.63–1.29)[99] to 1.02 (95% CI 0.93–1.12) ($\chi^2$ heterogeneity test $p = 0.79$) (*Figure 59*).[302] Individual accuracy results can be found in Appendix 5, *Table 103*.

### Accuracy of BV in symptomatic women

For predicting spontaneous preterm birth before 37 weeks' gestation, BV testing (using Nugent's criteria) 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) ($\chi^2$ 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) ($\chi^2$ heterogeneity test $p = 0.10$) (*Figure 60*). For predicting spontaneous preterm birth before 37 weeks' gestation, BV testing (using Spiegel's criteria) 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) ($\chi^2$ 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) ($\chi^2$ heterogeneity test $p = 0.04$) (*Figure 60*). Individual accuracy results can be found in Appendix 5, *Table 103*.

## Mammary stimulation test

The antenatal mammary stimulation test is a provocative test of uterine contractility, which



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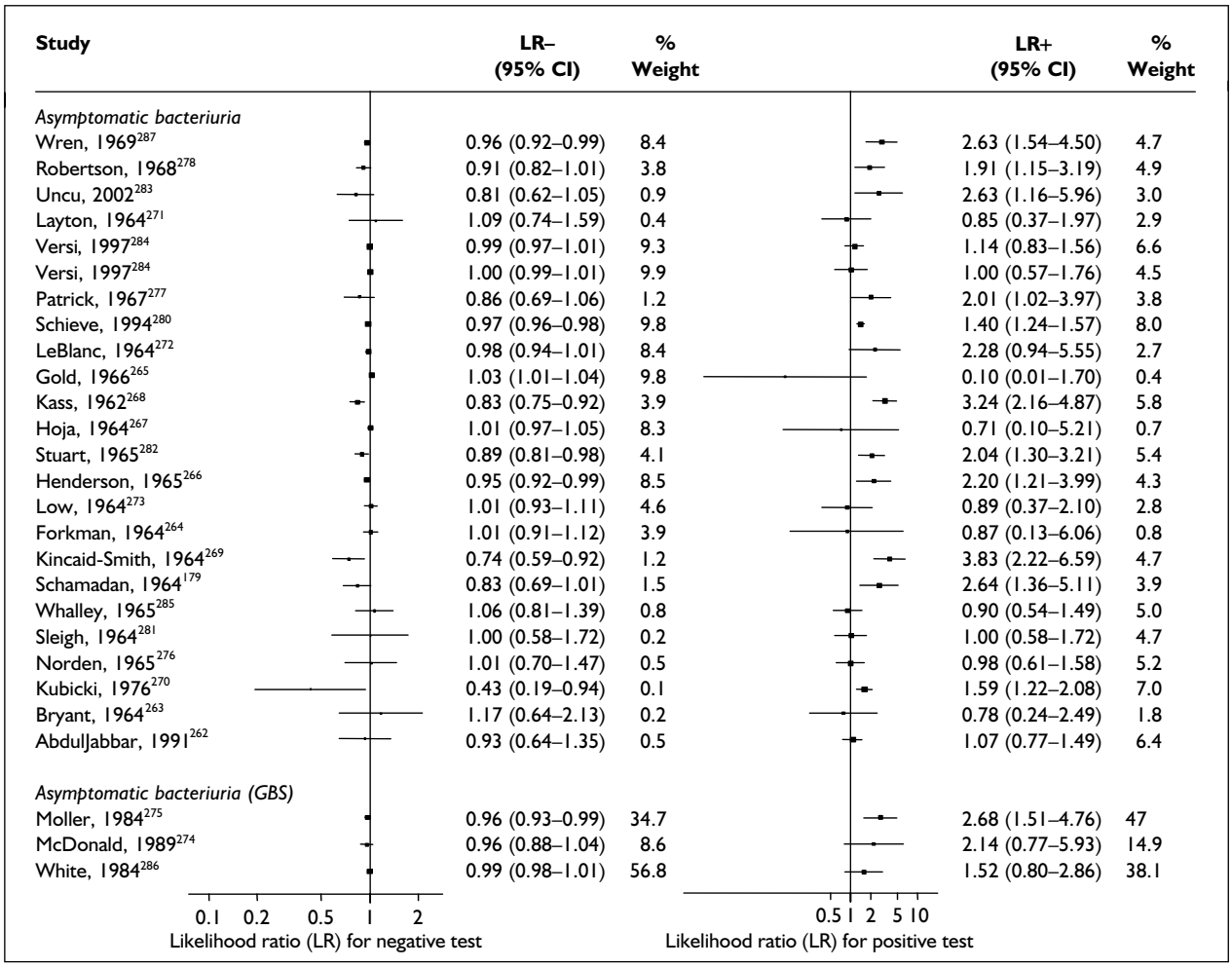


***FIGURE 55*** *Forest plots of likelihood ratios of asymptomatic bacteriuria assessment in asymptomatic women as a predictor of spontaneous preterm birth before 37 weeks' gestation stratified according to the type of asymptomatic bacteriuria. Studies are in descending order of quality. a. Caucasian population. b. Bangladeshi population. $\chi^2$ heterogeneity test for asymptomatic bacteriuria p = 0.00 for LR+ and p = 0.00 for LR–; for group B streptococcal asymptomatic bacteriuria p = 0.42 for LR+ and p = 0.16 for LR–.*

purported to identify asymptomatic women at high risk for spontaneous preterm birth. The presence of easily provoked uterine contractility is supposed to be an indication of higher risk of spontaneous preterm birth.

## Study characteristics and quality

There were two studies evaluating the mammary stimulation test, both in asymptomatic antenatal women ($n = 341$)[309,310] Both studies enrolled their population during the early third trimester. One study evaluated the accuracy in predicting spontaneous preterm birth before 34 weeks' gestation[310] while both evaluated the accuracy for prediction before 37 weeks' gestation. Neither of the studies fulfilled our criteria for an ideal quality study with consecutive enrolment being absent from both studies. *Figure 61* summarises the methodological quality of the included study. Both studies used the same test threshold. Individual study characteristics can be found in Appendix 5, *Table 104*.

## Accuracy of mammary stimulation test in asymptomatic women

For predicting spontaneous preterm birth before 34 weeks' gestation, the mammary stimulation test had an LR+ of 4.63 (95% CI 2.95–7.25) and LR– of 0.27 (0.08–0.91).[310] For predicting spontaneous preterm birth before 37 weeks' gestation the mammary stimulation test had a range of LR+ from 2.04 (95% CI 1.45–2.84)[309] to 3.30 (95% CI 1.54–7.08)[310] and LR– from 0.23 (0.06–0.85)[309] for those with a high Creasy risk score to 0.49

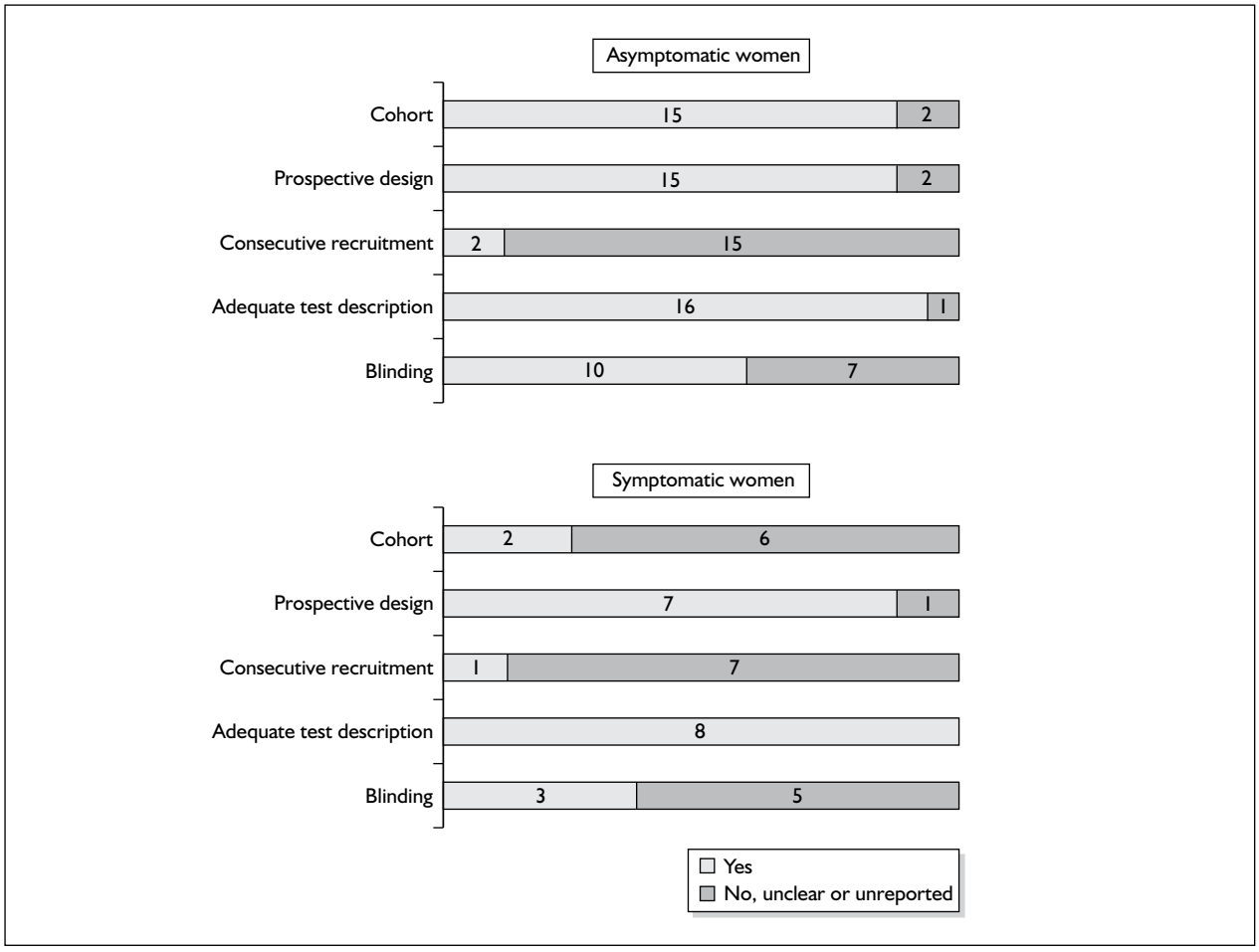


***FIGURE 56*** *Methodological quality of studies included in the systematic review of accuracy of bacterial vaginosis testing in predicting spontaneous preterm birth among asymptomatic antenatal women and symptomatic women who presented with threatened preterm labour. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

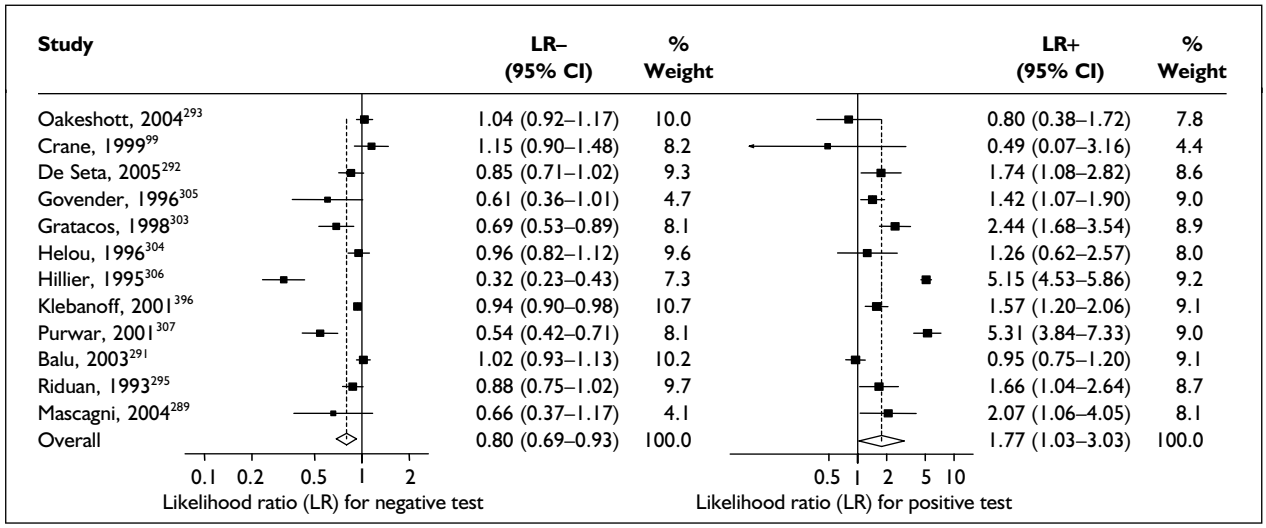


***FIGURE 57*** *Forest plots of likelihood ratios of a single second trimester bacterial vaginosis (BV) testing using Nugent's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test for Nugent's criteria p = 0.00 for LR+ and p 0.00 for LR–.*



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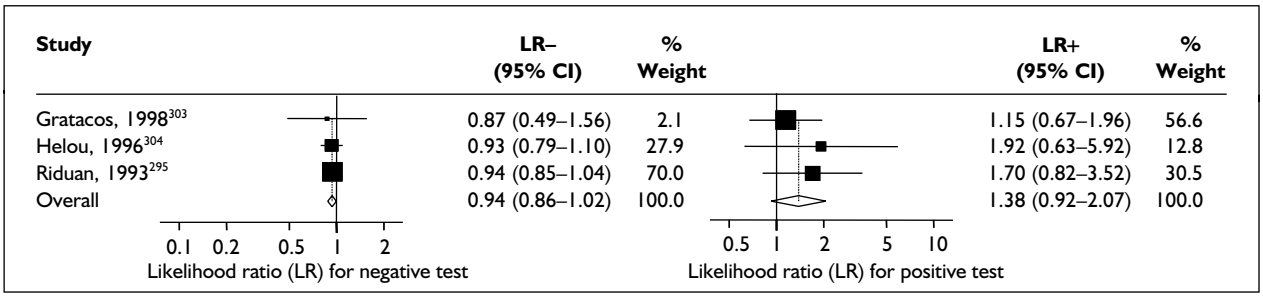


***FIGURE 58*** *Forest plots of likelihood ratios of serial bacterial vaginosis testing using Nugent's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test for Nugent's criteria p = 0.56 for LR+ and p 0.96 for LR–.*

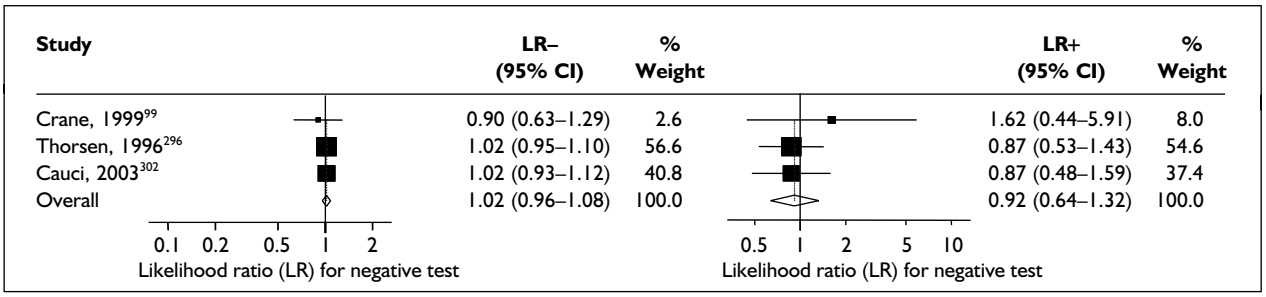


***FIGURE 59*** *Forest plots of likelihood ratios of a single second-trimester bacterial vaginosis testing using Amsel's criteria in asymptomatic pregnant women as a predictor of spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test for Amsel's criteria p = 0.67 for LR+ and p 0.79 for LR–.*

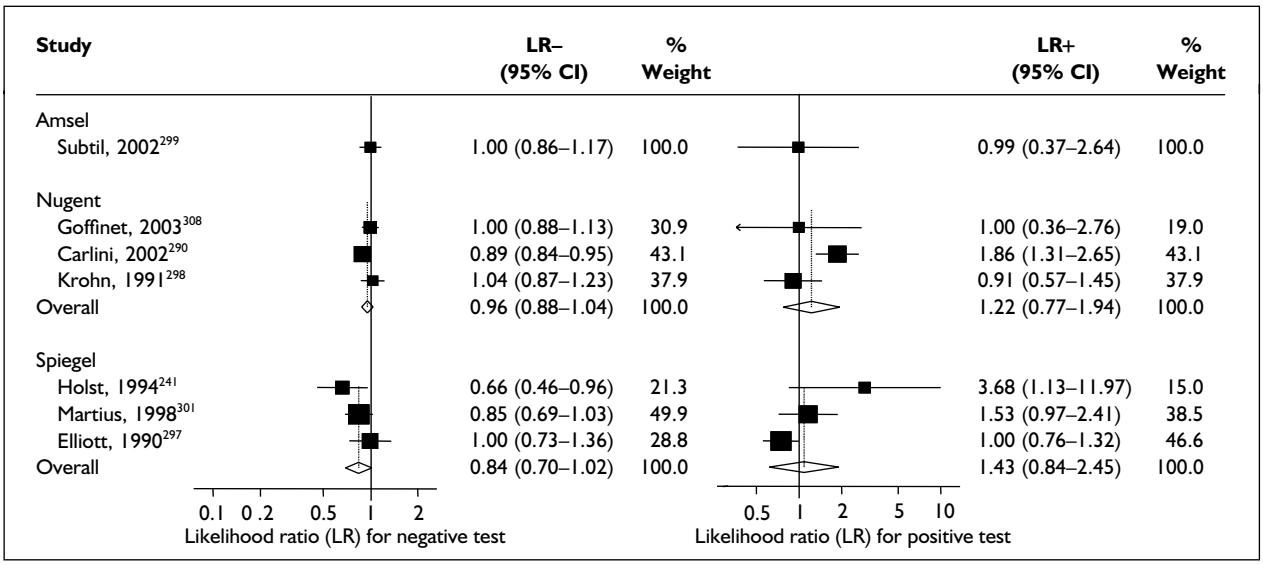


***FIGURE 60*** *Forest plots of likelihood ratios of bacterial vaginosis testing in symptomatic women as a predictor of spontaneous preterm birth before 37 weeks' gestation. $\chi^2$ heterogeneity test for Nugent's criteria p = 0.04 for LR+ and p = 0.010 for LR–; for Spiegel's criteria p = 0.25 for LR+ and p = 0.04 for LR–;*

(0.17–1.43) (*Figure 62*).[310] LRs from Guinn *et al.*[310] were used in the decision analyses because it represented the largest higher-quality study available. Individual accuracy results can be found in Appendix 5, *Table 105*.

## Uterine activity monitoring

The presence of increasingly co-ordinated, frequent and progressively stronger uterine activity often precedes the development of labour. It was thus purported that if uterine activities were monitored then advance warning of impending onset of labour, whether at term or specifically preterm, could be predicted.

### Study characteristics and quality

There were four studies evaluating uterine activities, two in asymptomatic antenatal women ($n = 370$) and two in symptomatic women with threatened preterm labour ($n = 114$).[76,311–313] Three studies used a tocograph while one used emerging technology involving electromyographic recording of uterine activities.[313] There was no consensus on the threshold defining abnormality. Aside from one study, which used birth before 35 weeks' gestation as its outcome,[76] the remaining studies used birth before 37 weeks' gestation. None of the studies fulfilled our criteria for ideal quality study, consecutive enrolment was absent from any of the studies and blinding was absent from three studies. *Figure 63* summarises the methodological quality of the included study. Individual study characteristics are summarised in Appendix 5, *Table 106*.

### 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)[76] when the threshold was set for detection of significant uterine activities during the day time, to 4.90 (95% CI 2.99–8.04)[312] when four significant contractions were detected within a 1-hour period, and a range of LR– from 0.15 (95% CI 0.04–0.56)[312] when four significant contractions were detected within a 1-hour period to 1.01 (95% CI 0.98–1.05)[76] for detection of significant uterine activities during the day time. LR+ of 2.41 (95% CI 0.76–7.68) and LR– of 0.95 (95% CI 0.86 –1.04) from Iams *et al.*[76] were used in the decision-analytic modelling because this study represented the higher-quality study. *Figure 64* summarises the accuracy results while Appendix 5, *Table 107* shows 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)[311] to 10.40 (95% CI 3.34–32.38)[313] and a range of LR– from 0.31 (95% CI 0.05–1.71)[311] to

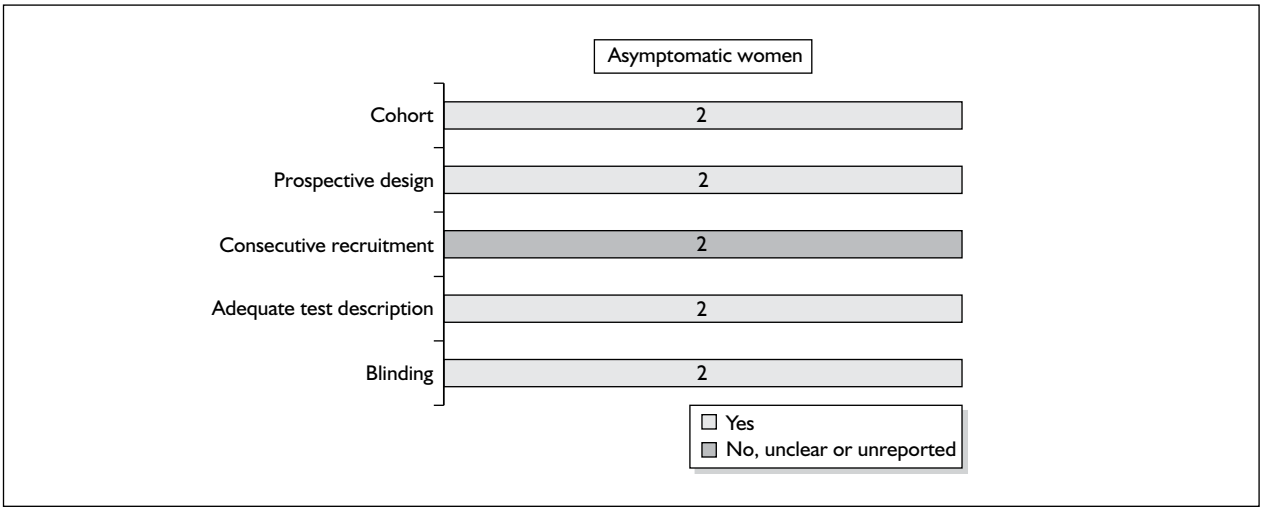


***FIGURE 61*** *Methodological quality of studies included in the systematic review of accuracy of mammary stimulation test in asymptomatic women for predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*



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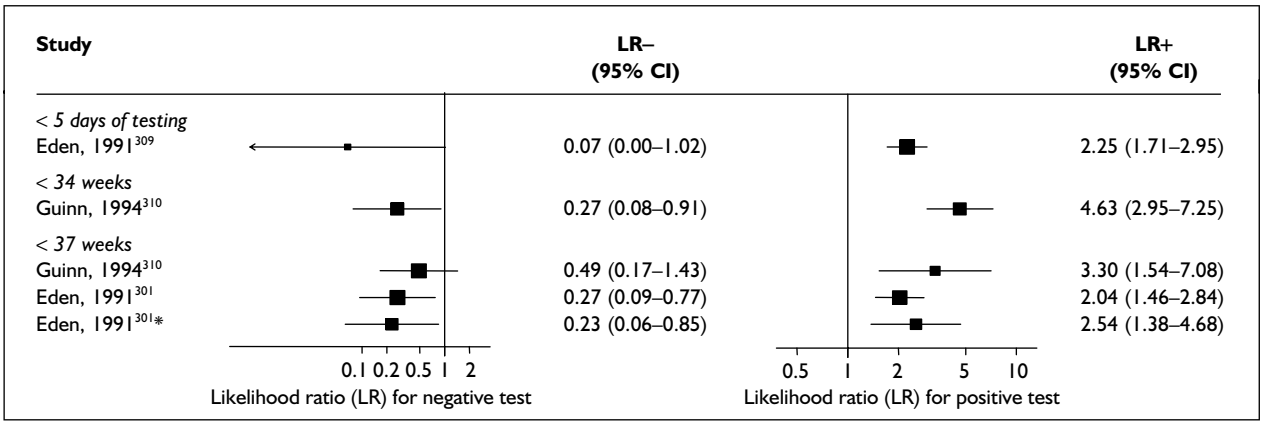


***FIGURE 62*** *Forest plots of likelihood ratios of mammary stimulation test as a predictor of spontaneous preterm birth in asymptomatic women stratified according to outcome. a, High-risk women according to Creasy's risk scoring system.*

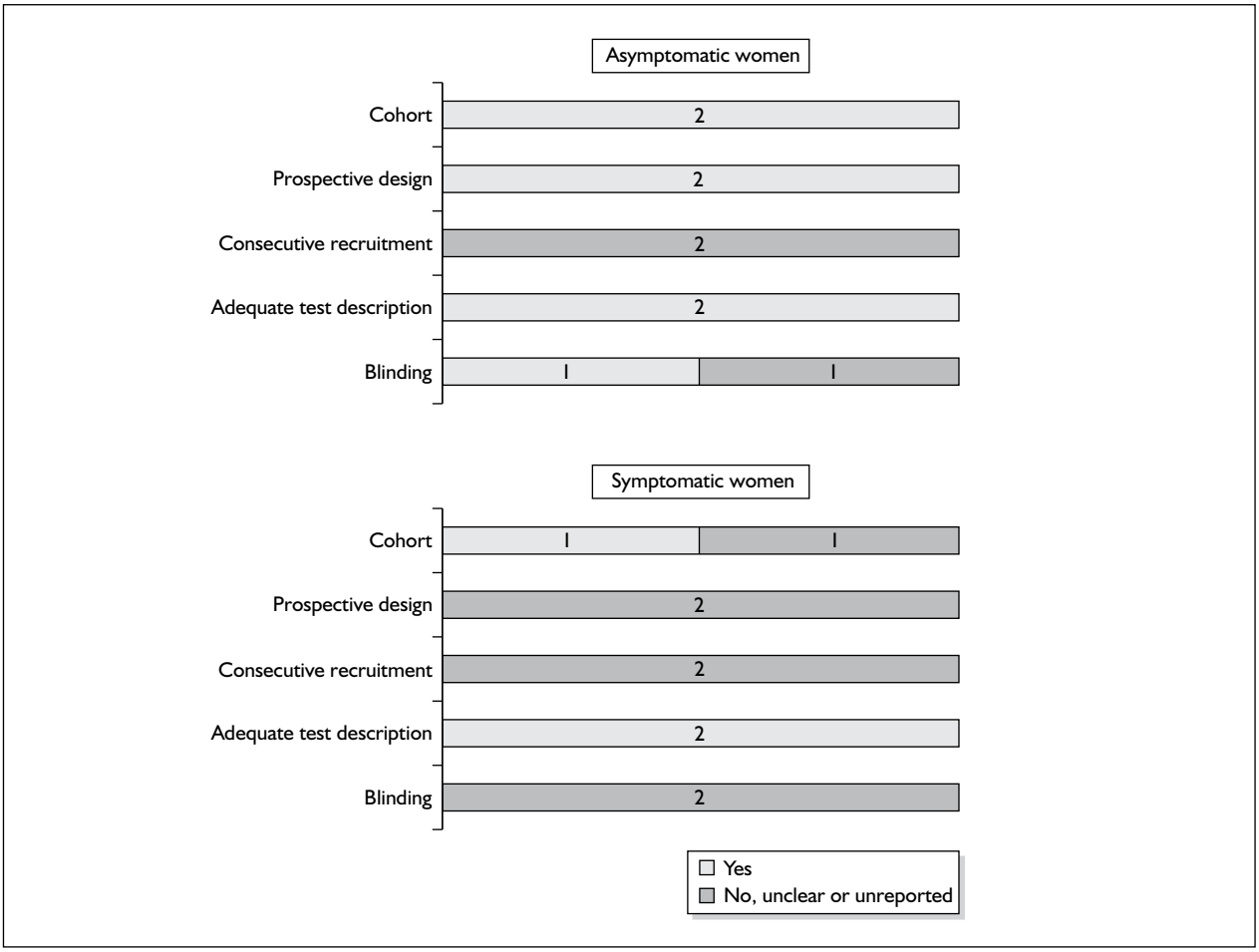


***FIGURE 63*** *Methodological quality of studies included in the systematic review of home uterine activity monitoring in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

0.48 (95% CI 0.34–0.67)[313] when using tocographic and electromyographic recording, respectively. LRs from Bell[311] were used for the decision-analytic modelling because this study represented the best available higher-quality study. *Figure 64* summarises the accuracy results while Appendix 5, *Table 107* shows individual accuracy results for each study.

## Rheobase

Rheobase in the context of a test to predict spontaneous preterm birth involves measurement of the minimal strength of electrical stimulus 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 strength to generate muscular excitation and hence the purported ability of rheobase to predict spontaneous preterm birth in symptomatic women with threatened preterm labour by detecting these greater electrical signals.

### Study characteristics and quality

There was only one study evaluating rheobase in symptomatic women with threatened preterm labour ($n = 176$).[314] 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 Appendix 5, *Table 108*. Methodological quality is summarised in *Figure 65*.

### Accuracy of rheobase measurement in symptomatic women

Depending on the thresholds being used, rheobase had an LR+ that ranged from 2.29 (95% CI 1.50–3.52) when 2.8 mA was used to 2.36 (95% CI 1.73–3.20) when 3.4 mA was used, and an LR– that ranged from 0.36 (95% CI 0.19–0.66) when 3.4 mA was used to 0.60 (95% CI 0.41–0.88) when 2.8 mA was used (*Figure 66*). Individual accuracy results are summarised in Appendix 5, *Table 109*. Both sets of LRs were used in the decision analyses.

## Absence of fetal breathing movements on ultrasound

A decrease in fetal breathing movements observed during a 20-minute 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.

### Study characteristics and quality

There were eight primary accuracy articles that met the selection criteria, which included a total of 328 women.[92,315–321] (Appendix 5, *Table 110*). All of them evaluated fetal breathing movements for

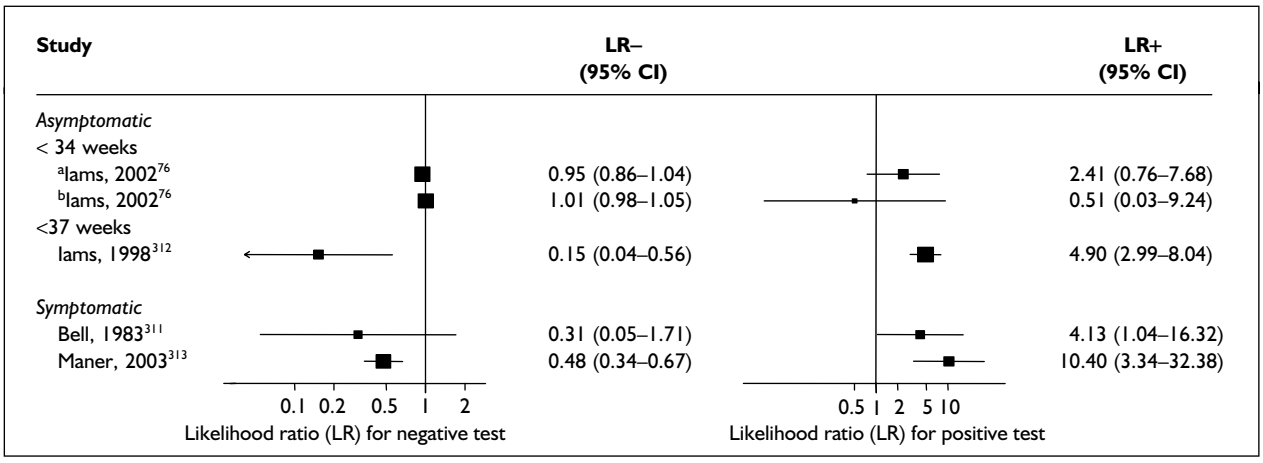


***FIGURE 64*** *Forest plots of likelihood ratios (LRs) of uterine activity monitoring as a predictor of spontaneous preterm birth before 37 weeks' gestation* stratified according to populations. a, Uterine activities at night-time. b, Uterine activities in day-time.*



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a sustained period of 15–20 seconds in a 30- to 45-minute period with real-time ultrasound. The absence of breathing movements, defined as no sustained fetal breathing movements noted during 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[317] to 70[321] women. One study fulfilled our ideal quality criteria.[92] Methodological quality was summarised in *Figure 67*.

## Accuracy of absence of fetal breathing movement in symptomatic women

For predicting preterm birth within 48 hours (*Figure 68*) and within 7 days of testing (*Figure 69*), 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 subgroup, the studies were of variable methodological quality and heterogeneity was present for the corresponding negative and positive LRs. The ideal quality study,[92] which was used in the decision-analytic modelling, showed a LR+ of 4.00 (95% CI 0.73–21.84) for a positive test result and a LR– of 0.67 (95% CI 0.32–1.38) when the test was negative, for predicting spontaneous preterm birth within 7 days of testing (*Figure 69*). For predicting preterm birth within 48 hours of testing, where the studies were lacking in one or more ideal quality features, the LR+ estimated from a better quality study was 16.08 (95% CI 5.22–49.55) and LR– was 0.16 (95%

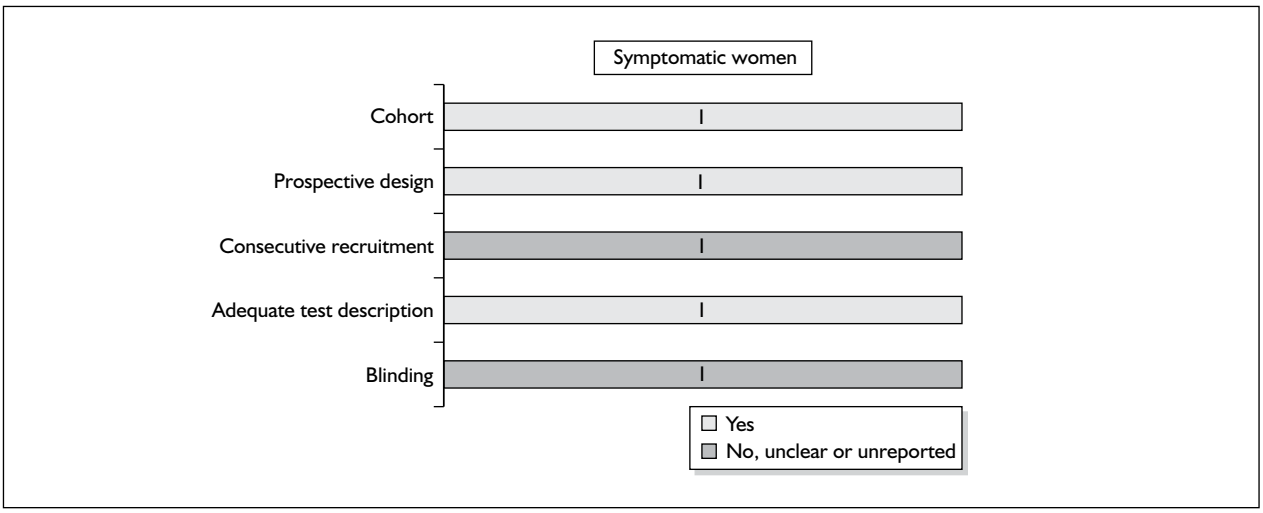


***FIGURE 65*** *Methodological quality of studies included in the systematic review of accuracy of rheobase testing in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*

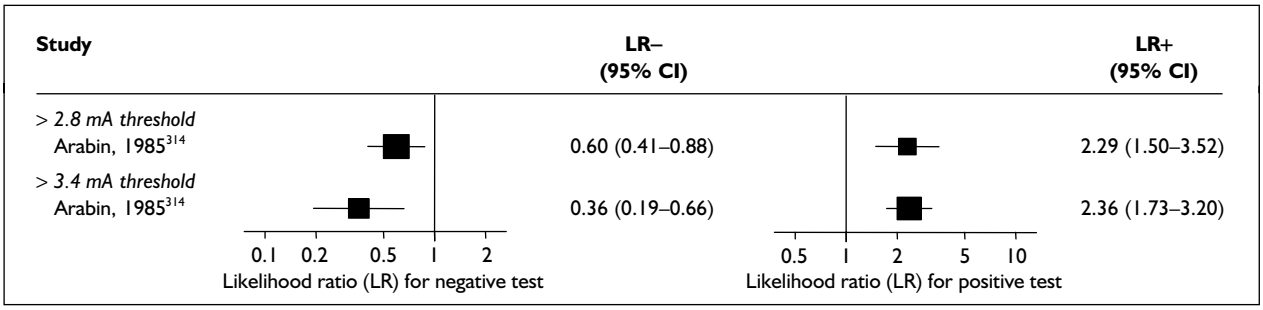


***FIGURE 66*** *Forest plots of likelihood ratios (LRs) of rheobase measurement as a predictor of spontaneous preterm birth in symptomatic women stratified according to thresholds.*

CI 0.05–0.58)[321] (*Figure 68*). This result was used for the decision-analytic modelling. Individual accuracy results from the included studies are summarised in Appendix 5, *Table 111*.

## Cervical ultrasound assessment

Antenatal cervical shortening[322] and opening of the internal os (funnelling)[323] have 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 ($n = 21,555$ women)[66,324–335] and 19 primary studies ($n = 2849$ women)[64,82,112,233,244,336–350] on symptomatic women with threatened preterm labour evaluating the accuracy of transvaginal ultrasound measurement of cervical length in predicting spontaneous preterm birth. Appendix 5, *Tables 112* and *113* summarise 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 six primary studies on asymptomatic women ($n = 12,855$ women)[322,325,329,330,332,334] and five primary studies ($n = 509$ women)[233,323,336,340,343] 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. Appendix 5, *Table 114* summarises 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 wide variation in the 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 out was in the late second trimester, between 20 and 24 weeks' gestation. The most common threshold used in asymptomatic women was 25 mm at this gestation and this was evaluated in two ideal quality studies.[322,325] The outcome frequently used by studies on asymptomatic women was birth before 37 weeks' gestation but among ideal quality studies, the outcome frequently used was spontaneous preterm birth before 34 weeks' gestation. Among symptomatic women, the most common threshold used was 15 mm and the most common outcome used was spontaneous preterm birth within 7 days of testing using this threshold.

There were five studies on asymptomatic women[325,326,329,331,335] and two studies on

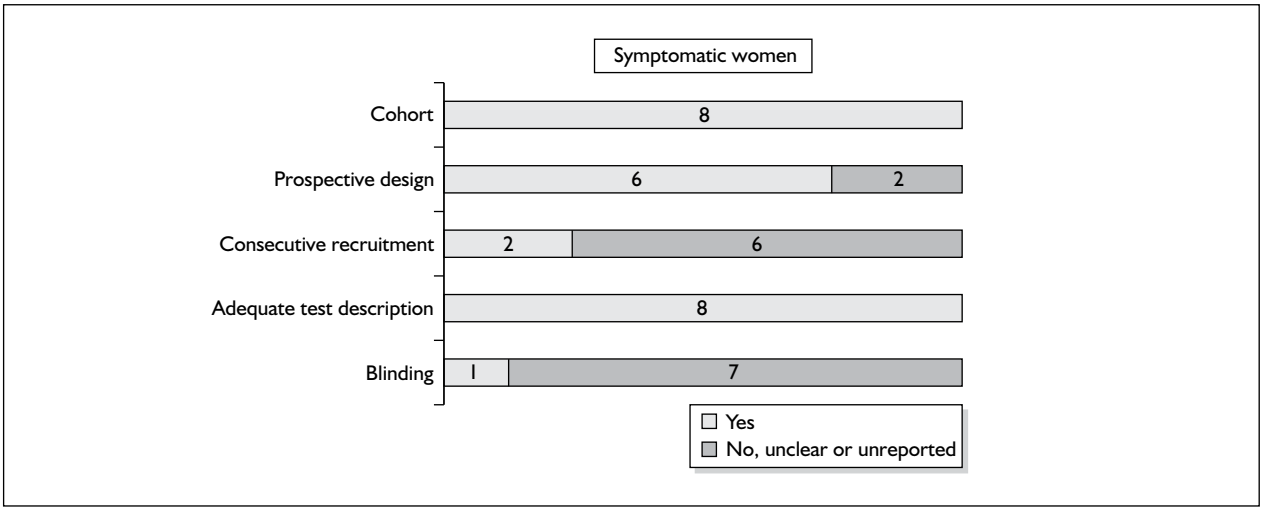


***FIGURE 67*** *Methodological quality of studies included in the systematic review of the accuracy of fetal breathing movements in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*



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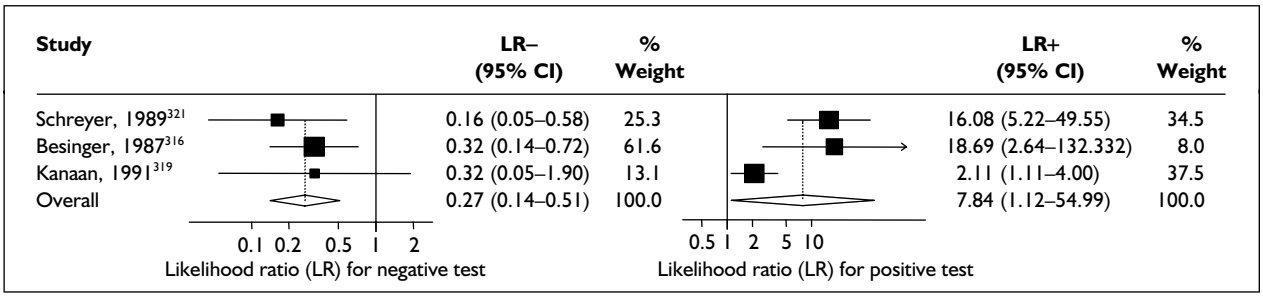


***FIGURE 68*** *Forest plots of likelihood ratios (LRs) for the absence of fetal breathing movements in predicting spontaneous preterm birth within 48 hours of testing in women presenting with threatened preterm labour. $\chi^2$ heterogeneity test = 17.44, p = 0.00 for LR+ and $\chi^2$ = 0.89, p = 0.64 for LR–. Studies are arranged in descending order of methodological quality.*

symptomatic women[336,340] on cervical length measurement that fulfilled the ideal definition of a high-quality study and three studies on asymptomatic women[322,325,329] and two studies on symptomatic women[336,340] evaluating cervical funnelling that fulfilled the ideal definition of a high-quality study. The methodological quality of the included primary studies is summarised in *Figure 70*.

## 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+ (summary LR+) of 13.38 (95% CI 6.90–25.96) ($\chi^2$ heterogeneity test $p = 0.07$) and sLR– of 0.80 (95% CI 0.71–0.90) ($\chi^2$ heterogeneity test $p = 0.91$).[325,329,331] *Figure 71* shows a 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 and 24 weeks' gestation, again using a threshold of 25 mm (commonest threshold evaluated at this gestation) it had sLR+ 4.68 (95% CI 3.64–6.03) ($\chi^2$ heterogeneity test $p = 0.54$) and sLR– 0.68 (95% CI 0.60–0.78) ($\chi^2$ heterogeneity test $p = 0.93$).[322,325] *Figure 71* shows a 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. Cervical funnelling screening in asymptomatic women had variable LRs depending on the chosen threshold (some studies did not indicate their threshold, merely indicating the presence of the 'funnelling' appearance on ultrasound imaging) (*Figure 75*). LR+ of 4.63 (95% CI 3.31–6.48) and LR– of 0.79 (95% CI 0.71–0.87)

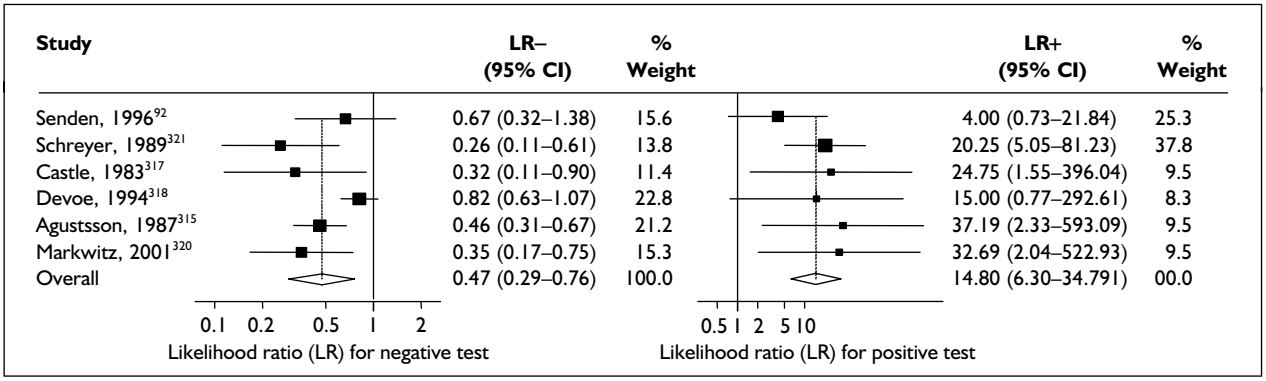


***FIGURE 69*** *Forest plots of likelihood ratios (LRs) for the absence of fetal breathing movements in predicting spontaneous preterm birth within 7 days of testing in women presenting with threatened preterm labour. $\chi^2$ heterogeneity test = 3.84, p = 0.57 for LR+ and $\chi^2$ = 21.10, p = 0.001 for LR–. Studies are arranged in descending order of methodological quality.*

from Iams *et al.*[322] using 5-mm protrusion of the amniotic membrane into the cervical canal as their threshold as a predictor for spontaneous preterm birth before 34 weeks' gestation was used for decision analysis because it represented the higher-quality study available for this threshold and reference standard.

There was no more than a single study of small sample size for any of the evaluated thresholds for cervical measurement performed before 20 weeks' gestation in predicting spontaneous preterm birth before 37 weeks (*Figure 73*), therefore this was not considered in the decision analysis. When cervical length was measured between 20 and 24 weeks' gestation for predicting birth before 37 weeks' gestation (*Figure 74*) using a threshold of 32.5 mm, it had an LR+ of 3.99 (95% CI 2.84–5.62) and LR– of 0.33 (95% CI 0.17–0.66).[335] Individual accuracy results are summarised in Appendix 5, *Tables 115* and *117*.

## 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 depending on the threshold abnormality chosen (*Figure 76*). LR+ of 6.43 (95% CI 5.17–8.00) and LR– of 0.027 (95% CI 0.0017–0.42) from Tsoi *et al.*[349] were chosen for decision analysis because their study represented the higher-quality study available for the most common threshold used (15 mm) and reference standard (birth within 48 hours of testing). For predicting spontaneous preterm birth within 7 days of testing, cervical length measurement in symptomatic women with threatened preterm labour had a variable LR depending on the threshold abnormality chosen (Appendix 5, *Table 116*). *Figure 77* shows the forest plot of LRs for the most commonly used threshold (< 15 mm) for the reference standard of spontaneous preterm birth

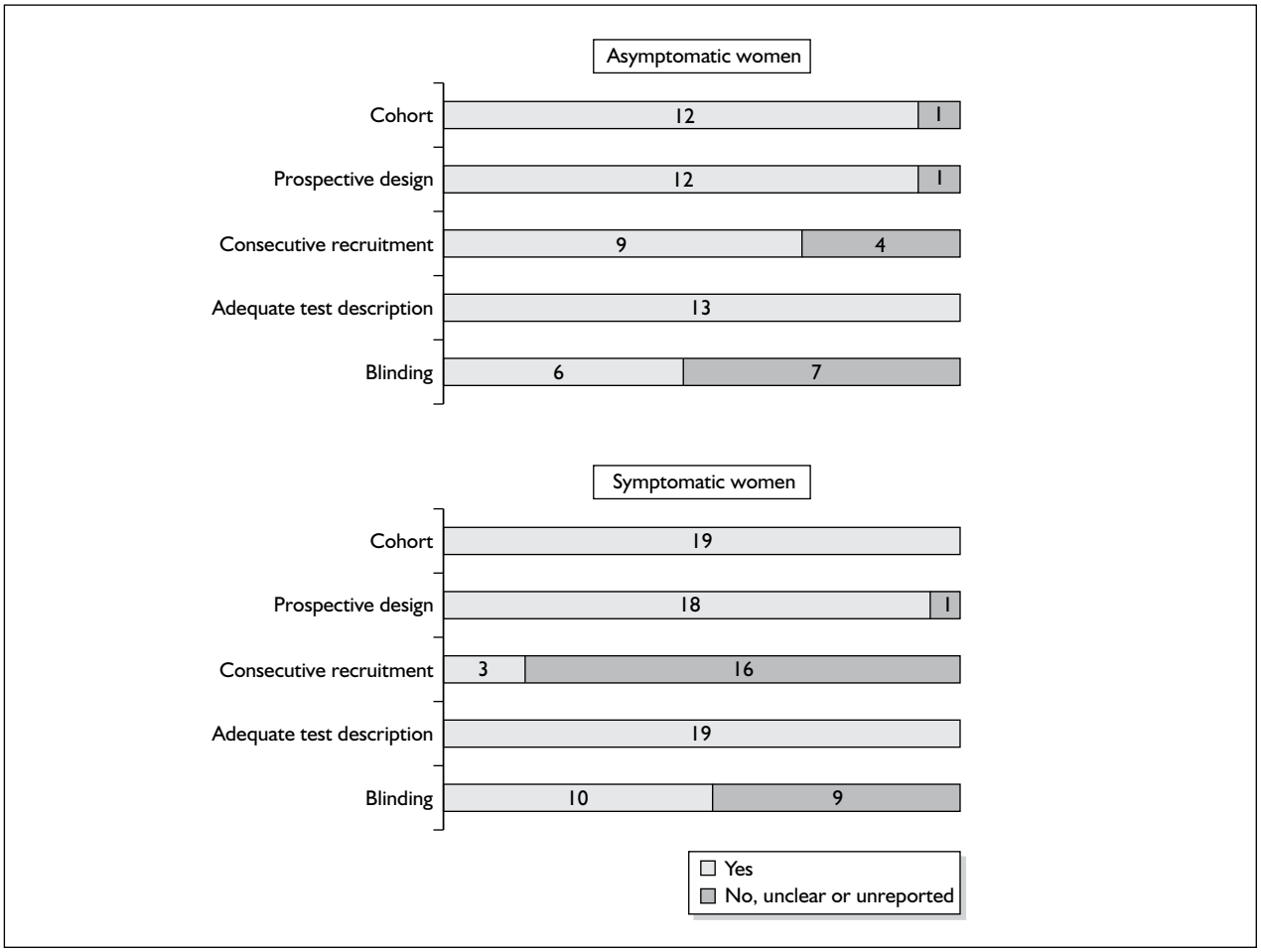


***FIGURE 70*** *Methodological quality of studies included in the systematic review of accuracy of cervical length in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies.*



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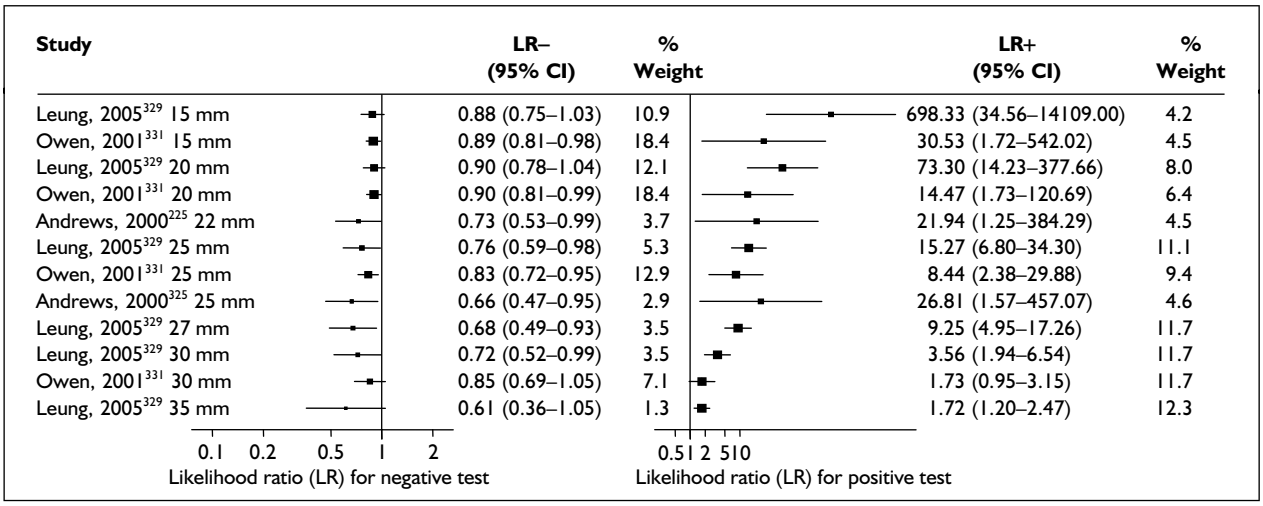


***FIGURE 71*** *Forest plots of likelihood ratios (LRs) from ideal quality studies for cervical length measurement before 20 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 34 weeks' gestation in asymptomatic antenatal women.*

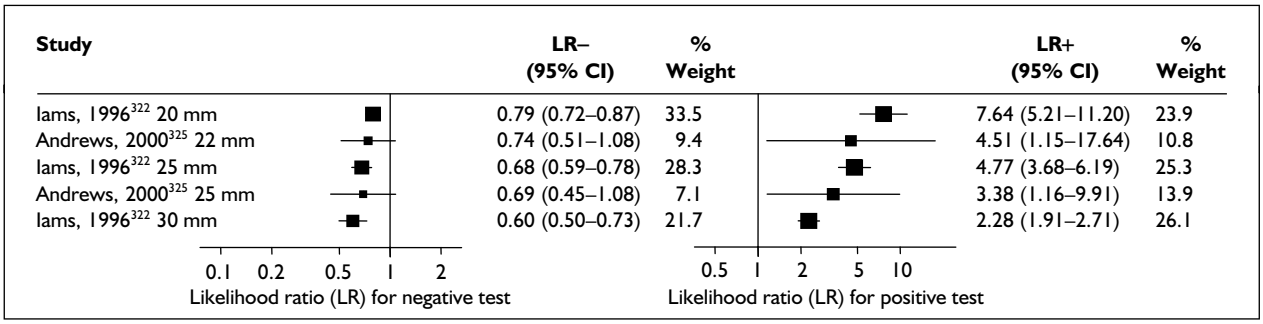


***FIGURE 72*** *Forest plots of likelihood ratios (LRs) from ideal quality studies for cervical length measurement between 20 and 24 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 34 weeks' gestation in asymptomatic antenatal women.*

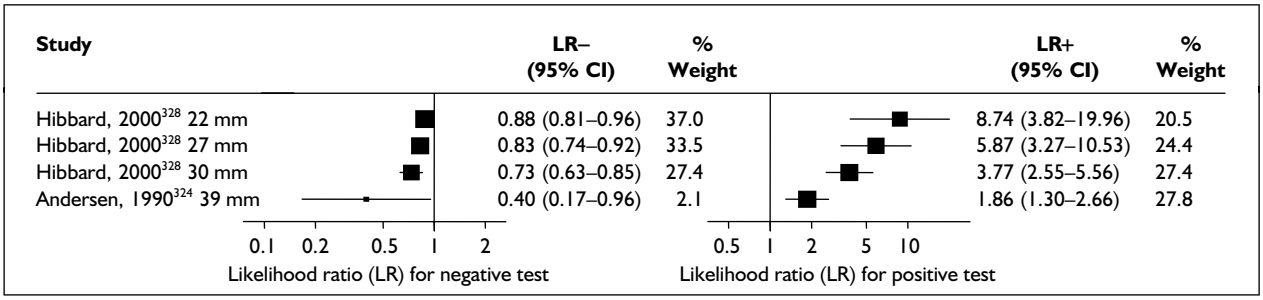


***FIGURE 73*** *Forest plots of likelihood ratios (LRs) from ideal quality studies for cervical length measurement before 20 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic antenatal women.*

within 7 days of testing. LR+ of 8.61 (95% CI 6.65–11.14) and LR– of 0.026 (95% CI 0.0038–0.182) from Tsoi *et al.*[349] were chosen for decision analysis again because the study was the higher-quality study available for the aforementioned threshold and reference standard.

For predicting spontaneous preterm birth before 34 weeks' gestation, cervical length measurement in symptomatic women with threatened preterm labour had a variable LR depending on the threshold abnormality chosen (Appendix 5, *Table 116*). *Figure 78* shows the forest plot of LRs for the most commonly used threshold (<30 mm) for the reference standard of spontaneous preterm birth before 34 weeks' gestation. LR+ of 1.879 (95% CI 1.36–2.59) and LR– of 0.30 (95% CI 0.083–1.07) from Crane *et al.*[336] were chosen for decision analysis because this study represented an ideal quality study for the aforementioned threshold and reference standard. For predicting spontaneous preterm birth before 37 weeks' gestation, cervical length measurement in symptomatic women with threatened preterm labour had a variable LR depending on the threshold abnormality chosen (*Figure 78*). LR+ of 3.36 (95% CI 1.73–6.54) and LR– of 0.35 (95% CI 0.17–0.70) from Gomez *et al.*[340] using a threshold <18 mm and LR+ of 2.29 (95% CI 1.68–3.12) and LR– of 0.29 (95% CI 0.15–0.58) from Crane *et al.*[336] with a threshold <30 mm were chosen for decision analysis because they represented ideal quality studies available for this reference standard (*Figure 79*). ROC plots of sensitivity versus specificity for cervical length measurement in symptomatic women predicting spontaneous preterm birth within 48 hours and

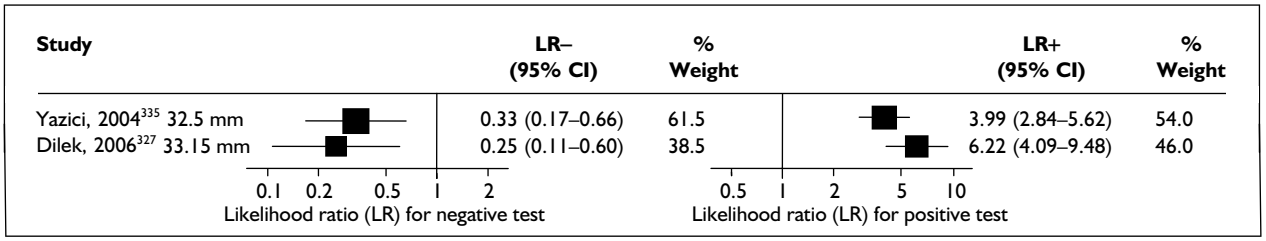


***FIGURE 74*** *Forest plots of likelihood ratios (LRs) from ideal quality studies for cervical length measurement between 20 and 24 weeks' gestation (listed in ascending order of thresholds of abnormality) in predicting spontaneous preterm birth before 37 weeks' gestation in asymptomatic antenatal women.*

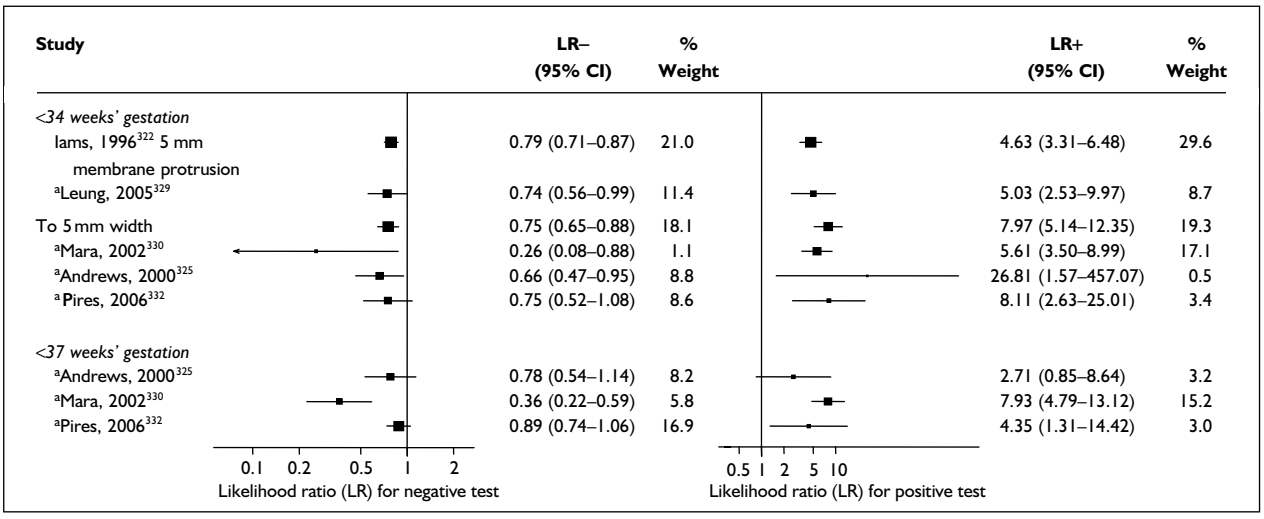


***FIGURE 75*** *Forest plots of likelihood ratios (LRs) for cervical funnelling between 20 and 24 weeks' gestation in predicting spontaneous preterm birth stratified according to reference standards (outcomes) in asymptomatic antenatal women. Studies are arranged in descending order of quality. a, Any definition of funnelling unless otherwise stated.*



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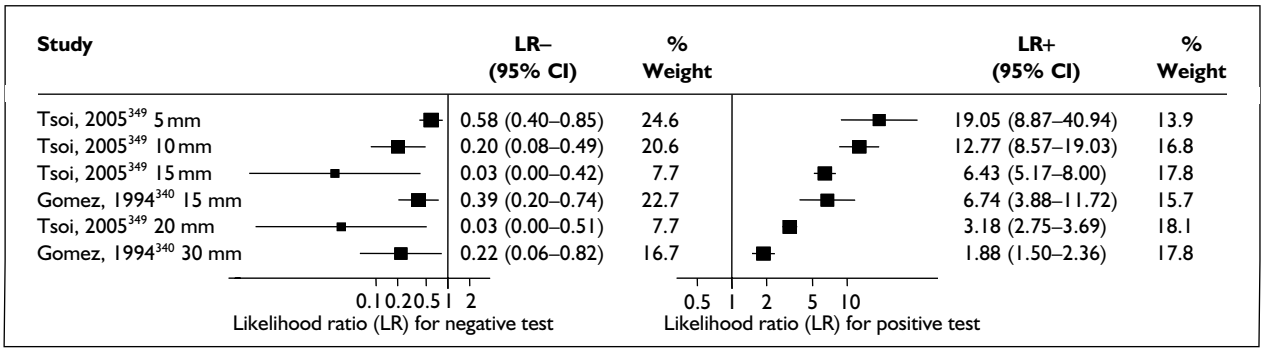


***FIGURE 76*** *Forest plots of likelihood ratios (LRs) from ideal quality studies for cervical length measurement in predicting spontaneous preterm birth within 48 hours of testing in symptomatic women with threatened preterm labour.*

7 days of testing, and before 34 weeks' gestation, are shown in *Figure 81*. Cervical funnelling screening in symptomatic women had variable LRs depending on the chosen threshold (some studies did not indicate their threshold, merely indicating presence of the 'funnelling' appearance on ultrasound imaging) (*Figure 80*). LR+ of 4.70 (95% CI 1.90–11.66) and LR– of 0.61 (95% CI 0.34–1.10) for predicting spontaneous preterm birth before 34 weeks' gestation and LR+ of 2.53 (95% CI 1.02–6.25) and LR– of 0.86 (95% CI 0.71–1.03) for predicting spontaneous preterm birth before 37 weeks' gestation from Crane *et al.*,[336] using the presence of 'V-shaped' ultrasonographic appearance as threshold for funnelling, were used for decision analysis because this study represented an ideal quality study available for this threshold and reference standard. Individual accuracy results for cervical length and funnelling measurement in symptomatic women can be found in Appendix 5, *Table 116* and *Table 117*.

# Summary of test accuracy systematic reviews

## Summary of test accuracy findings

This review assessed 22 tests aimed at the prediction of spontaneous preterm birth. The numbers of studies per test were small and of poor quality with few exceptions. The median number was 5 (range 0–26) for asymptomatic and 2 (range 0–40) for symptomatic women. We had planned to perform meta-analysis only for the highest-quality studies to improve the validity of our results. This meant that the number of tests suitable for meta-analysis was small (cervicovaginal fetal fibronectin and cervical ultrasound) and the number of studies per meta-analysis was similarly small (median = 3), introducing imprecision in estimation of accuracy.

The overall quality of studies within reviews was variable. There were deficiencies in many areas of methodology (*Figure 82*) but two quality items, consecutive enrolment and blinding, were more frequently unreported than the other items. No test had universally high quality data, but for some tests, e.g. fibronectin, cervicovaginal phIGFBP-1 and cervical length, a number of high-quality studies were available. Overall, the quality of test accuracy studies in symptomatic women tended to be better than that of studies in asymptomatic women (chi-squared 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 we restricted our reviews to singleton pregnancies, many studies included patients across the clinical risk spectrum, and did not provide separate results for specific parts of the spectrum, such as women without any particular risk factors. For this reason, when assessing the results we often could not be confident about the reported predictive ability of tests.

In evaluation of many tests, the limited number of quality studies and the limited number of cases with preterm birth per study seriously constrained the conclusions. As spontaneous preterm birth has prevalence, particularly for important outcomes such as birth before 34 weeks' gestation or birth within 48 hours of presentation, the small absolute numbers of affected cases introduced imprecision by increasing variance.

The main accuracy results are summarised in *Figures 83*, *84* and *85* 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.

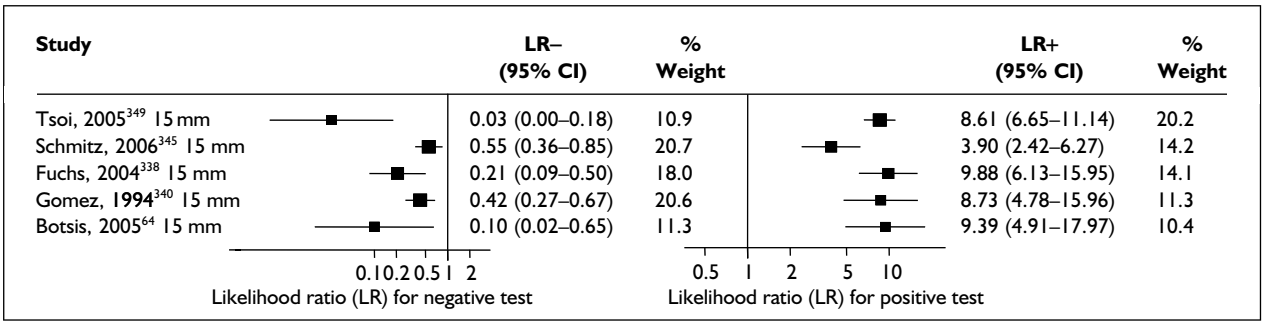


***FIGURE 77*** *Forest plots of likelihood ratios (LRs) for cervical length measurement using commonly chosen threshold (15 mm) in predicting spontaneous preterm birth within 7 days of testing in symptomatic women with threatened preterm labour. Studies are arranged in descending order of quality.*

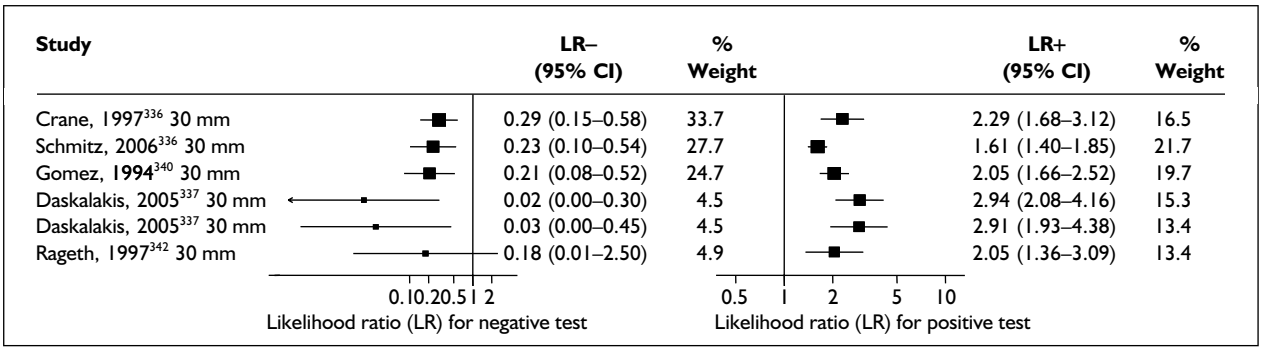


***FIGURE 78*** *Forest plots of likelihood ratios (LRs) for cervical length measurement using commonly chosen threshold (30 mm) in predicting spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour. Studies are arranged in descending order of quality.*

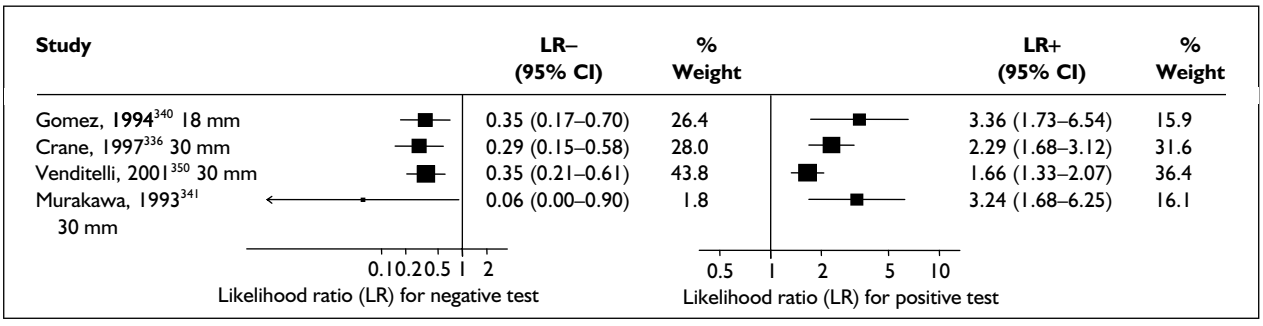


***FIGURE 79*** *Forest plots of likelihood ratios (LRs) from ideal quality studies for cervical length measurement in predicting spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*



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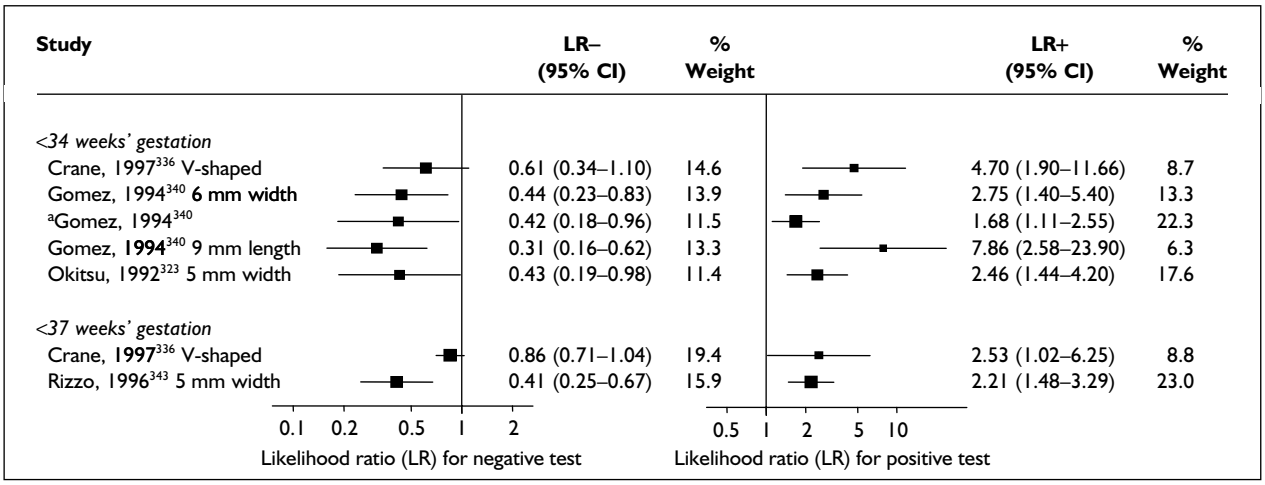


***FIGURE 80*** *Forest plots of likelihood ratios (LRs) for cervical funnelling between 24 and 36 weeks' gestation in predicting spontaneous preterm birth stratified according to reference standards (outcomes) in symptomatic women with threatened preterm labour. Studies are arranged in descending order of quality. a, Any definition of funnelling unless otherwise stated.*

For most of the tests evaluated the results were not pooled because of the lack of high-quality studies. Where studies were pooled, we used a random effects model. This method accounts for the statistical heterogeneity that is left unexplained after attempts to identify its sources, where feasible. It produced more conservative estimates of confidence intervals.

The forest plots shown in *Figures 83–85*, we believe, summarise suitably the valid information for consideration in clinical decision-making for each of the tests reviewed. These results have been put forward for decision-analytic modelling. The more the LR values depart from 1.0 the greater the change in post-test probability. As proposed by Jaeschke *et al.*[48] a useful test should have at least an accuracy of LR+ >5.0 and LR– <0.2 (*Table 1*). These estimates require at least 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

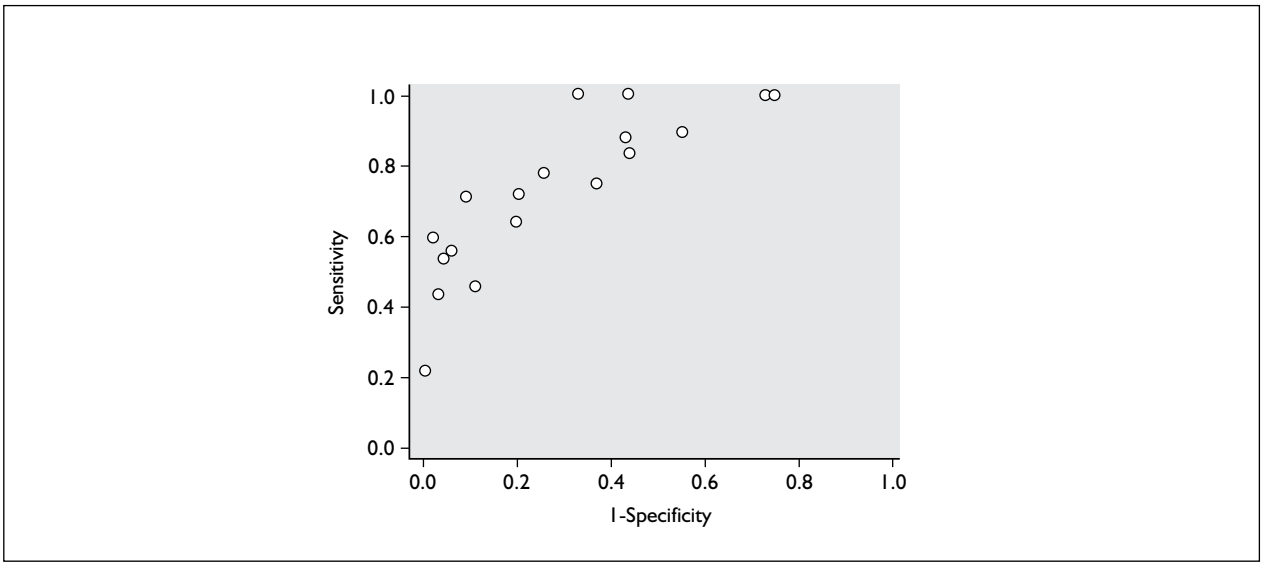


***FIGURE 81*** *Plot of sensitivity versus 1-specificity in ROC space for cervical length measurement studies in symptomatic women with threatened preterm labour in predicting spontaneous preterm birth within 48 hours and 7 days of testing (threshold 15 mm), and before 34 weeks' gestation (threshold 30 mm).*

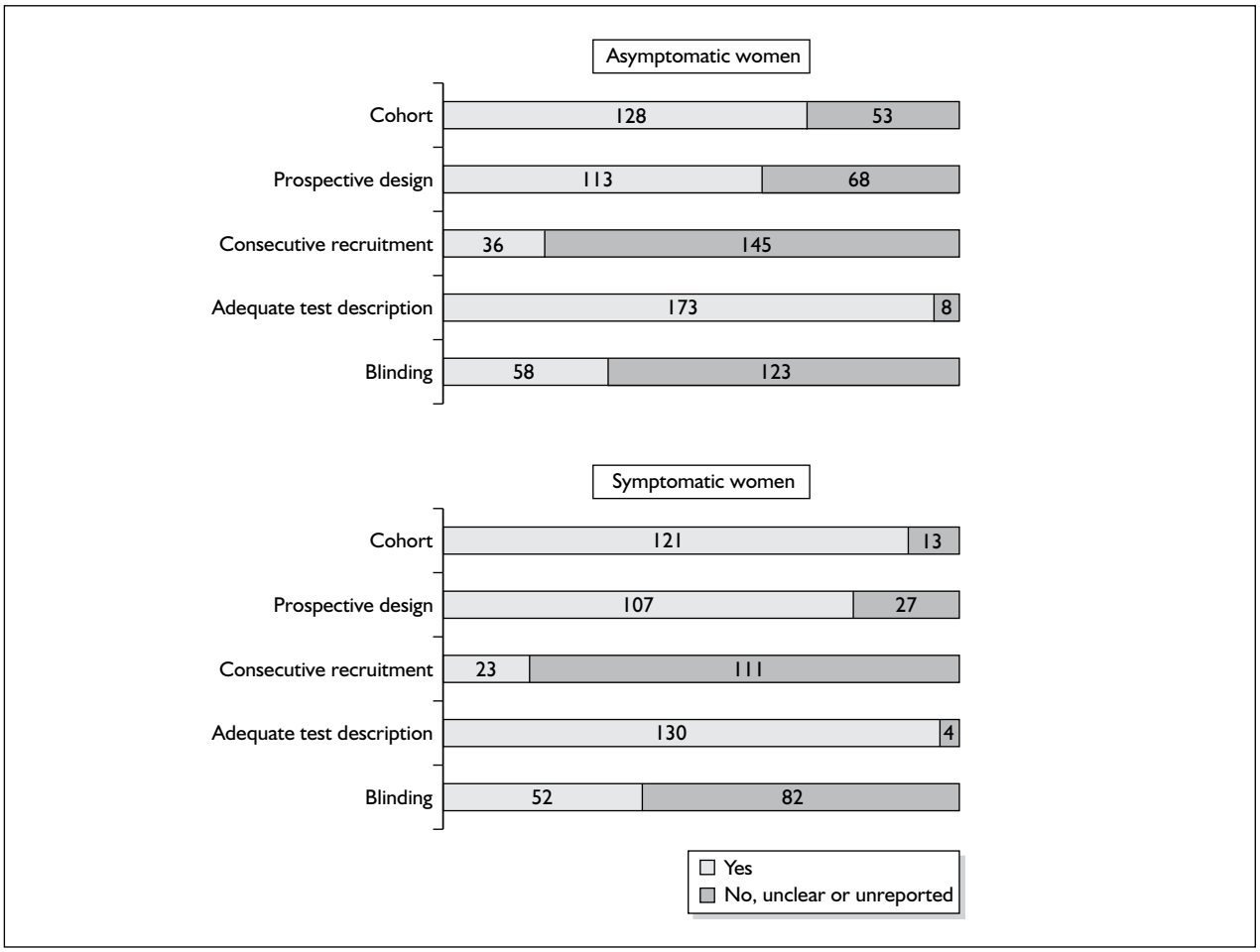


***FIGURE 82*** *Summary of methodological quality of studies included in the systematic review of accuracy of rheobase testing in predicting spontaneous preterm birth. Data presented as 100% stacked bars. Figures in the stacks represent number of studies. Some studies are reported twice because of their contributions to multiple reviews.*

the condition will probably not 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 in our accuracy reviews. Considering the point estimates of LRs, 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 than LR–. This meant that it was unlikely that the 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.

Screening typically involves the use of a confirmatory test after initial testing, before the institution of therapy. In this project, this is not the case because testing is used to identify a risk group in which preventative interventions (both intensive monitoring and or treatments) will be employed directly after test results become known. In this situation, for a test to serve as a good tool for screening, it should perform well.[48] 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 intervention(s). The consequences of false-positive results include both costs of intensive monitoring and treatment-associated morbidity and costs among otherwise normal women, so it is important that LR+ is suitably high, because 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 attributed to low LR+ values.



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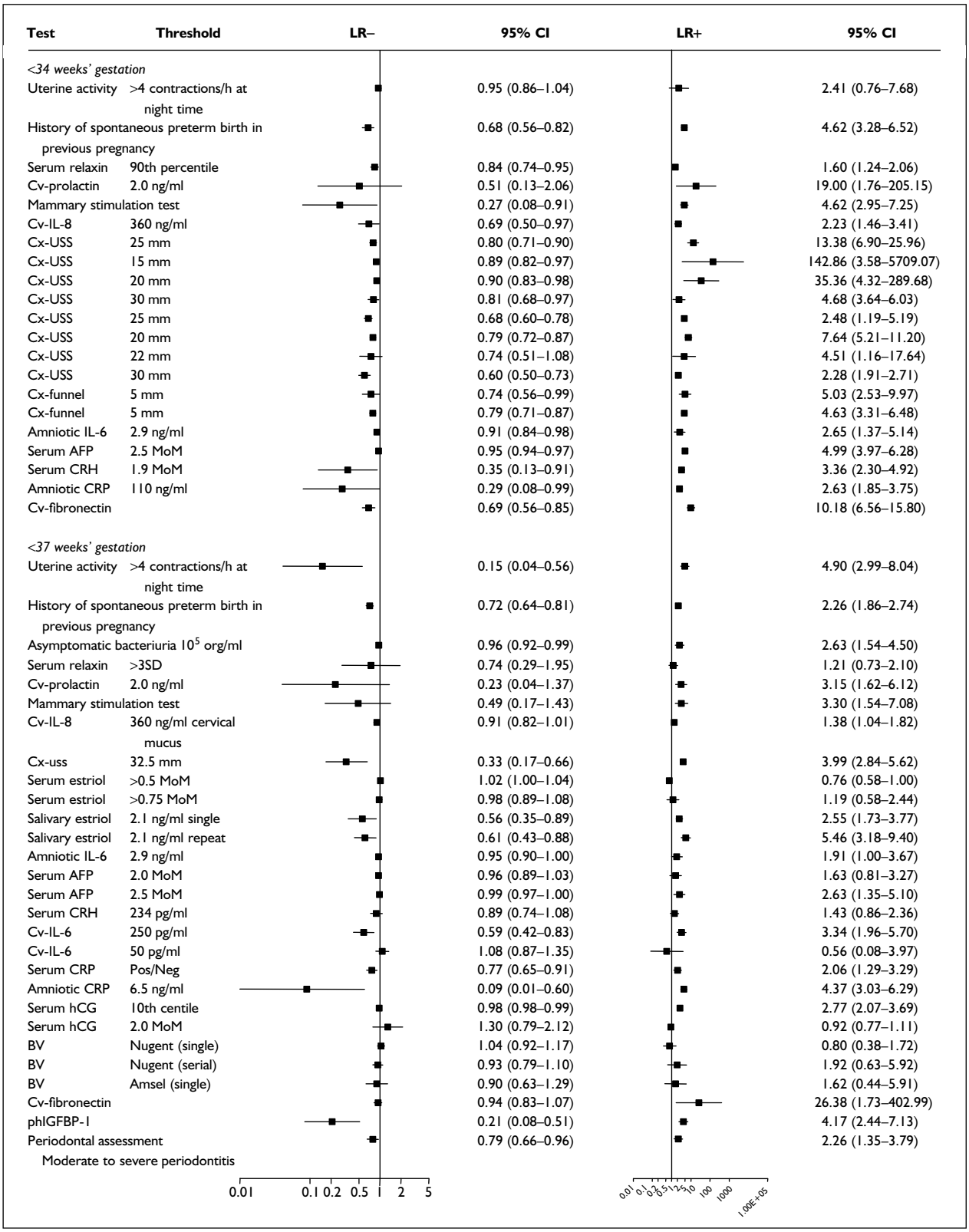


***FIGURE 83*** *Summary forest plots of likelihood ratios (LRs) of the accuracy of various tests as a predictor of spontaneous preterm birth in asymptomatic women stratified according to reference standards (outcomes of spontaneous birth before 34 and 37 weeks' gestation), tests and selected thresholds. LR values above are those that were considered for decision analyses. These estimates were based on the results of the highest-quality studies. AFP, α-fetoprotein; Cv, cervicovaginal; Cx, cervix; USS, ultrasound.*

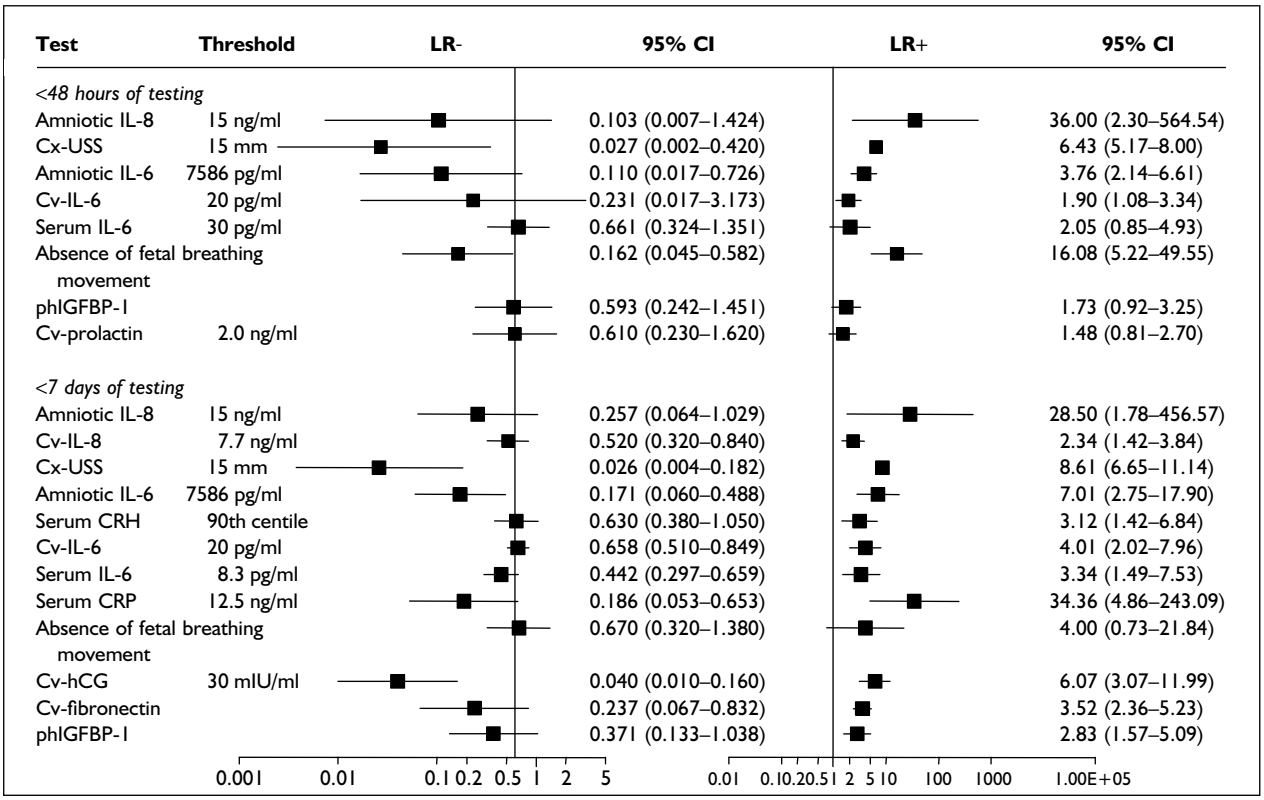


***FIGURE 84*** *Summary forest plots of likelihood ratios (LRs) of the accuracy of various tests as a predictor of spontaneous preterm birth in symptomatic women stratified according to reference standards (outcomes of spontaneous preterm birth within 48 hours and 7 days of testing), tests and selected thresholds. LR values above are those that were considered for decision analyses. These estimates were based on the results of the highest-quality studies. Cv, cervicovaginal; Cx, cervix.*

Given the consequences of false-negative results (both costs and morbidity of cases of spontaneous preterm birth as the result of lack of treatment), it is important that LR– is suitably low. This is because erroneously withholding effective interventions from falsely negative results leads to excessive morbidity and expense in the face of spontanenous preterm birth. If available effective interventions are convenient, inexpensive and without adverse effects (to both mother and child), then it is better to have the accuracy trade-offs in favour of LR–, i.e. a test with a low LR– rather than a high LR+.

*Figure 83*, *Figure 84* and *Figure 85* demonstrate that considering the point estimates of and imprecision in the LRs, most tests perform either poorly or the level of their performance is uncertain (i.e. has wide confidence intervals). A few tests in asymptomatic antenatal women reached LR+ >5, putting them in the useful tests category for predicting spontaneous preterm birth. These were ultrasonographic cervical length and funnelling measurement, and cervicovaginal fFN 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 than in asymptomatic women. These were absence of fetal breathing movements, cervical length and funnelling, amniotic fluid IL-6, serum CRP for predicting spontaneous preterm birth within 48 hours or 7 days of testing; and MMP-9, amniotic fluid IL-6, cervicovaginal fFN and cervicovaginal hCG testing for predicting spontaneous preterm birth before 34 or 37 weeks' gestation. For symptomatic women with threatened preterm labour, measurement of cervicovaginal IL-8, cervicovaginal hCG, cervical length measurement, absence of fetal breathing movement, amniotic fluid IL-6, and serum CRP all showed LR– <0.2 for predicting spontaneous preterm birth within 48 hours or 7 days of testing. Only cervicovaginal fFN and amniotic fluid IL-6 had an LR– <0.2 in predicting spontaneous preterm birth before 34 or 37 weeks' gestation. Depending on level of effectiveness of various interventions (Chapter 5) and their associated inconvenience, costs and



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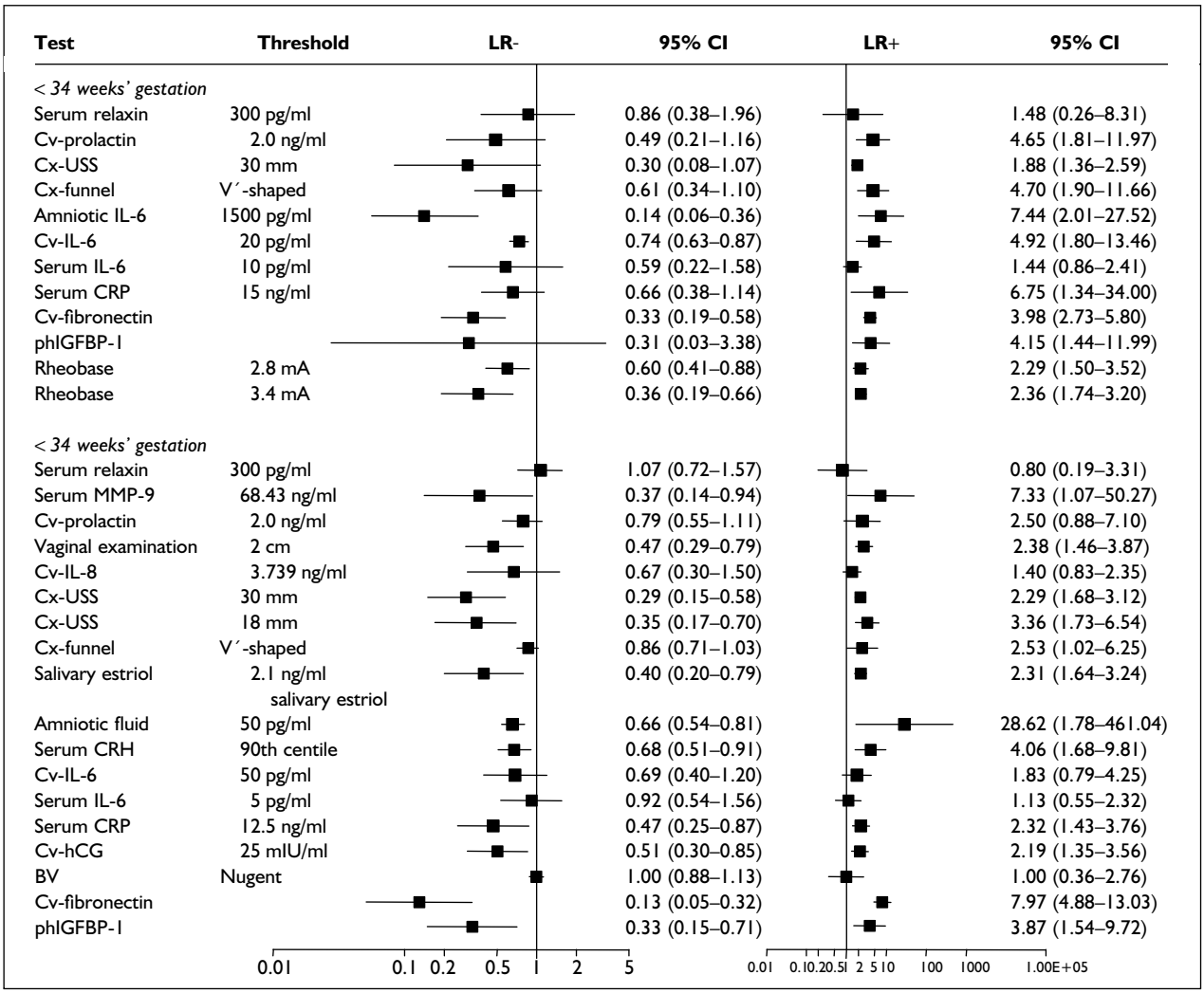


***FIGURE 85*** *Summary forest plots of likelihood ratios (LRs) of the accuracy of various tests as a predictor of spontaneous preterm birth in symptomatic women stratified according to reference standards (outcomes of spontaneous preterm birth before 34 and 37 weeks' gestation), tests and selected thresholds. LR values above are those that were considered for decision analyses. These estimates were based on the results of the highest-quality studies.*

morbidity, a threshold analysis (Chapter 6) will be required to determine which thresholds of accuracy are required to make testing cost-effective in prevention of spontaneous preterm birth. A summary of the more accurate tests (for clinically important outcomes) considered for the following threshold analysis (Chapter 5) is shown in *Table 2*.

## Provisos/limitations arising from problems with primary data

The interpretations of the accuracy data on tests are affected by threats to validity identified in the assessment of study quality (*Figure 82*). Only a few tests had been evaluated and reported in studies that met our definition of ideal study design as defined in our method section, both in asymptomatic and symptomatic women. The following tests were evaluated in at least one ideal quality study: cervical length and funnelling, IL-6 and cervicovaginal 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 82*). Association between design quality components and diagnostic performance has been empirically studied. 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. We

***TABLE 1*** *Guide to the interpretation of a test accuracy represented by likelihood ratio (LR)*

| 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 *et al.*;[48] Grimes and Schulz;[49] and Fagan.[50]
In any specific context, however, the value of LR below which a positive result and above which a negative result will be useless depends on how effective, safe and expensive the interventions that follow are relative to costs and outcome of false-negative cases – these will be explored in our economic evaluations.

accept, however, that our expectations of the level of detail that should be provided in the literature of the primary studies were perhaps unrealistic given that initiatives to improve test accuracy study design and its subsequent reporting are only recent phenomena.

Studies often did not conform to the standards of reporting for diagnostic studies. In particular, blinding and consecutive enrolment 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, absence of blinded assessment may lead to alteration(s) of the 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' where test-positive women are given effective treatments leading to prevention of spontaneous preterm birth, which makes an otherwise reasonable test appear inaccurate.

Lack of consecutive enrolment may have resulted in a 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). We tried to minimise this effect, notwithstanding the inherent study design and reporting inadequacy, by constraining our reviews to singleton and low-risk pregnancies.

Our discussion would not be complete without touching on the issue of interpreting a test's accuracy in the light of information obtained by any preceding test(s), which has so far been overlooked in diagnostic research. Diagnostic confounding can occur in this situation, which refers to one or more tests having predictive abilities that are related to each other and the outcome so that it is difficult to assess the independent prediction from each of the tests on the diagnosis of the outcome. Our reviews did not assess this issue. There may or may not be increased accuracy when two or more tests are combined in the prediction of spontaneous preterm birth depending on the overlap of information between tests. 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



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***TABLE 2*** *Summary of the more accurate tests (for clinically important outcomes) considered for the threshold analysis (see Chapter 6)*

| | LR+ (95% CI) | LR– (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|
| ***Symptomatic women*** | | | | |
| *Spontaneous preterm birth < 48 hours from testing* | | | | |
| Measurement of cervical length (15 mm) | 6.43 (5.17–8.00) | 0.027 (0.0017–0.42) | 0.98 (0.84–1.00) | 0.85 (0.81–0.88) |
| Amniotic fluid IL-6 | 3.76 (2.14–6.61) | 0.11 (0.0167–0.726) | 0.92 (0.62–0.99) | 0.76 (0.60–0.88) |
| Amniotic fluid IL-8 (15 ng/ml) | 36.00 (2.30–564.54) | 0.10 (0.0074–1.42) | 0.90 (0.40–1.00) | 0.98 (0.81–1.00) |
| Cervicovaginal IL-6 | 2.90 (1.08–3.34) | 0.23 (0.017–3.17) | 0.88 (0.29–1.00) | 0.54 (0.33–0.74) |
| Absence of fetal breathing movements | 7.84 (1.12–54.99) | 0.27 (0.14–0.51) | 0.76 (0.52–0.89) | 0.90 (0.79–0.99) |
| *Spontaneous preterm birth < 7 days from testing* | | | | |
| Measurement of cervical length (15 mm) | 8.61 (6.65–11.14) | 0.026 (0.0038–0.18) | 0.98 (0.88–1.00) | 0.89 (0.85–0.91) |
| Cervical β-hCG | 6.07 (3.07–11.99) | 0.04 (0.01–0.16) | 0.97 (0.88–1.00) | 0.84 (0.71–0.93) |
| Amniotic fluid IL-6 | 7.01 (2.75–17.90) | 0.17 (0.060–0.49) | 0.85 (0.62–0.97) | 0.88 (0.72–0.97) |
| Serum C-reactive protein | 34.36 (4.86–243.09) | 0.17 (0.05–0.62) | 0.82 (0.48–0.98) | 0.98 (0.87–1.00) |
| Fetal fibronectin | 3.52 (2.36–5.23) | 0.24 (0.067–0.83) | 0.82 (0.48–0.98) | 0.77 (0.69–0.83) |
| Amniotic fluid IL-8 (15 ng/ml) | 28.5 (1.78–456.57) | 0.26 (0.064–1.03) | 0.75 (0.28–0.99) | 0.97 (0.81–1.00) |
| phIGFBP-1 | 3.29 (2.24–4.83) | 0.20 (0.10–0.41) | 0.72 (0.56–0.87) | 0.74 (0.59–0.91) |
| *Spontaneous preterm birth < 34 weeks' gestation* | | | | |
| Amniotic fluid IL-6 | 7.44 (2.01–27.52) | 0.14 (0.06–0.36) | 0.88 (0.71–0.96) | 0.88 (0.64–0.99) |
| Measurement of cervical length (30 mm) | 2.48 (1.19–5.19) | 0.81 (0.68–0.97) | 0.83 (0.71–0.93) | 0.56 (0.48–0.61) |
| phIGFBP-1 | 2.96 (2.02–4.33) | 0.22 (0.08–0.64) | 0.75 (0.55–0.96) | 0.82 (0.48–0.98) |
| Fetal fibronectin | 3.98 (2.73–5.80) | 0.33 (0.19–0.58) | 0.73 (0.46–0.81) | 0.82 (0.68–0.96) |
| ***Asymptomatic women*** | | | | |
| *Spontaneous preterm birth < 34 weeks' gestation* | | | | |
| Mammary stimulation test | 4.62 (2.95–7.25) | 0.27 (0.079–0.91) | 0.78 (0.40–0.90) | 0.83 (0.78–0.88) |

95% CI, 95% confidence intervals; β-hCG, β-human chorionic gonadotrophin; IL-6, interleukin-6; LR+, likelihood ratio of positive test result; LR–, likelihood ratio of negative test result; phIGFBP-1, phosphorylated form of insulin-like growth factor binding protein 1.

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).

## Provisos/limitations arising from review methods

The accuracy review was carried out using a comprehensive search strategy to minimise the risk of missing tests and studies. Nevertheless the research identified for each test was often of variable quality and insufficient in amount 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, 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); and cervicovaginal fetal fibronectin (58 studies), cervical length and funnelling (42 studies), and IL-6 (22 studies) for symptomatic women. Where there was a scarcity of primary studies, it was not surprising that the some of the LR estimates were affected by imprecision. Therefore, when assessing their results we could not always be

confident about the range of reported predictive ability of tests, especially when there was only a small number of studies with small sample size in each.

Our review has already made explicit the deficiencies in the quality of studies. We would have preferred to base our inferences on high-quality studies, e.g. ideal quality features in asymptomatic antenatal women populations, using a single threshold and outcome (reference standard). To that end, we had planned a priori subgroup analyses according to study quality within our predefined populations and outcomes. However, because of the low number of included studies per test or per specific threshold, often compounded by a lack of reporting clarity, such subgroup analyses were often not possible or had insufficient power. In cases where it was possible, e.g. cervicovaginal fetal fibronectin and cervical length measurement, their subgroup analyses were based on a 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 because of violation of the principle that the compared study samples should be statistically independent. Recently, this issue was addressed in the literature, but the solution was based on the use of odds ratios, which has other drawbacks. For some other tests, e.g. CRP and interleukins, none of the studies had used the same thresholds, which limited our ability to compare and infer the accuracy estimates obtained. In these situations, we made a systematic attempt (see Methods section) at translating results in a summary ROC space into clinically relevant information. For pooling test results that we were able to pool, we used a random effects approach where unexplained statistical heterogeneity was formally taken into account. We could not explore the reasons for heterogeneity in detail largely because poor reporting and the small number of studies per test would have rendered the 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 we were not able to pool given the absence of high-quality studies, we have arbitrarily chosen accuracy estimates from the largest higher-quality study available for the particular test for our decision-analyses. Given also the uncertain impact of study design issues on the magnitudes of the accuracy estimates, our view is that the summaries we generated provide the best available results for clinical interpretation at the time of completing our work.

## Provisos/limitations arising from things not done (omissions)

For some tests we found so few studies [e.g. rheobase (one study), mammary stimulation test (two studies), MMP-9 (two studies)] that besides reporting their individual accuracy estimates no meaningful analyses could be carried out. We had expected, at the inception of our project, to find 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 our literature searching no studies were found on this aspect of physical examination, which forms the cornerstone of our 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 our understanding of the aetiology, physiology and pathology of spontaneous preterm birth evolves, more tests would appear that might not be included in our current review.

Where studies were available, absence of primary data in key areas (e.g. description of population, threshold, or outcome) limited our ability to extract and explore the data as completely as we would have liked. As an example, some studies reported mean ± SD for non-Gaussian distributions of index test results and did not provide $2 \times 2$ tables. Such studies had to be excluded from our review. We tried to minimise this problem by writing to the corresponding author(s) for the required data with variable results. We wrote an initial communiqué followed by another a week later in case of non-response. Generally, we obtained co-operation but for some, our time constraint and their work commitment schedule 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 or accessible, or we have simply had no response. Only after we exhausted this approach did we exclude studies that would otherwise have met our inclusion criteria. Indeed, from the preceding discussion, better quality



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primary test accuracy studies with better reporting would have improved our assessment of the test accuracy.

## Findings in the light of limitations

A confirmatory test usually follows the initial screening, before institution of therapy. In our project, 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 lead 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 parameter changes of the final common pathway of spontaneous preterm labour irrespective of the initial stimulus (e.g. be it subclinical infection or a cervical structural abnormality such as 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, we found that no single test emerged as a front runner 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 because of imprecision of the LR estimates, i.e. given a useful LR point estimate, its CIs should not be wide enough to make the LR less useful because of its imprecision. For example, absence of fetal breathing movement had an LR+ of 6.08 (95% CI 5.22–49.55), which would have made it a useful test to predict spontaneous preterm birth within 48 hours testing when the result is positive. However, it had an LR– of 0.16 (95% CI 0.05–0.58) where the upper limit of its confidence would have made it a less than useful test when the test result is negative. Had the estimate of the LR– including its CIs been $<0.2$, absence of fetal breathing movement would have been a useful test. It may well be that no single screening or testing modality would suffice in the prediction of spontaneous preterm birth and that individual patient data to better delineate the accuracy of test combinations has to be considered in the absence of a novel accurate test.

## Recommendations for an economic model

How accuracy results are incorporated into a model includes dealing with challenges relating to the systematic review process (covered above) and patient preferences. One of the key issues concerning screening or predictive tests in this project is that, if available, effective interventions are convenient, inexpensive, and without particular risk of harm or side effects (to both mother and fetus or newborn), 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 minimises both false-positive (high LR+) and false-negative (low LR–) results. Where screening and/or testing have lower 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 minimise the unwarranted cost and complications from exposure of women and the fetus to treatments. Depending on the economic threshold 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. We have only put forward data in *Figure 83–Figure 85* for decision-analytic modelling because we believe that it provided the most robust estimates, which were derived either from meta-analysis of ideal quality studies or from the largest higher quality study available for the particular test. Ultimately the threshold analysis (Chapter 6) will show what levels of LR+ and LR– will be required to make testing cost-effective in prevention of spontaneous preterm birth.

## Recommendations for practice

Considering cost-effectiveness, there are no practical recommendations for clinicians for prevention of spontaneous preterm birth with testing performed before preventative treatment.

## 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 a new test using multivariable analyses.
- Independent patient data diagnostic meta-analyses are required

## Conclusions of test accuracy reviews

The quality of studies and accuracy of tests was generally poor (*Figure 82*). Some tests were able to achieve high LR+, but at the expense of compromised LR–. Only a few tests reached LR+ >5 (minimising false positives) or LR– <0.2 (minimising false negatives) but not both. For LR+ >5 in asymptomatic antenatal women they are ultrasonographic cervical length measurement and cervicovaginal fetal fibronectin screening, while for LR– <0.2 in the corresponding population, they are detection of uterine contraction (by home uterine monitoring device) and amniotic fluid CRP measurement. For LR+ >5 in symptomatic women with threatened preterm labour they are absence of fetal breathing movements, cervical length and funnelling, amniotic fluid IL-6, serum CRP (for predicting spontaneous preterm birth within 2–7 days of testing); and MMP-9, amniotic fluid IL-6, cervicovaginal fetal fibronectin and cervicovaginal hCG (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation). For symptomatic women with threatened preterm labour, measurement of cervicovaginal IL-8, cervicovaginal hCG, cervical length measurement, absence of fetal breathing movement, amniotic fluid IL-6, and serum CRP all showed LR– <0.2 for predicting spontaneous preterm birth within 48 hours or 7 days of testing. Only cervicovaginal fetal fibronectin and amniotic fluid IL-6 had an LR– <0.2 in predicting spontaneous preterm birth before 34 or 37 weeks' gestation.



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# Chapter 5

# Results of reviews of effectiveness of interventions

## Identification of literature

We divided the literature into existing reviews and primary studies; the searches identified 257 potentially relevant reviews and 13,363 potentially relevant primary studies. On the basis of reviewing titles and abstracts 348 full text papers were ordered for further assessment (130 reviews and 218 primary studies). Once publications had been collated the total number of included reviews was 36, and the total number of included primary studies was 29 (*Figure 86*).

## Effectiveness of interventions among asymptomatic women

### Antibiotics for asymptomatic bacteriuria

Asymptomatic bacteriuria is a persistent bacterial growth in the urinary tract. It occurs in between 5 and 10% of all pregnancies and is associated with an increased risk of spontaneous preterm birth and a low-birthweight infant, although it is unclear whether this link is causal or whether the correlation results from a common underlying

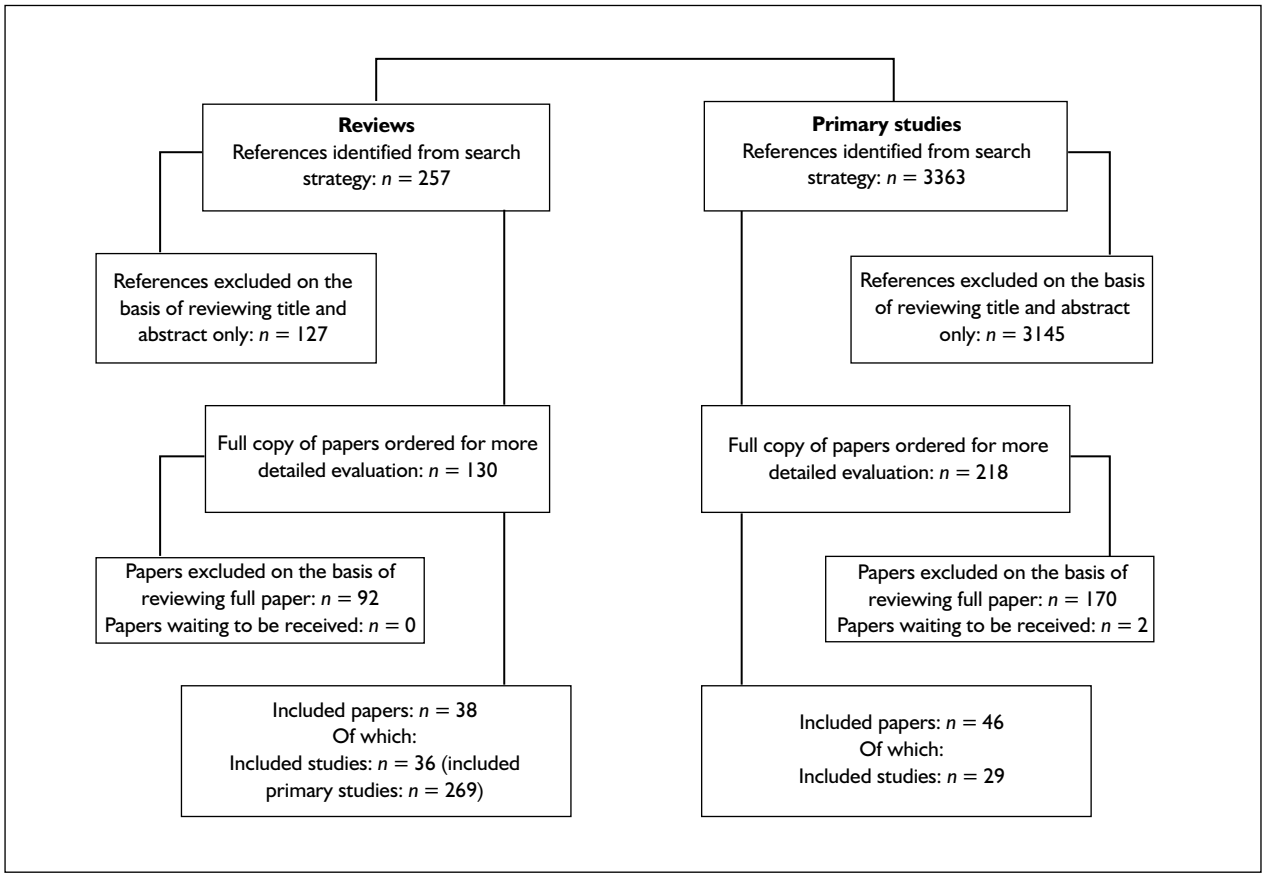


***FIGURE 86*** *Study selection for systematic review of interventions in preventing and delaying, and improving neonatal outcomes consequent on spontaneous preterm birth.*



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factor such as low socioeconomic status. Without treatment, approximately 30% of pregnant women with asymptomatic bacteriuria will develop pyelonephritis, with an associated risk of kidney damage.[351]

The review of antibiotics for asymptomatic bacteriuria[351] included 14 randomised or quasi-randomised controlled trials (RCTs). Further details of the review can be found in Appendix 6, *Table 118*.[265,272,287,352–362] No further trials were found when the searches were updated. Antibiotic therapy was compared with no therapy; and subgroups of continuous therapy and short-course (3–7 days) therapy were examined. The quality of the included studies was generally poor (*Figure 87*). Data were available on preterm birth before 37 weeks' gestation. However, many of the studies were published several decades ago, and defined preterm birth as a low-birthweight (<2500 g) infant, which is a surrogate outcome and may not be useful. Therefore, where preterm birth was defined in this way the study was excluded from the analysis. Six studies used appropriate definitions of preterm birth,[265,272,287,355,360,362] and these showed that antibiotic therapy was effective in preventing preterm birth at less than 37 weeks' gestation, both overall (*Figure 88*) and where continuous[265,272,355,362] (*Figure 89*) or short-course therapies[287,360] (*Figure 90*) were employed. This was the case whether only trials with a strict definition of preterm birth were included or not. Data on low birthweight from those studies using this as a surrogate for spontaneous preterm birth are shown in *Table 3*. As can be seen from the table there was no significant difference between the groups in incidence of low birthweight, either overall or for continuous or short-course therapy. As antibiotic therapy was effective in preventing preterm birth, this supports the view that low birthweight is not a useful surrogate outcome for preterm birth. In addition to reducing the risk of preterm birth, antibiotic therapy, either overall or where continuous or short-course therapy was used, was effective in reducing the incidence of pyelonephritis. Summary relative risks (RRs) from the forest plots presented were used in the decision analyses.

## Duration of treatment for asymptomatic bacteriuria

Asymptomatic bacteriuria is a persistent bacterial growth in the urinary tract. It occurs in between 5 and 10% of all pregnancies and is associated with an increased risk of spontaneous preterm birth and a low-birthweight infant. However, it is unclear whether this link is causal or whether the correlation results from a common underlying factor such as low socioeconomic status. Without treatment approximately 30% of pregnant women with asymptomatic bacteriuria will develop pyelonephritis, with an associated risk of kidney damage.

The review of duration of treatment for asymptomatic bacteriuria[363] included eight randomised[364–371] and two quasi-randomised[372,373] controlled trials. No further trials were found when the searches were updated. Further details of the review can be found in Appendix 6, *Table 118*. The quality of included studies is shown in *Figure 91*. Six trials compared different durations of the same antibiotic treatment,[364–367,369,372] while four compared different durations of treatment with different antibiotic treatments.[368,370,371,373] Data were available for the outcome of spontaneous preterm birth. There was no significant difference in occurrence of spontaneous preterm birth at less than 37 weeks' gestation between the groups where RR was 0.81 [95% confidence interval (95% CI) 0.26, 2.57] ($n = 101$) (*Figure 92*).[365] Other maternal outcomes are shown in *Table 4*. There were fewer side effects in the single-dose groups, both overall[364–367,369–373] and where different antibiotics were used[370,371,373] (*Table 4*). Overall the quality of the studies was poor, and there was little evidence on which to base an assessment of the effectiveness of different duration of antibiotic treatment for asymptomatic bacteriuria. The summary RR from the forest plot presented was not used in the decision analyses.

## Antibiotics for bacterial vaginosis

Bacterial vaginosis is an imbalance of the vaginal flora that results from a reduction in the normal lactobacillary bacterial population, and an increase in anaerobic flora including *Gardnerella vaginalis*. Usually asymptomatic, bacterial vaginosis is present in up to 35% of pregnancies.[374] Bacterial vaginosis has been linked to an increased risk of poor pregnancy outcome, including premature delivery with its concomitant risks.

The review of antibiotics for bacterial vaginosis in pregnancy[375] included 12 RCTs which compared antibiotic therapy with placebo or no treatment,[376–387] and one which compared a single daily dose with a double daily dose of a vaginal antibiotic.[388] Further details of the review can be found in Appendix 6, *Table 118*. No additional RCTs were found when the searches were updated,

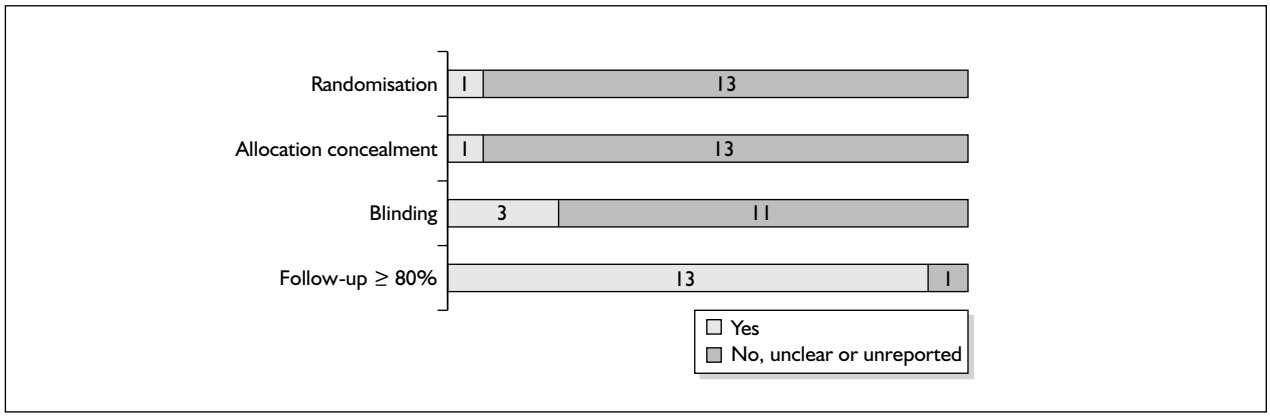


***FIGURE 87*** *Methodological quality of the included trials of antibiotic treatment for asymptomatic bacteriuria in preventing spontaneous preterm birth.*

| Study or subcategory | Treatment *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Preterm birth defined as <37 weeks | | | | | |
| Thomsen, 1987[360] | 2/37 | 12/32 | | 17.89 | 0.14 (0.03–0.60) |
| Subtotal (95% CI) | 37 | 32 | | 17.89 | 0.14 (0.03–0.60) |
| Total events: 2 (Treatment), 12 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 2.67$ ($p = 0.008$) | | | | | |
| 02 Preterm birth not defined | | | | | |
| Gold, 1966[265] | 2/35 | 0/30 | | 0.75 | 4.31 (0.21–86.32) |
| Kass, 1960[719] | 7/106 | 21/108 | | 28.91 | 0.34 (0.15–0.77) |
| LeBlanc, 1964[272] | 7/101 | 6/27 | | 13.16 | 0.31 (0.11–0.85) |
| Subtotal (95% CI) | 242 | 165 | | 42.82 | 0.40 (0.22–0.73) |
| Total events: 16 (Treatment), 27 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 2.81$, df = 2 ($p = 0.25$), $I^2 = 28.7\%$ | | | | | |
| Test for overall effect: $z = 3.00$ ($p = 0.003$) | | | | | |
| 03 Preterm birth defined as <38 weeks | | | | | |
| Furness, 1975[355] | 24/118 | 10/52 | | 19.29 | 1.06 (0.55–2.05) |
| Subtotal (95% CI) | 118 | 52 | | 19.29 | 1.06 (0.55–2.05) |
| Total events: 24 (Treatment), 10 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.17$ ($p = 0.87$) | | | | | |
| 04 Preterm birth defined as <37 weeks or LBW < 2500g | | | | | |
| Wren, 1969[287] | 5/83 | 15/90 | | 20.00 | 0.36 (0.14–0.95) |
| Subtotal (95% CI) | 83 | 90 | | 20.00 | 0.36 (0.14–0.95) |
| Total events: 5 (Treatment), 15 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 2.06$ ($p = 0.04$) | | | | | |
| Total (95% CI) | 480 | 339 | | 100.00 | 0.47 (0.33–0.69) |
| Total events: 47 (Treatment), 64 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 12.05$, df = 5 ($p = 0.03$), $I^2 = 58.5\%$ | | | | | |
| Test for overall effect: $z = 3.91$ ($p < 0.0001$) | | | | | |



***FIGURE 88*** *Forest plot of the effects of all antibiotic therapy versus no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*



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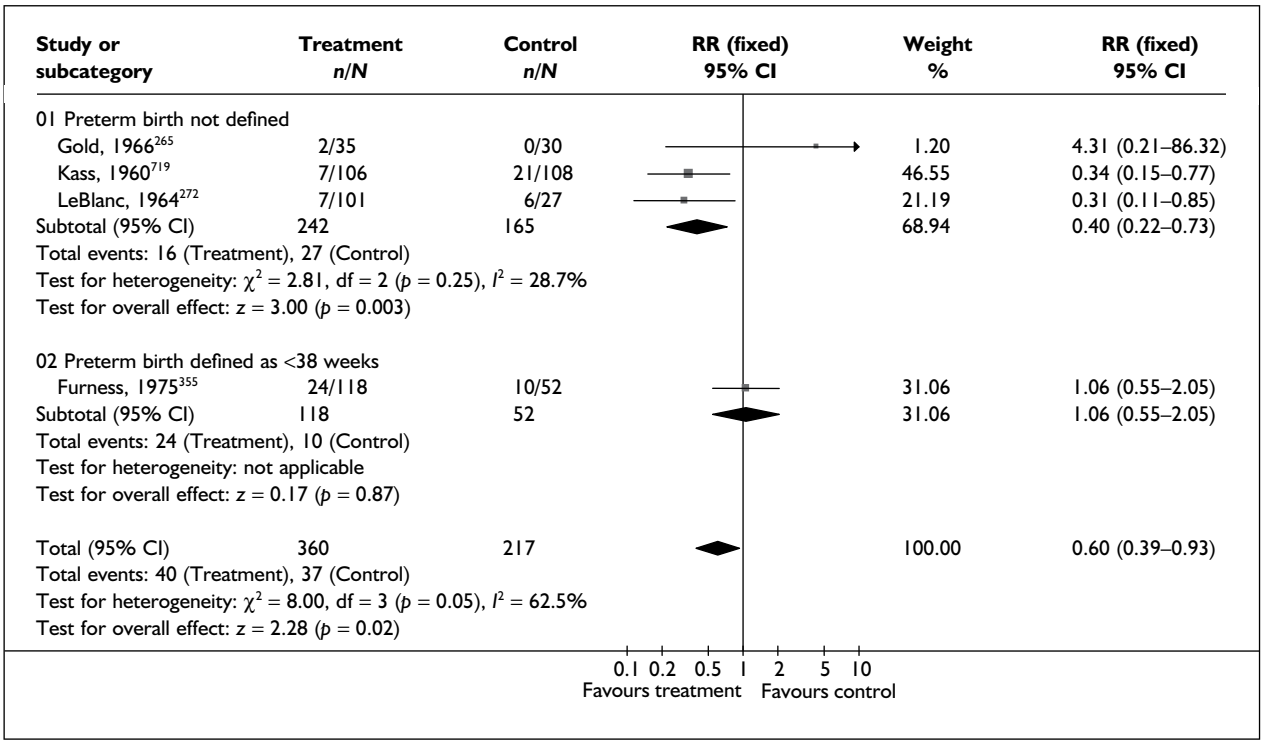


***FIGURE 89*** *Forest plot of the effects of continuous antibiotic therapy versus no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

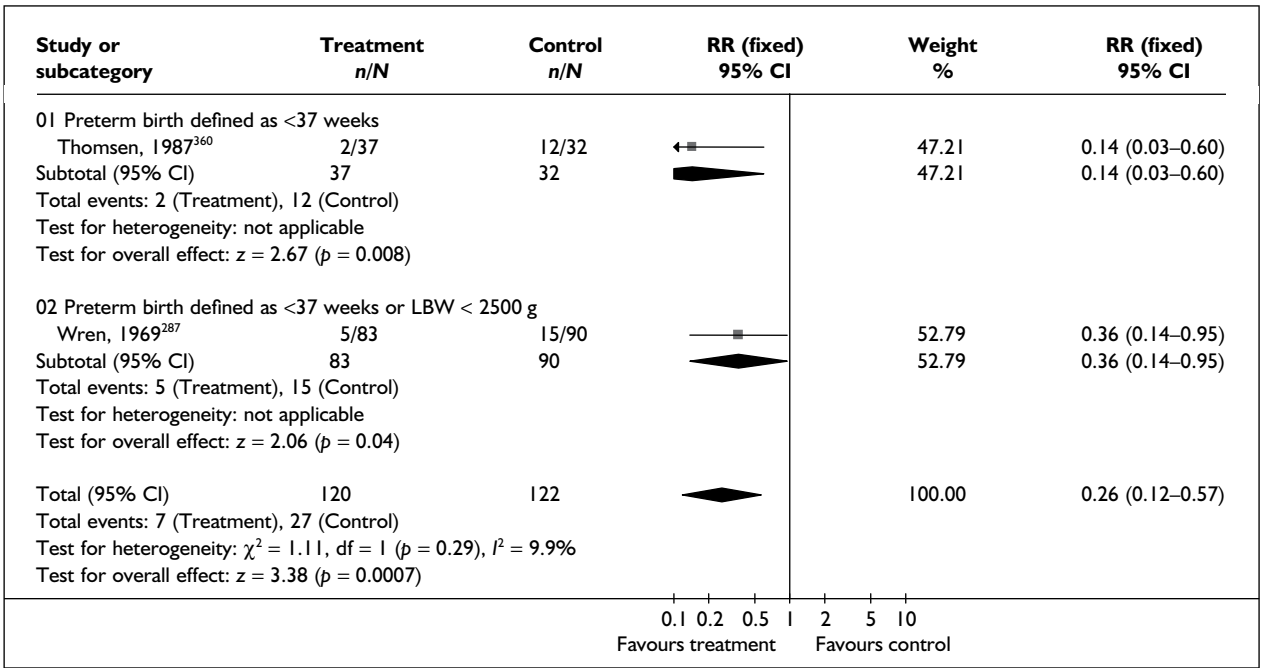


***FIGURE 90*** *Forest plot of the effects of continuous antibiotic therapy versus no treatment for the prevention of spontaneous preterm birth before 34 weeks' gestation.*

***TABLE 3*** *Effects of antibiotic therapies on other perinatal and maternal outcomes*

| Outcome (number of RCTs) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Low birthweight <2500 g*** | | | |
| Overall (4 studies, *n* = 1004) [352,353,356,357] | 0.81 | 0.55–1.19 | 0% (0.57) |
| Continuous (2 studies, *n* = 400) [356,357] | 0.93 | 0.58–1.49 | |
| Short-course (1 study, *n* = 281) [352] | 0.62 | 0.32–1.20 | |
| ***Pyelonephritis*** | | | |
| Overall (13 studies, *n* = 2189) [265,272,352–355–362] | 0.25 | 0.19–0.33 | 57.7% (0.005) |
| Continuous (6 studies, *n* = 1005) [265,272,355–357,362] | 0.22 | 0.14–0.33 | |
| Short-course (5 studies, *n* = 725) [352,354,358,360,361, | 0.38 | 0.23–0.62 | |

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk.

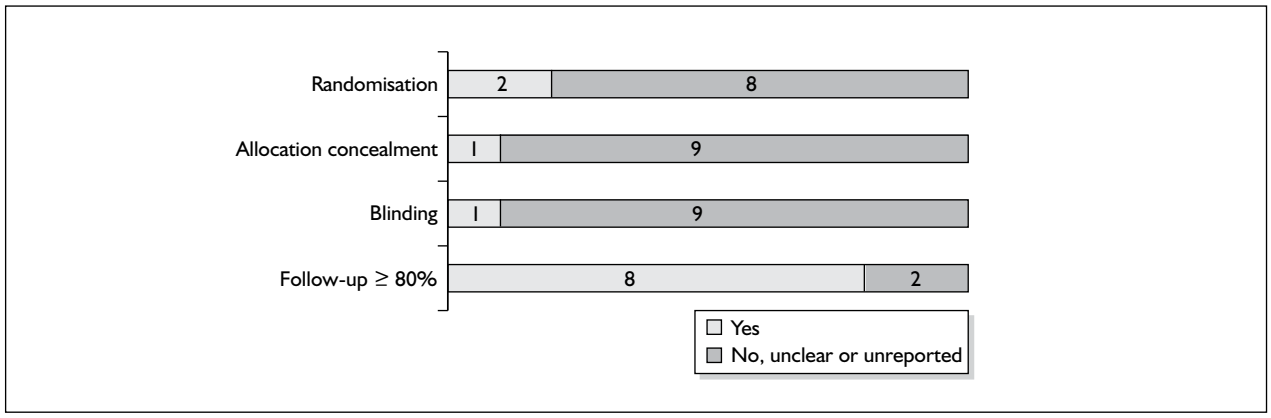


***FIGURE 91*** *Quality of the included trials of duration of treatment for asymptomatic bacteriuria.*

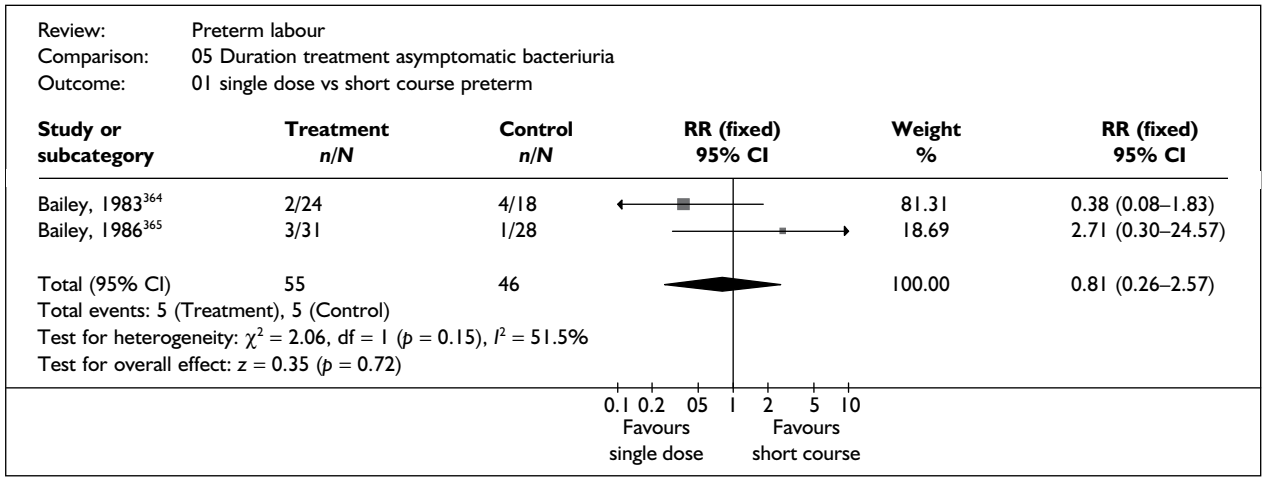


***FIGURE 92*** *Single-dose versus short-course antibiotics for prevention of spontaneous preterm birth before 37 weeks' gestation.*



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***TABLE 4*** *Effects of antibiotic therapies on other maternal outcomes*

| Outcome (number of RCTs) | RR | 95% CI | % Heterogeneity (*p* value) |
|---|---|---|---|
| ***Pyelonephritis*** | | | |
| (2 studies, n = 102)364,372 | 3.09 | 0.54–17.55 | 0% (0.67) |
| ***Maternal side effects*** | | | |
| Total (9 studies, n = 507) 364–368,370–373,714 | 0.52 | 0.32–0.85 | 0% (0.81) |
| Same antibiotic (6 studies, n = 353) 364–368,372,714 | 0.65 | 0.32–1.32 | 0% (0.70) |
| Different antibiotics (3 studies, n = 218) 370,371,373 | 0.44 | 0.23–0.84 | 0% (0.81) |

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk.

although one relevant RCT[389] was identified after the completion of this review. Both oral and vaginal antibiotics were used. High-risk and low-risk women were included in the review, as were women classified as having intermediate flora as well as bacterial vaginosis. *Figure 93* showed that, overall, the quality of the included studies was good with the exception of blinding. Data were available on spontaneous preterm birth before 34 weeks' and 37 weeks' gestation (*Figures 94–103*), perinatal mortality (*Figures 104–108*), and admission to neonatal intensive care (*Figure 109*). The following subgroups were examined:

1. Any antibiotic versus placebo (*Figure 94*, *Figure 98*, *Figure 104*).
2. Oral antibiotics versus placebo (*Figure 95*, *Figure 99*, *Figure 105*).
3. Vaginal antibiotics versus placebo (*Figure 96*, *Figure 100*, *Figure 106*).
4. Single daily dose versus double daily dose vaginal antibiotic (*Figure 102*).
5. Previous spontaneous preterm birth: antibiotics versus placebo (*Figure 97*, *Figure 101*, *Figure 107*).
6. Intermediate flora/bacterial vaginosis: antibiotics versus placebo (*Figure 103*, *Figure 108*, *Figure 109*).

Antibiotic therapy did not significantly affect the incidence of spontaneous preterm birth before 34 weeks' gestation, the incidence of perinatal mortality or the requirement for admission to neonatal intensive care. Spontaneous preterm birth before 37 weeks' gestation was significantly reduced in the subgroup of women with intermediate vaginal flora as well as bacterial vaginosis (*Figure 103*; RR 0.53, 95% CI 0.34, 0.83, based on two studies with 894 patients).[382,386] One study used oral administration[386] and one used vaginal

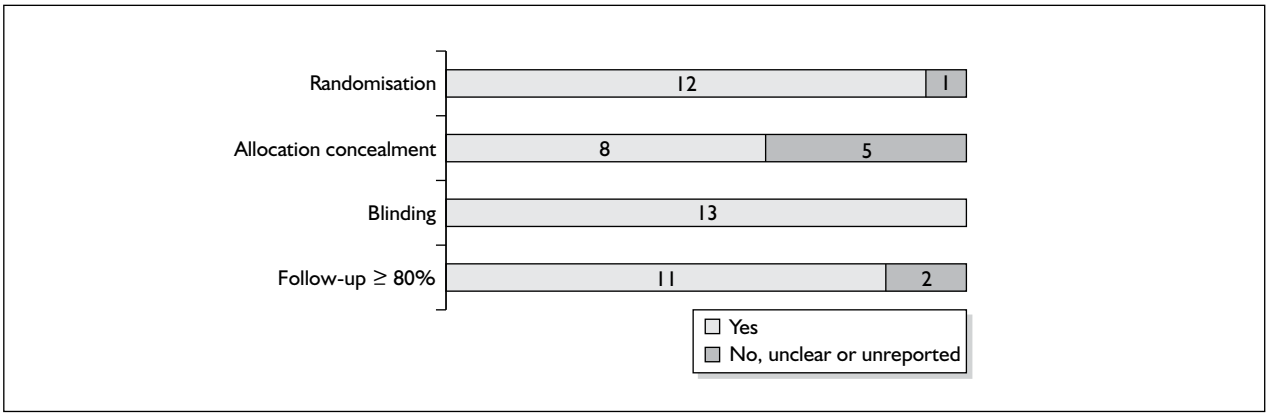


***FIGURE 93*** *Methodological quality of the included trials of antibiotic treatment for bacterial vaginosis.*

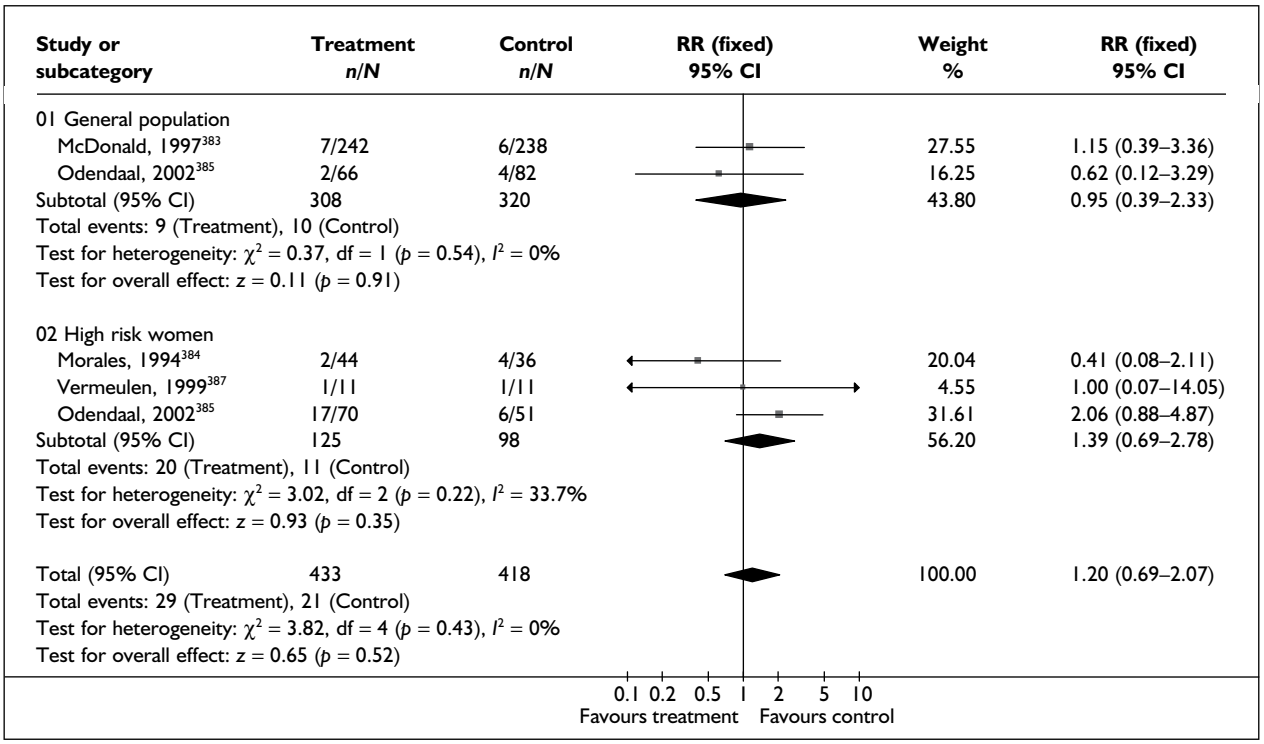


***FIGURE 94*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 34 weeks' gestation.*

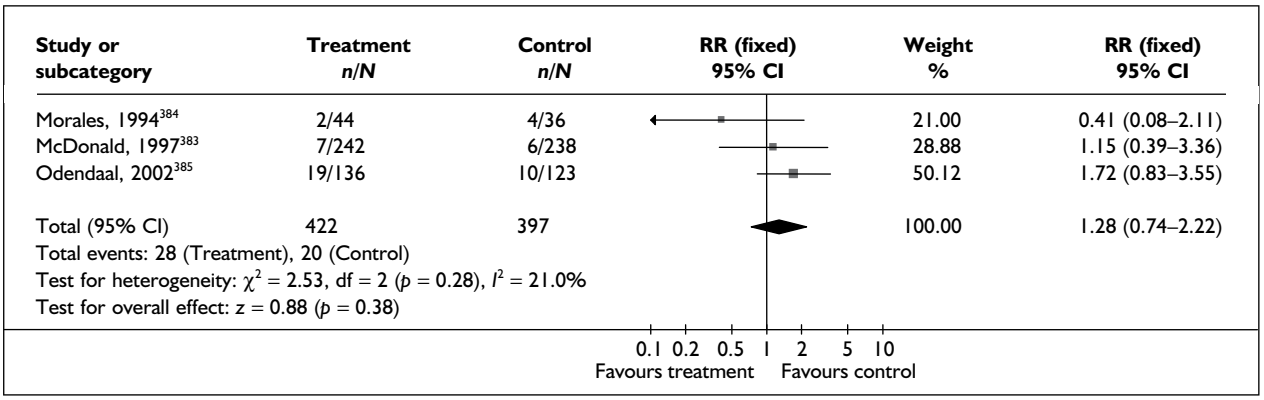


***FIGURE 95*** *Forest plot of the effects of oral antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 34 weeks' gestation.*

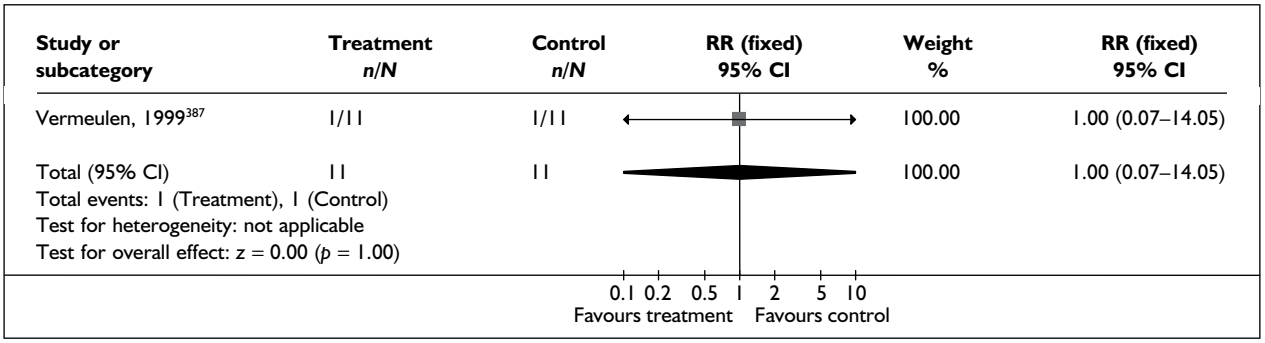


***FIGURE 96*** *Forest plot of the effects of vaginal antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 34 weeks' gestation.*



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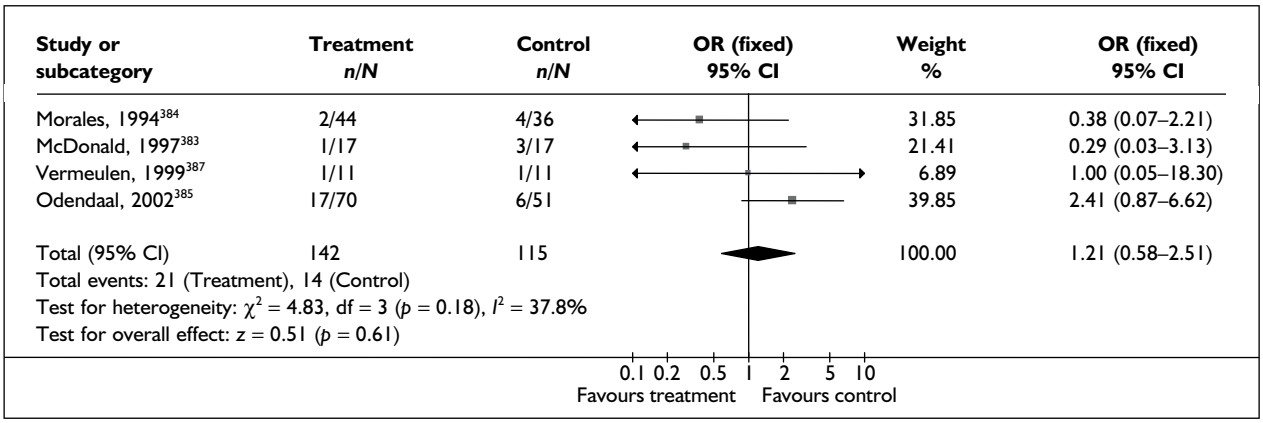


***FIGURE 97*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 34 weeks' gestation in women with previous preterm birth.*

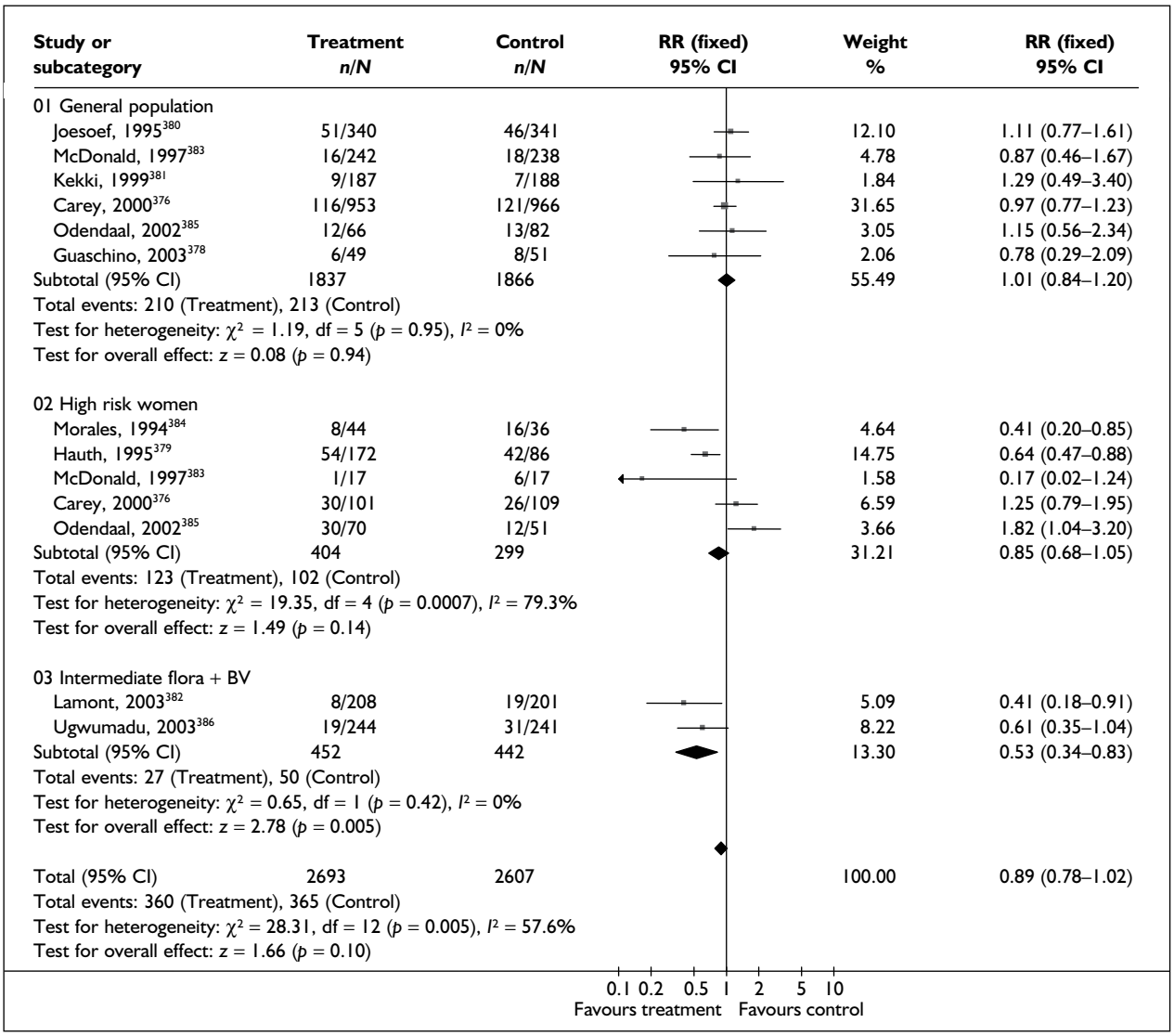


***FIGURE 98*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

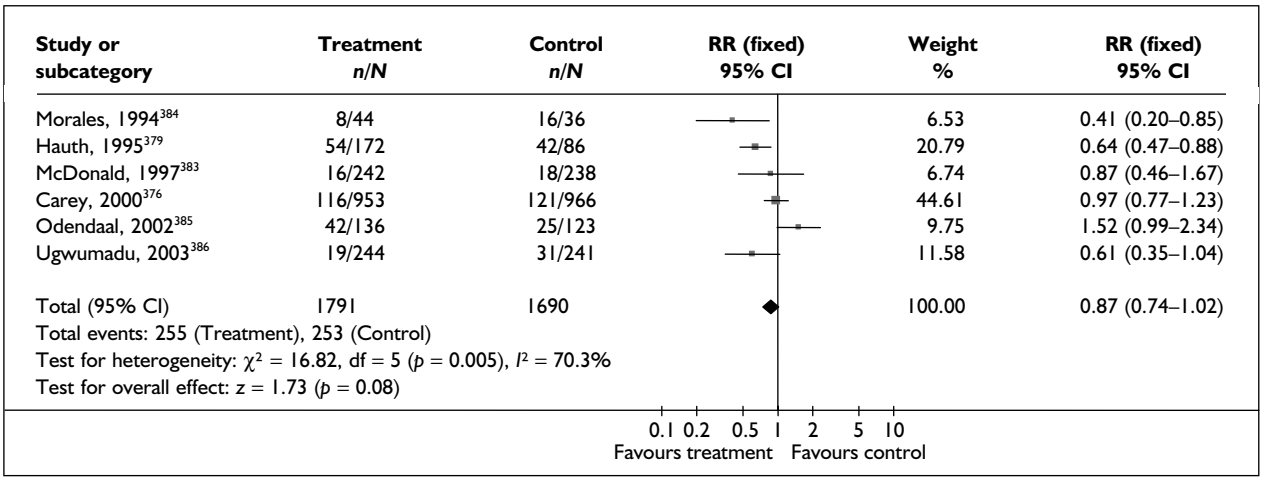


***FIGURE 99*** *Forest plot of the effects of oral antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

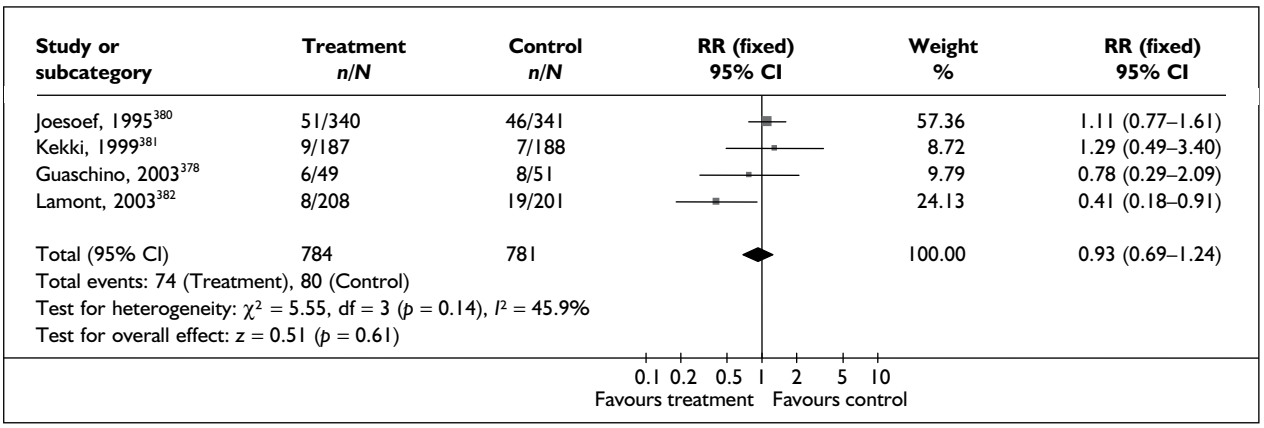


***FIGURE 100*** *Forest plot of the effects of vaginal antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

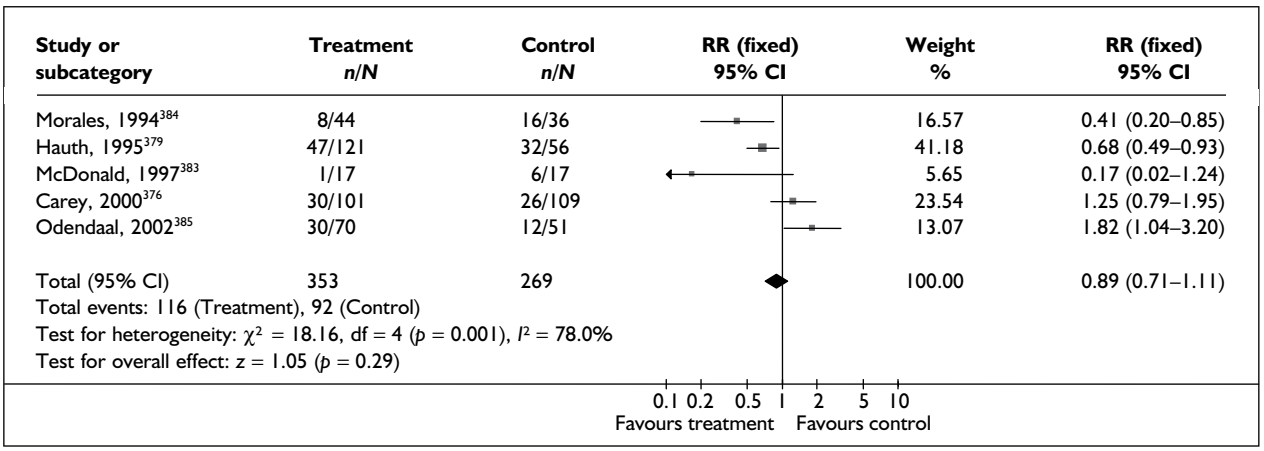


***FIGURE 101*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation in women with previous preterm birth.*



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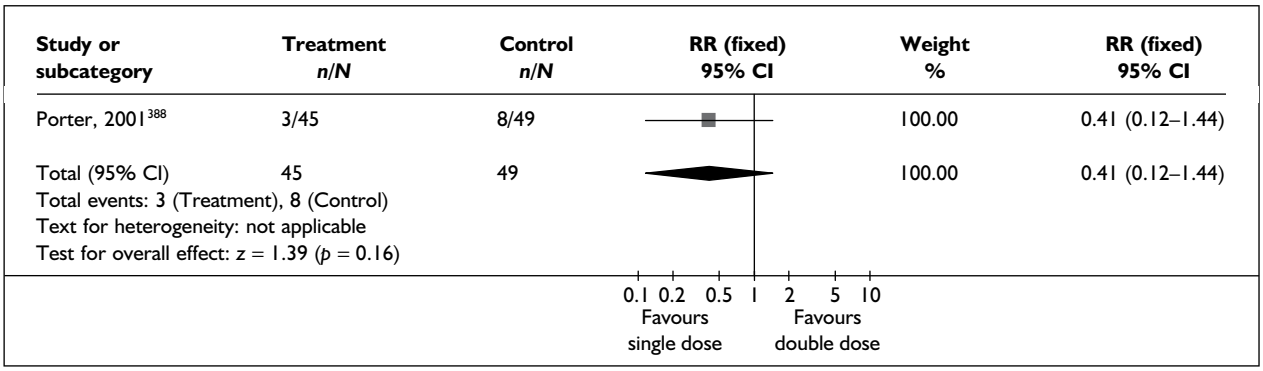


***FIGURE 102*** *Forest plot of the effects of single daily dose versus double daily dose of vaginal antibiotic for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

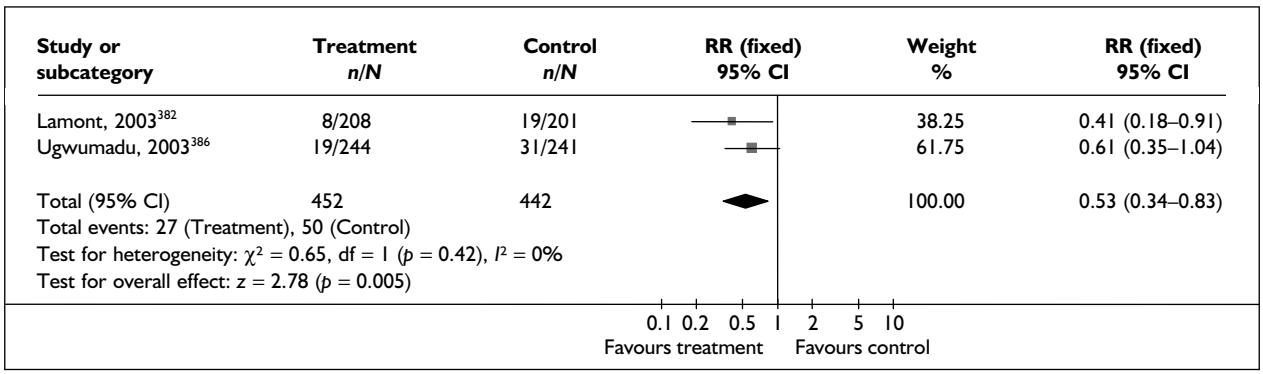


***FIGURE 103*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation in women with intermediate vaginal flora.*

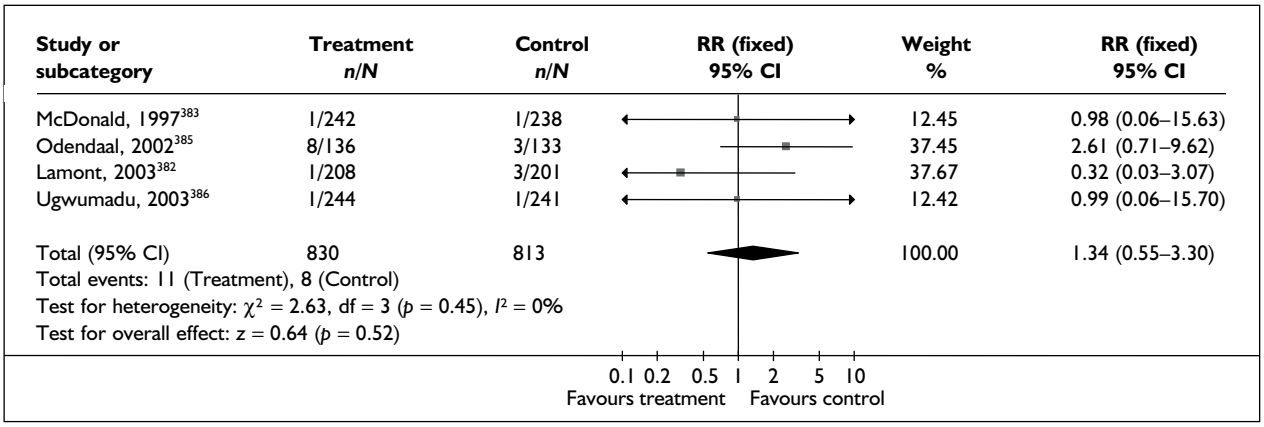


***FIGURE 104*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of perinatal mortality.*

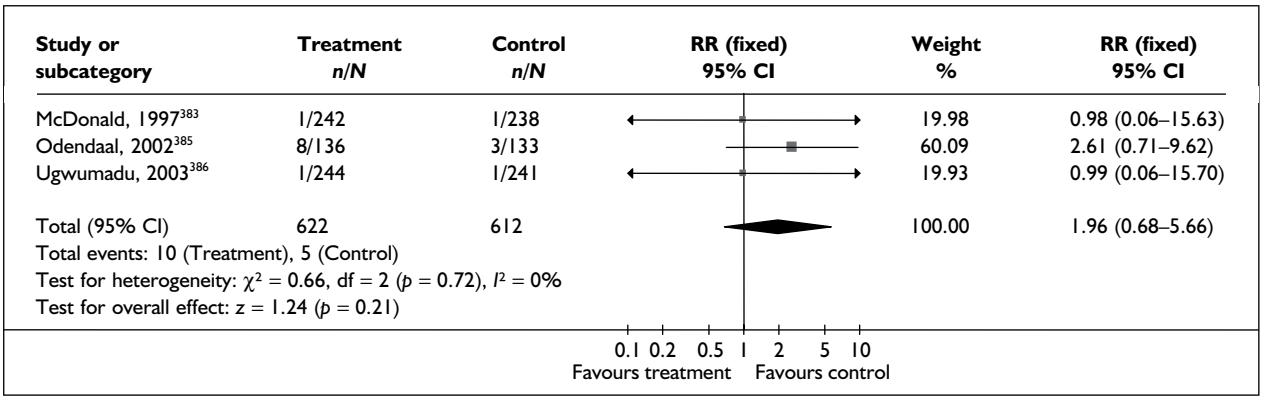


***FIGURE 105*** *Forest plot of the effects of oral antibiotic therapy versus placebo/no treatment for the prevention of perinatal mortality.*

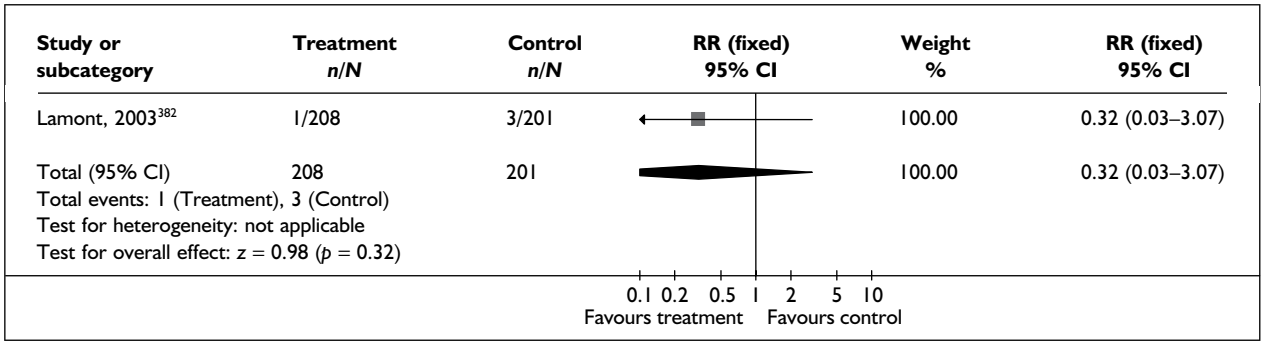


***FIGURE 106*** *Forest plot of the effects of vaginal antibiotic therapy versus placebo/no treatment for the prevention of perinatal mortality.*

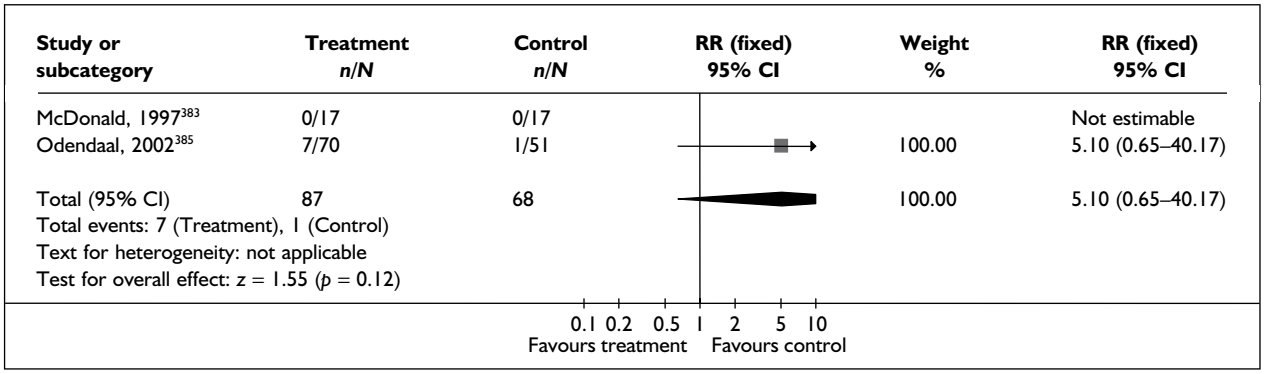


***FIGURE 107*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of perinatal mortality in women with previous preterm delivery.*



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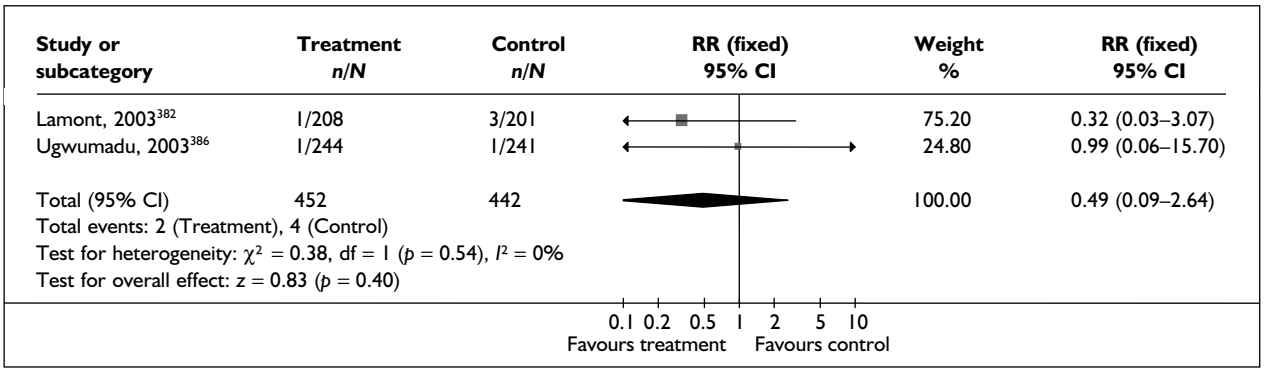


***FIGURE 108*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of perinatal mortality in women with intermediate vaginal flora.*

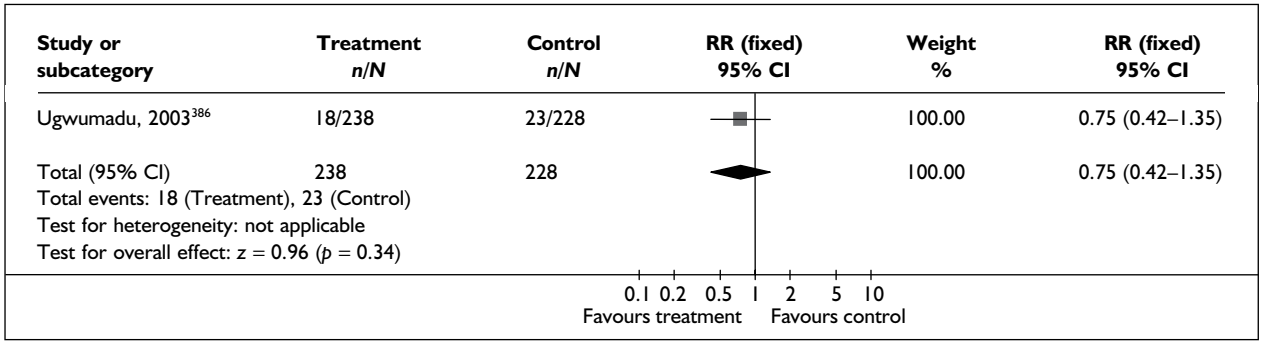


***FIGURE 109*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment in women with intermed1110iate vaginal flora for the prevention of admission to neonatal unit.*

administration of therapy.[382] This reduction in spontaneous preterm birth was not found in other subgroups or in the population as a whole (*Figure 98*). Other neonatal and maternal outcomes are shown in *Tables 5* and *6*. Summary RRs from the forest plots presented were used in the decision analyses.

## Antibiotics for gonorrhoea in pregnancy

Gonorrhoea is a sexually transmitted infection that, if transmitted from mother to child during birth, can result in gonococcal ophthalmia neonatorum. As with other genital bacterial infections, maternal gonorrhoea has been linked to increased risk of spontaneous preterm birth. Spontaneous preterm birth associated with such infections is of particular importance in developing countries where the prevalence of infection is high, with rates of gonorrhoeal infection in pregnant women ranging from 1.7 to 20%.[390]

The review of antibiotics for gonorrhoea in pregnancy[391] included two RCTs ($n = 346$).[392,393] Further details of the review can be found in Appendix 6, *Table 118*. Neither of these studies reported outcomes of spontaneous preterm birth, perinatal mortality or other relevant outcomes. The only outcomes reported were microbiological cure and adverse events. There were no significant differences between the antibiotic regimens used (amoxicillin plus probenecid; spectinomycin; ceftriaxone) in either microbiological efficacy or safety, with all treatments being highly effective and with few adverse events. No additional RCTs were found when the searches were updated. As there was no available evidence relating to the outcome of spontaneous preterm birth, it is not possible to form any conclusions about the efficacy of antibiotic treatment for gonorrhoea in the prevention of spontaneous preterm birth.

***TABLE 5*** *Effects of antibiotic therapies on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Premature birth <32 weeks*** | | | |
| Any antibiotic versus placebo/no treatment | | | |
| Total (4 studies, *n* = 3565) [376,380,383,386] | 1.13 | 0.77–1.68 | 0% (0.48) |
| General population (3 studies, *n* = 3080) [376,380,383] | 1.08 | 0.71–1.66 | 7.8% (0.34) |
| Women with intermediate flora (1 study, *n* = 485) [386] | 1.48 | 0.54–4.10 | NA |
| Oral antibiotic vs placebo/no treatment (3 studies, *n* = 2884) [376,383,386] | 0.98 | 0.62–1.54 | 0% (0.65) |
| Vaginal antibiotic vs placebo/no treatment (1 study, *n* = 681) [380] | 1.82 | 0.79–4.18 | NA |
| Previous preterm delivery: antibiotics vs placebo (1 study, *n* = 34) [383] | 0.50 | 0.05–5.01 | NA |
| Intermediate flora/bacterial vaginosis: antibiotics vs placebo (1 study, *n* = 485) [386] | 1.48 | 0.54–4.10 | NA |
| ***Late miscarriage*** | | | |
| Intermediate flora/bacterial vaginosis: antibiotics vs placebo (1 study, *n* = 485) [388] | 0.20 | 0.04–0.89 | NA |
| ***Low birthweight*** | | | |
| Any antibiotic vs placebo/no treatment | | | |
| Total (7 studies, *n* = 4107) [376,378,380,382–384,386] | 0.95 | 0.79–1.15 | 15.4% (0.31) |
| High-risk women (1 study, *n* = 80) [383] | 0.41 | 0.17–0.95 | NA |
| General population (4 studies, *n* = 3151) [376,378,380,383] | 1.00 | 0.80–1.24 | 0% (0.44) |
| Women with intermediate flora (2 studies, *n* = 876) [382,386] | 0.95 | 0.62–1.47 | 0% (0.44) |
| Oral antibiotic vs placebo/no treatment (4 studies, *n* = 2926) [376,383,384,386] | 0.90 | 0.72–1.11 | 17.3% (0.30) |
| Vaginal antibiotic vs placebo/no treatment (3 studies, *n* = 1181) [378,380,382] | 1.13 | 0.77–1.66 | 14% (0.31) |
| Single daily dose vs double daily dose vaginal antibiotic (1 study, *n* = 94) [388] | 1.19 | 0.58–2.42 | NA |
| Previous preterm delivery: antibiotics vs placebo (2 studies, *n* = 114) [383,384] | 0.39 | 0.18–0.82 | 0% (0.81) |
| Intermediate flora/bacterial vaginosis: antibiotics vs placebo (2 studies, *n* = 876) [382,386] | 0.95 | 0.62–1.47 | 0% (0.44) |
| ***Neonatal sepsis*** | | | |
| Any antibiotic vs placebo/no treatment (2 studies, *n* = 428) [383,387] | 0.95 | 0.06–15.12 | NA |
| Oral antibiotic vs placebo/no treatment (1 study, *n* = 406) [383] | 0.95 | 0.06–15.12 | NA |
| Vaginal antibiotic vs placebo/no treatment (1 study, *n* = 22) [387] | Not estimable | Not estimable | NA |
| Previous preterm delivery: antibiotics vs placebo (2 studies, *n* = 52) [383,387] | Not estimable | Not estimable | NA |
| ***Incidence of premature pre-labour rupture of membranes*** | | | |
| Any antibiotic vs placebo/no treatment (4 studies, *n* = 2579) [376,378,383,384] | 0.89 | 0.63–1.27 | 71.9% (0.01) |
| Oral antibiotic vs placebo/no treatment (3 studies, *n* = 2479) [376,383,384] | 0.81 | 0.56–1.18 | 76.4% (0.01) |
| Vaginal antibiotic vs placebo/no treatment (1 study, *n* = 100) [378] | 2.43 | 0.67–8.86 | NA |
| Previous preterm delivery: antibiotics vs placebo (2 studies, *n* = 114) [383,384] | 0.14 | 0.04–0.50 | 0% (0.98) |

*continued*



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***TABLE 5*** *Effects of antibiotic therapies on other perinatal and maternal outcomes (continued)*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Side effects sufficient to stop treatment*** | | | |
| Any antibiotic vs placebo/no treatment (3 studies, *n* = 1450) [377,383,386] | 1.55 | 0.95–2.54 | 0% (0.61) |
| Oral antibiotic vs placebo/no treatment (2 studies, *n* = 965) [377,383] | 1.29 | 0.69–2.40 | 0% (0.73) |
| Intermediate flora/bacterial vaginosis: antibiotics vs placebo (1 study, *n* = 485) [386] | 2.10 | 0.92–4.77 | NA |
| ***Side effects not sufficient to stop treatment*** | | | |
| Any antibiotic vs placebo/no treatment (3 studies, *n* = 1340) [377,381,383] | 1.27 | 0.76–2.13 | 29.3% (0.24) |
| Oral antibiotic vs placebo/no treatment (2 studies, *n* = 965) [377,383] | 1.49 | 0.72–3.06 | 58.5% (0.12) |
| Vaginal antibiotic vs placebo/no treatment (1 study, *n* = 375) [381] | 1.01 | 0.33–3.06 | NA |
| ***Postpartum infection*** | | | |
| Any antibiotic vs placebo/no treatment (2 studies, *n* = 618) [381,383] | 0.71 | 0.43–1.15 | 40.6% (0.19) |
| Oral antibiotic vs placebo/no treatment (1 study, *n* = 243) [383] | 2.93 | 0.31–27.75 | NA |
| Vaginal antibiotic vs placebo/no treatment (1 study, *n* = 375) [381] | 0.64 | 0.38–1.06 | NA |
| Previous preterm delivery: antibiotics vs placebo (1 study, *n* = 15) [383] | Not estimable | Not estimable | NA |
| Single daily dose vs double daily dose vaginal antibiotic (1 study, *n* = 94) [388] | 3.27 | 0.35,30.28 | NA |

CI, confidence interval; NA, not applicable; RCT, randomised controlled trial; RR, relative risk.

## Antibiotics for the treatment of syphilis

Syphilis is a serious sexually transmitted disease that can be transmitted by a pregnant woman to her baby, who may be born with serious disability as the result of the congenital form of the disease. Syphilis in pregnancy is also associated with increased risk of miscarriage, stillbirth, spontaneous preterm, perinatal mortality and intrauterine growth restriction. The incidence of syphilis has increased in a number of countries, and this is exacerbated by the spread of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). Syphilis in pregnancy is usually treated with penicillin.

The review of antibiotic treatment for syphilis[394] found no studies that met the inclusion criteria of randomised or quasi-randomised controlled trials of antibiotic treatment for syphilis in pregnant women. No additional RCTs were found when the searches were updated. Further details of the review can be found in Appendix 6, *Table 118*. As there was no available evidence it is not possible to form any conclusions about the efficacy of antibiotic treatment for syphilis in the prevention of spontaneous preterm birth.

## Antibiotics for trichomoniasis in pregnancy

Trichomoniasis is a sexually transmitted bacterial infection that causes vaginitis. It is not clear whether trichomonal infection during pregnancy is linked to spontaneous preterm birth, although some studies in the developing world have indicated that this may be the case. Infection with *Trichomonas* is also associated with acquisition of HIV/AIDS.

The review of interventions for trichomoniasis in pregnancy[395] included two studies (*n* = 842); one RCT[396] and one quasi-RCT.[397] Further details of the review can be found in Appendix 6, *Table 118*. The included RCT was of better quality than the quasi-randomised study. The quality of these studies is summarised in *Figure 110*. Women receiving treatment with metronidazole were more likely to experience spontaneous preterm birth before 37 weeks' gestation than women in the placebo

group. The summary RR from the forest plot presented was not used in the decision analyses (*Figure 111*).

## Antibiotics for symptomatic urinary tract infections

Urinary tract infections, including pyelonephritis, are common in pregnancy, occurring in up to 8% of pregnancies. Urinary tract infections are associated with an increased risk of spontaneous preterm birth and neonatal infection. A possible mechanism for this association is the bacterial production of arachidonic acid, phospholipases and prostaglandins, which cause cervical softening and an increase in levels of free calcium in the myometrium.

The review of antibiotics for symptomatic urinary tract infection in pregnancy[398] included eight RCTs.[399–406] Further details of the review can be found in Appendix 6, *Table 118*. The quality of the included studies was variable and poor in terms of blinding and allocation concealment (*Figure 112*). The numbers of participants in the trials were often quite small. No placebo-controlled trials were found; all trials compared one or more regimens of antibiotic treatment. Three studies provided data on spontaneous preterm birth before 37 weeks' gestation and/or neonatal intensive care admissions.[402,405,406] Data for at least one of these outcomes were available on the following comparisons:

1. Outpatient (intramuscular ceftriaxone) versus inpatient (intravenous ceftriaxone) antibiotic treatment.
2. Intravenous ampicillin plus gentamicin versus intravenous cephazolin.
3. Intravenous ampicillin plus gentamicin versus intramuscular ceftriaxone then oral cephalexin.
4. Intramuscular ceftriaxone then oral cephalexin versus intravenous cephazolin
5. Intravenous ceftriaxone once a day plus two doses placebo/day versus intravenous cephazolin every 8 hours.

Only one study was found for each comparison, with one study[406] contributing to three of the comparisons. There were no significant differences between antibiotic regimens in incidence of spontaneous preterm birth before 37 weeks (*Figures 113–117*), or in admission to neonatal intensive care units (*Figures 118–120*), or in other

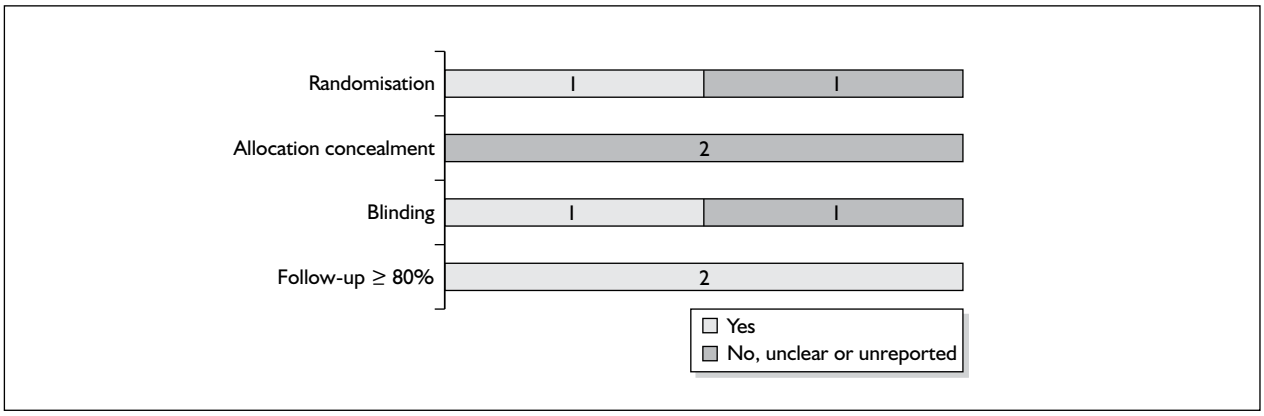


***FIGURE 110*** *Methodological quality of the included trials of metronidazole for the prevention of spontaneous preterm birth.*

| Study or subcategory | Metronidazole *n/N* | Placebo *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| Klebanoff, 2001[396] | 60/315 | 31/289 | | 100.00 | 1.78 (1.19–2.66) |

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

***FIGURE 111*** *Forest plot of the effects of metronidazole versus no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*



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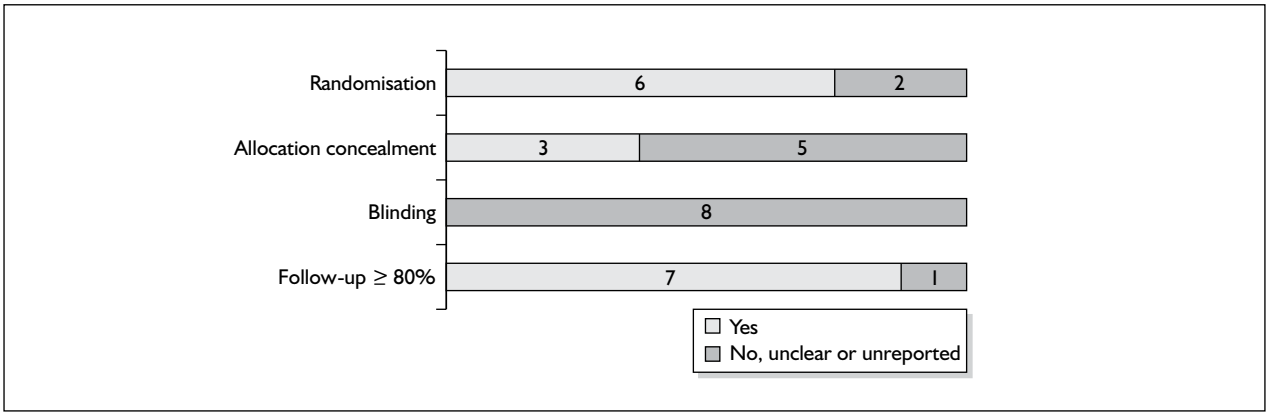


***FIGURE 112*** *Methodological quality of the included trials of antibiotic treatment for symptomatic urinary tract infections.*

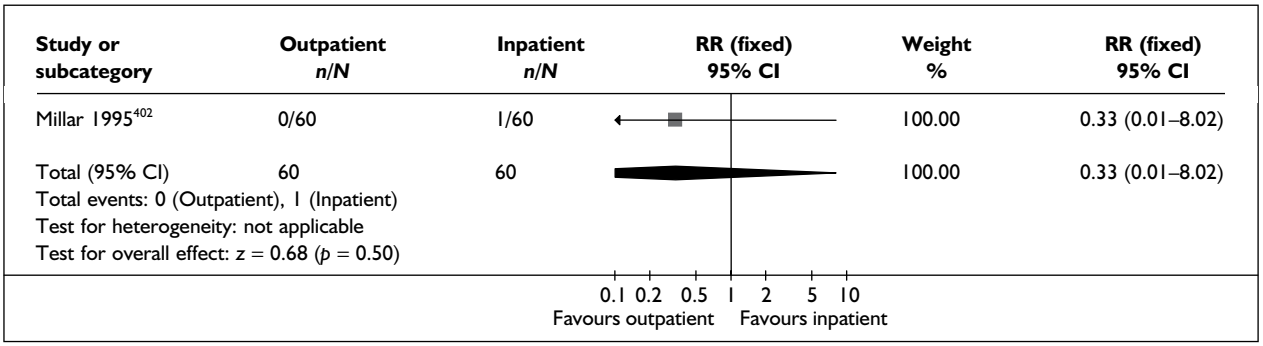


***FIGURE 113*** *Forest plot of the effects of outpatient versus inpatient antibiotics for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

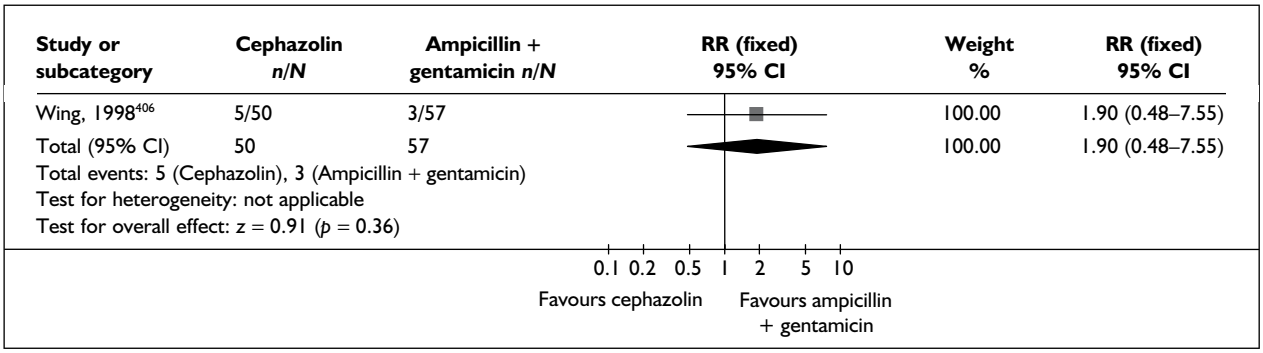


***FIGURE 114*** *Forest plot of the effects of intravenous cephalozin versus intravenous ampicillin plus gentamicin for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

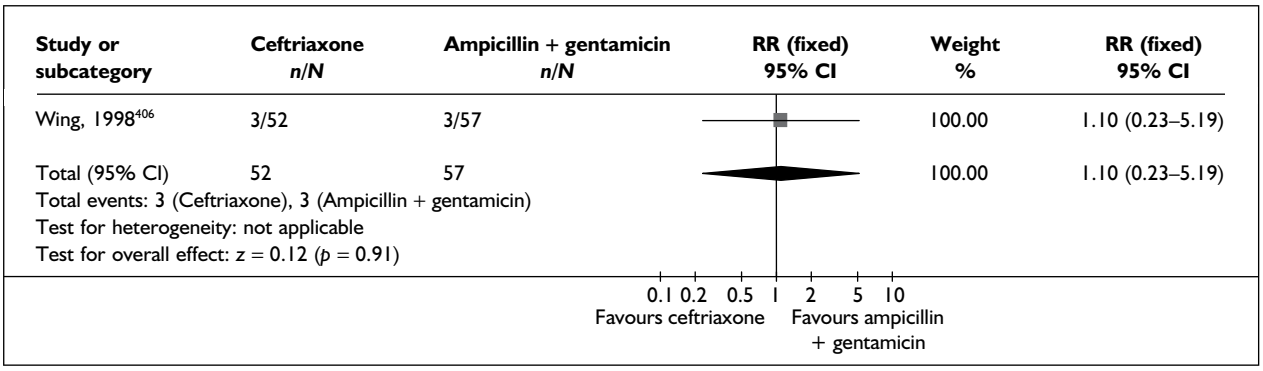


***FIGURE 115*** *Forest plot of the effects of intramuscular ceftriaxone versus intravenous ampicillin plus gentamicin for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

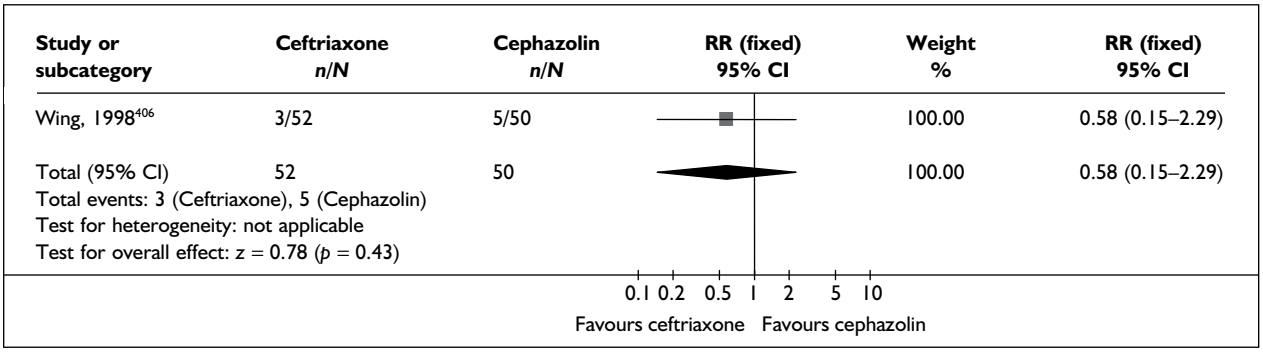


***FIGURE 116*** *Forest plot of the effects of intramuscular ceftriaxone versus intravenous cephazolin for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

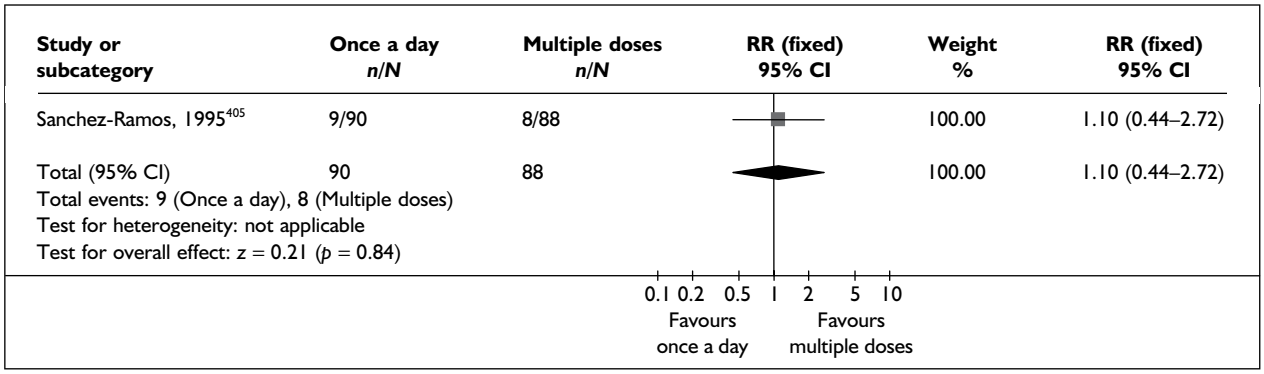


***FIGURE 117*** *Forest plot of the effects of cephalosporins once-a-day versus multiple doses for the prevention of spontaneous preterm birth before 37 weeks' gestation.*



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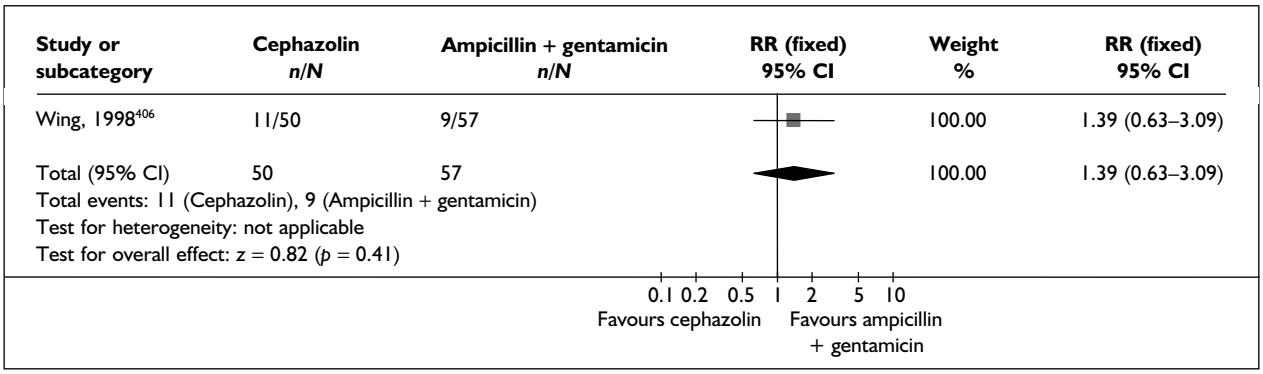


***FIGURE 118*** *Forest plot of the effects of intravenous cephazolin versus intravenous ampicillin plus gentamicin for the prevention of admission to neonatal intensive care unit.*

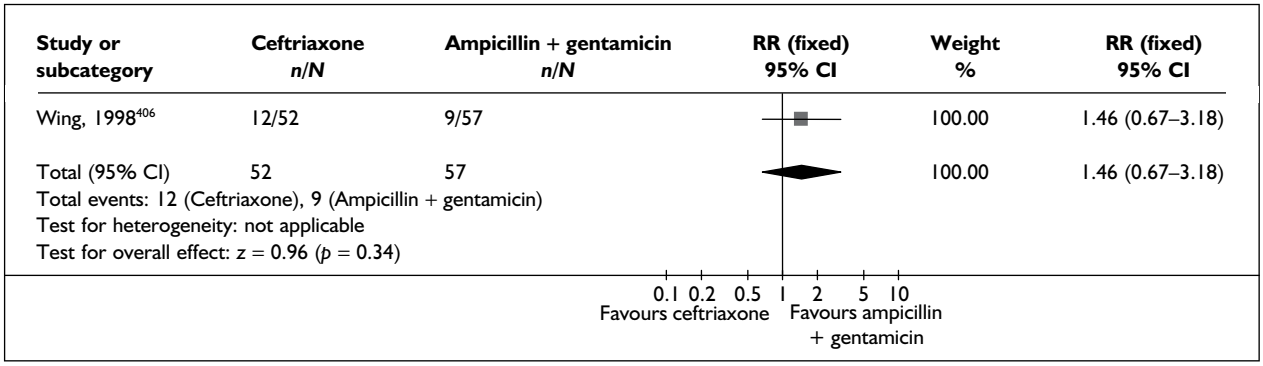


***FIGURE 119*** *Forest plot of the effects of intramuscular ceftriaxone versus intravenous ampicillin plus gentamicin for the prevention of admission to neonatal intensive care unit.*

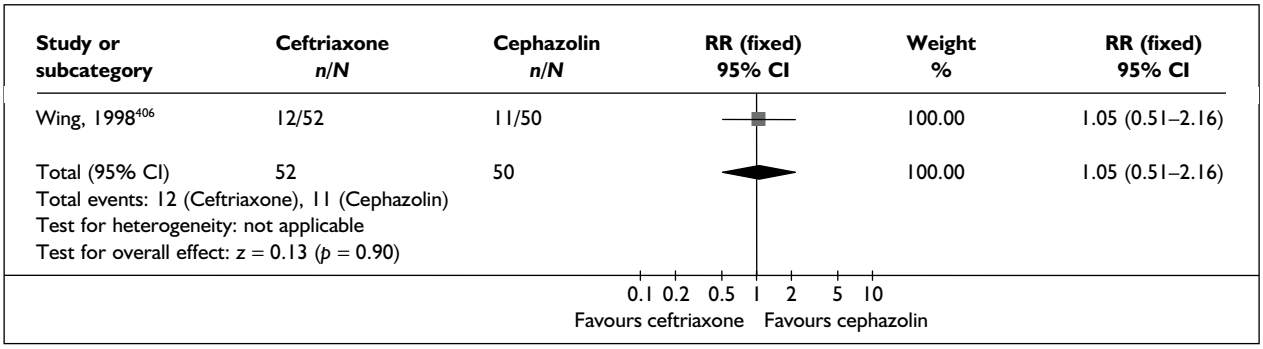


***FIGURE 120*** *Forest plot of the effects of intramuscular ceftriaxone versus intravenous cephazolin for the prevention of admission to neonatal intensive care unit.*

***TABLE 6*** *Other effects of antibiotic therapies on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Low birthweight <2500 g*** | | | |
| Ceftriaxone i.v. once a day vs cephazolin i.v. every 8 hours. (1 study, *n* = 172) [405] | 1.12 | 0.42–2.95 | NA |
| ***Intrauterine growth retardation*** | | | |
| Ceftriaxone i.v. once a day vs cephazolin i.v. every 8 hours. (1 study, *n* = 178) [405] | 0.78 | 0.22–2.82 | NA |
| ***Prolonged pyrexia*** | | | |
| Outpatient (ceftriaxone i.m.) vs inpatient (ceftriaxone i.v.) antibiotic treatment. (1 study, *n* = 120) [402] | 0.13 | 0.01–1.27 | NA |
| Cephazolin i.v. vs ampicillin i.v. + gentamicin (1 study, *n* = 120) [406] | 0.69 | 0.18–2.59 | NA |
| Ceftriaxone i.m. then cephalexin p.o. vs ampicillin i.v. + gentamicin (1 study, *n* = 121) [406] | 1.05 | 0.36–3.08 | NA |
| Ceftriaxone i.m. then cephalexin p.o. vs cephazolin i.v. (1 study, *n* = 117) [406] | 1.47 | 0.44–4.96 | NA |
| ***Need for change in treatment*** | | | |
| Outpatient (ceftriaxone i.m.) vs inpatient (ceftriaxone i.v.) antibiotic treatment. (1 study, *n* = 120) [402] | 0.08 | 0.00–1.34 | NA |
| Cephazolin i.v. ampicillin i.v. vs gentamicin. (1 study, *n* = 118) [406] | 5.17 | 0.25–105.42 | NA |
| Ceftriaxone i.m. then cephalexin p.o. vs ampicillin i.v. + gentamicin. (1 study, *n* = 121) [406] | 9.45 | 0.52–171.79 | NA |
| Ceftriaxone i.m. then cephalexin p.o. vs cephazolin i.v. (1 study, *n* = 117) [406] | 1,97 | 0.37–10.32 | NA |
| Ceftriaxone i.v. once a day vs cephazolin i.v. every 8 hours. (1 study, *n* = 178) [405] | 0.59 | 0.14–2.38 | NA |
| Ampicillin p.o. vs nitrofurantoin p.o. (1 study, *n* = 86) [404] | 1.44 | 0.22–7.08 | NA |

i.m., intramuscularly; i.v., intravenously; NA, not available; p.o., orally.

perinatal and maternal outcomes (*Table 6*). Overall, ampicillin and gentamicin appears to be the most promising treatment combination, as compared with cephazolin or ceftriaxone, but the evidence to support this is limited in terms of both the quantity and quality. Because of the lack of placebo/no treatment comparators, summary RRs were not used in the decision analyses.

## Antibiotics for ureaplasma

Ureaplasma in the vagina is an abnormal bacterial colonisation of the genital tract. Women who present with a high density of such abnormal flora in pregnancy are at increased risk of infections associated with spontaneous preterm birth. This is believed to be the result of an inflammatory cascade, which may lead to pre-labour rupture of membranes. It is unclear whether antibiotic treatment of asymptomatic ureaplasma is effective in preventing such a sequence of events.

The review of antibiotics for ureaplasma in the vagina in pregnancy[407] included one RCT (*n* = 1071).[408] Further details of the review can be found in Appendix 6, *Table 118*. This study did not report outcomes of spontaneous preterm birth or perinatal mortality. The only outcomes reported were low birthweight, <2500 g, and adverse events. There were no significant differences between the antibiotic regimens used (erythromycin estolate, erythromycin sterate, clindamycin hydrochloride) and placebo in either incidence of low birthweight (RR 0.70; 95% CI 0.46–1.07) or safety (RR 1.25; 95% CI 0.85–1.85). No additional RCTs were found when the searches were updated. As there



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was no available evidence relating to the outcome of spontaneous preterm birth, it is not possible to form any conclusions about the efficacy of antibiotic treatment for vaginal ureaplasma in the prevention of spontaneous preterm birth. RRs for this intervention were not included in the decision analysis.

## Prophylactic antibiotics for the prevention of spontaneous preterm birth

Infections, such as maternal genital tract infection or colonisation by some infectious organisms, have been implicated in the aetiology of preterm birth, and associated with maternal and perinatal mortality and morbidity. A strategy of routine antibiotic prophylaxis has been suggested as an alternative to routine antenatal detection and treatment of infections.

The review of prophylactic antibiotics during the second and third trimester for the prevention of infectious morbidity and mortality[409] included five RCTs ($n = 1560$), which compared antibiotic therapy (oral erythromycin, metronidazole, cefetamet-pivoxil, and parenteralceftriaxone and clindamycin vaginal cream) with placebo or no treatment.[387,410–413] Further details of the review can be found in Appendix 6, *Table 118*. No additional RCTs were found when the searches were updated; although one trial was removed from the original review because it appeared to include women with a diagnosis of bacterial vaginosis before randomisation. High-risk and unspecified or unselected pregnant women with singleton gestations were included in the review. In general, few of the included studies were considered to be of high quality because of deficiencies in allocation concealment and follow-up (*Figure 121*). No beneficial affect of antibiotic prophylaxis was reported for incidence of spontaneous preterm birth less than 37 weeks' gestation in high-risk women; results did not change when subgroups for unselected and high-risk women were considered (*Figure 122*). Prophylactic antibiotic therapy did not reduce the risk of perinatal mortality compared to placebo/no treatment (*Figure 123*). No data were reported for preterm birth less than 34 weeks' gestation or requirement of neonatal intensive care. Prophylactic antibiotic therapy was also found to reduce the risk of pre-labour rupture of membranes in unselected women, and infection (puerperal sepsis) and low birthweight in high-risk women (*Table 7*). Summary RRs were used in the decision analysis for all primary end points. Although this review appears to support the use of prophylactic antibiotics in high-risk women for the prevention of spontaneous preterm birth, further research is needed to determine the best type and dose of antibiotic therapy for routine use in pregnant women.

## Antioxidants

The use of antioxidants, such as vitamin C, vitamin D, vitamin E and zinc, during pregnancy may offer protection against the development of pregnancy complications, including spontaneous preterm birth,[414] pre-eclampsia, and pre-labour rupture of fetal membranes. Antioxidants are loosely defined as any substance that when present in low concentrations compared to that of an oxidisable substrate, significantly delays or inhibits oxidation of that substrate. Antioxidants are thought to protect proteins and enzymes from oxidation and destruction by free radicals, and help to maintain cellular membrane integrity. In addition to its

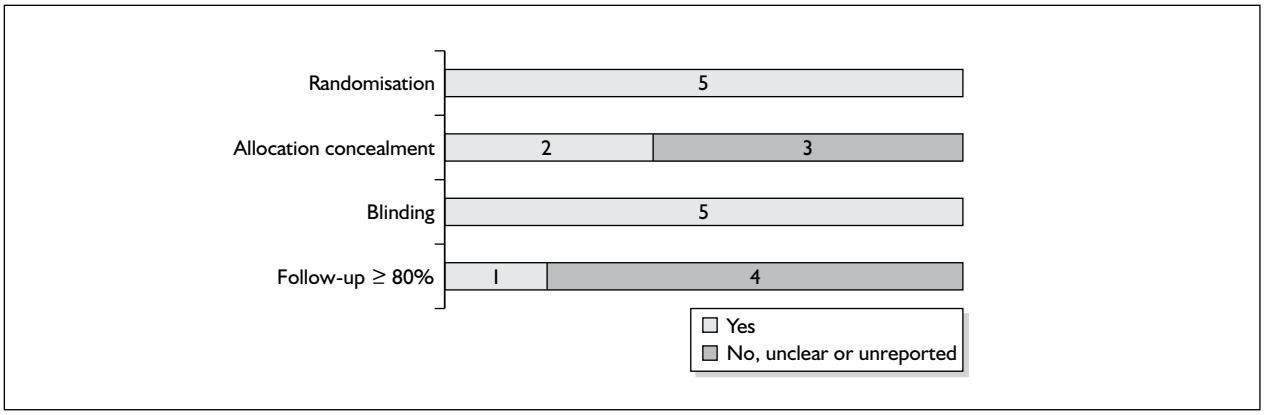


***FIGURE 121*** *Quality of the included trials of prophylactic antibiotic therapy for the prevention of spontaneous preterm birth.*

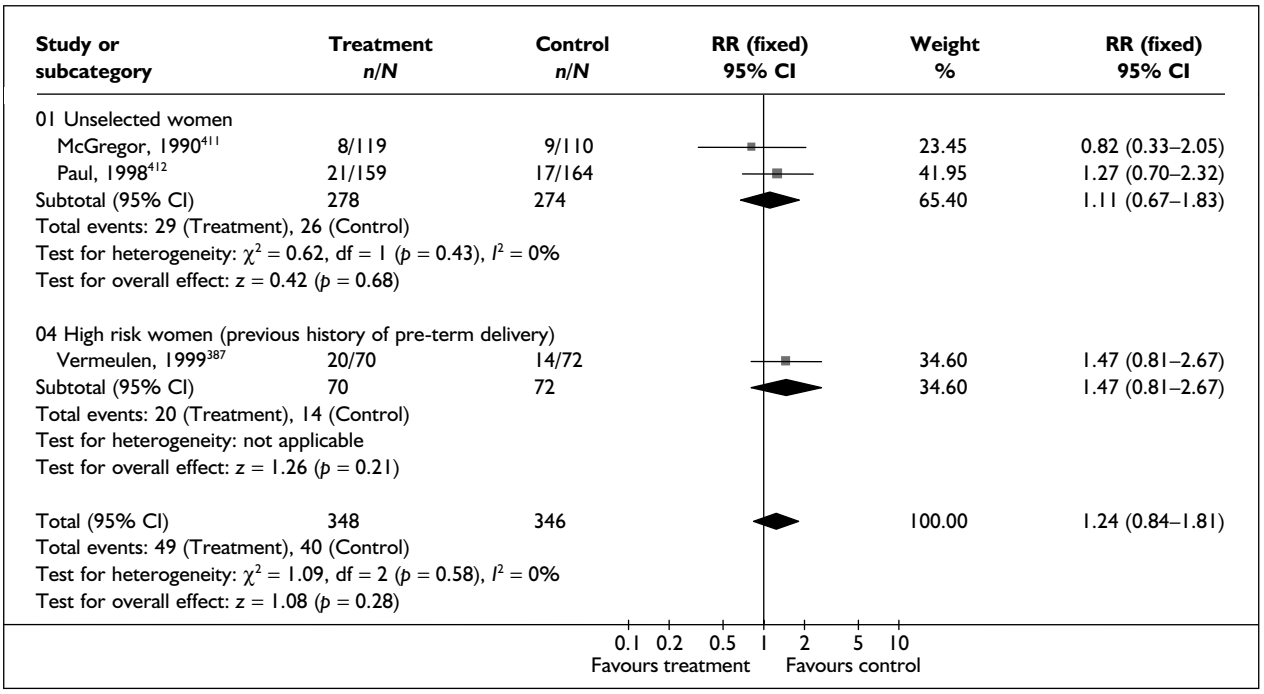


***FIGURE 122*** *Forest plot of the effects of any antibiotic therapy versus no treatment for the prevention of spontaneous preterm birth (birth gestation undefined).*

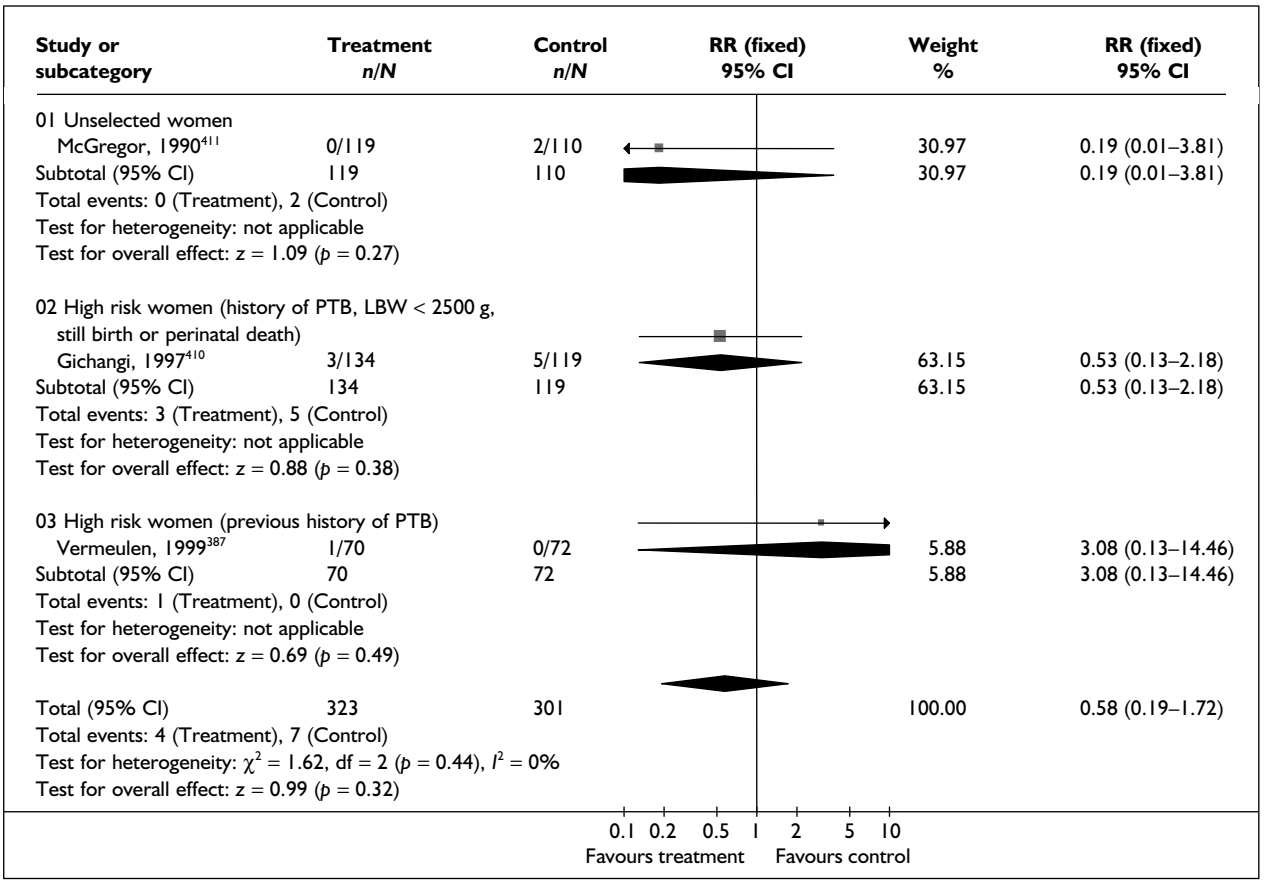


***FIGURE 123*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of perinatal mortality.*



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***TABLE 7*** *Effects of antibiotic therapies on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Chorioamnionitis*** | | | |
| Unselected women (1 study, $n = 229$)[411] | 0.62 | 0.10–3.62 | NA |
| ***Puerperal sepsis/postpartum endometritis*** | | | |
| Unselected women (2 studies, $n = 431$)[411,413] | 0.51 | 0.24–1.08 | 0% (0.40) |
| High-risk women (previous history of preterm delivery, LBW < 2500 g, stillbirth or perinatal death) (1 study, $n = 196$)[410] | 0.55 | 0.33–0.92 | NA |
| ***Low birthweight*** | | | |
| Unselected women (2 studies, $n = 555$)[412,413] | 1.03 | 0.69–1.55 | 70.8% (0.06) |
| High-risk women (history of preterm delivery, LBW < 2500 g, stillbirth or perinatal death) (1 study, $n = 253$)[460] | 0.57 | 0.37–0.88 | NA |
| ***Neonatal sepsis*** | | | |
| High-risk women (previous history of preterm delivery) (1 study, $n = 142$)[387] | 11.31 | 0.64–200.79 | NA |
| ***Congenital abnormality*** | | | |
| Unselected women (2 studies, $n = 463$)[411,413] | 1.49 | 0.20–11.14 | 0% (0.59) |
| ***Small for gestational age*** | | | |
| Unselected women (1 study, $n = 239$)[411] | 1.29 | 0.42–3.96 | NA |
| ***PROM*** | | | |
| Unselected women (1 study, $n = 229$)[411] | 0.34 | 0.15–0.78 | NA |
| ***Gonococcal infection detected postpartum*** | | | |
| High-risk women (1 study, $n = 204$)[410] | 0.35 | 0.13–0.94 | NA |

CI, confidence interval; LBW, low birthweight; NA, not applicable; PROM, pre-labour rupture of membranes; RCT, randomised controlled trial; RR, relative risk.

antioxidant properties zinc plays an important role in normal growth and development and biological functions such as protein synthesis and nucleic acid metabolism.[415,416] Since these are involved in cell division and growth, zinc is believed to be important for fetal growth and development.[417]

The review of antioxidants (vitamins C, E and D, and zinc) included 15 RCTs ($n = 4763$)[418–421] with one RCT[422] added to the primary studies identified in these earlier reviews. Further details of these reviews and the RCT can be found in Appendix 6, *Table 119*. Clinical heterogeneity precluded a quantitative summary of the primary studies relating to zinc supplementation because of variation in dosages, populations and duration of intervention. The quality of the primary studies is shown in *Figure 124* where criteria for blinding and follow-up appeared to be met in most of the included trials. Compared to placebo, supplementation with vitamin C, either in combination with vitamin E or alone, or supplementation with zinc did not significantly reduce the risk of spontaneous preterm birth before 37 weeks' gestation (*Figure 125*) or perinatal mortality (*Figure 126*). No statistically significant between group differences were shown in the incidence of admission to neonatal intensive care (*Figure 127*). Subgroup analyses based on trial quality or gestation at time of study entry did not alter these results (*Table 8*).

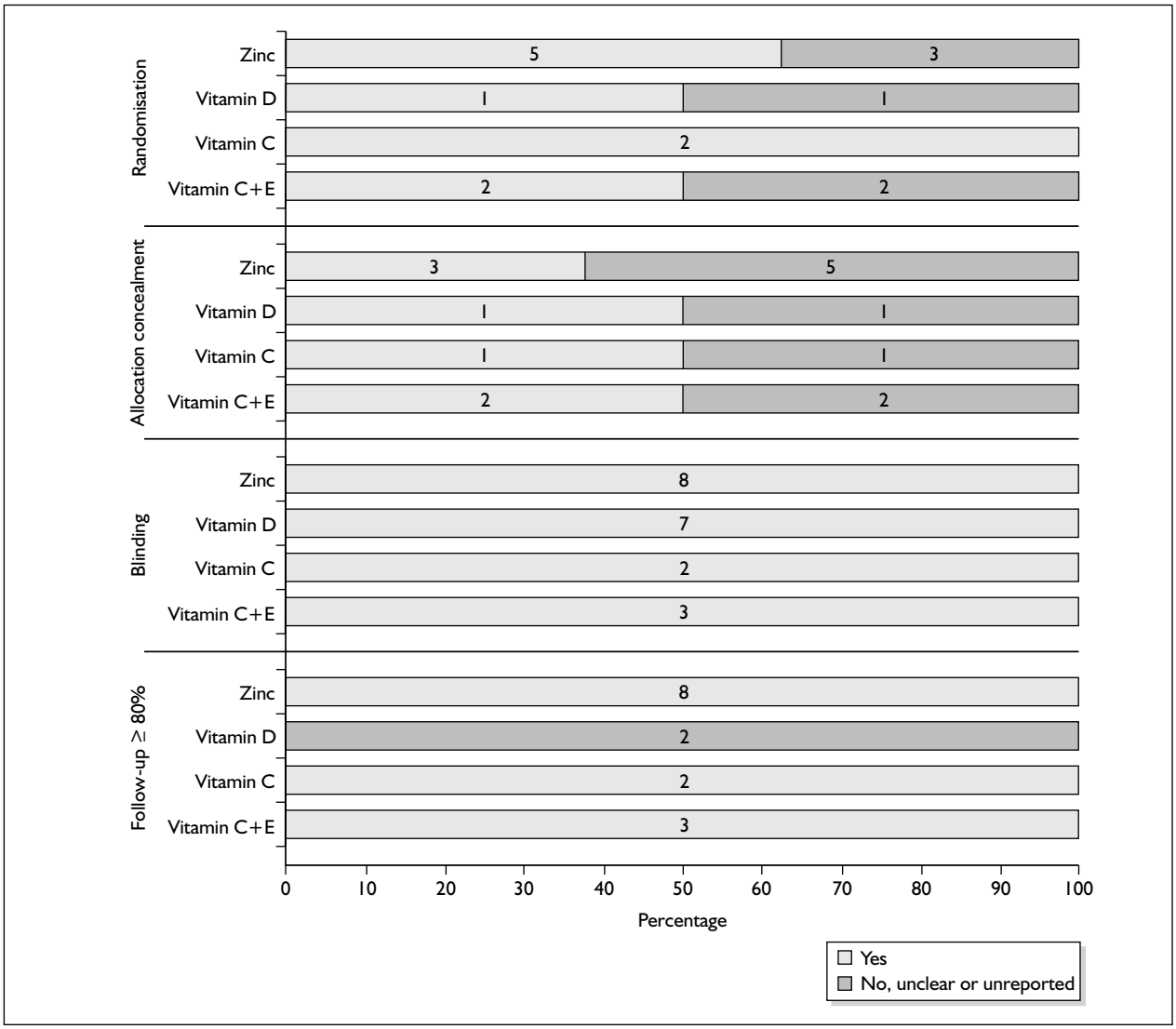


***FIGURE 124*** *Methodological quality of RCTs of antioxidants in the prevention of spontaneous preterm birth.*

The effect on other perinatal or maternal outcomes is shown in *Table 9*. The results do not appear to support the prophylactic use of antioxidants for the prevention of spontaneous preterm birth. In addition there is limited evidence about the safety of giving antioxidants to women during pregnancy. When interpreting these results it should be noted that it is unclear whether the primary studies relating to vitamin D and zinc supplementation included women with multiple pregnancies. RRs less than one in the forest plots presented were included in the decision analysis. RRs from the highest-quality study with gestationally defined spontaneous preterm birth outcome were used for the zinc subgroup, and in all other subgroups summary RRs were used.

## Energy and protein intake

Observational studies have indicated that gestational weight gain and energy intake are positively associated with fetal growth, and may even prevent spontaneous preterm birth.[423,424] Furthermore, higher weight for gestational age has been associated with a reduced risk of morbidity related to type 2 diabetes and heart disease in late adulthood.[425] On the other hand, rapid maternal weight gain during pregnancy has been associated with increased pregnancy complications.[426] A number of strategies designed to optimise energy and protein intake during pregnancy have been developed, but the fetal, infant and maternal health implications are not clear.



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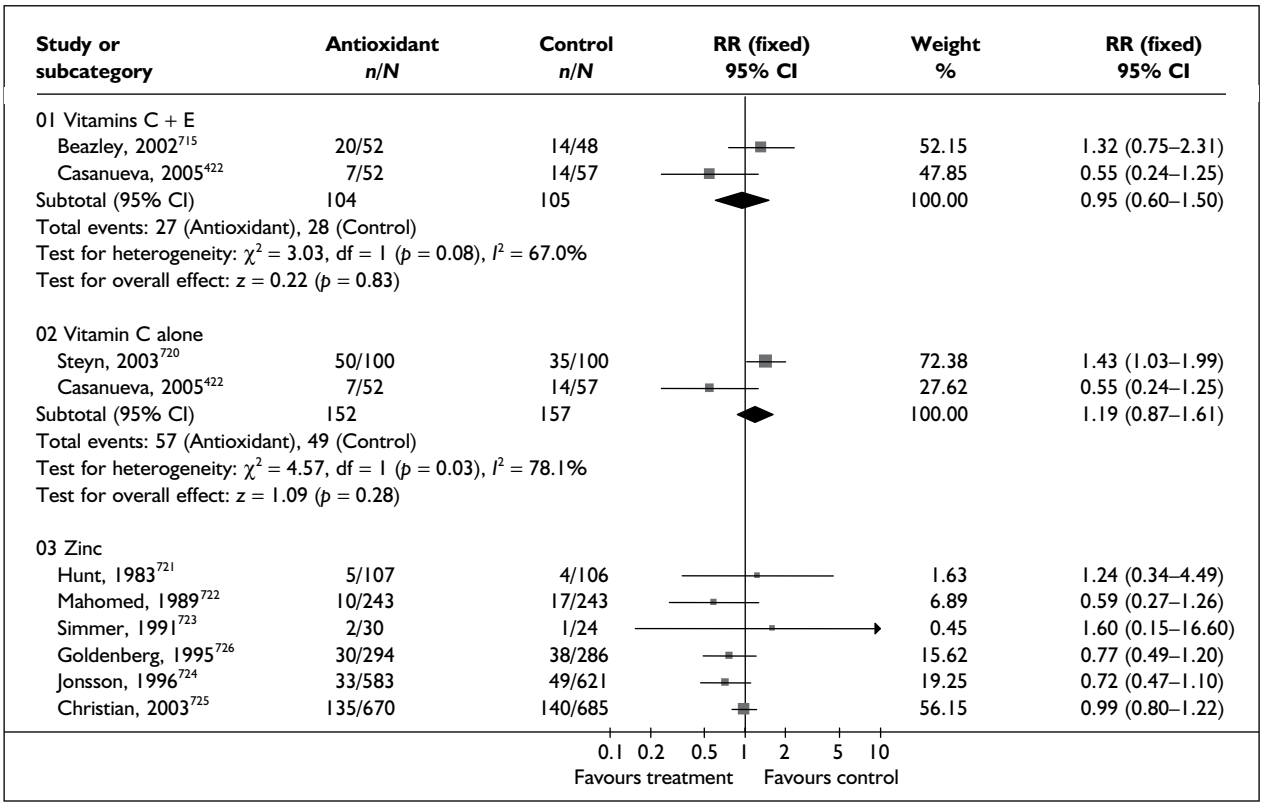


***FIGURE 125*** *Forest plot of the effects of antioxidants in the prevention of preterm birth before 37 weeks' gestation.*

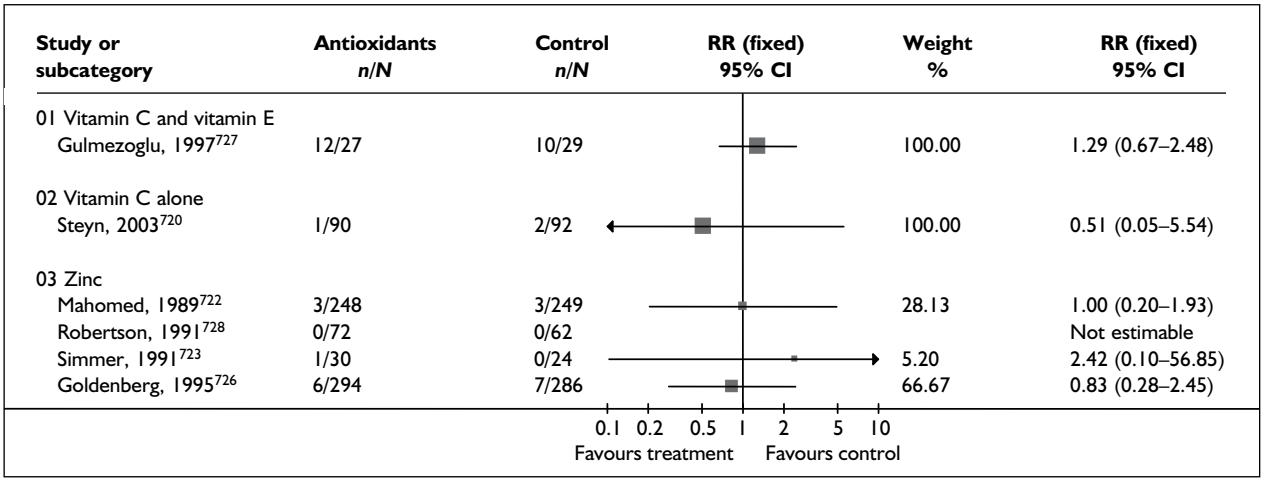


***FIGURE 126*** *Forest plot of the effects of antioxidants on perinatal mortality.*

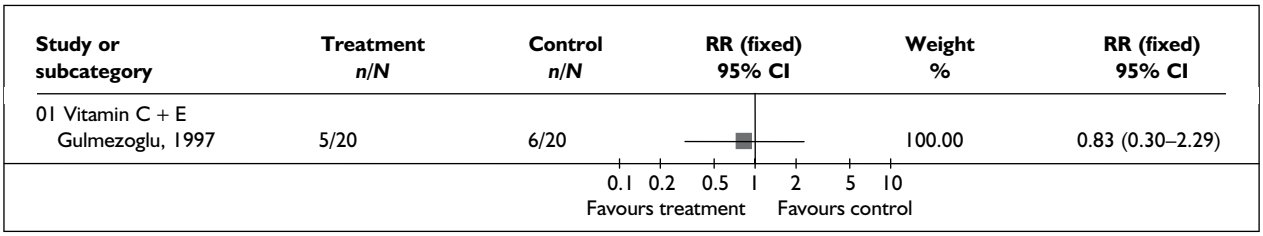


***FIGURE 127*** *Forest plot of the effects of antioxidants on admission to neonatal intensive care unit.*

***TABLE 8*** *Subgroup analyses*

| Subgroup analyses | RR | 95% CI | Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Trial quality (high quality)***[a] | | | |
| *Preterm birth <37 weeks* | | | |
| Vitamin C+E (1 study, *n* = 283)[421] | 1.21 | 0.38–3.387 | NA |
| Vitamin C alone (1 study, *n* = 200)[422] | 1.43 | 1.03–1.99 | NA |
| Zinc (1 study, *n* = 580)[418] | 0.77 | 0.49–1.20 | NA |
| *Perinatal mortality* | | | |
| Vitamin C+E (1 study, *n* = 56)[421] | 1.29 | 0.67–2.48 | NA |
| Vitamin C alone (1 study, *n* = 182)[420] | 1.70 | 0.05–5.54 | NA |
| Zinc (1 study, *n* = 580)[418] | 0.83 | 0.28–2.45 | NA |
| ***Gestation at trial entry [≤20 weeks, >20 weeks, unclassified (<20 weeks + >20 weeks)]*** | | | |
| *Preterm birth <37 weeks* | | | |
| Vitamin C+E (unclassified) (1 study, *n* = 283)[421] | 1.21 | 0.38–3.87 | NA |
| (≤20 weeks) (1 study, *n* = 100)[715] | 1.32 | 0.75–2.31 | NA |
| Vitamin C alone (unclassified) (1 study, *n* = 200)[422] | 1.43 | 1.03–1.99 | NA |
| (≤20 weeks) (1 study, n = 109)422 | 0.55 | 0.24–1.25 | NA |
| Zinc (≤20 weeks) (1 study, *n* = 580)[418] | 0.77 | 0.49–1.20 | NA |
| *Perinatal mortality* | | | |
| Vitamin C+E (>20 weeks) (1 study, *n* = 56)[421] | 1.29 | 0.67–2.48 | NA |
| Vitamin C alone (unclassified) (1 study, *n* = 200)[422] | 0.51 | 0.05–5.54 | NA |
| Zinc (≤20 weeks) (1 study, *n* = 580)[418] | 0.83 | 0.28–1.45 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.
a High quality: Adequate allocation concealment, use of placebo and < 3% exclusions.

The review of energy and protein intake (nutritional advice, energy restriction, isocaloric balanced protein supplementation, high protein supplementation and balanced protein supplementation)[427] included 23 studies (*n* = 5784 women).[428–450] Further details of the review can be found in Appendix 6, *Table 123*. Overall, the methodological quality of many of the included studies was poor or unclear; results are shown in *Figure 128*. A small but statistically significant reduction in the risk of spontaneous preterm birth was shown in women receiving dietary advice to increase energy and protein intake compared to women who did not receive nutritional advice (*Figure 129*). However, it should be noted that this estimate was based on two RCTs, of which one study was very small; results are therefore dominated by a study undertaken in rural Greece in which spontaneous preterm birth was not defined. The risk of spontaneous preterm birth was not shown to statistically differ between groups for the other nutritional strategies assessed.

None of the included studies reported incidence of perinatal mortality; however, women receiving a balanced energy/protein supplementation demonstrated a reduction in the risk of stillbirth compared to women receiving mineral/vitamin-only supplementation or no supplementation (*Table 10*). Women receiving a balanced energy/protein supplementation also demonstrated a small reduction in the risk of giving birth to an infant defined as 'small-for-gestational-age', compared to controls (*Table 10*). Conversely, women receiving a high protein supplementation or an isocaloric supplementation were significantly more likely to give birth to a 'small-for-gestational-age' infant compared to women not receiving



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***TABLE 9*** *Perinatal and maternal outcomes with antenatal maternal antioxidant treatment*

| Outcome (number of RCTs) | RR | 95% CI | Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Stillbirth*** | | | |
| Vitamin C+E (2 studies, *n* = 339) [420,421] | 0.77 | 0.35–1.71 | 0% (0.69) |
| Vitamin C (1 study, *n* = 200) [420] | 3.00 | 0.12–72.77 | NA |
| ***Neonatal death*** | | | |
| Vitamin C+E (1 study, *n* = 40) [421] | 5.00 | 0.64–39.06 | NA |
| Vitamin C (1 study, *n* = 181) [422] | 0.69 | 0.12–4.03 | NA |
| ***Stillbirth + neonatal death*** | | | |
| Zinc[a] (1 study, *n* = 580)[418] | 0.83 | 0.28–2.45 | NA |
| ***Low birthweight (<2500 g)*** | | | |
| Vitamin D (1 study, *n* = 128)[419] | 0.55 | 0.24–1.25 | NA |
| ***Low birthweight (unspecified)*** | | | |
| Zinc[a] (1 study, *n* = 580)[418] | 0.62 | 0.38–1.02 | NA |
| ***Intrauterine growth restriction*** | | | |
| Vitamin C+E (2 studies, *n* = 383)[420,421] | 0.72 | 0.49–1.04 | 0% (0.59) |
| ***Bleeding episodes (placental abruption)*** | | | |
| Vitamin C+E (2 studies, *n* = 339)[420,421] | 0.35 | 0.10–1.23 | 0% (0.96) |
| ***Antepartum haemorrhage + placental abruption*** | | | |
| Vitamin C (1 study, *n* = 200)[420] | 7.00 | 0.88–55.86 | NA |
| ***Measures of serious maternal morbidity*** | | | |
| *Eclampsia:* vitamin C+E (1 study, *n* = 56)[421] | 1.07 | 0.07–16.33 | NA |
| *Renal failure:* vitamin C+E (1 study, *n* = 56)[421] | 0.36 | 0.02–8.41 | NA |
| *Disseminated intravascular coagulation:* vitamin C+E (1 study, *n* = 56)[421] | 0.36 | 0.02–8.41 | NA |
| *Pulmonary oedema*: vitamin C+E (1 study, *n* = 56)[421] | 0.54 | 0.05–5.59 | NA |
| ***5-min Apgar score <7*** | | | |
| Vitamin C+E (1 study, *n* = 49)[421] | 0.63 | 0.21–1.90 | NA |
| ***Adverse side effects of supplementation*** | | | |
| *Acne:* vitamin C+E (1 study, *n* = 56)[421] | 3.21 | 0.14–75.68 | NA |
| *Transient weakness:* vitamin C+E (1 study, *n* = 56)[421] | 5.36 | 0.27–106.78 | NA |
| *Skin rash:* vitamin C+E (1 study, *n* = 56)[421] | 3.21 | 0.14–75.68 | NA |
| ***Neonatal hypocalcaemia*** | | | |
| Vitamin D (2 studies, *n* = 203)[419] | 0.13 | 0.02–0.65 | 0% (0.75) |
| ***Use of mechanical ventilation*** | | | |
| Vitamin C+E (1 study, *n* = 40)[421] | 0.33 | 0.08–1.46 | NA |
| ***Neonatal sepsis*** | | | |
| Zinc (1 study, *n* = 580)[418] | 0.19 | 0.02–1.66 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.
a Datum taken from the largest, highest quality trial.

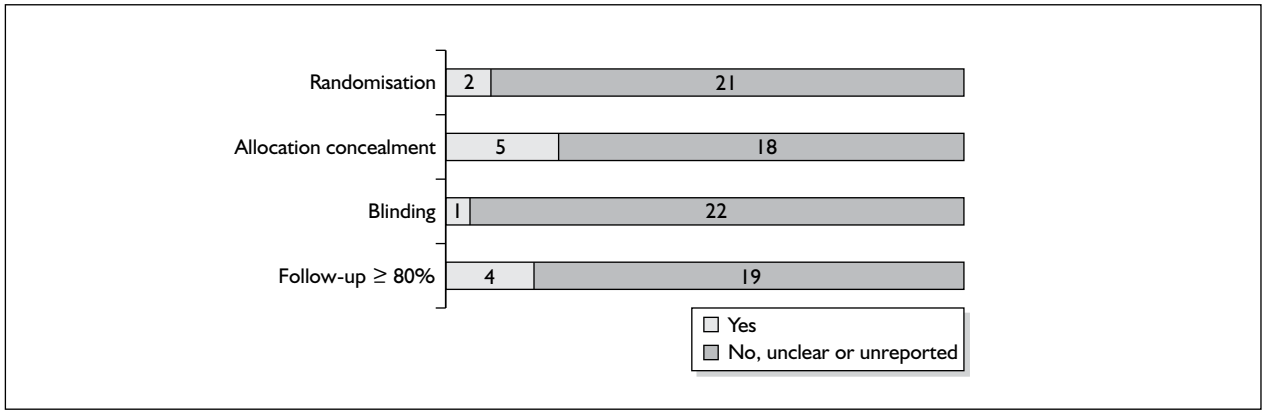


***FIGURE 128*** *Methodological quality of trials of energy and protein intake for the prevention of spontaneous preterm birth.*

| Study or subcategory | Treatment *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Nutritional advice | | | | | |
| Kafatos, 1989[441] | 9/228 | 17/201 | | 92.34 | 0.47 (0.21–1.02) |
| Briley, 2002[431] | 0/10 | 1/10 | | 7.66 | 0.33 (0.02–7.32) |
| Subtotal (95% CI) | 238 | 211 | | 100.00 | 0.46 (0.21–0.98) |
| Total events: 9 (Treatment), 18 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.04$, df = 1 ($p = 0.84$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 2.02$ ($p = 0.04$) | | | | | |
| 02 Balanced energy/protein supplementation | | | | | |
| Blackwell, 1973[430] | 3/94 | 6/88 | | 5.29 | 0.47 (0.12–1.81) |
| Mora, 1978[444] | 22/221 | 25/222 | | 21.28 | 0.88 (0.51–1.52) |
| [a]Rush, 1980[447] | 56/256 | 69/264 | | 57.97 | 0.84 (0.62–1.14) |
| [a]Elwood, 1981[436] | 9/557 | 10/539 | | 8.67 | 0.87 (0.36–2.13) |
| Campbell, 1983[433] | 7/97 | 8/98 | | 6.79 | 0.88 (0.33–2.34) |
| Subtotal (95% CI) | 1225 | 1211 | | 100.00 | 0.83 (0.65–1.06) |
| Total events: 97 (Treatment), 118 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.77$, df = 4 ($p = 0.94$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 1.46$ ($p = 0.14$) | | | | | |
| 03 High protein supplementation | | | | | |
| [a]Rush, 1980[447] | 62/249 | 56/256 | | 100.00 | 1.14 (0.83–1.56) |
| Subtotal (95% CI) | 249 | 256 | | 100.00 | 1.14 (0.83–1.56) |
| Total events: 62 (Treatment), 56 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.80$ ($p = 0.42$) | | | | | |
| 04 Isocaloric supplementation | | | | | |
| Mardones, 1988[443] | 40/391 | 38/391 | | 100.00 | 1.05 (0.69–1.60) |
| Subtotal (95% CI) | 391 | 391 | | 100.00 | 1.05 (0.69–1.60) |
| Total events: 40 (Treatment), 38 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.24$ ($p = 0.81$) | | | | | |
| 05 Energy/protein restriction | | | | | |
| Campbell, 1983[433] | 2/91 | 4/91 | | 100.00 | 0.50 (0.09–2.66) |
| Subtotal (95% CI) | 91 | 91 | | 100.00 | 0.50 (0.09–2.66) |
| Total events: 2 (Treatment), 4 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.81$ ($p = 0.42$) | | | | | |



***FIGURE 129*** *Forest plot of the effect of energy and protein intake interventions for the prevention of spontaneous preterm birth (not defined). a, Appropriate randomisation and allocation concealment methods used.*



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***TABLE 10*** *Other perinatal and maternal outcomes of interest for antenatal maternal energy and protein intake supplementation*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Stillbirth*** | | | |
| Nutritional advice (1 study, *n* = 431) [441] | 0.37 | 0.07–1.90 | NA |
| Balanced energy/protein supplementation (4 studies, n = 2206) [435,437,444,447] | 0.55 | 0.31–0.97 | 19.6% (0.29) |
| High protein supplementation (1 study, *n* = 529) [447] | 0.81 | 0.31–2.15 | NA |
| ***Neonatal mortality*** | | | |
| Nutritional advice (1 study, *n* = 448) [441] | 1.28 | 0.35–4.72 | NA |
| Balanced energy/protein supplementation (4 studies, *n* = 2206) [435,437,444,447] | 0.62 | 0.37–1.05 | 0% (0.81) |
| High protein supplementation (1 study, *n* = 529) [447] | 2.78 | 0.75–10.36 | NA |
| Isocaloric protein supplementation (1 study, *n* = 782) [443] | 0.50 | 0.05–5.49 | NA |
| ***Small for gestational age*** | | | |
| Nutritional advice (1 study, *n* = 404) [441] | 0.97 | 0.45–2.11 | NA |
| Balanced energy/protein supplementation (6 studies, *n* = 3396) [435–437,444,447] | 0.68 | 0.56–0.84 | 0% (0.66) |
| High protein supplementation (1 study, *n* = 505) [447] | 1.58 | 1.03–2.41 | NA |
| Isocaloric protein supplementation (1 study, *n* = 782) [443] | 1.35 | 1.12–1.61 | NA |
| ***Pre-eclampsia*** | | | |
| Nutritional advice (1 study, *n* = 136) [438] | 0.89 | 0.42–1.88 | NA |
| Balanced energy/protein supplementation (3 studies, *n* = 516) [437,444,445] | 1.20 | 0.77–1.89 | 47.0% (0.17) |
| Isocaloric protein supplementation (1 study, *n* = 782) [443] | 1.00 | 0.57–1.75 | NA |
| Energy restriction (2 studies, *n* = 284) [432,433] | 1.13 | 0.59–2.18 | 53.8% (0.14) |
| ***Pregnancy-induced hypertension*** | | | |
| Energy restriction (3 studies, *n* = 384) [429,432,433] | 0.97 | 0.75–1.26 | 0% (0.82) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

supplementation; results were based on one trial. No statistically significant between-group differences were shown for any of the nutritional strategies reporting neonatal mortality (*Table 10*). The effect of energy and protein intake interventions on admission to neonatal intensive care units was not reported. Other perinatal and maternal outcomes are shown in *Table 10*. Given the methodological uncertainty of the majority of the included studies, there is insufficient evidence to support the use of these energy and protein intake interventions. Summary RRs for perinatal mortality (stillbirth) were used in the decision analyses.

## Fish oil supplements

Supplementation with marine oils, rich in the long chain n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, may be useful in prolonging the duration of gestation. Two possible mechanisms have been proposed: fish oil fatty acids could delay delivery by reducing the activity of eicosanoid promoters of the parturition process (particularly prostaglandins F2α and E2), they may also relax the myometrium by increasing the production of prostacyclins PGI2 and PGI3. Some concerns have been raised regarding the safety of fish oil supplementation in pregnancy, particularly with regard to bleeding complications.

The review of marine oil for the prevention of spontaneous preterm birth included one multicentre intervention study[369] (consisting of a series of six RCTs) and one further RCT[451] (*n* = 1997). Further details of the review can be found in Appendix 6, *Table 124*. The quality of the included studies is presented in *Figure 130*. Overall,

the quality of the studies was good. Compared to placebo/no treatment, marine oil supplementation was shown to reduce the incidence of spontaneous preterm birth before 34 and 37 weeks' gestation (*Figures 131* and *132*); however, this did not reach statistical significance in the docosahexaenoic acid supplement trial. No statistically significant between-group differences were found in the incidence of neonatal mortality or admission to neonatal intensive care units between women receiving marine oil and women receiving placebo or no treatment (*Figures 133, 134*). Results for other perinatal and maternal variables are shown in *Table 11;* it should be noted that two twin gestation trials were included in the aggregated trial data presented. Overall, fish oil supplements for women at risk of spontaneous preterm birth appear promising, but results are largely based on one multicentre trial. Further research would be required to confirm these findings. RRs presented for eicosapentaenoic acid plus docosahexaenoic acid were used in the decision analysis.

## Bed rest

Bed rest in hospital or at home is widely recommended as a first-step treatment for the prevention of spontaneous preterm birth. This advice is largely based on observational studies that hard work and hard physical activity during pregnancy could be associated with spontaneous preterm birth,[452,453] and that bed rest could reduce uterine activity.[454]

The review[455] of bed rest (hospital or home) for the prevention of spontaneous preterm birth included one quasi-RCT ($n = 1266$).[456] Further details of the review can be found in Appendix 6, *Table 120*.

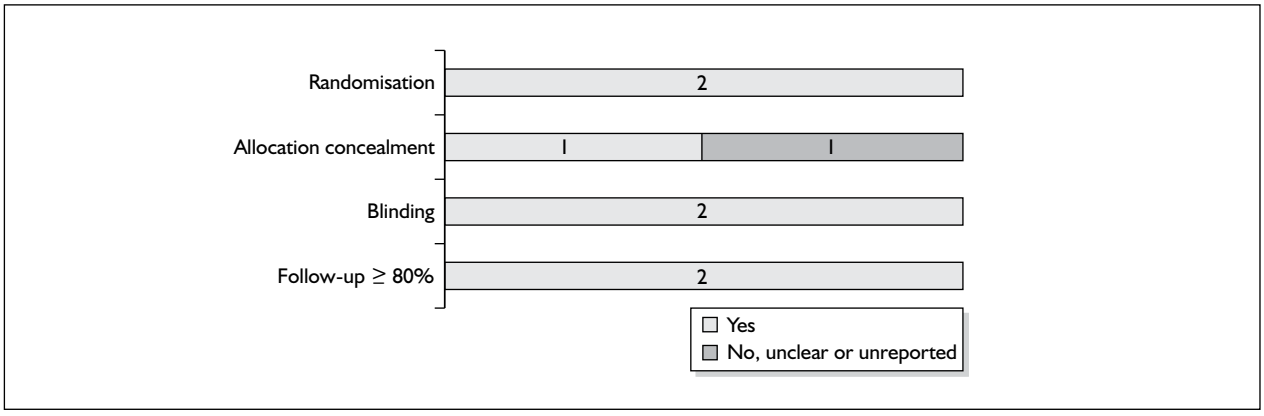


***FIGURE 130*** *Methodological quality of trials of fish oil for the prevention of spontaneous preterm birth.*

| Study or subcategory | Marine oil n/N | Control n/N | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Eicosapentaenoic acid + Docosahexaenoic acid supplement vs placebo (olive oil) | | | | | |
| Olsen, 2000[369] | 23/108 | 40/120 | | 100.00 | 0.64 (0.41–0.99) |
| Total events: 23 (Marine oil), 40 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 1.99$ ($p = 0.05$) | | | | | |
| 02 Docosahexaenoic acid supplement vs no treatment | | | | | |
| Smuts, 2003[451] | 14/142 | 17/149 | | 100.00 | 0.86 (0.44–1.69) |
| Total events: 14 (Marine oil), 17 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.43$ ($p = 0.67$) | | | | | |



***FIGURE 131*** *Forest plot of fish oil versus placebo for the prevention of spontaneous preterm birth in singleton pregnancies before 37 weeks' gestation.*



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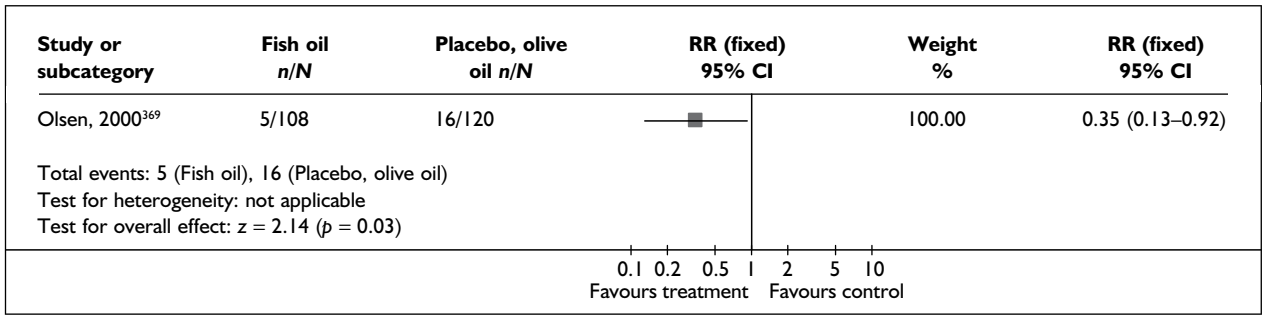


***FIGURE 132*** *Forest plot of fish oil versus placebo for the inhibition of spontaneous preterm birth in singleton pregnancies before 34 weeks' gestation.*

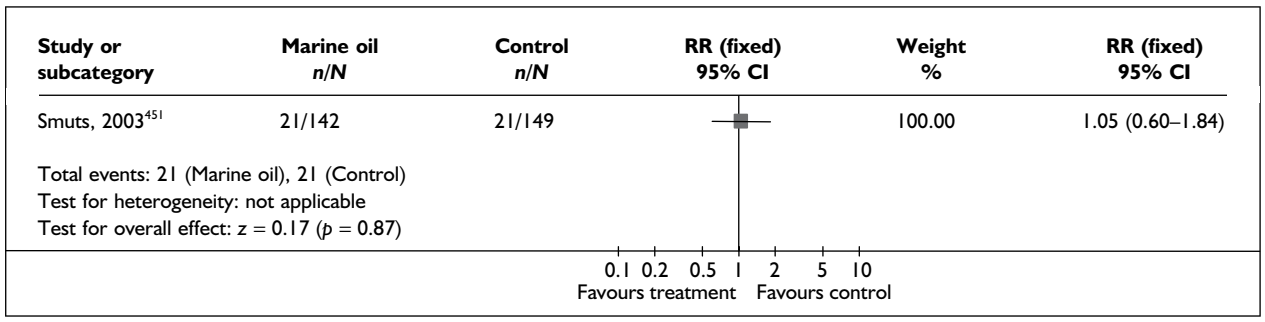


***FIGURE 133*** *Forest plot of fish oil versus placebo for transfer to intensive neonatal care unit.*

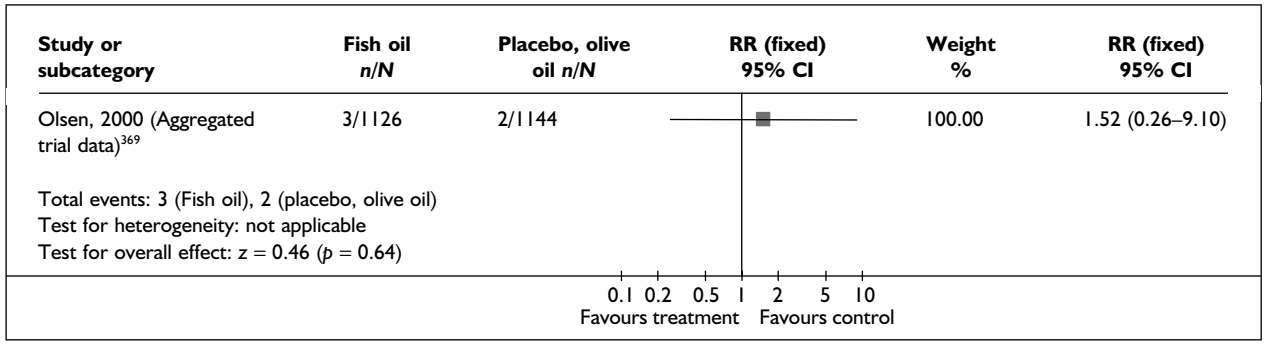


***FIGURE 134*** *Forest plot of fish oil versus placebo for incidence of early neonatal mortality.*

***TABLE 11*** *Perinatal and maternal effects of fish oil supplementation during pregnancy*

| Outcome (number of RCTs) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| Spontaneous abortion (aggregated trials: 6 RCTs, *n* = 1619)[369] | 0.58 | 0.17–1.97 | Not reported |
| Stillbirths (aggregated trials: 6 RCTs, *n* = 2141)[369] | 0.87 | 0.45–1.67 | Not reported |
| Intracranial haemorrhage in infant (aggregated trials: 6 RCTs, *n* = 2226) | 2.36 | 0.61–9.10 | Not reported |
| Admission to neonatal care unit (1 RCT, *n* = 2138)[369] | 0.92 | 0.80–1.07 | Not reported |
| Low birthweight (3 RCTs, *n* = 559)[369] | 1.18 | 0.83–1.67 | 2.7%, 0.36 |
| Duration of hospital stay after delivery (infant) (aggregated trials: 6 RCTs)[369] | WMD 0.11 | –1.40 to 1.62 | Not reported |
| Duration of hospital stay after delivery (mother) (aggregated trials: 6 RCTs)[369] | WMD –0.33 | –2.47 to 1.81 | Not reported |
| Vaginal bleeding (aggregated trials: 6 RCTs, *n* = 1618)[369] | 0.94 | 0.60–1.48 | Not reported |
| Maternal anaemia (aggregated trials: 6 RCTs, *n* = 846)[369] | 1.16 | 0.91–1.48 | Not reported |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD weighted mean difference.

Of note, is the fact that high risk of spontaneous preterm birth as defined by the review included previous history of spontaneous preterm birth as well as threatened preterm labour. The quality of the included trial was unclear, as shown in *Figure 135*. No statistically significant difference was shown between women prescribed bed rest and women who received no treatment for risk of spontaneous preterm birth before 37 weeks (7.9% and 8.5%, respectively) (*Figure 136*). No other results were available. There is insufficient evidence to support or refute the use of bed rest in hospital or at home for the prevention of spontaneous preterm birth. This intervention should be prescribed with caution until effective evidence becomes available. The RR presented in the forest plot below was used in the economic model

## Elective cervical cerclage

Cervical cerclage, or stitch, is a surgical procedure used to keep the cervix closed during pregnancy to prevent delivery in women at risk of spontaneous preterm birth. It is used for the treatment of a weak or incompetent cervix, which may shorten or open without labour too early in a pregnancy. A cervical cerclage is applied after the first trimester to prevent these early changes in a woman's cervix and subsequent premature labour.

This review of elective cervical cerclage for the prevention of spontaneous preterm birth included eight trials (*n* = 2511); two RCTs[457,458] were added to the primary studies identified in an earlier review.[22] Two studies were excluded from the original review; one trial that focused on twin gestations, and one trial that was considered likely to have already been included within another study. Further details of the review can be found in Appendix 6, *Table 121*. The quality of all studies is shown in *Figure 137*. Overall, the quality was good, although there were problems with some of the studies not reporting sufficient detail about how participants were allocated to treatment groups (i.e. randomisation). As cerclage is a surgical procedure, blinding is problematic and only one study fulfilled this criterion.

Clinical heterogeneity precluded a quantitative summary because of variation in population and surgical procedure (i.e. type of cerclage used). Two RCTs demonstrated a small but significant reduction in the incidence of spontaneous preterm birth before 34 weeks' gestation in women receiving cerclage,[459,460] compared to standard treatment (*Figure 138*), although it should be noted that the dataset in one of these trials was extremely small. No statistically significant between-group differences were found in the included trials for incidence of spontaneous preterm birth before 37 weeks' gestation (*Figure 139*), or perinatal mortality (*Figure 140*). The three trials reporting data on the development of postpartum fever all show a greater incidence of maternal pyrexia in the cerclage group compared to the control group, although the difference was not statistically significant in two of the trials. The effect of cervical cerclage on other perinatal and maternal outcomes is shown in *Table 12*.

Results are dominated by the largest high-quality trial of elective cerclage, which demonstrates a



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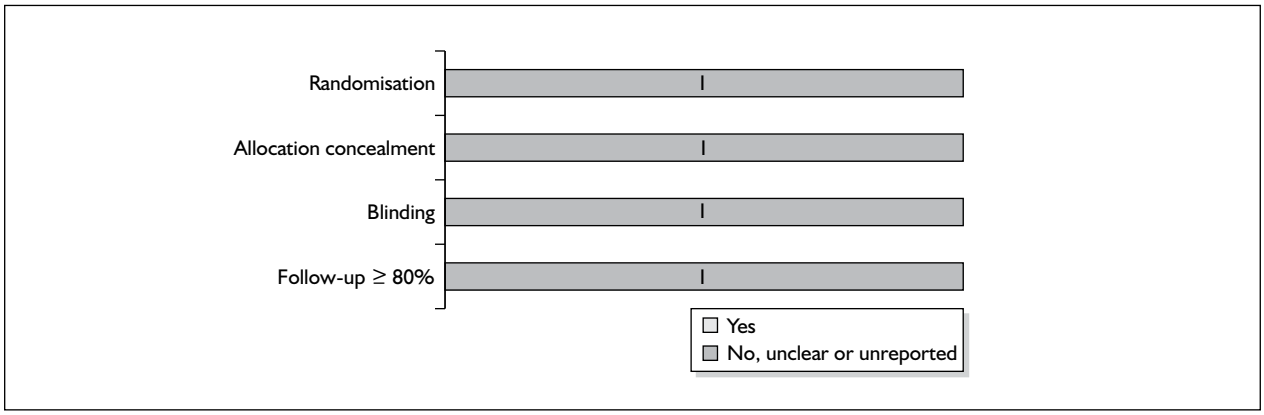


***FIGURE 135*** *Methodological quality of trials of bed rest for the prevention of spontaneous preterm birth.*

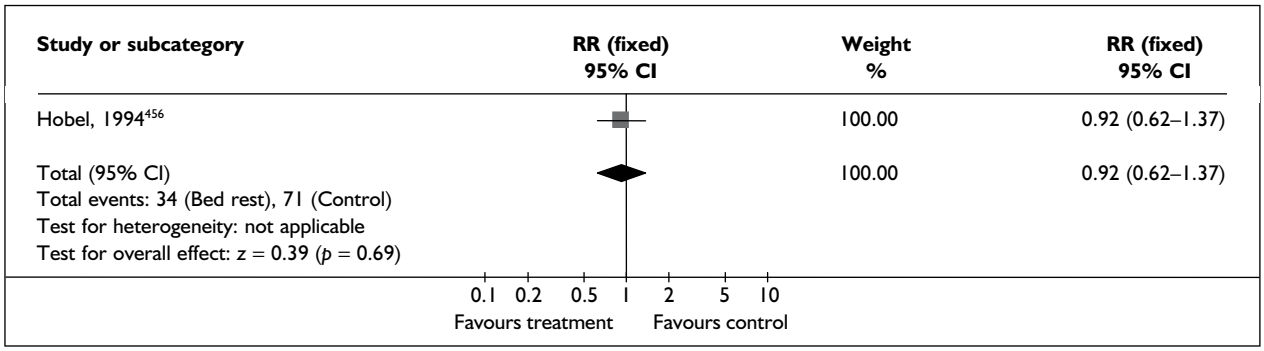


***FIGURE 136*** *Forest plot of bed rest versus no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

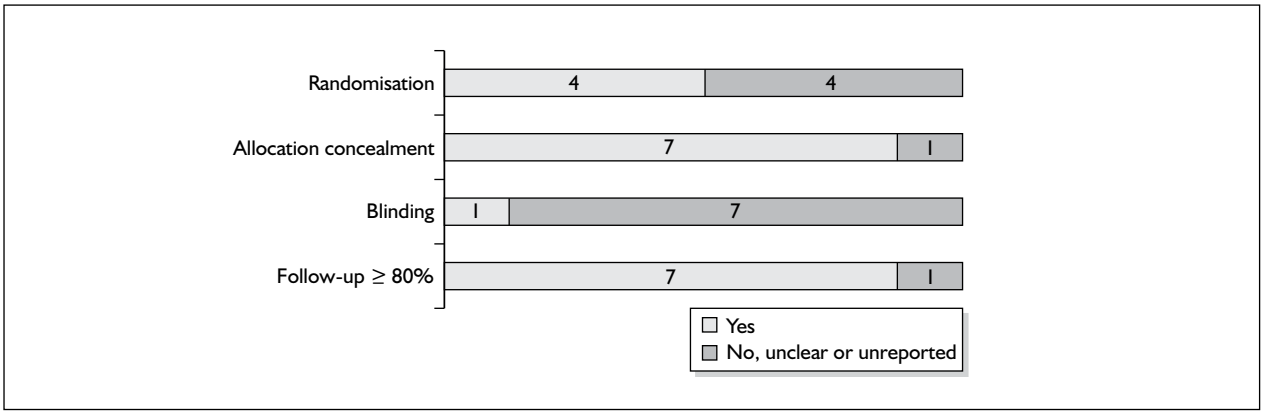


***FIGURE 137*** *Methodological quality of included trials of elective cervical cerclage for the prevention of spontaneous preterm birth.*

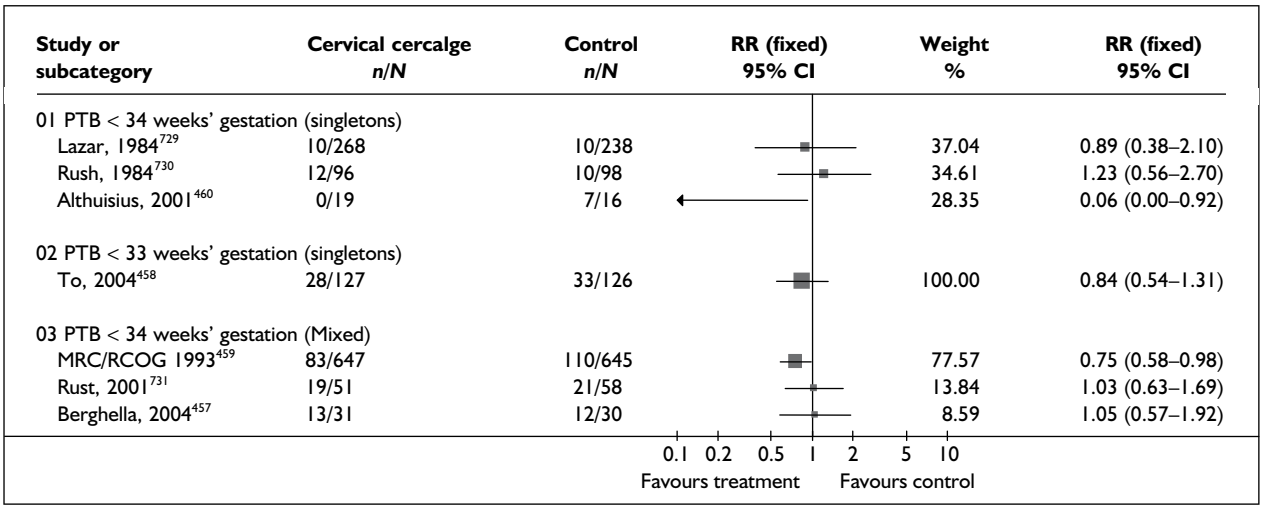


***FIGURE 138*** *Forest plot of the effects of cervical cerclage versus standard care for the prevention of spontaneous preterm birth before 34 weeks' gestation.*

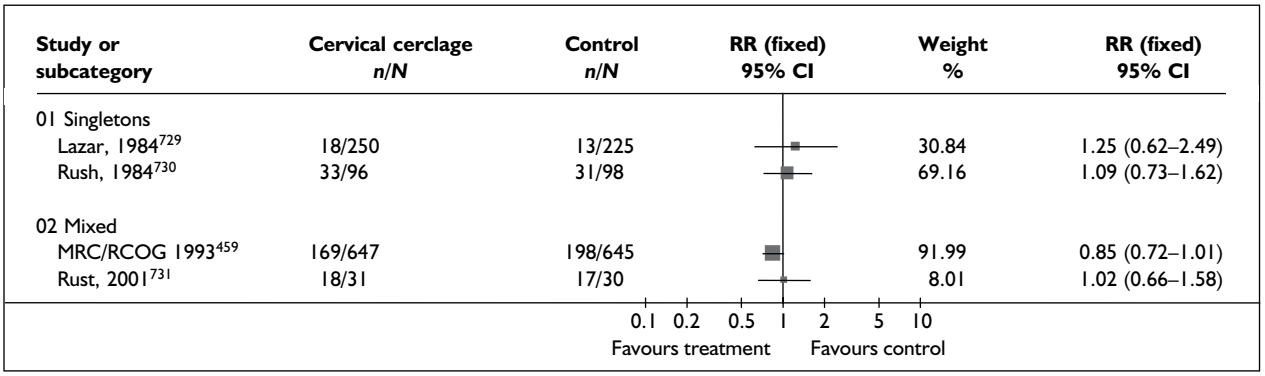


***FIGURE 139*** *Forest plot of the effects of cervical cerclage versus standard care for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

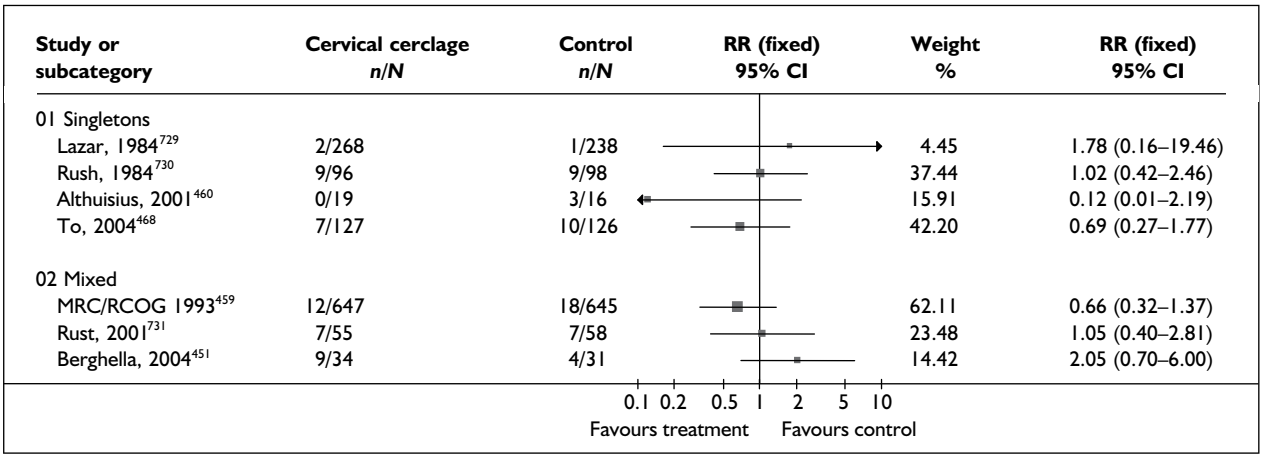


***FIGURE 140*** *Forest plot of the effects of cervical cerclage versus standard care on perinatal mortality.*



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reduction in the risk of spontaneous preterm birth before 34 weeks' gestation in women with a mixed population of singleton and multiple pregnancies at risk of spontaneous preterm birth. A trend toward cerclage preventing preterm birth was shown at before 37 weeks' gestation in the same population. Other infant and maternal outcomes are less well reported and further research is needed regarding the use of cervical cerclage on the incidence of neonatal or maternal complications. Summary RRs for spontaneous preterm birth and perinatal mortality were included in the decision analysis.

## Antenatal educational programmes

Educational programmes for the prevention of spontaneous preterm birth have been developed to promote early recognition and treatment of spontaneous preterm birth. The programmes focus on increasing the awareness of women and their providers of spontaneous preterm contractions and the importance of early intervention. In some strategies, periodic home uterine monitoring is also included.

The review of educational programmes[461] for the prevention of preterm birth included six RCTs[462–467] ($n = 6445$). Further details of the review can be found in Appendix 6, *Table 122*. Poor reporting meant that the methodological quality of the included studies was unclear; results are presented in *Figure 141*. Spontaneous preterm birth prevention educational programmes did not significantly reduce the incidence of spontaneous preterm birth, compared to no intervention (*Figure 142*); furthermore, no statistically significant difference was found in neonatal mortality between women receiving an educational programme and women who did not (*Table 13*). The incidence of admission to neonatal care units was not reported. Overall, educational programmes do not appear to beneficially affect the incidence of spontaneous preterm birth in women at risk. It should be noted, however, that two potentially relevant RCTs were not received in time.[468,469] Summary RRs were not included in the decision analyses.

## In utero transfer

In utero transfer occurs when a woman at risk of spontaneous preterm birth is transported before delivery to a unit with more specialised facilities for neonates, such as intensive care or care in a particular specialism. In some cases tocolytics are administered to the mother to temporarily delay threatened spontaneous preterm birth, facilitating maternal antenatal corticosteroid administration (to accelerate fetal lung maturity and so prevent respiratory distress syndrome) and the transfer. Some evidence from retrospective cohort studies[470,471] suggests that there is an increased risk of neonatal mortality with extrauterine transfer. However, there is no existing systematic review of the efficacy and safety of this intervention, and no

***TABLE 12*** *Effect of cervical cerclage on other perinatal and maternal outcomes*

| Outcome (RCT) | Cerclage group % | Control group % | *p*-value |
|---|---|---|---|
| ***PROM*** | | | |
| Rush 1984, $n = 193$[22] | 18 | 12 | 0.50 |
| To 2004, $n = 253$[458] | 18 | 15 | Not reported |
| ***Chorioamnionitis*** | | | |
| Rust 2001, $n = 113$ | 20 | 10.3 | 0.20 |
| ***Postpartum fever*** | | | |
| MRC/COG 1993, $n = 1292$[459] | 5.8 | 2.6 | 0.03 |
| Rush 1984, $n = 193$[22] | 10.4 | 3.1 | 0.06 |
| To 2004, $n = 253$[458] | 3.9 | 0.8 | 0.14 |
| ***Placental abruption*** | | | |
| Rust 2001, $n = 113$[22] | 10.9 | 13.8 | 0.80 |

PROM, pre-labour rupture of membrane; RCT, randomised controlled trial; RR, relative risk.

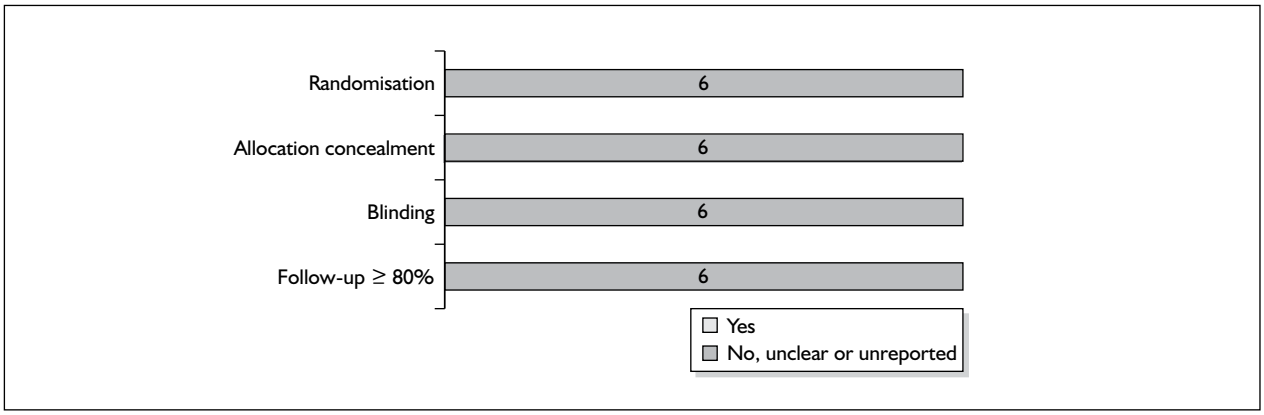


***FIGURE 141*** *Methodological quality of trials of educational programmes for the prevention of spontaneous preterm birth.*

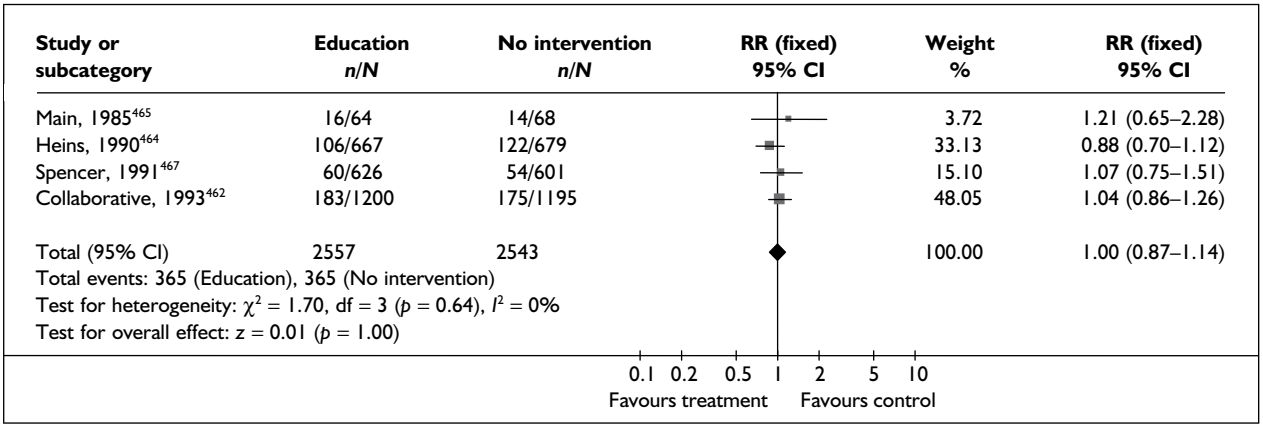


***FIGURE 142*** *Forest plot of the effect of educational programmes for the inhibition of spontaneous preterm labour (length of gestation not defined).*

***TABLE 13*** *Other infant outcomes following educational programmes*

| Outcome (number of RCTs) | RR | 95% CI | *p*-value |
|---|---|---|---|
| Low birthweight (4 studies, $n$ = 4130) [462,465–467] | 0.99 | 0.88–1.11 | 0.84 |
| Neonatal survival (3 studies, $n$ = 2949) [464,466,467] | 1.00 | 0.99–1.01 | 0.47 |

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk.



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randomised trials were retrieved when primary studies were sought. It was therefore not possible to evaluate the impact of in utero transfer on perinatal or maternal outcomes.

## Home uterine monitoring

Early detection of threatened preterm labour may increase the proportion of women who receive care while suppression is still a viable option. Clinically the onset of threatened preterm labour is usually preceded by a period of increased uterine activity that can be detected by tocodynamometry (home uterine activity monitoring device).[472]

The review of home uterine activity monitoring included three trials ($n = 618$).[473–475] Further details of the review can be found in Appendix 6, *Table 125*. The overall quality of these studies, shown in *Figure 143*, was poor with only one trial considered to be of good quality. Clinical heterogeneity precluded a quantitative summary. No statistically significant difference across trials was shown for the incidence of spontaneous preterm birth before 34 weeks' or 37 weeks' gestation in women who received home uterine activity monitoring compared to controls (*Figures 144* and *145*). Similarly, no statistically significant between-group difference was shown for admission to neonatal intensive care across the primary studies (*Figure 146*). Other infant and maternal outcomes are less well reported (*Table 14*) and further research is needed regarding the effect of home uterine activity monitoring on the incidence of neonatal or maternal complications.

In the largest, high-quality trial, home uterine monitoring did not show significant reduction in spontaneous preterm birth before 37 weeks' gestation in women at risk of spontaneous preterm birth; however, a reduction was shown in the incidence of admission to neonatal intensive care units.[474] It should be noted that this trial compared home uterine monitoring to standard care, whereas the other included trials compared home uterine monitoring to an educational or increased nursing

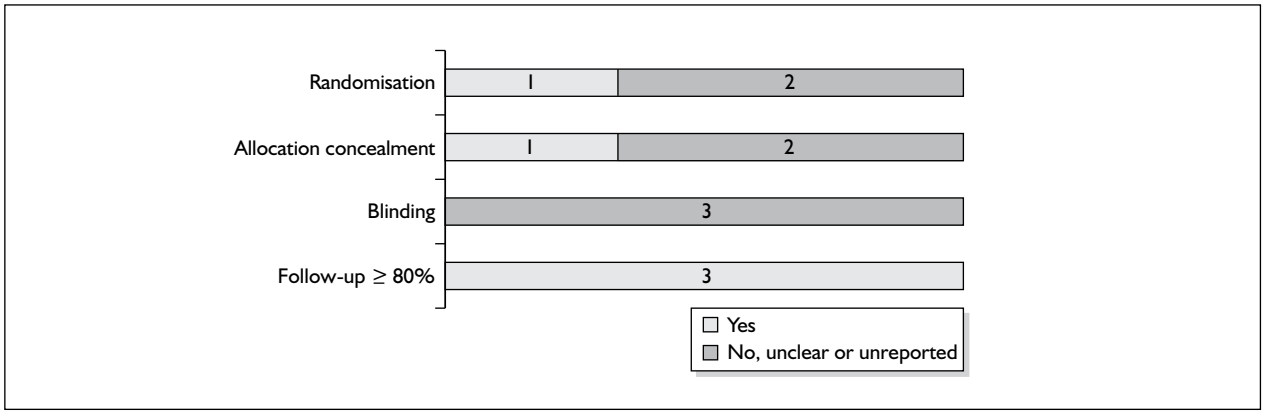


***FIGURE 143*** *Methodological quality of included trials of home uterine activity monitoring for the prevention of spontaneous preterm birth.*

| Study or subcategory | Treatment n/N | Control n/N | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Asymptomatic women at risk of pre-term birth | | | | | |
| Corwin, 1996[474] | 22/164 | 35/154 | | 100.00 | 0.59 (0.36–0.96) |
| 02 Women treated for idiopathic preterm labour | | | | | |
| Brown, 1999[473] | 40/82 | 48/80 | | 100.00 | 0.81 (0.61–1.08) |

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

***FIGURE 144*** *Forest plot of the effects of home uterine activity monitoring versus no monitoring for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

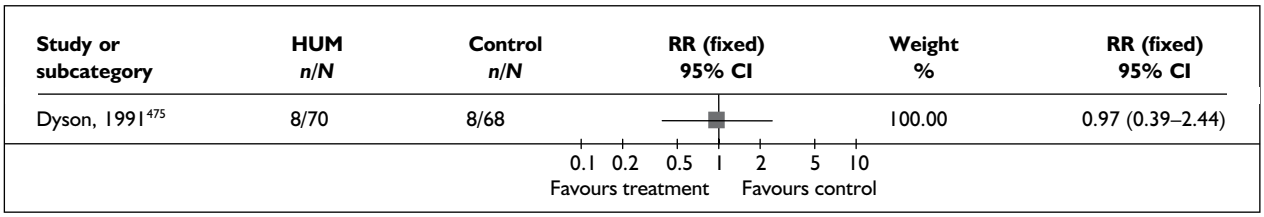


***FIGURE 145*** *Forest plot of the effects of home uterine activity monitoring versus no monitoring for the prevention of spontaneous preterm birth before 34 weeks' gestation.*

control group. Overall, there was very limited good quality evidence to support the use of home uterine monitoring. RRs for the largest, high-quality study were used in the decision analyses.

## Home visits

A number of studies have suggested that pregnancy outcomes may be influenced by women's psychological well-being during pregnancy and labour, indicating stress and lack of social support as potential risk factors.[476–478] The objective of many home-care programmes is to provide support and care in a familiar environment.

This review of home visits included ten RCTs ($n = 9274$ women);[479–488] two RCTs were added to the primary studies identified in an earlier review.[489] Further details of the review and the two additional RCTs can be found in Appendix 6, *Table 126*. The quality of these studies was generally poor; results are shown in *Figure 147*. When compared with women who do not receive a home-visit program, home visits during pregnancy do not significantly reduce the incidence of spontaneous preterm birth before 37 weeks' gestation or neonatal admission to intensive care (*Figures 148* and *149*. The effect of home visits on spontaneous preterm birth before 34 weeks' gestation was not reported in the primary studies. The effect of home visits on other perinatal or maternal outcomes is shown in *Table 15*. The results do not support a beneficial effect of home visits for the inhibition of spontaneous preterm birth. The summary RR for spontaneous preterm birth before 37 weeks' gestation was included in the decision analysis.

## Hypnosis

Stress may be a factor in triggering spontaneous preterm labour. Hypnosis is a technique that may help to relax the mother and as such has been suggested as a treatment for threatened preterm labour. However, there is no existing systematic review of its use for this indication, and no randomised primary studies where found. It was not therefore possible to evaluate this intervention.

## Periodontal care

Evidence indicates that infections can be a major risk factor in spontaneous preterm birth. Case–

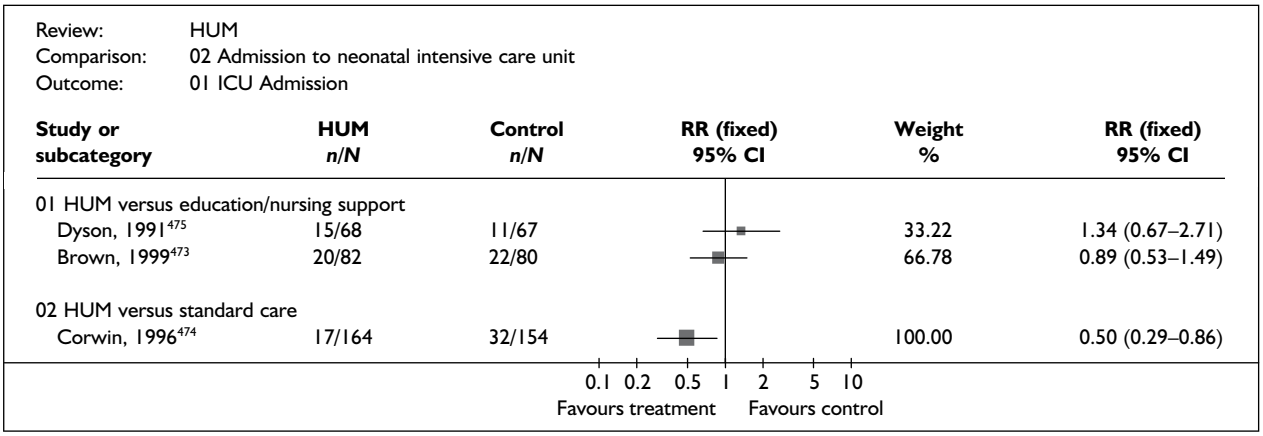


***FIGURE 146*** *Forest plot of the effects of home uterine activity monitoring versus control on admission to neonatal intensive care unit.*



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***TABLE 14*** *Effect of home uterine activity monitoring on other perinatal and maternal outcomes*

| Outcome (number of RCTs) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| Birthweight < 2500 g | | | |
| 1 study, *n* = 133[475] | 1.11 | 0.56–2.18 | NA |
| 1 study, *n* = 279[474] | 0.47 | 0.28–0.78 | NA |
| Birthweight < 1500 g | | | |
| 1 study, *n* = 133[475] | 0.69 | 0.20–2.33 | NA |
| 1 study, *n* = 279[474] | Not estimable | – | – |
| Neonates receiving mechanical ventilation (1 study, *n* = 162)[473] | 0.65 | 0.11–3.79 | NA |
| Length of hospital stay (1 study, *n* = 162)[473] | WMD 3.60 | 2.92–4.28 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

control, and prospective cohort studies point to an association between periodontal infection and increased rates of spontaneous preterm birth. This rapid review examines whether periodontal therapy reduces the risk of spontaneous preterm birth.

The review of periodontal therapy included one quasi-RCT (*n* = 400 women).[490] Further details of the review can be found in Appendix 6, *Table 127*. The quality of the primary study was poor (*Figure 150*). When compared with no treatment, periodontal therapy reduced the incidence of spontaneous preterm birth before 37 weeks' gestation (*Figure 151*). In addition, when compared with no treatment, fewer infants with low birthweight (<2500 g) were delivered to the periodontal therapy group (*Table 16*). Incidence of spontaneous preterm birth before 34 weeks' gestation, perinatal mortality and neonatal admission to intensive care were not reported. Although the results support a beneficial effect of periodontal therapy for prevention of spontaneous preterm birth before 37 weeks' gestation, the methodological quality of the trial and uncertain accounting of residual confounders warrant caution in the interpretation of these results. Further well-controlled, large trials are needed. The RR from the forest plot presented was used in the decision analyses.

## Progestational agents

Progesterone is a hormone that inhibits the uterus from contracting and has been advocated for the prevention of spontaneous preterm birth.[491]

This review of progesterone included six RCTs (*n* = 988 women).[492–497] Further details of the

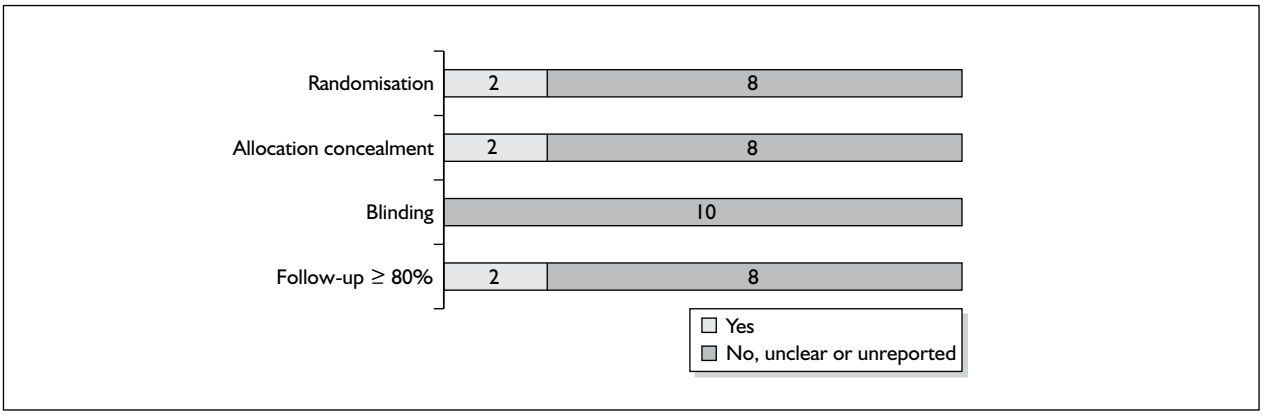


***FIGURE 147*** *Methodological quality of included trials of home visits for the prevention of spontaneous preterm birth.*

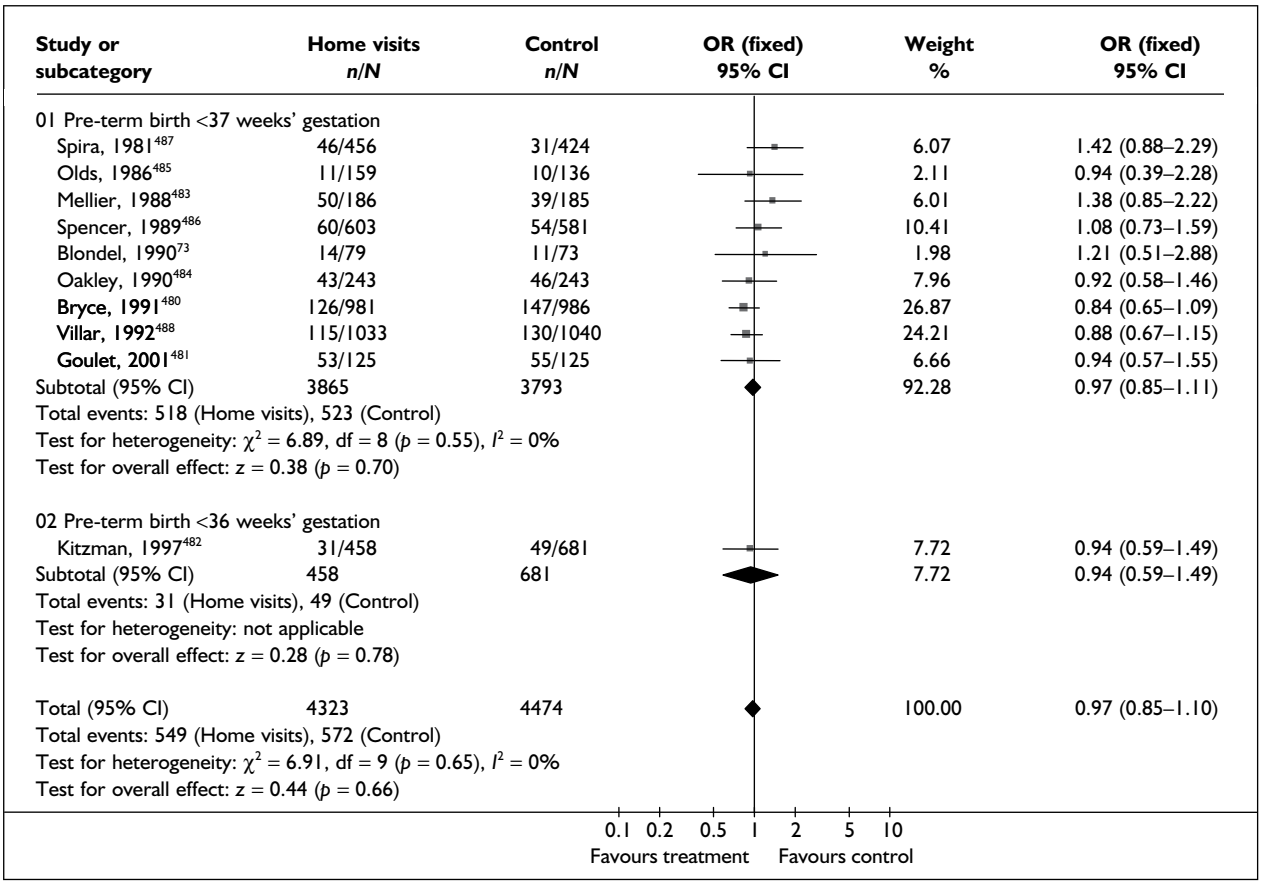


***FIGURE 148*** *Forest plot of the effects of home visits versus usual care for the inhibition of spontaneous preterm labour before 37 weeks' gestation.*

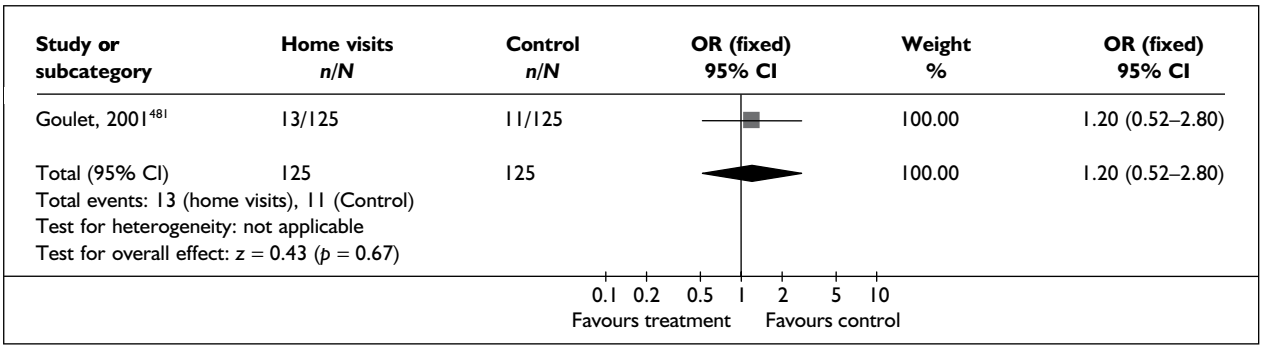


***FIGURE 149*** *Forest plot of the effects of home visits versus usual care on neonatal admission to intensive care.*

***TABLE 15*** *Effect of home visits on perinatal and maternal outcomes*

| Outcome (RCTs) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| ***Hospital admission during pregnancy*** | | | |
| All home visits (4 studies, $n = 1893$)[478,479,483,487] | 0.88 | 0.77–1.00 | 47.4%, 0.13 |
| Social support (1 study, $n = 486$)[478] | 0.79 | 0.65–0.95 | NA |
| Medical care (3 studies, $n = 1407$)[479,483,487] | 0.94 | 0.75–1.12 | 45.0%, 0.16 |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.



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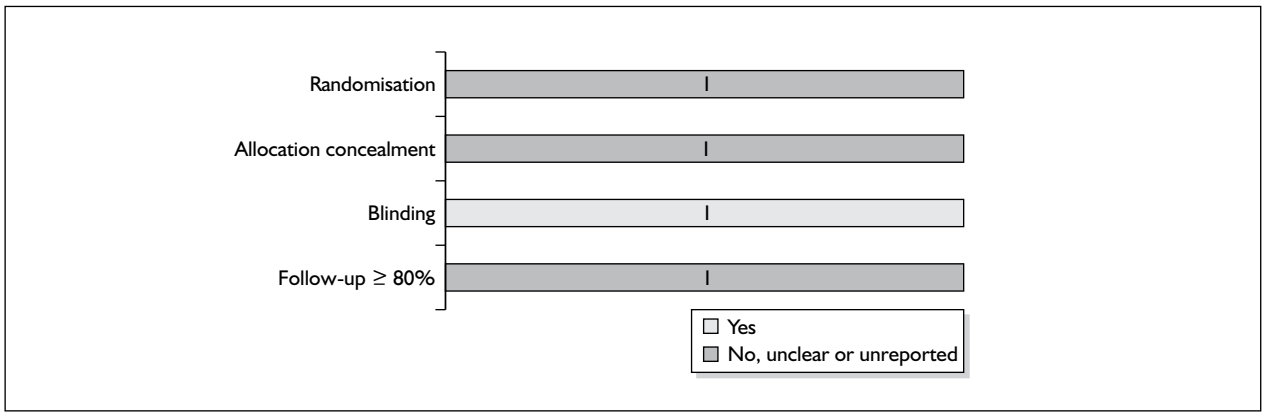


***FIGURE 150*** *Methodological quality of included trials of periodontal therapy for the prevention of spontaneous preterm birth.*

review can be found in Appendix 6, *Table 128*. An additional review of progesterone was identified after the final searches had been completed,[498] which included six RCTs and three quasi-RCTs. The quality of the primary studies is shown in *Figure 152*. Overall, the quality of the studies was reasonable, although poor reporting meant that randomisation and allocation concealment were difficult to assess in some cases. There was a reduction in risk of spontaneous preterm birth before 34 and 37 weeks' gestation (*Figures 153* and *154*). No statistically significant between-group difference was found for incidence of perinatal mortality (*Figure 155*). Delivery within 24 hours, 48 hours or 7 days after treatment initiation was not reported. The effect of progesterone on other perinatal and maternal outcomes is shown in *Table 17*. Planned subgroup analyses were also performed; the effect of route of administration, timing of treatment initiation, dose and plurality of the pregnancy for risk of spontaneous preterm birth before 37 weeks' gestation is shown in *Table 18*. Overall, the results support the superiority of intramuscular progesterone over placebo in preventing spontaneous preterm birth before 37 weeks' gestation. However, further research is needed to evaluate the use of vaginal progesterone in the prevention of spontaneous preterm birth, because although there appeared to be a significant benefit, this was based on only one trial. In addition, there is currently no appropriate intramuscular formulation available in the UK. Further studies are required to confirm the effectiveness of this intervention. Other infant and maternal outcomes are less well reported, with most outcomes taken from a single study. Further research is needed regarding the use of vaginal progesterone in the prevention of spontaneous preterm birth. Summary RRs for spontaneous preterm birth before 34 and 37 weeks' gestation, shown in the forest plots presented, were used in the decision analyses.

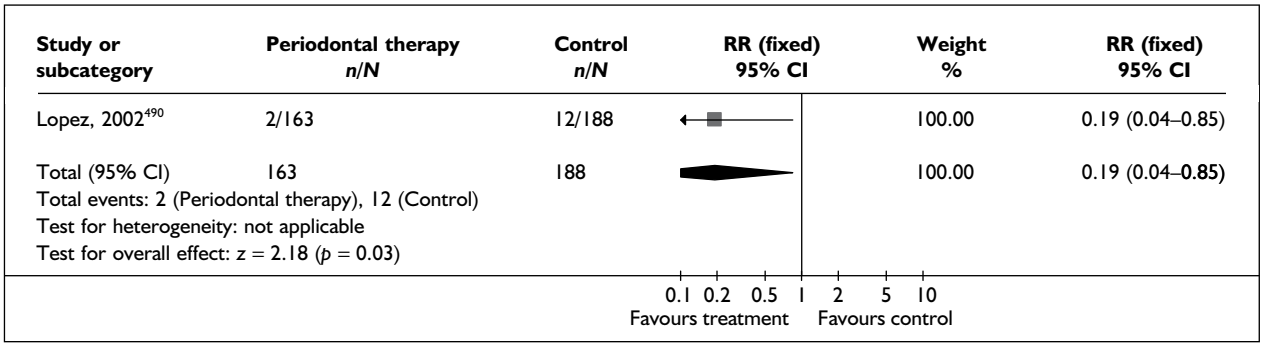


***FIGURE 151*** *Forest plot of the effects of periodontal therapy versus no treatment for the inhibition of spontaneous preterm birth before 37 weeks' gestation.*

***TABLE 16*** *Effects of periodontal therapy versus no treatment on other perinatal and maternal outcomes*

| Outcome (number of RCTs) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| Low birthweight < 2500 g (1 study, *n* = 351) [490] | 0.16 | 0.02–1.33 | NA |
| Spontaneous abortion (1 study, *n* = 400) [490] | 1.33 | 0.47–3.77 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

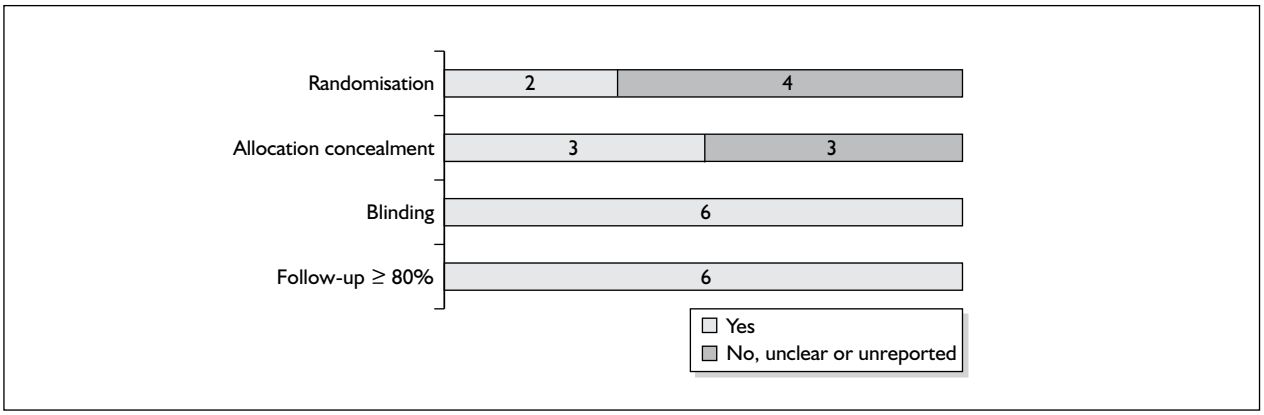


***FIGURE 152*** *Methodological quality of randomised controlled trials of progestogens in the prevention of spontaneous preterm birth.*

## Smoking cessation programmes in pregnancy

The prevalence of smoking during pregnancy is high with between 20 and 33% of pregnant women engaging in the practice. Smoking is significantly more frequent among women with low socioeconomic status. There is strong evidence linking maternal smoking to an increased risk of adverse pregnancy outcomes, including spontaneous preterm birth and perinatal death.[499]

The review of smoking cessation interventions[500] included 64 randomised trials. Fifteen of these trials reported outcomes related to maternal and perinatal health.[501–515] Further details of the review are in Appendix 6, *Table 129*. No additional studies were found when the searches were updated. The quality of the 15 included studies was generally poor (*Figure 156*). Data were available for the outcomes of spontaneous preterm birth before 37 weeks' gestation (*Figure 157*) and perinatal

| Study or subcategory | Progesterone *n/N* | Placebo *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| Papiernik, 1970[497] | 2/50 | 9/49 | | 5.50 | 0.22 (0.05–0.96) |
| Johnson, 1975[495] | 2/18 | 12/25 | | 6.08 | 0.23 (0.06–0.91) |
| Hartikainen, 1980[493] | 15/39 | 9/38 | | 5.52 | 1.62 (0.81–3.25) |
| Hauth, 1983[494] | 5/80 | 5/88 | | 2.88 | 1.10 (0.33–3.66) |
| Meis, 2003[496] | 111/306 | 84/153 | | 67.76 | 0.66 (0.54–0.81) |
| da Fonseca 2003[492] | 10/72 | 20/70 | | 12.27 | 0.49 (0.25–0.96) |
| Total (95% CI) | 565 | 423 | | 100.00 | 0.65 (0.54–0.79) |
| Total events: 145 (Progesterone), 139 (Placebo) | | | | | |
| Test for heterogeneity: $\chi^2$ = 12.35, df = 5 ($p$ = 0.03), $I^2$ = 59.5% | | | | | |
| Test for overall effect: $z$ = 4.42 ($p$ < 0.00001) | | | | | |



***FIGURE 153*** *Forest plot of the effects of prenatal administration of progesterone for the prevention of spontaneous preterm birth before 37 weeks' gestation.*



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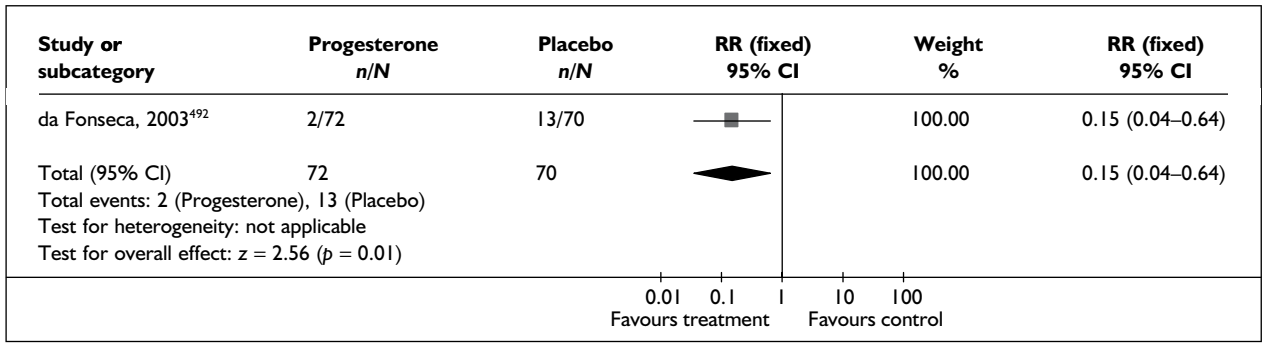


***FIGURE 154*** *Forest plot of the effects of prenatal administration of progesterone versus placebo for the prevention of spontaneous preterm birth before 34 weeks' gestation.*

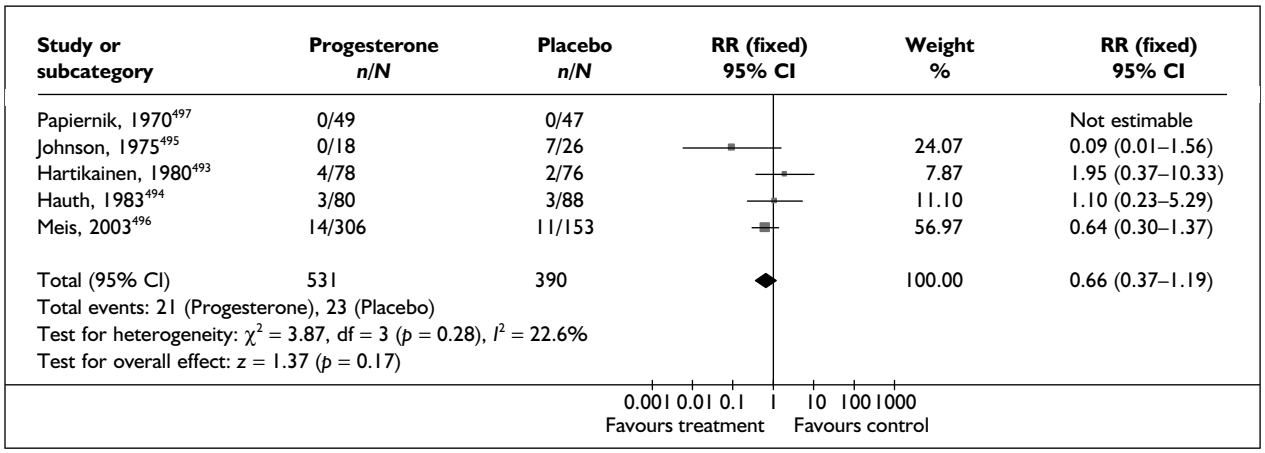


***FIGURE 155*** *Forest plot of the effects of prenatal administration of progesterone versus placebo on the incidence of perinatal death.*

***TABLE 17*** *Effects of progesterone versus placebo on other perinatal and maternal outcomes*

| Outcome (number of RCTs) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| Neonatal death (3 studies, $n = 671$) [494–496] | 0.59 | 0.27–1.30 | 25.2%, 0.26 |
| Intrauterine death (3 studies, $n = 671$) [494–496] | 0.56 | 0.19–1.61 | 24.3%, 0.27 |
| Threatened preterm labour (2 studies, $n = 601$) [492,496] | 0.92 | 0.64–1.33 | 63.6%, 0.10 |
| Use of antenatal corticosteroids (1 study, $n = 459$) [496] | 0.87 | 0.58–1.30 | NA |
| Use of antenatal tocolytics (2 studies, $n = 503$) [494,496] | 1.12 | 0.73–1.72 | NA |
| Birthweight <2500 g (4 studies, $n = 763$) [492,494–496] | 0.63 | 0.49–0.81 | 0%, 0.56 |
| Infant respiratory distress syndrome (1 study, $n = 457$) [496] | 0.63 | 0.38–1.05 | NA |
| Mechanical ventilation (1 study, $n = 454$) [496] | 0.59 | 0.35–1.00 | NA |
| Intraventricular haemorrhage (1 study, $n = 458$) [496] | 0.25 | 0.08–0.82 | NA |
| Retinopathy of prematurity (1 study, $n = 457$) [496] | 0.50 | 0.15–1.70 | NA |
| Necrotising enterocolitis (1 study, $n = 457$) [496] | 0.06 | 0.00–1.03 | NA |
| Neonatal sepsis (1 study, $n = 457$) [496] | 1.12 | 0.35–3.58 | NA |
| Patent duct arteriosus (1 study, $n = 456$) [496] | 0.43 | 0.16–1.17 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

***TABLE 18*** *Subgroup analyses of the effects of progesterone versus placebo on spontaneous preterm birth before 37 weeks' gestation*

| Stratification (number of studies) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| ***Preterm birth <37 weeks' gestation*** | | | |
| *Route of administration* | | | |
| Intramuscular injection (4 studies, $n = 771$)[492,494–496] | 0.61 | 0.50–0.75 | 42.4%, 0.16 |
| Vaginal pessary (1 study, $n = 140$)[498] | 0.49 | 0.25–0.96 | NA |
| *Timing of treatment* | | | |
| <20 weeks' gestation (3 studies, $n = 672$)[494,496,492] | 0.64 | 0.52–0.79 | 32.7%, 0.23 |
| >20 weeks' gestation (2 studies, $n = 239$)[495,498] | 0.40 | 0.22–0.75 | 0%, 0.33 |
| *Cumulative weekly dose* | | | |
| ≥500 mg (3 studies, $n = 409$)[495,496,498] | 0.50 | 0.29–0.86 | 30.3%, 0.24 |
| <500 mg (2 studies, $n = 502$)[492,494] | 0.63 | 0.51–0.77 | 56.5%, 0.13 |
| ***Perinatal mortality*** | | | |
| *Timing of treatment* | | | |
| <20 weeks' gestation (3 studies, $n = 671$)[492,494,496] | 0.55 | 0.29–1.06 | 16.6%, 0.30 |
| >20 weeks' gestation (1 study, $n = 96$)[495] | Not estimable | Not estimable | Not estimable |
| *Cumulative weekly dose* | | | |
| ≥500 mg (1 study, $n = 168$)[496] | 1.10 | 0.23–5.29 | NA |
| <500 mg (2 studies, $n = 503$)[492,494] | 0.48 | 0.23–0.98 | 45.4%, 0.18 |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

death (*Figure 158*). Smoking cessation programmes in general, and low intensity programmes in particular, significantly reduced the incidence of spontaneous preterm birth before 37 weeks' gestation (*Figure 157*) but there were no differences between the groups for perinatal mortality. Women on smoking cessation programmes also had significantly fewer low-birthweight (<2500 g) infants (*Table 19*). Data for other perinatal outcomes are also shown in *Table 19*. Summary RRs from the forest plots presented were used in the decision analyses. Overall, reductions in spontaneous preterm birth and low birthweight suggest that smoking cessation programmes may have beneficial perinatal outcomes, but the quality of the studies is poor and the significance is unclear. Additionally, it is unclear whether changes in smoking behaviour are a consequence of the intervention programmes because there was no direct assessment of smoking cessation. Further good quality research that directly measures the effects of smoking cessation programmes on spontaneous preterm birth is required.

# Effectiveness of interventions among symptomatic women

## Hydration

Hydration has been proposed as a treatment for women presenting with threatened preterm labour contractions.[516] One possible mechanism of action is that volume expansion inhibits contractions by increasing uterine blood flow, so stabilising decidual lysosomes and decreasing prostaglandin production,[517] and by decreasing pituitary secretion of antidiuretic hormone and oxytocin.[517,518]

The review of hydration (intravenous or oral) for the prevention or delay of threatened preterm labour included two randomised controlled trials ($n = 228$ women).[517,519] Further details of the review can be found in Appendix 6, *Table 130*. The quality of the included studies is presented in *Figure 159*. Overall, the methodological quality of the included studies was good, although the trials were small. Compared to bed rest alone, intravenous hydration did not reduce the incidence of spontaneous



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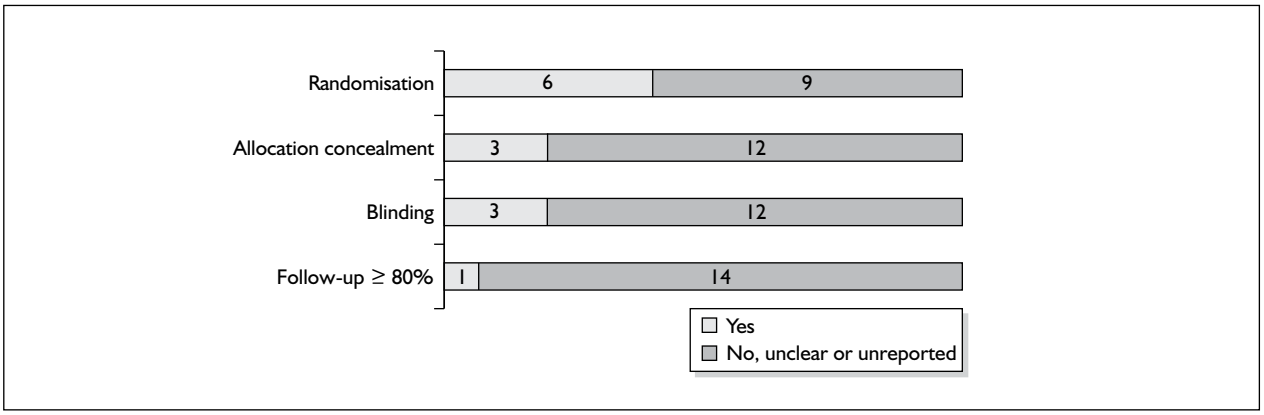


***FIGURE 156*** *Methodological quality of trials of smoking cessation programmes for the prevention of spontaneous preterm birth.*

| Study or subcategory | Treatment *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 High intensity intervention | | | | | |
| Ershoff, 1989[502] | 7/118 | 7/109 | | 2.14 | 0.92 (0.33–2.55) |
| Thornton, 1997[514, 732] | 14/209 | 8/209 | | 2.35 | 1.75 (0.75–4.08) |
| Panjari, 1999[509] | 18/339 | 34/391 | | 9.28 | 0.61 (0.35–1.06) |
| Tappin, 2000[513] | 5/48 | 4/49 | | 1.16 | 1.28 (0.36–4.47) |
| Wisborg, 2000[515] | 10/120 | 12/122 | | 3.50 | 0.85 (0.38–1.89) |
| Hegaard, 2003[504] | 7/327 | 10/320 | | 2.97 | 0.69 (0.26–1.78) |
| Subtotal (95% CI) | 1161 | 1200 | | 21.40 | 0.85 (0.61–1.18) |
| Total events: 61 (Treatment), 75 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 4.79$, df = 5 ($p = 0.44$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.95$ ($p = 0.34$) | | | | | |
| 02 Medium intensity intervention | | | | | |
| Donovan, 1977[501] | 16/263 | 17/289 | | 4.76 | 1.03 (0.53–2.00) |
| Hjalmarson, 1991[505] | 13/421 | 8/197 | | 3.20 | 0.76 (0.32–1.80) |
| Subtotal (95% CI) | 684 | 486 | | 7.96 | 0.92 (0.55–1.56) |
| Total events: 29 (Treatment), 25 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.31$, df = 1 ($p = 0.58$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.30$ ($p = 0.77$) | | | | | |
| 03 Low intensity intervention | | | | | |
| MacArthur, 1987[507] | 32/493 | 37/489 | | 10.92 | 0.86 (0.54–1.35) |
| Haddow, 1991[503] | 109/1423 | 137/1425 | | 40.23 | 0.80 (0.63–1.01) |
| LeFevre, 1995[506] | 57/1768 | 67/1803 | | 19.49 | 0.87 (0.61–1.23) |
| Subtotal (95% CI) | 3684 | 3717 | | 70.64 | 0.83 (0.69–0.99) |
| Total events: 198 (Treatment), 241 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.19$, df = 2 ($p = 0.91$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 2.07$ ($p = 0.04$) | | | | | |
| Total (95% CI) | 5529 | 5403 | | 100.00 | 0.84 (0.72–0.96) |
| Total events: 288 (Treatment), 341 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 5.46$, df = 10 ($p = 0.86$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 2.26$ ($p = 0.02$) | | | | | |



***FIGURE 157*** *Forest plot of the effects of smoking cessation interventions for the prevention of spontaneous preterm birth before 36 or 37 weeks' gestation, subgrouped by intensity of intervention.*

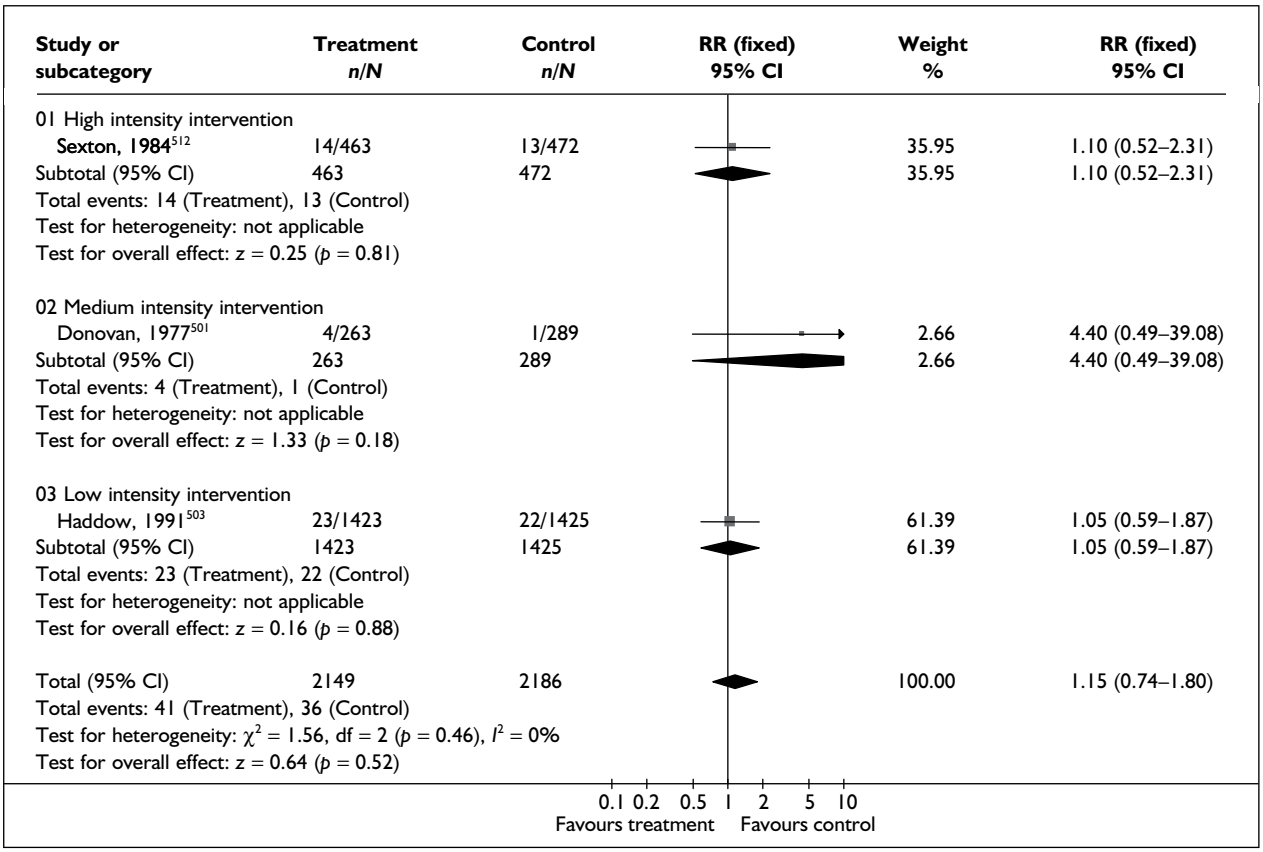


***FIGURE 158*** *Forest plot of the effects of smoking cessation interventions for the prevention of perinatal mortality.*

***TABLE 19*** *Effects of smoking cessation interventions on other perinatal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Stillbirth (5 studies, n = 4525)[502,503,512–514]*** | ***1.16*** | ***0.71–1.88*** | ***0% (0.86)*** |
| High-intensity intervention (4 studies, *n* = 1677)[502,512–514] | 1.08 | 0.52–2.26 | 0% (0.75) |
| Low-intensity intervention (1 study, *n* = 2848)[503] | 1.24 | 0.66–2.33 | NA |
| ***Neonatal death (3 studies, n = 4143)[503,512,514]*** | ***1.17*** | ***0.34–4.01*** | ***25.7% (0.26)*** |
| High-intensity intervention (2 studies, *n* = 1333)[503,512] | 2.36 | 0.61–9.08 | 0% (0.87) |
| Low-intensity intervention (1 study, *n* = 2810)[514] | 0.40 | 0.08–2.07) | NA |
| ***Low birthweight < 2500 g (13 studies, n = 8930)[501–505,507–512,514,515]*** | ***0.82*** | ***0.70–0.95*** | ***0% (0.67)*** |
| High-intensity intervention (8 studies, *n* = 3652)[501–509] | 0.79 | 0.62–1.00 | 0% (0.43) |
| Medium-intensity intervention (3 studies, *n* = 1448)[510–512] | 0.84 | 0.57–1.23 | 12.1% (0.32) |
| Low-intensity intervention (2 studies, *n* = 3830)[514,515] | 0.83 | 0.67–1.03 | 0% (0.90) |
| ***Low birthweight < 1500 g (3 studies, n = 4765)[505,507.512]*** | ***1.26*** | ***0.69–2.32*** | ***0% (0.61)*** |
| High-intensity intervention (1 study, *n* = 620)[505] | 1.83 | 0.69–2.32 | NA |
| Medium-intensity intervention (1 study, *n* = 982)[507] | 0.89 | 0.34–2.30 | NA |
| Low-intensity intervention (1 study, *n* = 935)[512] | 1.39 | 0.44–4.35 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.



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preterm birth before 34 or 37 weeks' gestation (*Figures 160* and *161*). Delivery within 48 hours and 7 days of treatment initiation was not estimable; delivery within 24 hours of treatment initiation was not reported. No statistically significant difference was found in admission to neonatal intensive care between women receiving intravenous hydration and women receiving bed rest alone (*Figure 162*). A separate analysis of women included before 34 weeks' gestation did not demonstrate any beneficial effect of hydration during the period of evaluation soon after admission; results were based on one study.[517] Overall, there is insufficient evidence to support the use of intravenous hydration for the treatment of women presenting with threatened preterm labour. No eligible studies were found for oral hydration. Summary RRs for spontaneous preterm birth before 34 weeks' gestation and admission to neonatal intensive care were used in the decision analysis.

## Prophylactic antibiotics in women with intact membranes

Subclinical and clinical infections have been implicated in the aetiology of spontaneous preterm birth, which has led to the suggestion that women with threatened preterm labour should be treated with antibiotics to reduce the incidence of spontaneous preterm birth. As rupture of the membranes can also be a significant factor in threatened preterm labour, it is important to establish if prophylactic antibiotic treatment has an effect before membrane rupture.

The review of prophylactic antibiotics in pregnant women with intact membranes[520] included eleven RCTs that compared antibiotic therapy with placebo or no treatment.[521–531] Further details of the review can be found in Appendix 6, *Table 131*. No additional RCTs were found when the searches were updated. All women included in

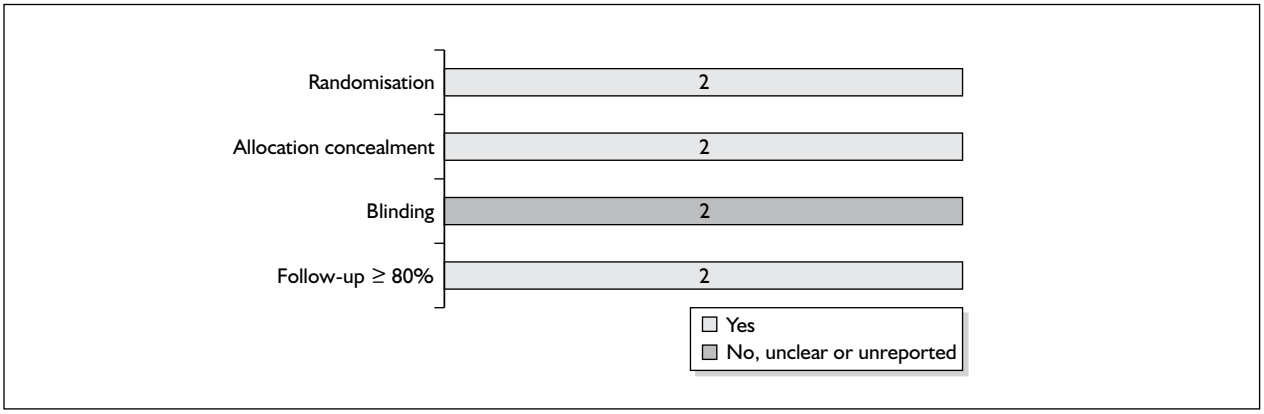


***FIGURE 159*** *Methodological quality of trials of hydration for the prevention of spontaneous preterm birth.*

| Study or subcategory | Hydration n/N | Control n/N | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| Helfgott, 1994[519] | 19/73 | 11/37 | | 51.66 | 0.88 (0.47–1.64) |
| Guinn, 1997[517] | 19/62 | 13/56 | | 48.34 | 1.32 (0.72–2.42) |
| Total (95% CI) | 135 | 93 | | 100.00 | 1.09 (0.71–1.68) |
| Total events: 38 (Hydration), 24 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.85$, df = 1 ($p = 0.36$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.39$ ($p = 0.70$) | | | | | |

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

***FIGURE 160*** *Forest plot of intravenous hydration versus bed rest alone for the inhibition of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*

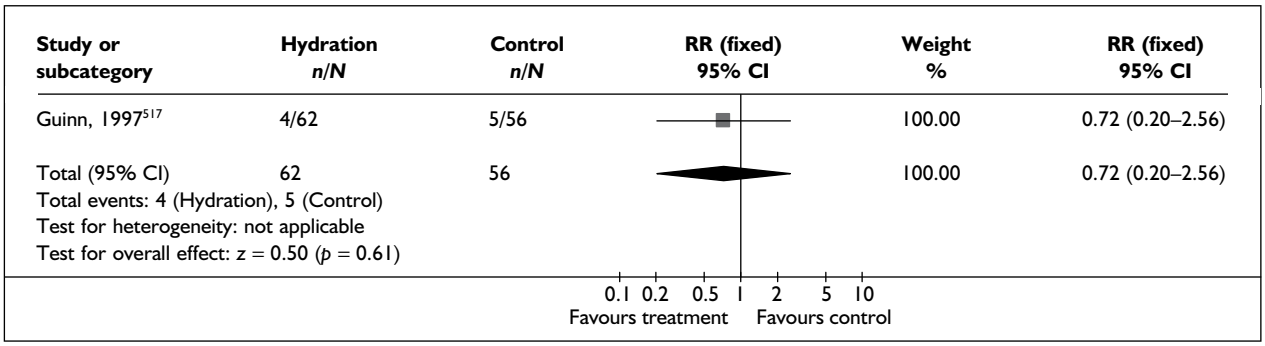


***FIGURE 161*** *Forest plot of intravenous hydration versus bed rest alone for the inhibition of spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour.*

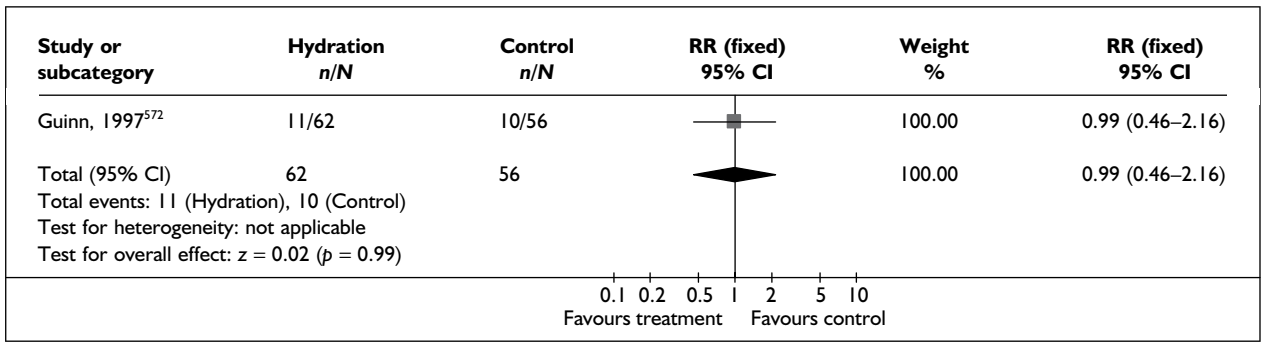


***FIGURE 162*** *Forest plot of intravenous hydration versus bed rest alone on neonatal admission to intensive care unit.*

the trials were experiencing, or thought to be experiencing, symptoms of threatened preterm labour. The original review included trials with multiple pregnancies, which we have subgrouped where possible. The quality of the included studies is shown in *Figure 163;* overall this was considered good. The following subgroups were examined: any antibiotic versus no antibiotics; betalactam antibiotic alone versus no antibiotics; macrolide alone versus no antibiotics; betalactam and macroclide versus no antibiotics; and antibiotics active against anaerobic bacteria.

Antibiotic prophylaxis did not significantly affect the incidence of spontaneous preterm birth before 37 weeks' gestation (*Figures 164–168*), although a reduced risk of maternal infection was shown for prophylactic antibiotic therapy compared to no antibiotic therapy across all subgroups (*Table 20*). A trend toward an increase in risk of perinatal mortality (*Figures 170* and *171*) and neonatal mortality (*Table 20*) was found for women receiving prophylactic antibiotic therapy, which was demonstrated across all subgroups. Antibiotics active against anaerobic bacteria were shown to significantly affect the incidence of delivery within 7 days of treatment and incidence of admission to neonatal intensive care unit; however, this reduction in risk was not found in other subgroups or the population as a whole (*Figures 169*, *172* and *173*). No studies reported spontaneous preterm birth before 34 weeks' gestation or delivery within 24 hours of treatment.

Other neonatal and maternal outcomes are shown in *Table 20*. Summary RRs of any antibiotic therapy versus placebo/no treatment from the forest plots presented were used in the decision analyses. The ORACLE II trial, as the largest included trial, dominates the results of this review, and fails to demonstrate any clear benefit of prophylactic antibiotic therapy for the prevention of spontaneous preterm birth in women with intact membranes and no evidence of clinical infection. Overall, the review did not find any clear evidence of a beneficial effect of prophylactic antibiotic therapy for the prevention of spontaneous preterm birth in women with intact membranes.



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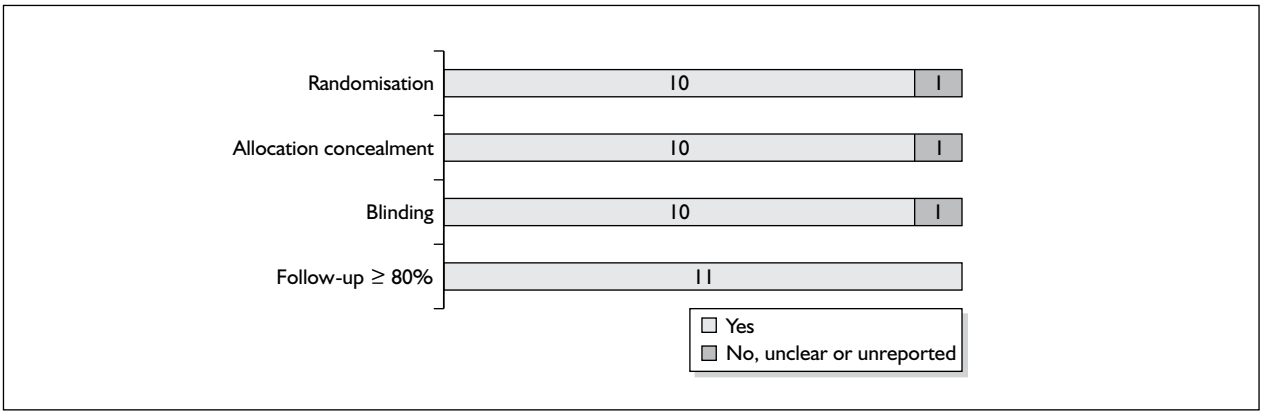


***FIGURE 163*** *Methodological quality of the included trials of prophylactic antibiotic therapy for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*

## Betamimetics for tocolysis

Betamimetics were commonly used to arrest threatened premature labour thus delaying spontaneous preterm birth. They act on uterine $\beta_2$-receptors to induce the relaxation of smooth muscle cells. However stimulation of β-adrenergic receptors may also produce a number of cardiovascular and biochemical disturbances as side effects.

The review of betamimetics (ritodrine, terbutaline, isoxuprine, fenoterol, hexoprenaline) for the prevention of spontaneous preterm birth[532] included 16 RCTs ($n = 21{,}782$);[533–548] no additional

| Study or subcategory | Treatment n/N | Control n/N | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Singletons only | | | | | |
| Newton, 1989[525] | 18/48 | 21/47 | | 1.88 | 0.84 (0.52–1.36) |
| McGregor, 1991[524] | 38/58 | 37/58 | | 3.28 | 1.03 (0.78–1.34) |
| Romero, 1993[529] | 69/131 | 74/144 | | 6.24 | 1.02 (0.82–1.29) |
| **Svare, 1997**[530] | 25/59 | 33/51 | | 3.13 | 0.65 (0.46–0.94) |
| Oyarzun, 1998[528] | 38/83 | 45/90 | | 3.82 | 0.92 (0.67–1.25) |
| Subtotal (95% CI) | 379 | 390 | | 18.36 | 0.92 (0.80–1.05) |
| Total events: 188 (Treatment), 210 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 5.07$, df = 4 ($p = 0.28$), $I^2 = 21.2\%$ | | | | | |
| Test for overall effect: $z = 1.20$ ($p = 0.23$) | | | | | |
| 02 Other | | | | | |
| Newton, 1991[526] | 23/43 | 27/43 | | 2.39 | 0.85 (0.59–1.22) |
| Gordon, 1995[522] | 35/58 | 34/59 | | 2.99 | 1.05 (0.77–1.42) |
| **Cox, 1996**[121] | 23/39 | 22/39 | | 1.95 | 1.05 (0.71–1.53) |
| ORACLE II 2001[523] | 1687/4685 | 559/1556 | | 74.32 | 1.00 (0.93–1.08) |
| Subtotal (95% CI) | 4825 | 1697 | | 81.64 | 1.00 (0.93–1.08) |
| Total events: 1768 (Treatment), 642 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.90$, df = 3 ($p = 0.83$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.02$ ($p = 0.99$) | | | | | |
| Total (95% CI) | 5204 | 2087 | | 100.00 | 0.99 (0.92–1.05) |
| Total events: 1956 (Treatment), 852 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 6.85$, df = 8 ($p = 0.55$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.44$ ($p = 0.66$) | | | | | |



***FIGURE 164*** *Forest plot of the effects of any antibiotic therapy versus no treatment for the prevention of preterm birth before 36 or 37 weeks' gestation.*

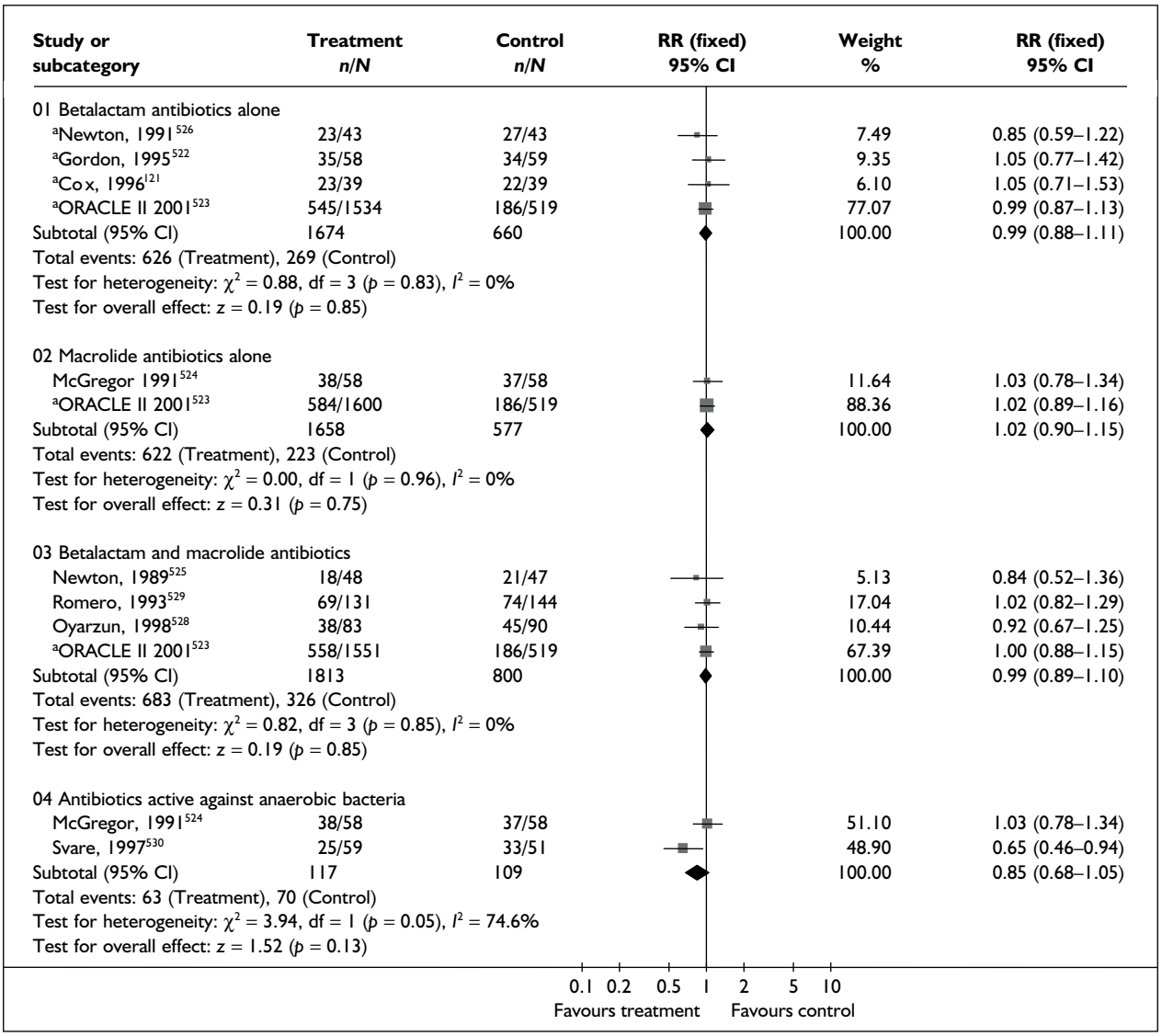


***FIGURE 165*** *Forest plot of the effects of antibiotic therapy subgrouped by type of antibiotic versus no treatment for the prevention of spontaneous preterm birth before 36 or 37 weeks' gestation. a, Multiple gestations included in trial or not excluded from trial.*

studies were found when the searches were updated. Further details of the review can be found in Appendix 6, *Table 132*. The quality of these studies was mixed as shown in *Figure 174;* few trials reported adequate allocation concealment. No statistically significant benefit was found on the risk of spontaneous preterm birth before 37 weeks' gestation when betamimetics were compared with placebo (*Figure 175*). When grouped by type of betamimetic, terbutaline was found to significantly reduce risk of spontaneous preterm birth before 37 weeks' gestation in two small trials, one of unclear methodological quality. The summary RR was put forward for use in the decision analysis. A reduction in the risk of delivery within 48 hours after treatment was shown when ritodrine and terbutaline were compared with placebo (*Figure 176*). The pooled RR for ritodrine and terbutaline combined was put forward for use in the decision analysis. Compared with ritodrine, terbutaline was found to reduce the incidence of birth within 48 hours of treatment, although this did not reach statistical significance (*Figure 177*). A reduction in the risk of delivery within 7 days after treatment was shown for ritodrine and terbutaline when compared with placebo (*Figure 178*).The pooled RR for all betamimetics versus placebo was used in the decision analysis. When compared with ritodrine, terbutaline demonstrated a non-significant reduction in risk of delivery within 7 days (*Figure*



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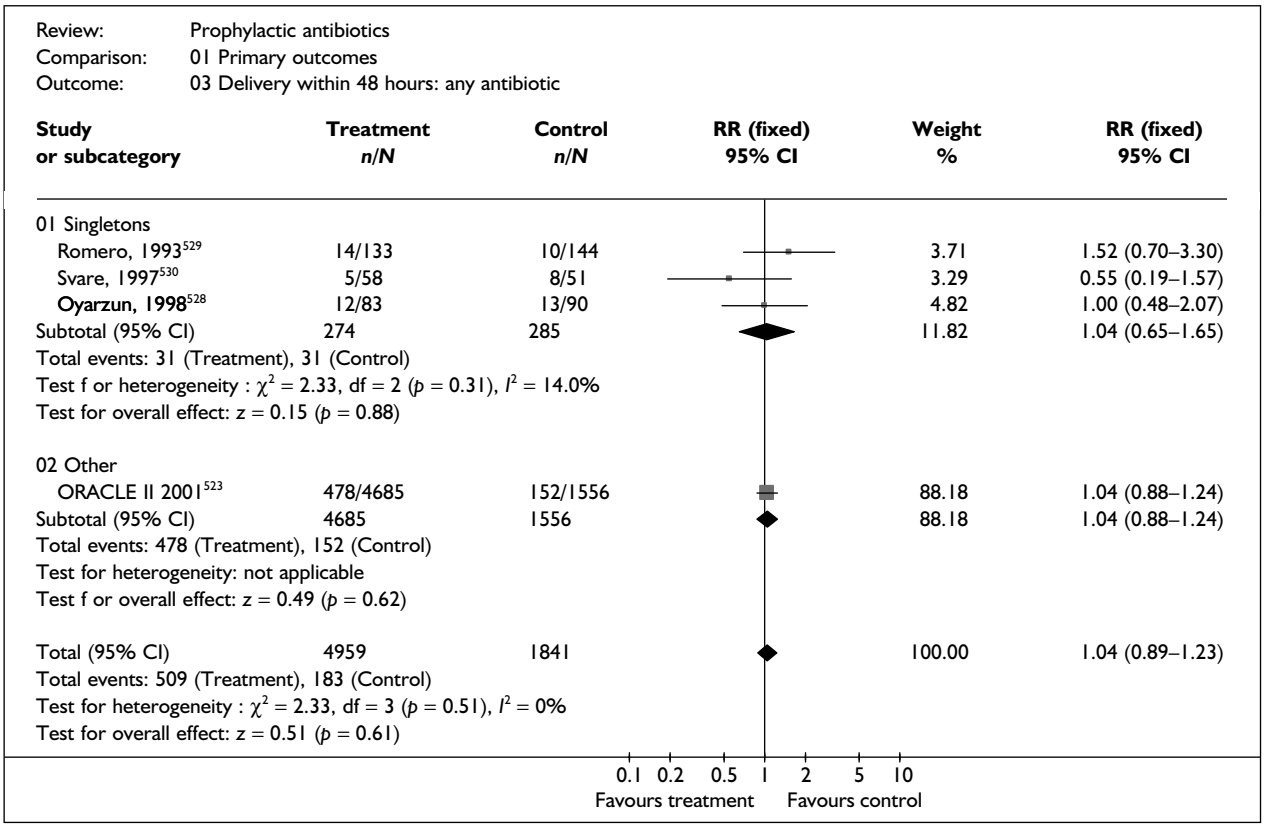


***FIGURE 166*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for delivery within 48 hours of treatment.*

*179*). Incidence of admission to neonatal care unit was not reported. Neither placebo nor betamimetic comparisons had a statistically significant relative risk on perinatal mortality (Figures *180* and *181*). As can be seen from *Table 21* a greater number of cardiovascular changes, and adverse events leading to the discontinuation of therapy were reported in the betamimetics group compared to placebo. There were insufficient data to indicate whether one betamimetic agent was superior to another, with most head-to-head comparisons based on a single trial.

Of the included studies, only one trial does not appear to have used a maintenance regimen as part of its study protocol; however, the dataset for this study is very small.[537] It is therefore not possible to separate the influence of acute treatment with betamimetics from the effect of any maintenance regimen, except for birth within 48 hours of treatment. This should be considered when interpreting these results. In addition, only one trial explicitly states that multiple gestations were excluded. While betamimetics appear to be able to prolong gestation up to 7 days compared to placebo, the risk of adverse effects must also be considered. Indeed, the use of betamimetics as tocolysis is no longer recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) because of the risk of adverse events.

## Oral betamimetics maintenance

Oral tocolytic maintenance therapy can be given after an episode of threatened preterm labour to maintain uterine quiescence. Betamimetics are one of several tocolytic agents that may be offered.

The review of oral betamimetics for maintenance therapy after threatened preterm labour [549] included 11 RCTs ($n = 1238$);[550–560] no additional studies were found when the searches were updated. Further details of the review can be found in Appendix 6, *Table 132*. The quality of these studies is shown in *Figure 182;* few of the included trials were considered to be of high quality. Oral betamimetics for maintenance therapy after acute tocolytic treatment of threatened preterm labour did not significantly affect the risk of spontaneous preterm birth before either 34 or 37 weeks' gestation (*Figure 183* and *Figure 184*, respectively), delivery within 24 or 48 hours after

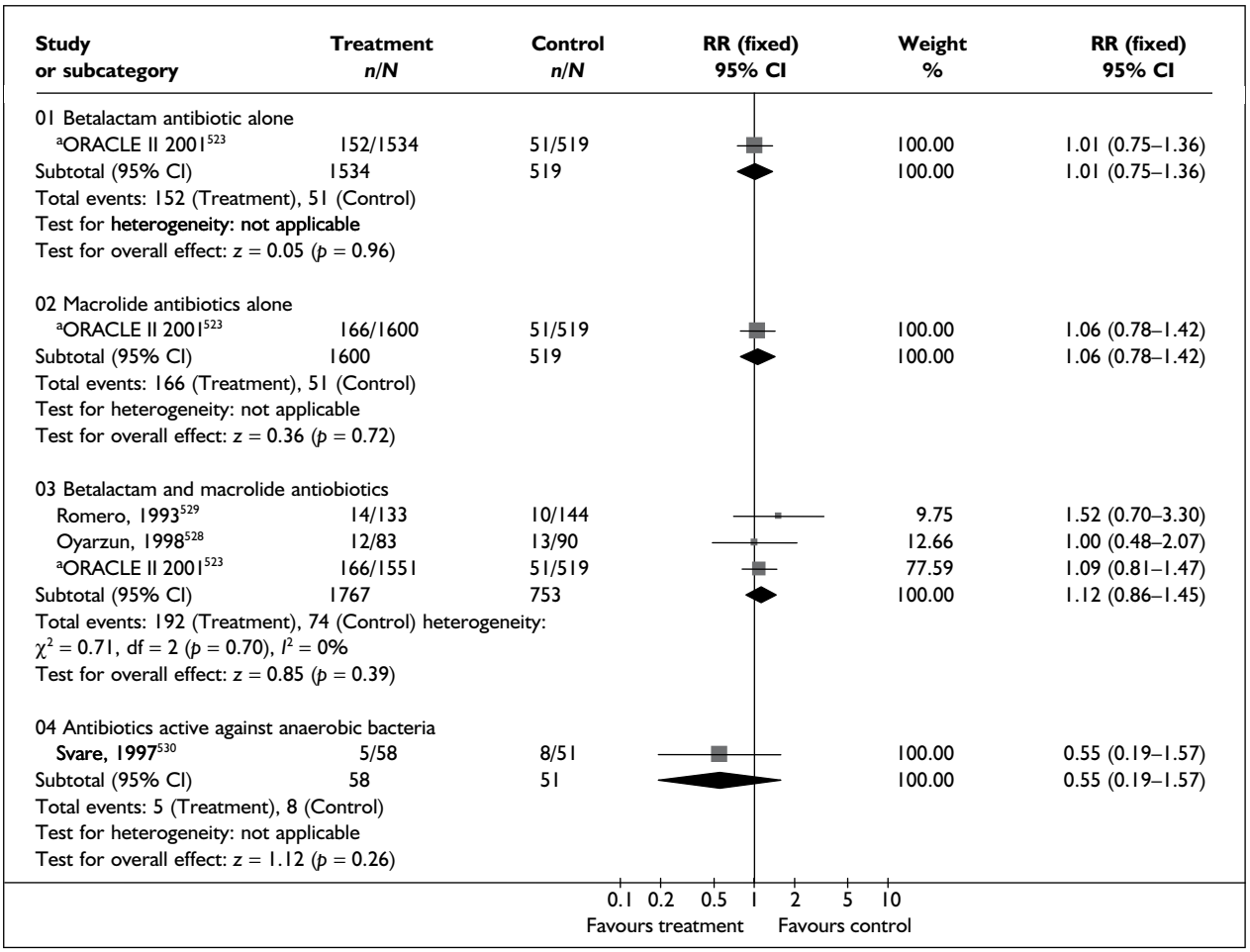


***FIGURE 167*** *Forest plot of the effects of antibiotic therapy subgrouped by type of antibiotic versus placebo/no treatment for delivery within 48 hours of treatment. Multiple gestations included in trial or not excluded from trial.*

treatment (*Figure 185* and *Figure 186*, respectively), delivery within 7 days after treatment (*Figure 187*) or requirement for admission to neonatal intensive care unit (*Figure 188*) compared to placebo/no treatment. Pooled RRs for betamimetics versus placebo/no treatment presented in the forest plots were used in the decision analyses for all primary outcomes. Although perinatal mortality was reported, it was defined as death before discharge among all live births, as this may include mortality beyond the first week after birth, summary RRs were not used in the decision analysis for perinatal mortality. Compared with placebo/no treatment, an increase in perinatal mortality (defined as death before discharge among live births) was reported, although this was not statistically significant. A greater number of adverse events, and in particular cardiovascular changes, were reported in the betamimetic maintenance group compared with placebo (*Table 22*). There were insufficient data to indicate whether one betamimetic agent was superior to another, with most head-to-head comparisons based on a single trial for the available information for delaying spontaneous preterm birth before 37 weeks' gestation and within 7 days of treatment with betamimetic maintenance therapy (*Figures 189* and *190*, respectively). It was unclear in the majority of the primary studies whether trials included both singletons and multiple gestations. Overall, the evidence does not support the use of oral betamimetics for maintenance therapy after threatened preterm labour.

## Terbutaline subcutaneous pump maintenance tocolysis

Women who are undelivered after 48 hours of tocolysis remain at increased risk of spontaneous preterm birth. A number of different drugs have been administered beyond 48 hours in the hope of maintaining uterine quiescence, including



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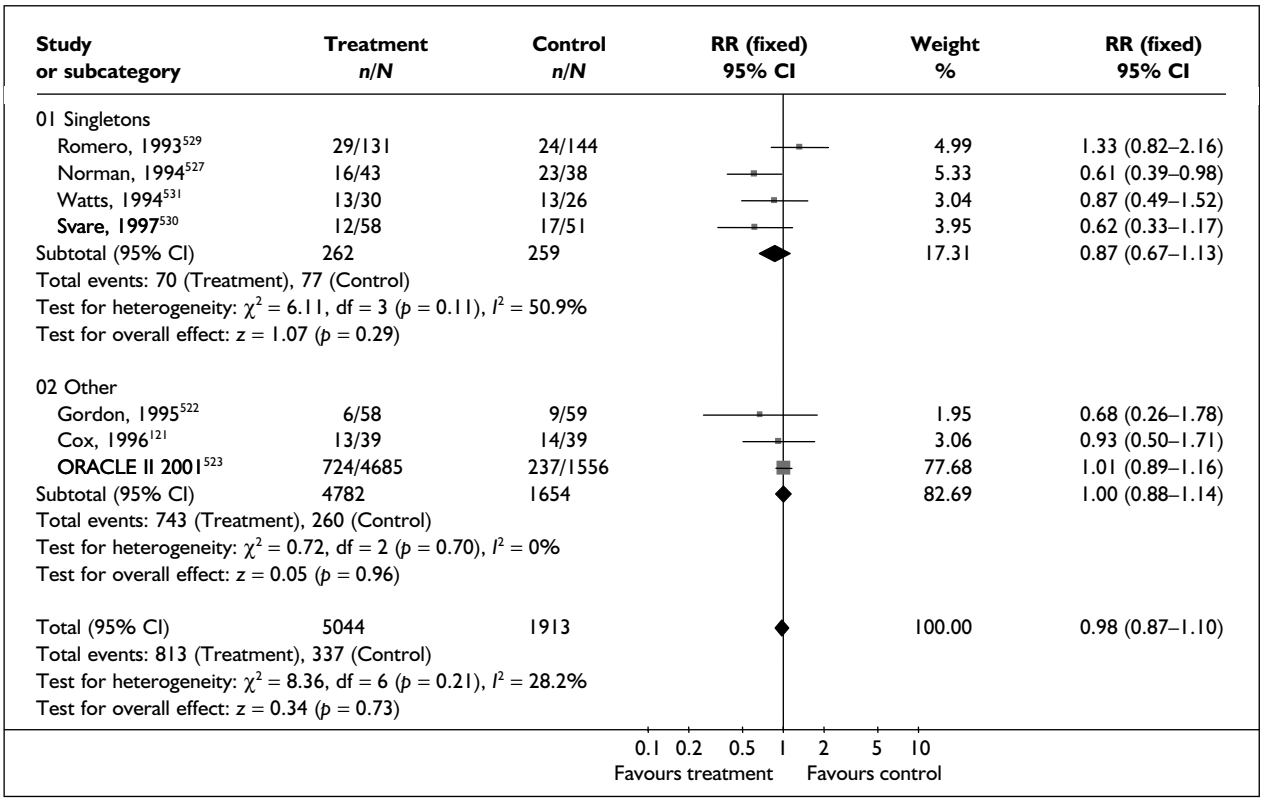


***FIGURE 168*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for delivery within 7 days of treatment.*

terbutaline, which is a relatively selective $\beta_2$-adrenergic blocker that inhibits uterine muscle contractility. It is administered via a portable subcutaneous pump. Advantages of pump administration include good subcutaneous absorption; steady, lower, more regular doses; and the ability to titrate the infusion rate against contractions.

The review of terbutaline pump maintenance[561] for the prevention of spontaneous preterm birth included two RCTs ($n = 94$);[562,563] no additional studies were identified. Further details of the review can be found in Appendix 6, *Table 132*. The quality of these studies is shown in *Figure 191* and is generally good. No statistically significant differences were found between terbutaline pump maintenance and saline pump for prolongation of pregnancy (*Figure 192*), or admission to neonatal intensive care unit (*Figure 193*). Similarly, no statistically significant differences were found between terbutaline pump maintenance and saline pump or oral terbutaline therapy in terms of birthweight, risk of respiratory distress syndrome or incidence of early discontinuation (*Table 23*). Neither of these studies reported outcomes of perinatal mortality. RRs presented in *Figures 192* and *193* below were used in the decision analyses. Overall, there is insufficient evidence to demonstrate any benefit from prolonged treatment with subcutaneous administration of terbutaline sulphate, and its safety has not been adequately addressed. Furthermore, one study included multiple births but it was not clear how many.[563]

## Calcium channel blockers

Dihydropyridines are a class of L-type calcium channel blockers that cause non-specific smooth muscle relaxation by preventing extracellular calcium, required for muscle contractility, from entering muscle cells. Myometrial drugs from this class, including nifedipine and nicardipine, are employed as tocolytics for the treatment of threatened preterm labour.[564]

The review of inhibition of threatened preterm labour with calcium channel blockers[565] included 12 RCTs.[566–577] Updating the searches retrieved a further five RCTs.[578–582] Further details of the review can be found in Appendix 6, *Table 133*. The quality of the included studies is generally good (*Figure 194*). Calcium channel blockers used were nifedipine and nicardipine and comparators were magnesium sulphate,[569,574,580,581] a betamimetic (ritodrine, terbutaline, salbutamol),[566–568,570–573,575–579]

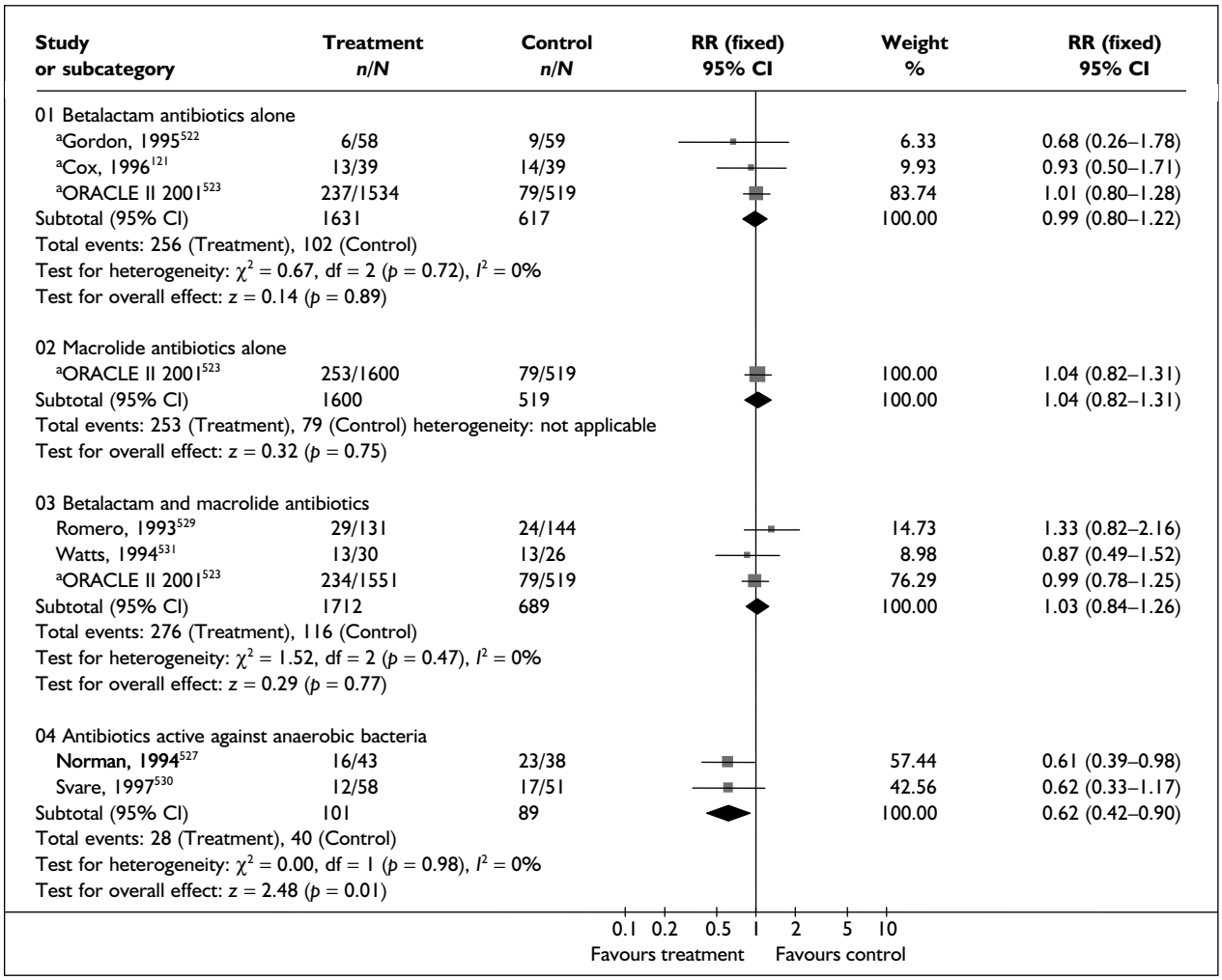


***FIGURE 169*** *Forest plot of the effects of antibiotic therapy subgrouped by type of antibiotic versus placebo/no treatment for delivery within 7 days of treatment. a, Multiple gestations included in trial or not excluded from trial.*

and an oxytocin antagonist (atosiban).[582] No placebo-controlled trials were found. Maintenance therapy was used in 12 of the trials (*Table 24*).[566–569,571–575,578–580] Twelve studies excluded women with multiple gestations.[566–569,571,574–578,580,581] Studies that included women with multiple gestations are denoted with an asterisk in the forest plots.[570,572,573,579,582] Data were available on the following outcomes: birth within 48 hours of intervention, birth within 7 days of intervention, spontaneous preterm birth before 37 weeks' gestation, spontaneous preterm birth before 34 weeks' gestation, perinatal mortality and admission to neonatal intensive care. Other maternal and neonatal outcomes are shown in *Table 25*.

Calcium channel antagonists were significantly more effective than betamimetics in studies where maintenance therapy was employed in preventing spontaneous preterm birth before 37 weeks' gestation (*Figure 195*). There were no other differences in interventions for this outcome. They were significantly more effective than any other tocolytic in preventing spontaneous preterm birth before 34 weeks' gestation (*Figure 196*), and were more effective than betamimetics both in general and where maintenance therapy was employed (*Table 24*). Calcium channel antagonists were also more effective in preventing spontaneous preterm birth within 7 days of intervention (*Figure 197*) but not within 48 hours (*Figure 198*) than any other tocolytic and any betamimetic, both overall and where maintenance therapy was employed (*Table 24*). This was also the case for admission to neonatal intensive care where there were fewer admissions in the calcium channel antagonist groups than in those given any other tocolytic (*Figure 199*), any betamimetic and any betamimetic where maintenance therapy was employed (*Table 24*). There were no significant differences between the groups in incidence of perinatal mortality



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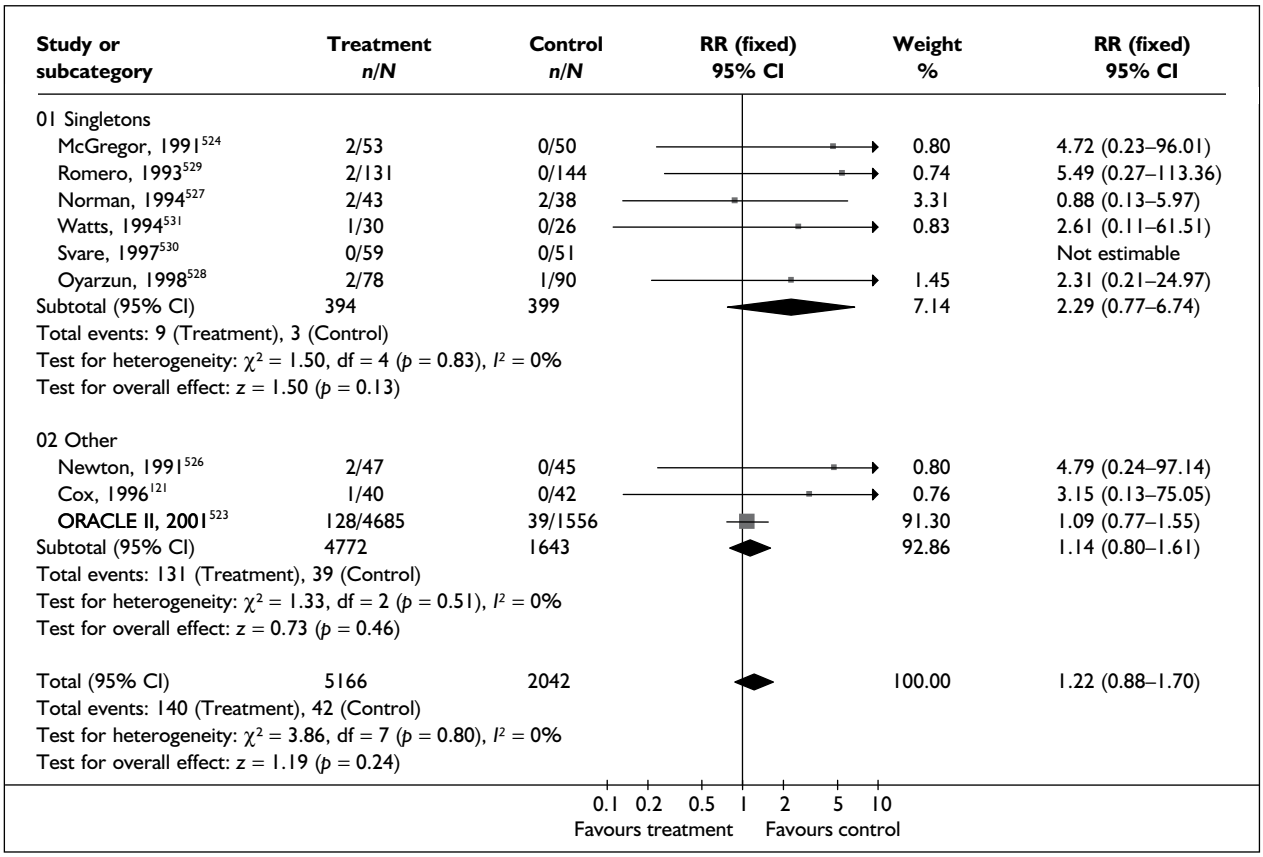


***FIGURE 170*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of perinatal mortality.*

following the interventions with calcium channel blockers for prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour (*Figure 200*).

Other maternal and perinatal outcomes are shown in *Table 25*. There were fewer instances of low-birthweight infants (<2500 g) in groups given calcium channel antagonists than in groups given other tocolytics. The following outcomes were significantly more favourable in calcium channel antagonist groups than for other tocolytics overall and betamimetics in general: respiratory distress syndrome, neonatal jaundice, neonatal sepsis, necrotising enterocolitis, intraventricular haemorrhage (all grades), maternal adverse drug reaction and maternal adverse drug reaction requiring cessation of treatment. The summary RRs shown were not used in the decision analyses because they did not include a placebo/no treatment comparison. Overall, calcium channel blockers appear to have a reasonable efficacy and safety profile compared to other tocolytics. They appeared to be superior to betamimetics in both respects.

## Calcium channel blocker maintenance

Uterine contractions are thought to be initiated by increasing intracellular calcium levels of myometrial cells. Calcium channel blockers are a type of tocolytic agent that counteracts this process and so prevents contractions. Maintenance therapy is used to prevents further contractions after the symptoms of threatened preterm labour have been successfully treated with an initial dose of tocolytic therapy.

The review[583] of calcium channel blocker maintenance therapy (nifedipine) for the prevention of spontaneous preterm birth included two RCTs ($n = 147$).[584,585] One trial[585] was added to the primary study[584] identified in an earlier review.[583] Further details of the review can be found in Appendix 6, *Table 133*. The quality of the included studies is presented in *Figure 201*. Only one small study was considered to be of good quality.[585] No reduction in the risk of spontaneous preterm birth before 34 or 37 weeks' gestation was shown when calcium channel blocker maintenance therapy was compared with no treatment (Figures

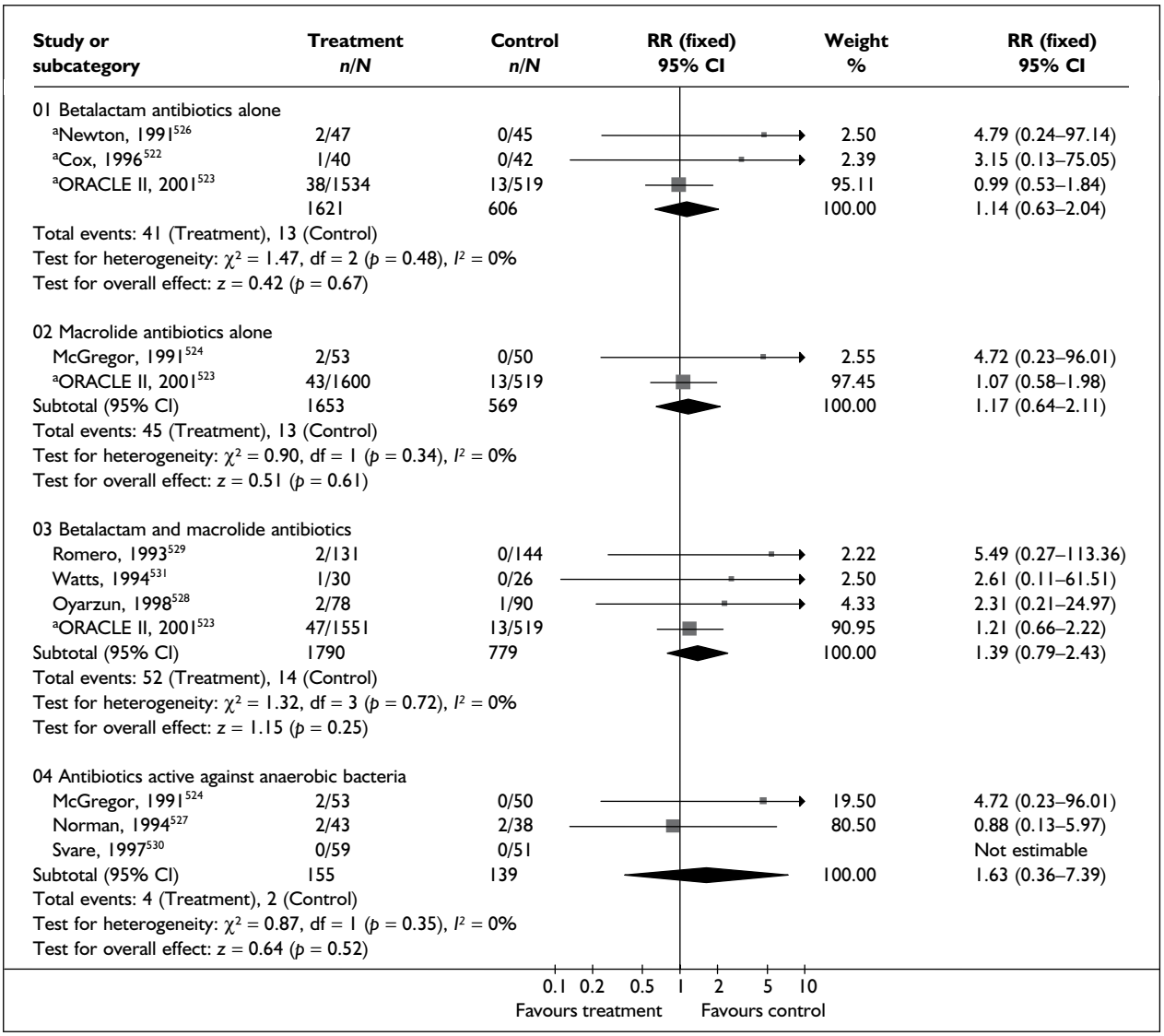


***FIGURE 171*** *Forest plot of the effects of antibiotic therapy subgrouped by type of antibiotic versus placebo/no treatment for the prevention of perinatal mortality. a, Multiple gestations included in trial or not excluded from trial.*

202 and *203*). There was no difference in admission to neonatal intensive care units with nifedipine versus no treatment (*Figure 204*). Delivery within 24 hours and 48 hours of treatment initiation was omitted from the review because maintenance therapy was aimed at a longer duration than this. Delivery within 7 days of treatment initiation was not reported. The effect of nifedipine on other outcomes is shown in *Table 26*. No RCTs were found comparing calcium channel blockers for maintenance therapy with other maintenance tocolytic agents for the prevention of spontaneous preterm birth following acute tocolytic therapy for threatened preterm labour. The review does not provide sufficient evidence to assess the use of calcium channel blockers as maintenance therapy for the prevention of spontaneous preterm birth following acute tocolytic therapy for threatened preterm labour. Summary RRs presented in the forest plots below were not used in the decision analysis because only RRs that appear to be beneficial were entered into the main model.

## Oxytocin receptor antagonists

Oxytocin receptor antagonists are competitive antagonists of human oxytocin receptors within the uterus and potentially the decidual and fetal membranes. They act to reduce the level of oxytocin, which is believed to initiate uterine contractibility, and as such have been proposed as effective tocolytic agents for women symptomatic of



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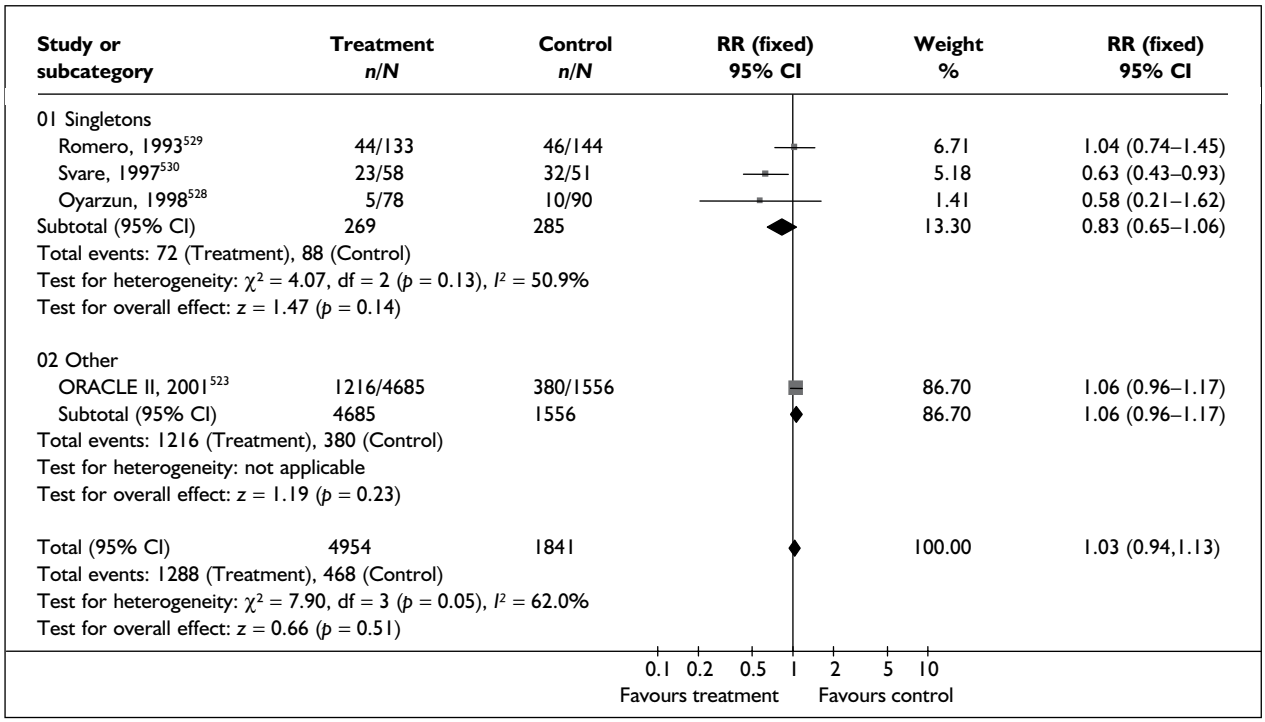


***FIGURE 172*** *Forest plot of the effects of any antibiotic therapy versus placebo/no treatment for the prevention of admission to neonatal unit.*

threatened preterm labour to postpone birth. The oxytocin receptor antagonist atosiban is the only treatment currently licensed for the treatment of threatened preterm labour in the UK.

The review[586] of oxytocin receptor antagonists (atosiban) included six RCTs ($n = 1695$).[587–592] Further details of the review can be found in Appendix 6, *Table 138*. Overall, the quality of included primary studies was good (*Figure 205*). When compared with placebo, atosiban did not reduce the incidence of spontaneous preterm birth before 37 weeks' gestation, or the incidence of delivery within 48 hours of treatment initiation (*Figures 206* and *207*, respectively). No statistically significant difference was found in the incidence of neonatal mortality or admission to neonatal intensive care between women receiving atosiban and women receiving placebo (*Figures 208* and *209*, respectively). When compared to betamimetics, atosiban did not significantly differ in the incidence of spontaneous preterm birth before 37 weeks' gestation or incidence of delivery within 48 hours, or 7 days, of treatment initiation (*Figures 210–212*). No statistically significant difference was found in the incidence of neonatal mortality or admission to neonatal intensive care between women receiving atosiban and women receiving betamimetics (*Figures 213* and *Figure 214*, respectively). Delivery within 24 hours of treatment initiation was not reported. The effect of atosiban on other outcomes is shown in *Table 27*. Summary RRs presented in the forest plots below were not used in the decision analyses. Overall, the results do not support the superiority of atosiban over betamimetics or placebo in terms of tocolytic efficacy or infant outcomes; however, some outcomes were based on only one small trial, so large trials with placebo comparators are recommended. Importantly, rescue tocolysis was employed in all the included trials; because these women received additional treatment the comparison of neonatal outcomes is not appropriate.

## Non-steroidal anti-inflammatories and cyclo-oxygenase inhibitors

Cyclo-oxygenase (COX) inhibitors are a subgroup of the class of non-steroidal anti-inflammatories (NSAIDs). They have a tocolytic effect, inhibiting uterine contractions, and are therefore an option in the treatment of threatened preterm labour. Uterine contractions are the result of an influx of extracellular calcium – COX (and in particular COX type 2) synthesises prostaglandins from arachidonic acid, resulting in the opening of myometrial cell membrane calcium channels; COX inhibitors block this effect.[593] Neither NSAIDs

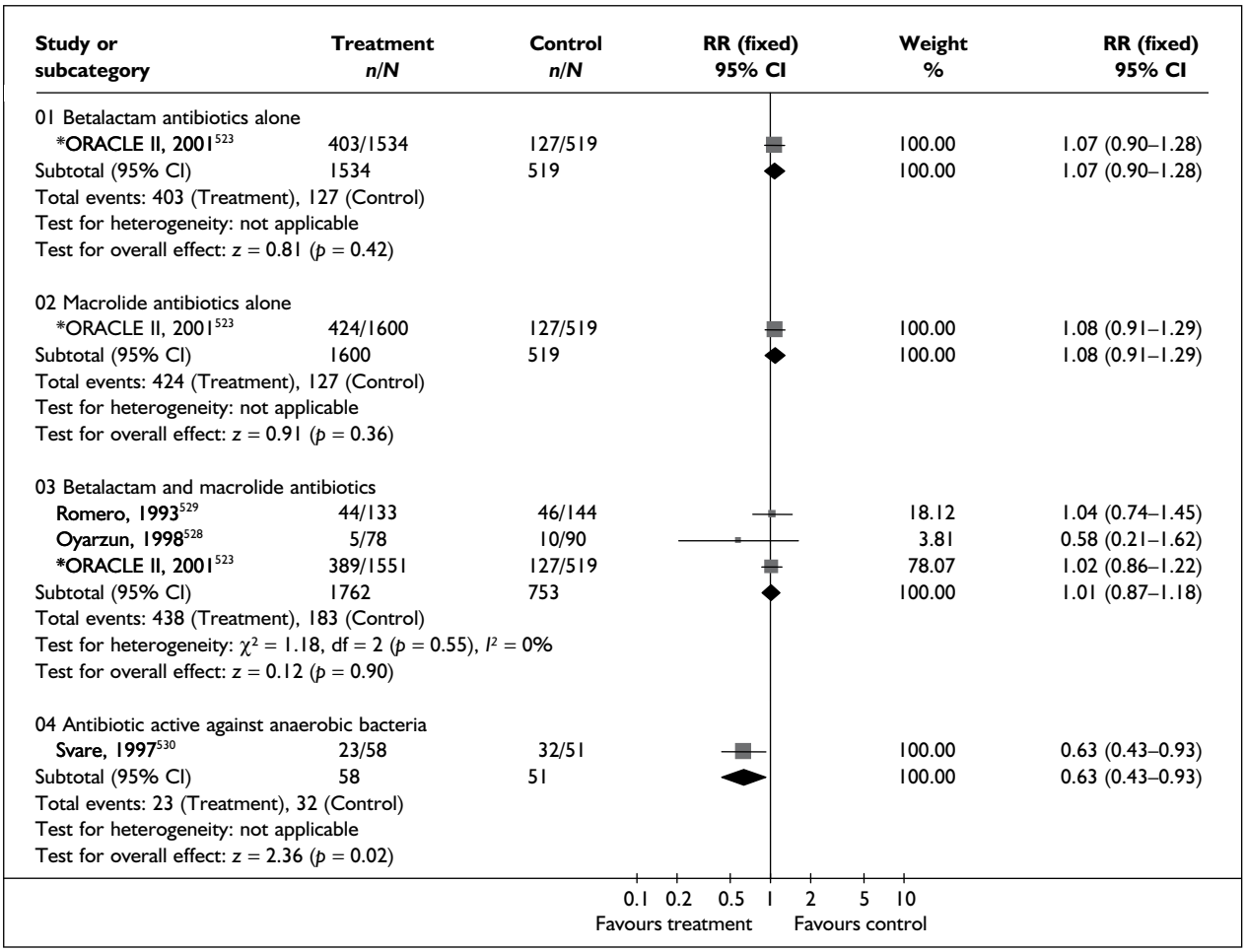


***FIGURE 173*** *Forest plot of the effects of antibiotic therapy subgrouped by type of antibiotic versus placebo/no treatment for the prevention of admission to neonatal unit. a, Multiple gestations included in trial or not excluded from trial.*

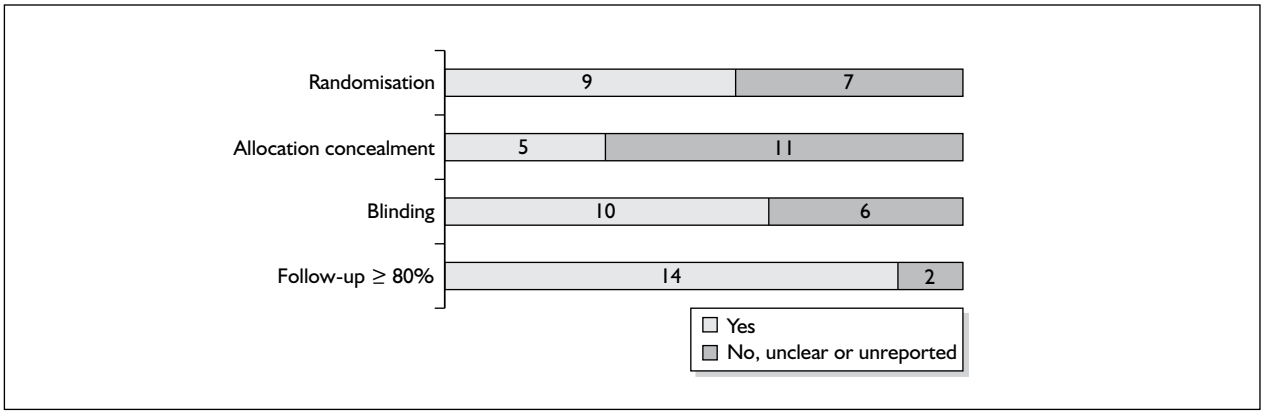


***FIGURE 174*** *Methodological quality of the included trials of betamimetic therapy for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*



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***TABLE 20*** *Effects of antibiotic therapies on other perinatal and maternal outcomes (studies contain singleton and multiple births unless stated otherwise)*

| Outcome (RCT) | RR | 95% CI | Heterogeneity ($I^2$, *p*-value) |
|---|---|---|---|
| ***Fetal death*** | | | |
| Any antibiotic (mixed): (7 studies, $n = 6986$)[121,523,524,526,527,529,530] | 0.72 | 0.42–1.25 | 0% (0.38) |
| Betalactam antibiotics alone: (3 studies, $n = 2227$)[121,526,523] | 0.90 | 0.37–2.21 | 0% (0.44) |
| Macrolide antibiotics alone: (2 studies, $n = 2222$)[523,524] | 0.54 | 0.20–1.48 | NA, 1 study not estimable |
| Betalactam + macrolide: (2 studies, $n = 2347$)[523,529] | 0.73 | 0.28–1.90 | NA, 1 study not estimable |
| ***Neonatal death*** | | | |
| Any antibiotic (singletons): (4 studies, $n = 462$)[524,527,528,530] | 1.81 | 0.51–6.45 | 0% (0.62) |
| Any antibiotic (mixed): (3 studies, $n = 6415$)[121,523,526] | 1.49 | 0.94–2.36 | 0% (0.82) |
| Betalactam antibiotics alone: (3 studies, $n = 2227$)[121,523,526] | 1.32 | 0.61–2.86 | 0% (0.74) |
| Macrolide antibiotics alone: (2 studies, $n = 2222$)[523,524] | 1.68 | 0.77–3.64 | 0% (0.48) |
| Betalactam + macrolide: (2 studies, $n = 2238$)[523,528] | 1.68 | 0.78–3.61 | 0% (0.78) |
| Active against anaerobic bacteria: (3 studies, $n = 294$)[524,527,530] | 1.63 | 0.36–7.39 | 0% (0.35) |
| ***Birthweight <2500 g*** | | | |
| Any antibiotic (singletons): (2 studies, $n = 213$)[524] | 0.75 | 0.56–1.01 | 0% (0.91) |
| Any antibiotic (mixed): (3 studies, $n = 6415$)[121,523,526] | 1.06 | 0.97–1.16 | 12.7% (0.32) |
| Betalactam antibiotics alone: (3 studies, $n = 2227$)[121,523,526] | 1.08 | 0.94–1.24 | 13.4% (0.32) |
| Macrolide antibiotics alone: (2 studies, $n = 2222$)[523,524] | 1.05 | 0.90–1.22 | 0% (0.13) |
| Betalactam + macrolide: (1 study, $n = 2070$)[523] | 1.02 | 0.87–1.20 | NA |
| Active against anaerobic bacteria: (2 studies, $n = 213$)[524,530] | 0.75 | 0.56–1.01 | 0% (0.91) |
| ***Respiratory distress syndrome*** | | | |
| Any antibiotic (singletons): (5 studies, $n = 689$)[527–531] | 1.17 | 0.78–1.76 | 0% (0.49) |
| Any antibiotic (mixed): (3 studies, $n = 2227$)[121,523,526] | 0.96 | 0.81–1.14 | 0% (0.95) |
| Betalactam antibiotics alone: (3 studies, $n = 2227$)[121,523,526] | 0.94 | 0.71–1.24 | 0% (0.95) |
| Macrolide antibiotics alone: (1 study, $n = 2119$)[523] | 0.94 | 0.68–1.29 | NA |
| Betalactam + macrolide: (4 studies, $n = 2569$)[523,528,529] | 1.12 | 0.87–1.46 | 0% (0.69) |
| Active against anaerobic bacteria: (2 studies, $n = 190$)[531,527,530] | 0.49 | 0.17–1.40 | 0% (0.80) |
| ***Mechanical ventilation*** | | | |
| Any antibiotic (mixed): (1 study, $n = 6241$)[523] | 1.02 | 0.84–1.24 | NA |
| Betalactam antibiotics alone: (1 study, $n = 2053$)[523] | 1.01 | 0.71–1.42 | NA |
| Macrolide antibiotics alone: (1 study, $n = 2119$)[523] | 1.02 | 0.73–1.44 | NA |
| Betalactam + macrolide: (1 study, $n = 2070$)[523] | 1.05 | 0.75–1.48 | NA |
| ***Chronic lung disease*** | | | |
| Any antibiotic (mixed): (1 study, $n = 6241$)[523] | 1.17 | 0.78–1.76 | NA |
| Betalactam antibiotics alone: (1 study, $n = 2053$)[523] | 0.81 | 0.39–1.69 | NA |
| Macrolide antibiotics alone: (1 study, $n = 2119$)[523] | 1.17 | 0.58–2.34 | NA |
| Betalactam + macrolide: (1 study, $n = 2070$)[523] | 1.41 | 0.71–2.78 | NA |
| ***Neonatal sepsis*** | | | |
| Any antibiotic (singletons): (5 studies, $n = 736$)[524,527–530] | 0.65 | 0.41–1.02 | 11.7% (0.34) |
| Any antibiotic (mixed): (4 studies, $n = 2227$)[121,522,523,526] | 1.05 | 0.71–1.54 | 0% (0.92) |

***TABLE 20*** *Effects of antibiotic therapies on other perinatal and maternal outcomes (studies contain singleton and multiple births unless stated otherwise)*

| Outcome (RCT) | RR | 95% CI | Heterogeneity ($I^2$, *p*-value) |
|---|---|---|---|
| Betalactam antibiotics alone: (4 studies, *n* = 2366)[121,522,523,526] | 1.01 | 0.54–1.90 | 0% (0.91) |
| Macrolide antibiotics alone: (2 studies, *n* = 2222)[523,524] | 0.97 | 0.51–1.83 | 0% (0.35) |
| Betalactam + macrolide: (3 studies, *n* = 2513)[523,528,529] | 0.89 | 0.56–1.42 | 45% (0.16) |
| Active against anaerobic bacteria: (3 studies, *n* = 293)[527,529,530] | 0.56 | 0.29–1.11 | 0% (0.74) |
| ***Necrotising enterocolitis*** | | | |
| Any antibiotic (singletons): (3 studies, *n* = 465)[527,529,530] | 0.33 | 0.11–1.00 | 0% (0.40) |
| Any antibiotic (mixed): (3 studies, *n* = 2227)[121,523,526] | 148 | 0.82–2.67 | 21.7% (0.27) |
| Betalactam antibiotics alone: (3 studies, *n* = 2227)[121,523,526] | 1.31 | 0.52–3.32 | 0% (0.65) |
| Macrolide antibiotics alone: (1 study, *n* = 2119)[523] | 1.30 | 0.44–3.86 | NA |
| Betalactam + macrolide: (2 studies, *n* = 2345)[523,529] | 1.36 | 0.60–3.11 | 29.8% (0.23) |
| Active against anaerobic bacteria: (2 studies, *n* = 190)[527,530] | 0.13 | 0.02–1.01 | 0% (0.55) |
| ***Neonatal positive blood cultures*** | | | |
| Any antibiotic (singletons): (1 study, *n* = 168)[528] | 0.58 | 0.05–6.24 | NA |
| Any antibiotic (mixed): (2 studies, *n* = 6358)[522,523] | 1.03 | 0.69–1.52 | 0% (0.99) |
| Betalactam antibiotics alone: (2 studies, *n* = 2170)[522,523] | 0.96 | 0.49–1.87 | 0% (0.95) |
| Macrolide antibiotics alone: (1 study, *n* = 2119)[523] | 1.10 | 0.55–2.22 | NA |
| Betalactam + macrolide: (2 studies, *n* = 2238)[523,528] | 1.08 | 0.55–2.10 | 0% (0.59) |
| ***Intraventricular haemorrhage*** | | | |
| Any antibiotic (singletons): (2 studies, *n* = 384)[523,526] | 0.32 | 0.07–1.49 | 7.2% (0.89) |
| Any antibiotic (mixed): (2 studies, *n* = 6333)[529,530] | 0.84 | 0.52–1.35 | 0% (0.55) |
| Betalactam antibiotics alone: (2 studies, *n* = 2145)[523,527] | 0.84 | 0.38–1.87 | 0% (0.89) |
| Macrolide antibiotics alone: (1 study, *n* = 2119)[523] | 0.83 | 0.35–1.99 | NA |
| Betalactam + macrolide: (2 studies, *n* = 2345)[523,529] | 0.97 | 0.43–2.19 | 0% (0.92) |
| Active against anaerobic bacteria: (1 study, *n* = 109)[530] | 0.18 | 0.02–1.46 | NA |
| ***Major cerebral abnormality*** | | | |
| Any antibiotic (mixed): (1 study, *n* = 6241)[523] | 1.00 | 0.66–1.51 | NA |
| Betalactam antibiotics alone: (1 study, *n* = 2053)[523] | 0.91 | 0.45–1.87 | NA |
| Macrolide antibiotics alone: (1 study, *n* = 2119)[523] | 0.84 | 0.41–1.74 | NA |
| Betalactam + macrolide: (1 study, *n* = 2070)[523] | 1.14 | 0.57–2.29 | NA |
| ***Maternal adverse drug reaction*** | | | |
| Any antibiotic (singletons): (4 studies, *n* = 544)[524,529–531] | 1.30 | 0.90–1.87 | 0% (0.43) |
| Any antibiotic (mixed): (1 study, *n* = 82)[121] | 3.15 | 0.13–75.05 | NA |
| Betalactam antibiotics alone: (1 study, *n* = 82)[121] | 3.15 | 0.13–75.05 | NA |
| Macrolide antibiotics alone: (1 study, *n* = 103)[524] | 0.88 | 0.49–1.59 | NA |
| Betalactam + macrolide: (2 studies, *n* = 331)[529,531] | 1.49 | 0.93–2.40 | 0% (0.97) |
| Active against anaerobic bacteria: (2 studies, *n* = 213)[524,530] | 1.04 | 0.59–1.83 | 32.6% (0.22) |

*continued*



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***TABLE 20*** *Effects of antibiotic therapies on other perinatal and maternal outcomes (studies contain singleton and multiple births unless stated otherwise) (continued)*

| Outcome (RCT) | RR | 95% CI | Heterogeneity ($I^2$, *p*-value) |
|---|---|---|---|
| ***Maternal infection*** | | | |
| Any antibiotic (singletons): (6 studies, $n = 798$)[524,527–531] | 0.53 | 0.32–0.89 | 0% (0.45) |
| Any antibiotic (mixed): (3 studies, $n = 6444$)[522,523,526] | 0.77 | 0.66–0.91 | 7.7% (0.33) |
| Betalactam antibiotics alone: (3 studies, $n = 2227$)[522,523,526] | 0.74 | 0.56–0.98 | 6.2% (0.34) |
| Macrolide antibiotics alone: (2 studies, $n = 2222$)[523,524] | 0.81 | 0.62–1.07 | 0% (0.40) |
| Betalactam + macrolide: (4 studies, $n = 2563$)[523,528,529,531] | 0.75 | 0.59–0.95 | 0% (0.53) |
| Active against anaerobic bacteria: (3 studies, $n = 294$)[524,527,530] | 0.76 | 0.25–2.34 | 37.8% (0.20) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

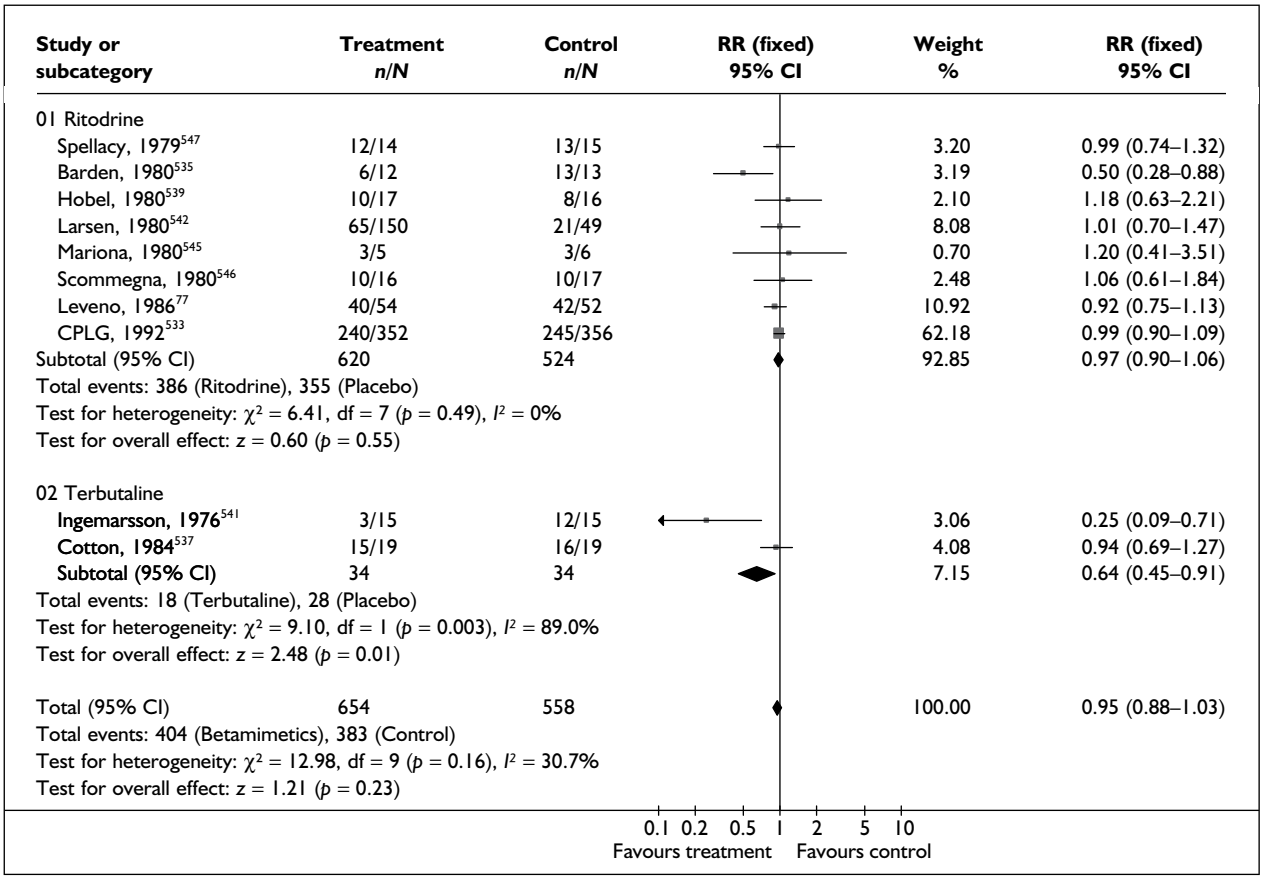


***FIGURE 175*** *Forest plot of the effects of betamimetics versus placebo for the prevention of spontaneous preterm birth before 37 weeks gestation.*

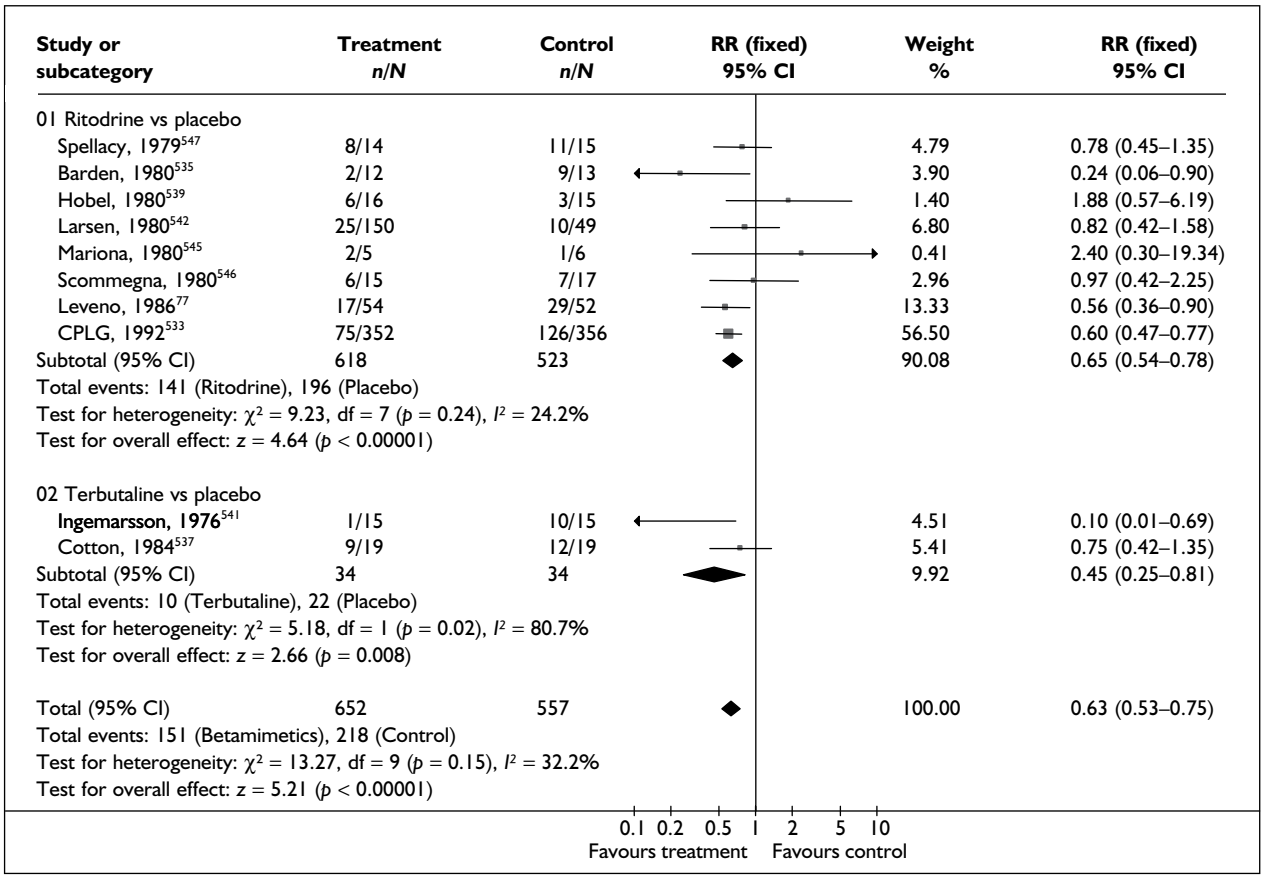


***FIGURE 176*** *Forest plot of the effects of betamimetics versus placebo or an alternative betamimetic for the prevention of spontaneous preterm birth within 48 hours of treatment.*

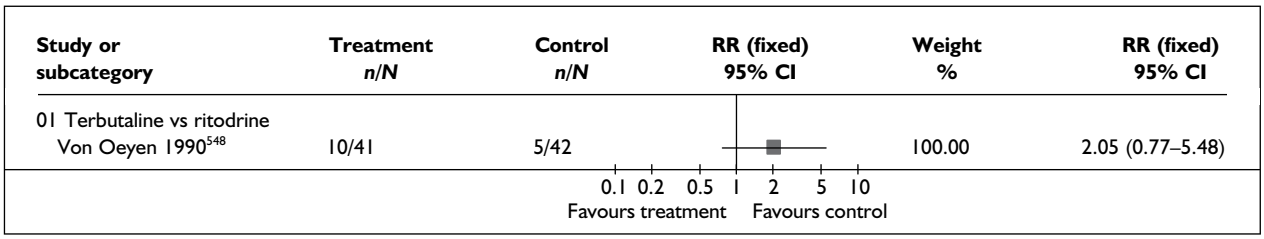


***FIGURE 177*** *Forest plot of the effects of betamimetics versus an alternative betamimetic for the prevention of spontaneous preterm birth within 48 hours of treatment.*



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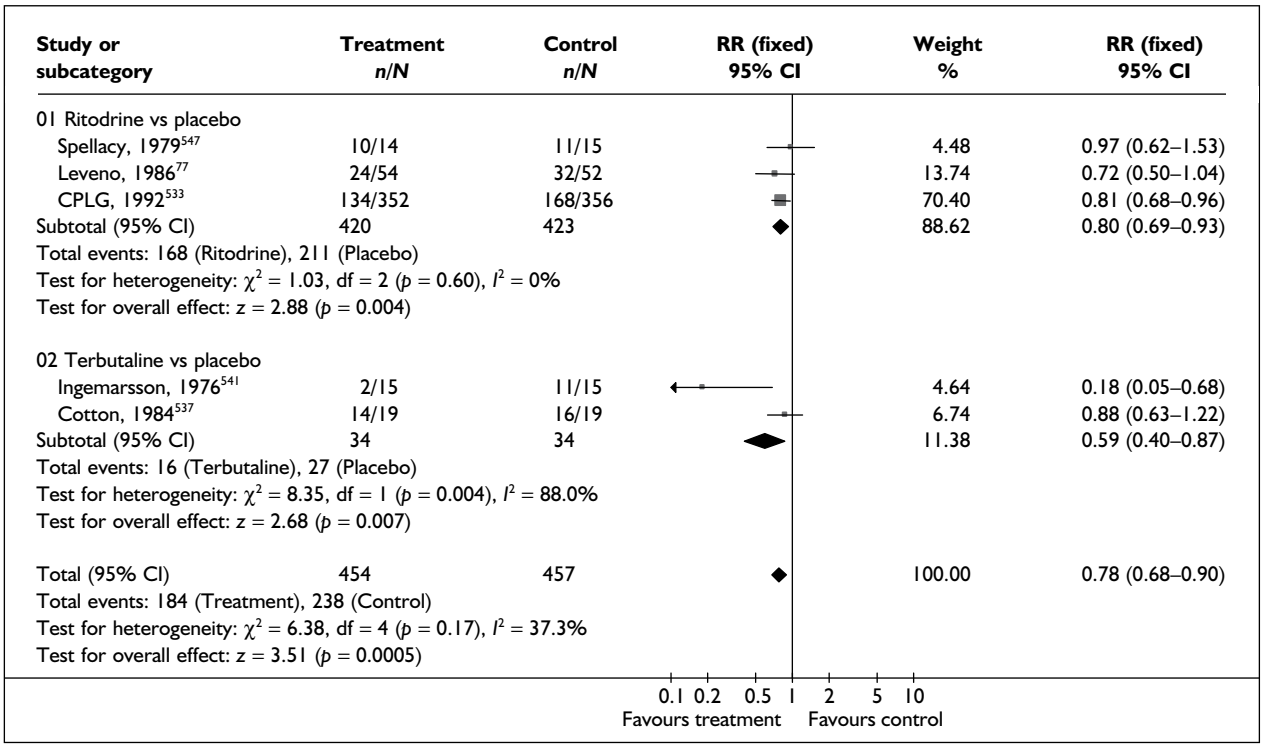


***FIGURE 178*** *Forest plot of the effects of betamimetics versus placebo or an alternative betamimetic for the prevention of spontaneous preterm birth within 7 days of treatment.*

nor COX inhibitors specifically are currently recommended for tocolytic use by the RCOG because of concerns over their fetal adverse events profile. This assessment included the use of NSAIDs for the prevention as well as treatment of threatened preterm labour to prevent spontaneous preterm birth. In addition to acute treatment, chronic maintenance therapy is also included in the review.

The review of NSAIDs[594] for treating threatened preterm labour included 13 RCTs.[595–607] A further three RCTs were added when the searches were updated and expanded to include all NSAIDs.[608–610] The quality of the studies included in the review and of the additional studies was generally high (*Figure 215*). Further details of the review can be found in Appendix 6, *Table 134*. The studies included in the review examined NSAIDs and COX inhibitors for treating threatened preterm labour.[595–607] Data were available on the following comparisons:

1. COX inhibitors versus placebo (*Figures 216, 218, 219, 222, 223, 226, 228, 231, 234*).
2. COX inhibitors versus any other tocolytic (*Figures 217, 220, 224, 229, 232*).
3. Non-selective COX inhibitors versus any COX-2 inhibitors (*Figures 221, 225, 233*).

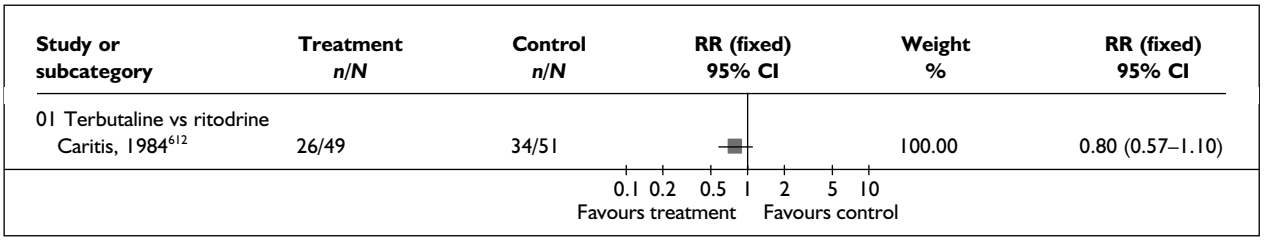


***FIGURE 179*** *Forest plot of the effects of betamimetics versus an alternative betamimetic for the prevention of spontaneous preterm birth within 7 days of treatment.*

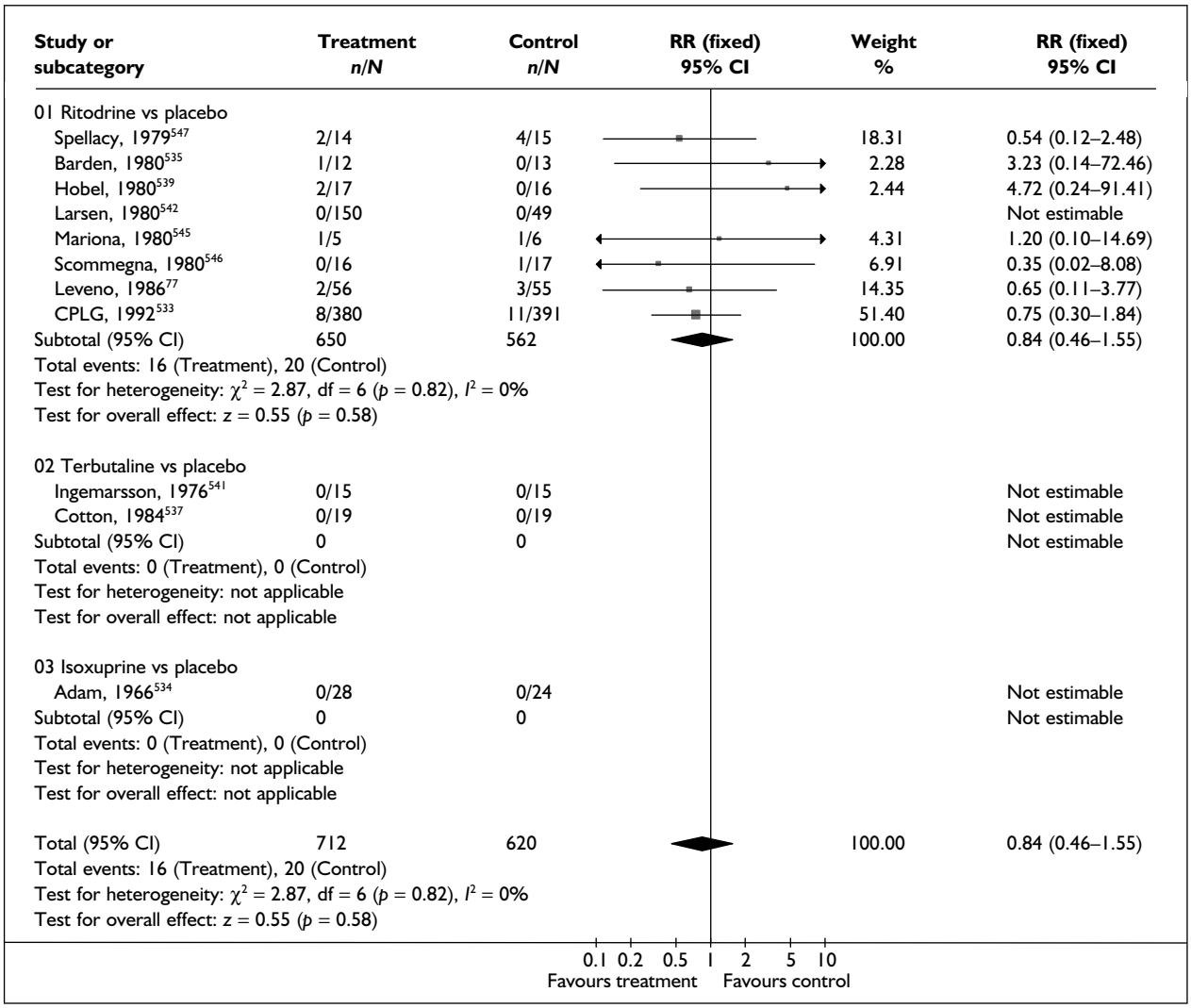


***FIGURE 180*** *Forest plot of the effects of betamimetics versus placebo on perinatal mortality.*

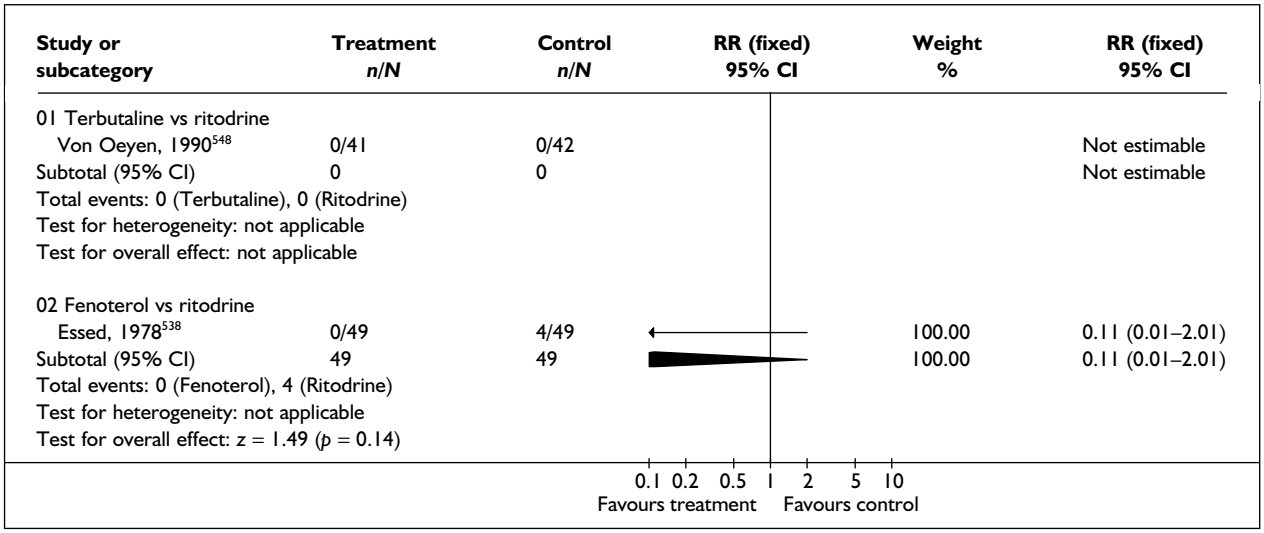


***FIGURE 181*** *Forest plot of the effects of betamimetics versus an alternative betamimetic on perinatal mortality.*



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***TABLE 21*** *Effect of betamimetic therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Preterm birth <28 weeks gestation*** | | | |
| Terbutaline vs ritodrine: (1 study, $n = 100$)[535] | 2.08 | 0.55–7.87 | NA |
| ***Neonatal death*** | | | |
| All betamimetics vs placebo: (5 studies, $n = 1144$)[532,536,537,541,542] | 1 | 0.48–2.09 | 43.2% (0.13) |
| Terbutaline vs ritodrine: (1 study, $n = 83$)[535] | 1.27 | 0.42–3.91 | NA |
| Fenoterol vs ritodrine: (1 study, $n = 98$)[533] | 0.13 | 0.02–0.96 | NA |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 222$)[539] | 0.11 | 0.01–2.04 | NA |
| ***Respiratory distress syndrome*** | | | |
| All betamimetics vs placebo: (8 studies, $n = 1239$)[533,535,537,539542,543,546,547] | 0.87 | 0.71–1.08 | 22.0% (0.25) |
| Terbutaline vs ritodrine: (1 study, $n = 101$)[535] | 1.99 | 0.93–4.27 | NA |
| Fenoterol vs ritodrine: (1 study, $n = 98$)[533] | 2 | 0.38–10.42 | NA |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 222$)[539] | 0.71 | 0.35–1.41 | NA |
| ***Periventricular haemorrhage (grades 3 and 4)*** | | | |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 222$)[539] | 0.14 | 0.01–2.73 | NA |
| ***Cerebral palsy*** | | | |
| All betamimetics vs placebo: (1 study, $n = 246$ [537] | 0.19 | 0.02–1.63 | NA |
| ***Treatment cessation due to side effects*** | | | |
| All betamimetics vs placebo: (4 studies, $n = 1051$)[536,537,541,542] | 11.38 | 5.21–24.86 | 0% (0.48) |
| Terbutaline vs ritodrine: (1 study, $n = 100$)[535] | 0.83 | 0.24–2.92 | NA |
| Hexoprenaline vs ritodrine: (1 study, $n = 466$)[543] | 0.28 | 0.08–0.93 | NA |
| Any maternal treatment side effects | | | |
| Terbutaline vs ritodrine: (1 study, $n = 183$)[548] | 0.95 | 0.84–1.07 | NA |
| Hexoprenaline vs ritodrine: (1 study, $n = 466$)[543] | 0.83 | 0.76–0.91 | NA |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 203$)[539] | 0.69 | 0.43–1.11 | NA |
| ***Palpitations*** | | | |
| All betamimetics vs placebo: (4 studies, $n = 1042$)[537,541,542,547] | 10.11 | 6.56–15.58 | 0% (0.99) |
| Terbutaline vs ritodrine: (1 study, $n = 83$)[548] | 1.18 | 0.78–1.79 | NA |
| Hexoprenaline vs ritodrine: (1 study, $n = 466$)[543] | 0.75 | 0.60–0.94 | NA |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 203$)[539] | 0.5 | 0.23–1.13 | NA |
| ***Tachycardia*** | | | |
| All betamimetics vs placebo: (1 study, $n = 199$)[541] | 4.08 | 1.55–10.73 | NA |
| Terbutaline vs ritodrine: (1 study, $n = 100$)[535] | 0.66 | 0.43–1.00 | NA |
| Fenoterol vs ritodrine: (1 study, $n = 96$)[533] | 0.71 | 0.35–1.45 | NA |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 203$)[539] | 0.88 | 0.33–2.35 | NA |

***TABLE 21*** *Effect of betamimetic therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Cardiac arrhythmia*** | | | |
| All betamimetics vs placebo: (1 study, $n = 708$)[537] | 3.54 | 0.74–16.92 | NA |
| Terbutaline vs ritodrine: (1 study, $n = 100$)[535] | 0.35 | 0.04–3.22 | NA |
| ***Pulmonary oedema*** | | | |
| [a]All betamimetics vs placebo: (3 studies, $n = 852$)[533,537,543] | 3.03 | 0.12–74.23 | NA |
| ***Myocardial ischemia*** | | | |
| All betamimetics vs placebo: (1 study, $n = 106$)[542] | 12.53 | 0.72–21.91 | NA |
| ***Chest pain*** | | | |
| All betamimetics vs placebo: (2 studies, $n = 814$)[537,542] | 11.29 | 3.81–33.46 | 0% (0.52) |
| Terbutaline vs ritodrine: (2 studies, $n = 183$)[535.548] | 1.11 | 0.55–2.25 | 51.9% (0.15) |
| ***Dyspnoea/Shortness of breath*** | | | |
| All betamimetics vs placebo: (2 studies, $n = 814$)[537,542] | 3.86 | 2.21–6.77 | 0% (0.88) |
| Terbutaline vs ritodrine: (2 studies, $n = 183$)[535,548] | 0.83 | 0.41–1.67 | 0% (0.76) |
| ***Tremor*** | | | |
| All betamimetics vs placebo: (1 study, $n = 708$)[537] | 10.74 | 6.20–18.59 | NA |
| ***Hypotension*** | | | |
| All betamimetics vs placebo: (2 studies, $n = 136$)[540,542] | 1.77 | 0.39–8.06 | 49.1% (0.16) |
| Terbutaline vs ritodrine: (2 studies, $n = 183$)[535,548] | 1 | 0.67–1.49 | 74.5% (0.05) |
| Hexoprenaline vs ritodrine: (1 study, $n = 466$)[543] | 0.77 | 0.61–0.96 | NA |
| ***Hyperglycaemia*** | | | |
| All betamimetics vs placebo: (1 study, $n = 708$)[537] | 2.9 | 2.05–4.09 | NA |
| Terbutaline vs ritodrine: (1 study, $n = 100$)[535] | 1.78 | 1.05–3.03 | NA |
| Fenoterol vs ritodrine: (1 study, $n = 98$)[533] | 1.33 | 0.31–5.65 | NA |
| ***Hypokalaemia*** | | | |
| All betamimetics vs placebo: (1 study, $n = 708$)[537] | 6.07 | 4.00–9.20 | NA |
| ***Nausea/vomiting*** | | | |
| All betamimetics vs placebo: (3 studies, $n = 932$)[537,542,547] | 1.76 | 1.29–2.42 | 0% (0.93) |
| Terbutaline vs ritodrine: (1 study, $n = 100$)[535] | 1.5 | 0.71–3.20 | NA |
| Hexoprenaline vs ritodrine: (1 study, $n = 466$)[543] | 0.63 | 0.45–0.89 | NA |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 203$)[539] | 1.21 | 0.38–3.84 | NA |
| ***Headaches*** | | | |
| All betamimetics vs placebo: (3 studies, $n = 936$)[533,542,547] | 4.07 | 2.60–6.35 | 6.35 |
| Terbutaline vs ritodrine: (1 study, $n = 83$)[548] | 0.48 | 0.23–0.99 | NA |
| Ritodrine loading dose vs incremental dose: (1 study, $n = 203$)[539] | 1.01 | 0.06–15.93 | NA |

*continued*



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***TABLE 21*** *Effect of betamimetic therapy on other perinatal and maternal outcomes (continued)*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Fetal hypoglycaemia*** | | | |
| All betamimetics vs placebo: (3 studies, n = 857)536,537,542 | 1.89 | 0.35–10.04 | NA |
| ***Fetal tachycardia*** | | | |
| All betamimetics vs placebo: (1 study, n = 30)540 | 2.4 | 1.12–5.13 | NA |
| ***Sepsis/infection*** | | | |
| All betamimetics vs placebo: (2 studies, n = 809)536,537 | 2.72 | 0.19–39.63 | 73.9% (0.05) |
| Ritodrine loading dose vs incremental dose: (1 study, n = 222)539 | 0.71 | 0.23–2.18 | NA |
| ***Necrotising enterocolitis*** | | | |
| All betamimetics vs placebo: (2 studies, n = 149)536,542 | 0.42 | 0.06–2.78 | 0% (0.42) |
| Terbutaline vs ritodrine: (1 study, n = 101)535 | 0.53 | 0.05–5.67 | NA |
| ***Increase in fetal heart rate*** | | | |
| Hexoprenaline vs ritodrine: (1 study, n = 466) 543 | 0.74 | 0.56–0.98 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.
a Only one study estimable.

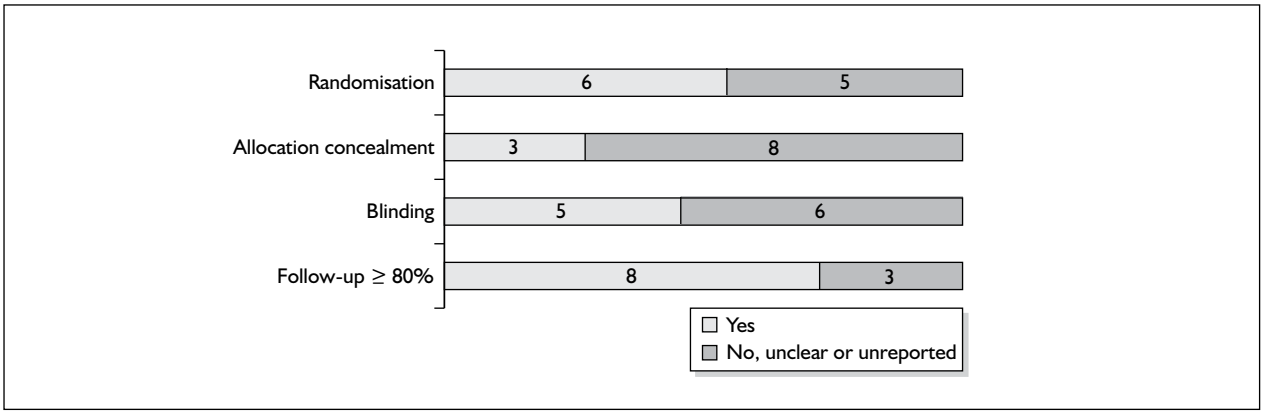


***FIGURE 182*** *Methodological quality of the included trials of oral betamimetics for maintenance therapy for the prevention of spontaneous preterm birth following acute tocolytic therapy in symptomatic women with threatened preterm labour.*

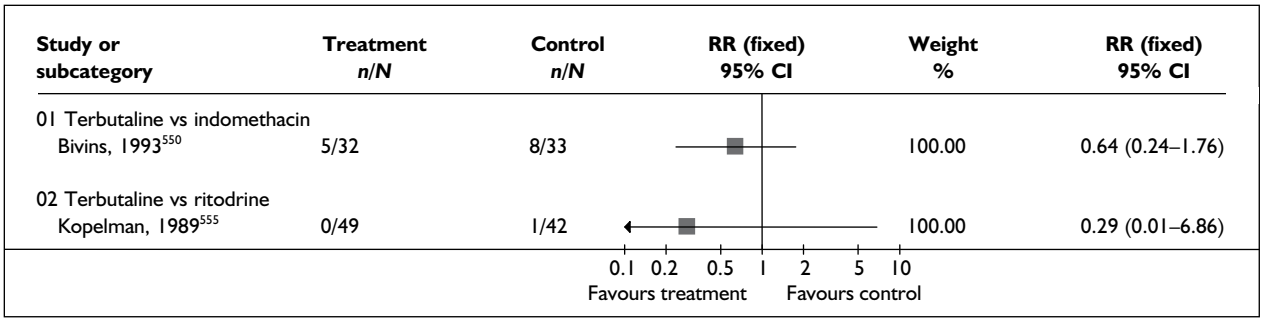


***FIGURE 183*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus other tocolytic treatment for the prevention of spontaneous preterm birth before 34 weeks' gestation.*

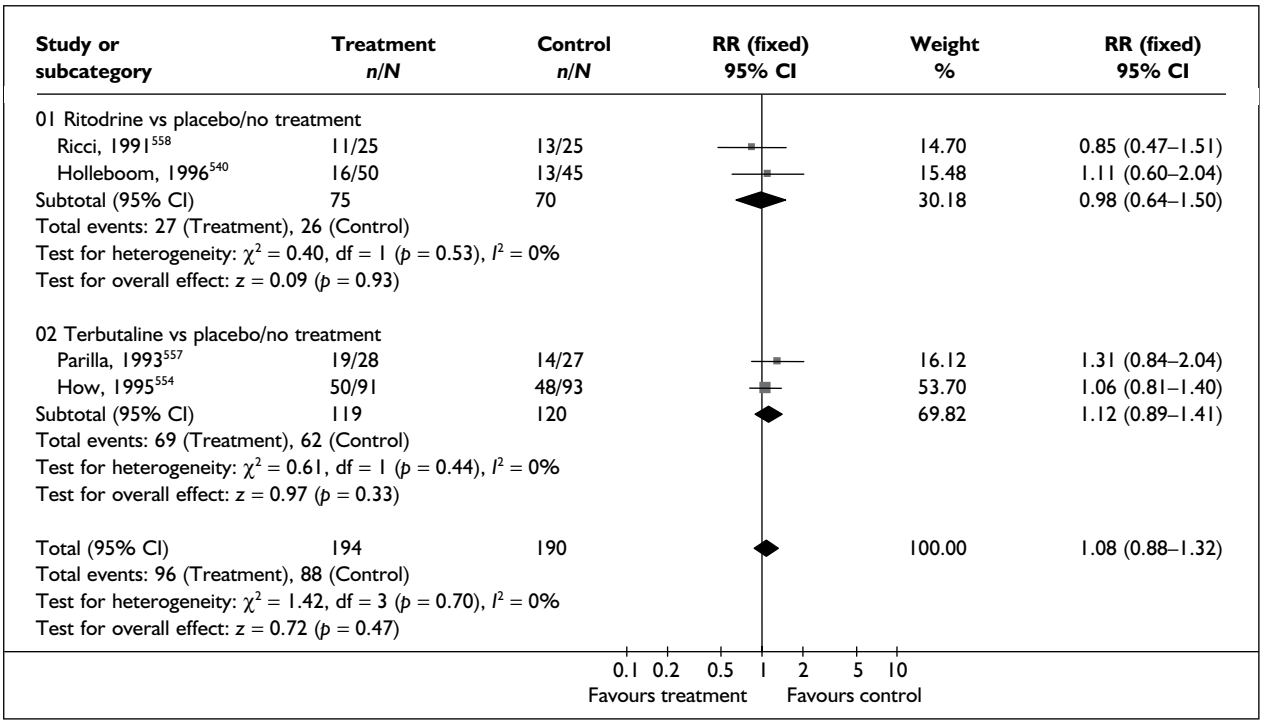


***FIGURE 184*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus placebo/no treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

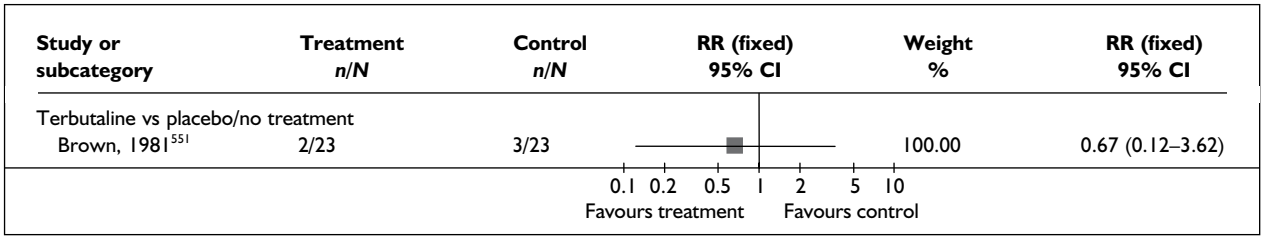


***FIGURE 185*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus placebo/no treatment on spontaneous preterm birth within 24 hours of treatment.*

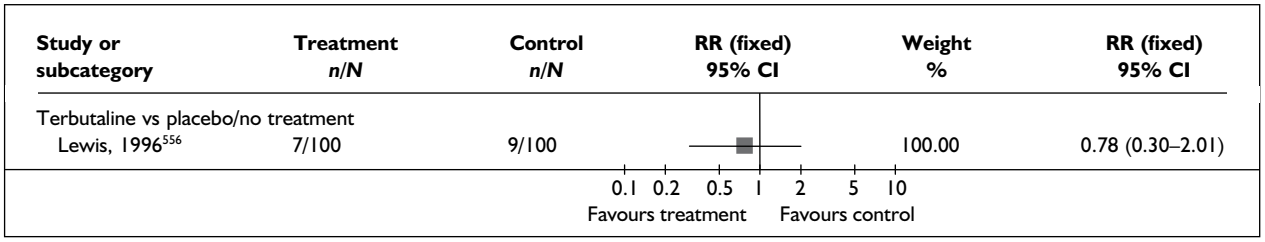


***FIGURE 186*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus placebo/no treatment on spontaneous preterm birth within 48 hours of treatment.*



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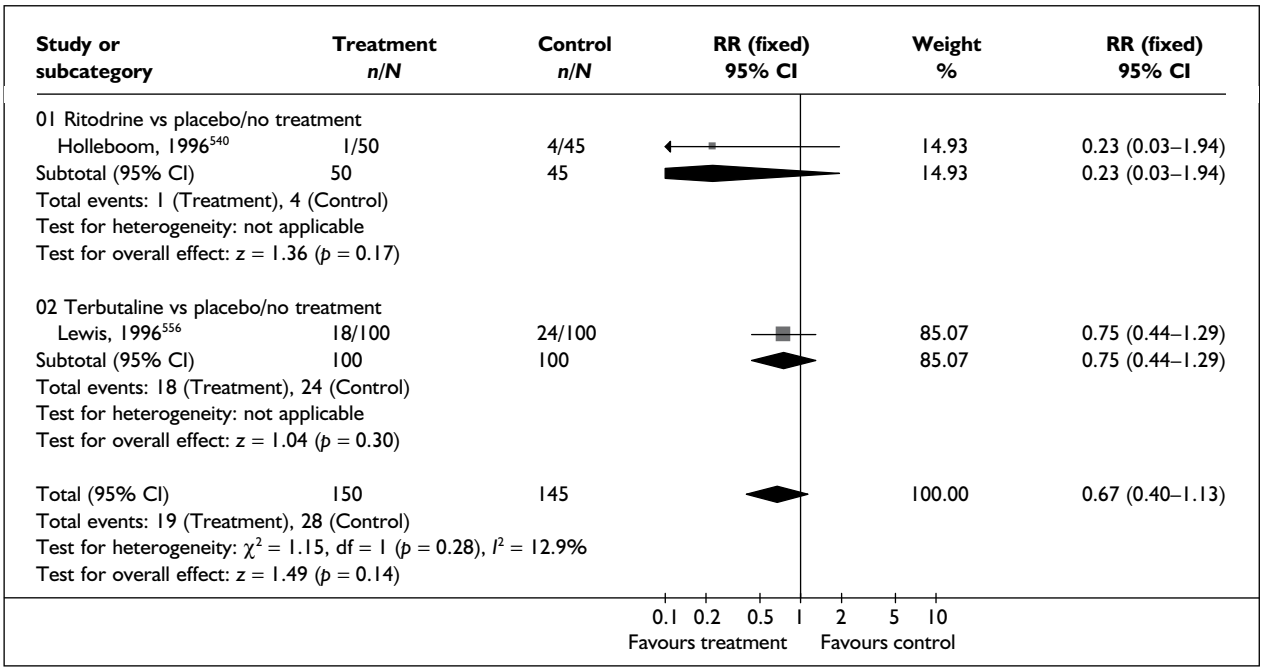


***FIGURE 187*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus placebo/no treatment on spontaneous preterm birth within 7 days of treatment.*

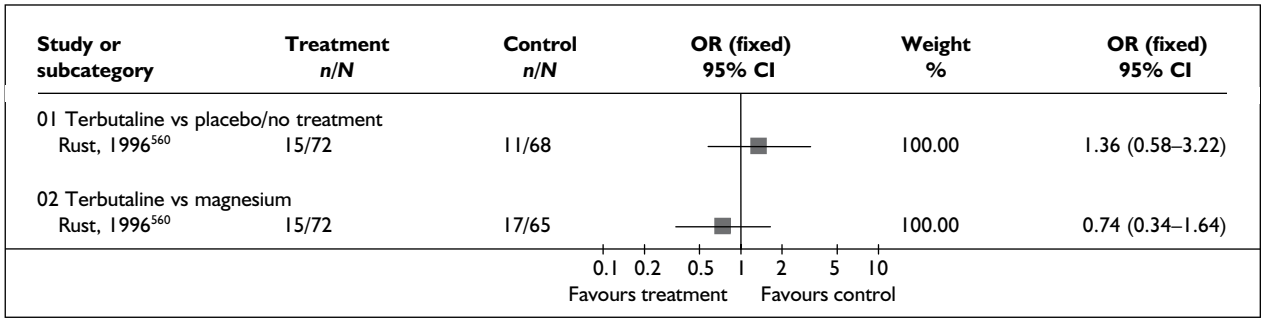


***FIGURE 188*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus placebo/no treatment or another tocolytic agent on admission to neonatal intensive care unit.*

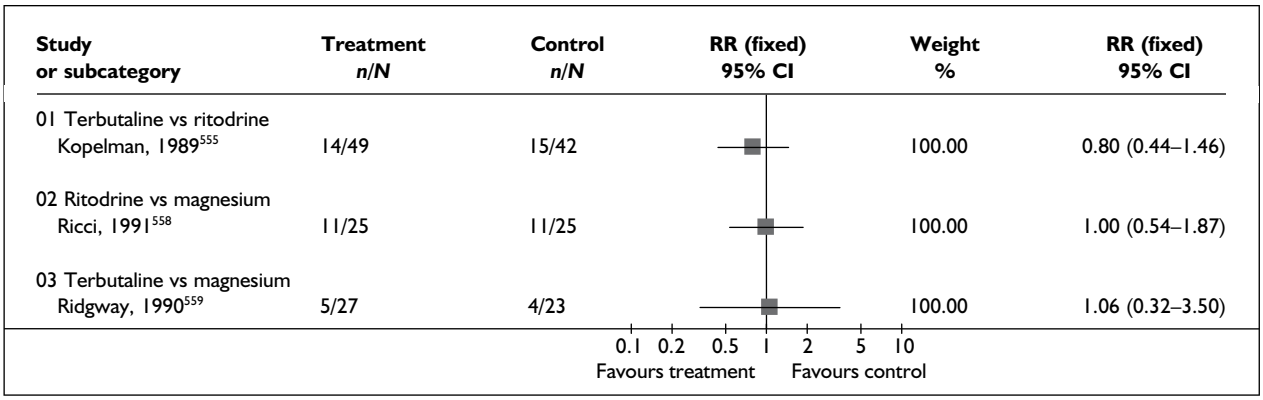


***FIGURE 189*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus other tocolytic treatment for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

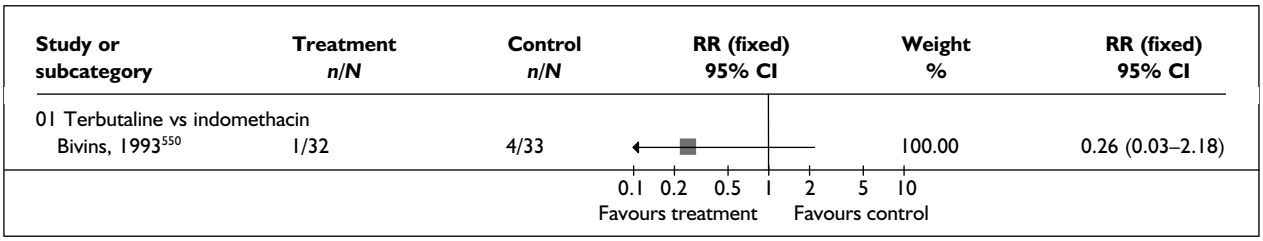


***FIGURE 190*** *Forest plot of the effects of oral betamimetics for maintenance therapy versus other tocolytic treatment on spontaneous preterm birth within 7 days of treatment.*

***TABLE 22*** *Effect of maintenance betamimetic therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Perinatal mortality (before discharge among live births)*** | | | |
| Betamimetic vs placebo/no treatment: (6 studies, $n = 681$)[551–554,556,558] | 2.41 | 0.86–6.74 | 0% (0.97) |
| Betamimetic vs magnesium: (1 study, $n = 50$)[558] | 0.2 | 0.01–3.97 | NA |
| ***Respiratory distress syndrome*** | | | |
| Betamimetic vs placebo/no treatment: (5 studies, $n = 577$) [551,552,554,556,558] | 1.1 | 0.61–1.98 | 17.5% (0.30) |
| Betamimetic vs magnesium: (1 study, $n = 50$) [558] | 2 | 0.19–20.67 | NA |
| ***Necrotising enterocolitis*** | | | |
| Betamimetic vs placebo/no treatment: (2 studies, $n = 416$)[554,556] | 0.98 | 0.22–4.28 | 0% (0.44) |
| ***Intraventricular haemorrhage*** | | | |
| Betamimetic vs placebo/no treatment: (3 studies, $n = 466$)[554,556,558] | 0.97 | 0.27–3.58 | 0% (0.44) |
| Betamimetic vs magnesium: (1 study, $n = 50$[558] | 1 | 0.07–15.12 | NA |
| ***Neonatal jaundice*** | | | |
| Betamimetic vs placebo/no treatment: (1 study, $n = 50$ [558] | 1.67 | 0.71–3.89 | NA |
| Terbutaline vs ritodrine: (1 study, $n = 91$ [555] | 1.45 | 0.84–2.51 | NA |
| Betamimetic vs magnesium: (1 study, $n = 50$)[558] | 0.91 | 0.47–1.75 | NA |
| ***Mechanical ventilation*** | | | |
| Terbutaline vs indomethacin: (1 study, $n = 65$)[550] | 0.34 | 0.01–8.13 | NA |
| ***Length of neonatal intensive care stay (days)*** | | | |
| Terbutaline vs indomethacin: (1 study, $n = 65$)[550] | WMD –1.17 | –2.93–0.59 | NA |
| ***Treatment cessation due to side effects*** | | | |
| Betamimetic vs placebo/no treatment: (1 study, $n = 95$)[553] | 2.71 | 0.11–64.79 | NA |
| Terbutaline vs indomethacin: (1 study, $n = 65$)[550] | 3.09 | 0.13–73.19 | NA |
| Betamimetic vs magnesium: (2 studies, $n = 100$)[558,559] | 0.9 | 0.24–3.46 | 0% (0.52) |
| ***Palpitations*** | | | |
| Betamimetic vs placebo/no treatment: (1 study, $n = 140$) [560] | 5.67 | 1.32–24.40 | NA |

*continued*



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***TABLE 22*** *Effect of maintenance betamimetic therapy on other perinatal and maternal outcomes (continued)*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Tachycardia*** | | | |
| Betamimetic vs placebo/no treatment: (2 studies, *n* = 101)[551,552] | 1.55 | 1.02–2.37 | 0% (0.87) |
| Terbutaline vs ritodrine: (1 study, *n* = 91)[555] | 0.57 | 0.22–1.47 | NA |
| Betamimetic vs magnesium: (3 studies, *n* = 237)[558,559,560] | 5.61 | 2.41–13.04 | 0% (0.62) |
| ***Tachypnoea*** | | | |
| Betamimetic vs placebo/no treatment: (1 studies, *n* = 140) [560] | 2.83 | 0.59–13.56 | NA |
| Terbutaline vs ritodrine: (1 study, *n* = 91)[555] | 2.57 | 0.55–12.07 | NA |
| Betamimetic vs magnesium: (1 study, *n* = 137)[560] | 1.35 | 0.40–4.59 | NA |
| ***Hypotension*** | | | |
| Betamimetic vs placebo/no treatment: (1 study, *n* = 46) [552] | 1.8 | 1.08–3.01 | NA |
| ***Nausea*** | | | |
| Betamimetic vs placebo/no treatment: (2 studies, *n* = 186)[552,560] | 0.95 | 0.43–2.13 | 31.5% (0.23) |
| Betamimetic vs magnesium: (3 studies, *n* = 237 [558,559,560] | 1.07 | 0.57–1.98 | 0% (0.75) |
| ***Vomiting*** | | | |
| Betamimetic vs placebo/no treatment: (2 studies, *n* = 235)[553,560] | 1.28 | 0.44–3.70 | 0% (0.61) |
| Terbutaline vs ritodrine: (1 study, *n* = 91)[555] | 0.57 | 0.17–1.89 | NA |
| Betamimetic vs magnesium: (2 studies, *n* = 187)[559,560] | 0.88 | 0.39–1.98 | 4.7% (0.31) |
| ***Headaches*** | | | |
| Betamimetic vs placebo/no treatment: (1 study, *n* = 95)[554] | 2.71 | 0.11–64.79 | NA |
| ***Maternal readmission to hospital*** | | | |
| Betamimetic vs placebo/no treatment: (4 studies, *n* = 335)[552,554,557,558] | 1.11 | 0.76–1.62 | 35.8% (0.20) |
| Terbutaline vs indomethacin: (1 study, *n* = 65)[551] | 0.6 | 0.34–1.05 | NA |
| Terbutaline vs ritodrine: (1 study, *n* = 91)[555] | 1.71 | 0.56–5.29 | NA |
| Betamimetic vs magnesium: (1 study, *n* = 50)[558] | 1.09 | 0.60–1.99 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

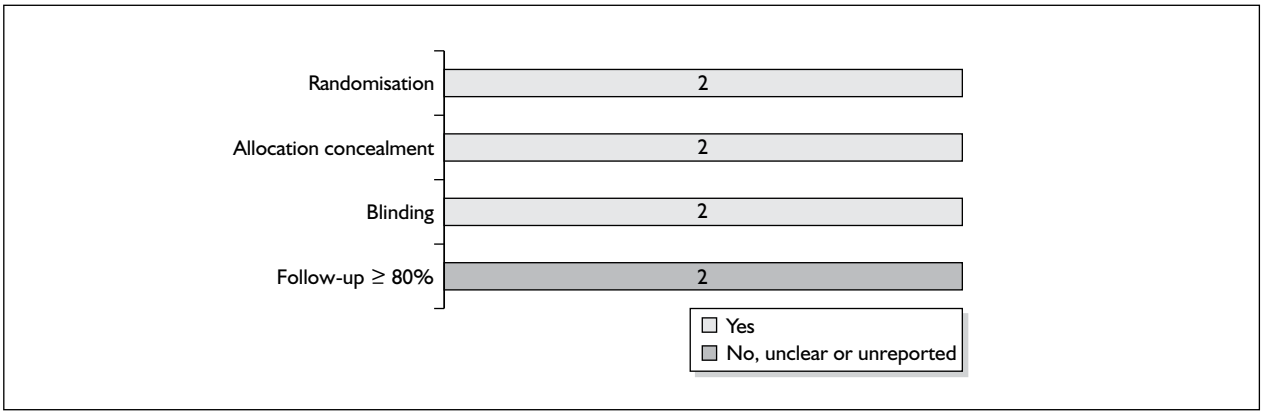


***FIGURE 191*** *Methodological quality of the included trials of terbutaline pump maintenance therapy for the prevention of spontaneous preterm birth following acute tocolytic therapy in symptomatic women with threatened preterm labour.*

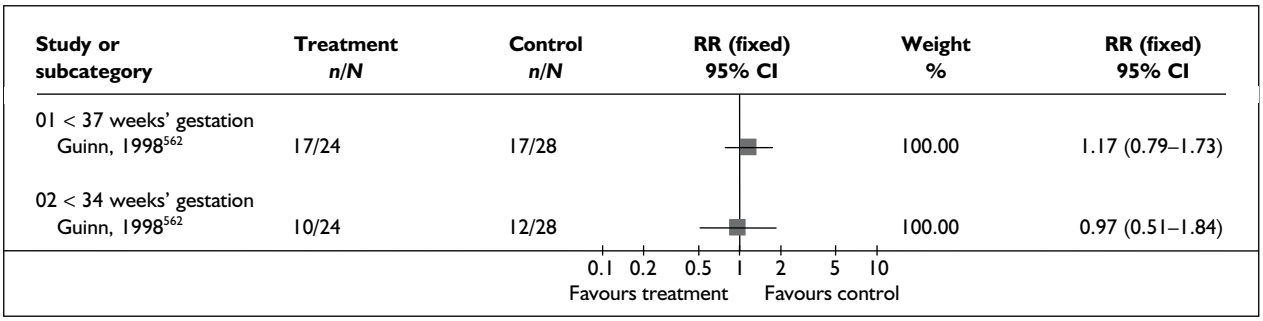


***FIGURE 192*** *Forest plot of the effects of terbutaline pump maintenance versus saline pump for the prevention of spontaneous preterm birth before 34 and 37 weeks' gestation.*

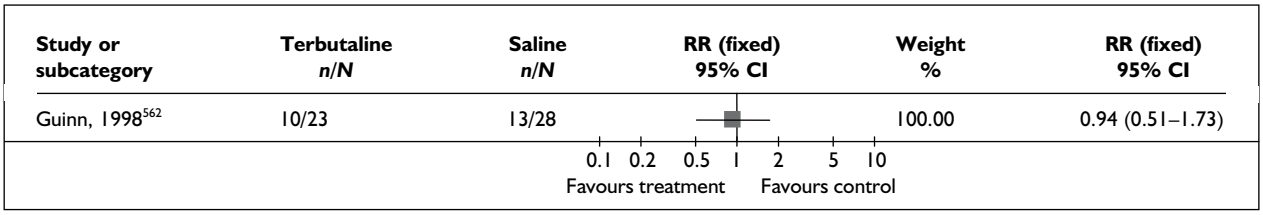


***FIGURE 193*** *Forest plot of the effects of terbutaline pump maintenance versus saline pump on admission to neonatal intensive care unit.*

***TABLE 23*** *Effect of terbutaline pump maintenance on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | Heterogeneity ($I^2$, *p*-value) |
|---|---|---|---|
| ***Respiratory distress syndrome*** | | | |
| Terbutaline pump vs saline pump: (2 studies, $n = 79$)[562,563] | 0.85 | 0.23–2.93 | 0% (0.48) |
| Terbutaline pump vs oral terbutaline: (1 study, $n = 30$)[562] | 1 | 0.16–6.20 | NA |
| ***Early discontinuation of treatment*** | | | |
| Terbutaline pump vs saline pump: (2 studies, $n = 79$)[562,563] | 1.15 | 0.68–1.95 | 8.1% (0.30) |
| Terbutaline pump vs oral terbutaline: (1 study, $n = 30$)[562] | 3 | 0.72–12.55 | NA |
| ***Birthweight*** | | | |
| Terbutaline pump vs saline pump: (2 studies, $n = 79$)[562,563] | WMD 107.90 | –216.25–432.04 | 0% (0.54) |
| Terbutaline pump vs oral terbutaline: (1 study, $n = 30$)[562] | WMD 484.00 | –25.01–993.01 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.



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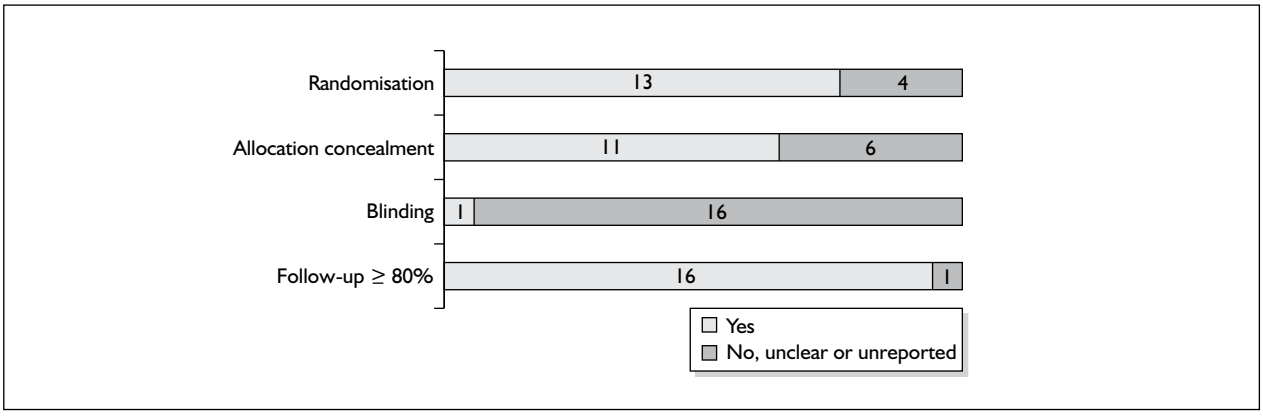


***FIGURE 194*** *Methodological quality of the included trials of calcium channel antagonists for the treatment of preterm labour to delay spontaneous preterm birth.*

Five of the studies included in the review employed maintenance tocolysis (*Table 28*); three compared a COX inhibitor with a betamimetic,[595,596,599] and two with magnesium sulphate.[600,605] Rescue tocolysis was employed in eight studies.[595,598–601,603,605,607] One additional study examined a COX inhibitor (sulindac) for the prevention of recurrence of spontaneous preterm birth (*Figures 218, 222*)[610] a second additional study compared a COX-2 inhibitor (rofecoxib) with placebo in prevention of spontaneous preterm birth in high-risk women (*Figures 226, 234*)[609] and the remaining additional study compared the use of another NSAID (aspirin) with placebo in prevention of spontaneous preterm birth labour in the general population (*Figures 227, 230, 235*).[608] Data were available on the following outcomes: birth within 48 hours of treatment, birth within 7 days of treatment, spontaneous preterm

| Study or subcategory | Treatment *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Versus betamimetic | | | | | |
| Ferguson, 1990[567] | 24/33 | 19/33 | | 9.64 | 1.26 (0.88–1.81) |
| Jannet, 1997[571] | 4/43 | 12/43 | | 6.09 | 0.33 (0.12–0.95) |
| Papatsonis, 1997[575] | 66/95 | 72/90 | | 37.51 | 0.87 (0.73–1.03) |
| Garcia-Velasco, 1998[568] | 4/26 | 3/26 | | 1.52 | 1.33 (0.33–5.38) |
| Al-Qattan, 2000[578] | 20/30 | 19/23 | | 10.91 | 0.81 (0.59–1.11) |
| Weerakul, 2002[577] | 28/45 | 24/44 | | 12.31 | 1.14 (0.80–1.62) |
| Subtotal (95% CI) | 272 | 259 | | 77.98 | 0.92 (0.80–1.05) |
| Total events: 146 (Treatment), 149 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 9.39$, df = 5 ($p = 0.09$), $I^2 = 46.8\%$ | | | | | |
| Test for overall effect: $z = 1.24$ ($p = 0.22$) | | | | | |
| 02 Versus magnesium sulphate (maintenance therapy employed) | | | | | |
| Glock, 1993[569] | 23/39 | 24/41 | | 11.87 | 1.01 (0.70–1.45) |
| Floyd, 1995[580] | 18/50 | 18/40 | | 10.15 | 0.80 (0.48–1.32) |
| Subtotal (95% CI) | 89 | 81 | | 22.02 | 0.91 (0.67–1.23) |
| Total events: 41 (Treatment), 42 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.54$, df = 1 ($p = 0.46$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.60$ ($p = 0.55$) | | | | | |
| Total (95% CI) | 361 | 340 | | 100.00 | 0.92 (0.81–1.04) |
| Total events: 187 (Treatment), 191 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 9.93$, df = 7 ($p = 0.19$), $I^2 = 29.5\%$ | | | | | |
| Test for overall effect: $z = 1.37$ ($p = 0.17$) | | | | | |



***FIGURE 195*** *Forest plot of the effects of calcium channel antagonists versus any other tocolytic for the prevention of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*

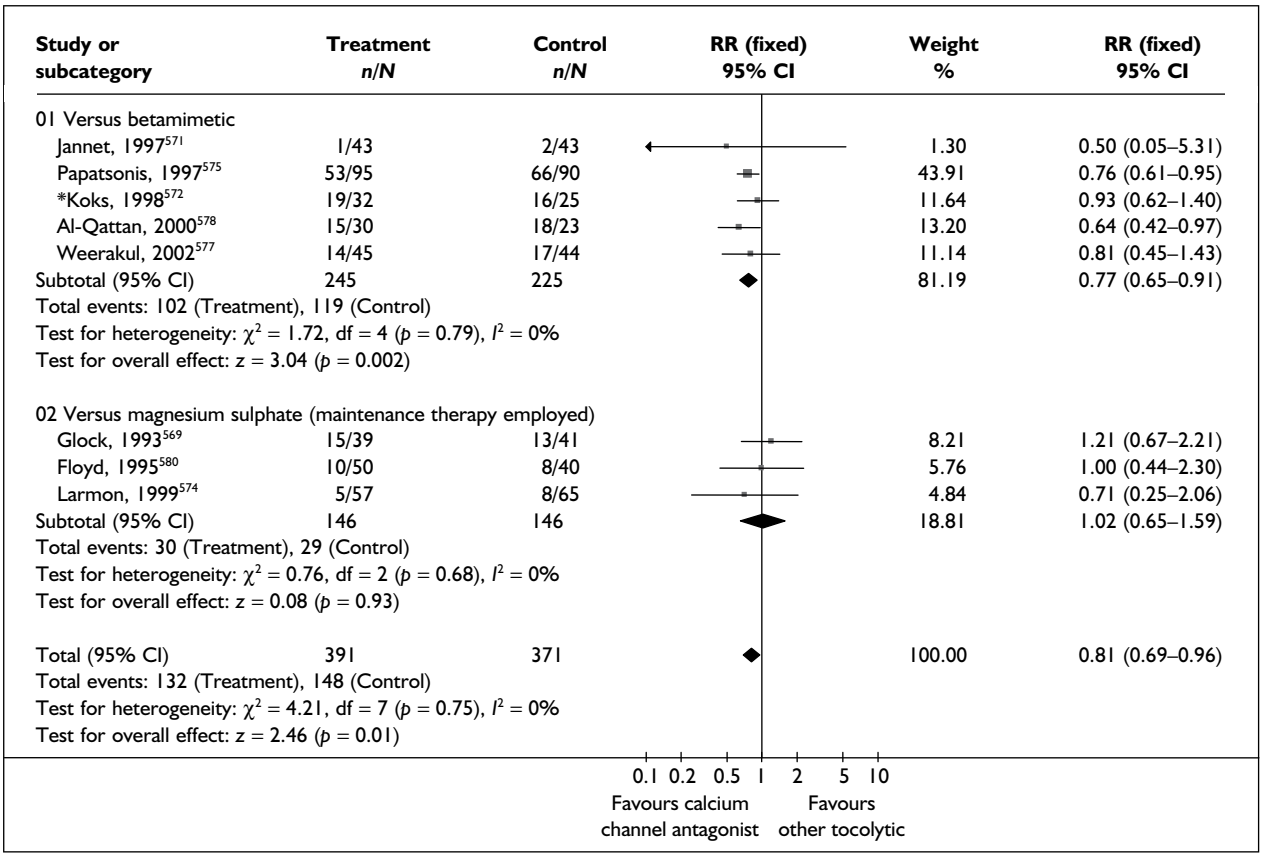


***FIGURE 196*** *Forest plot of the effects of calcium channel antagonists versus any other tocolytic for the prevention of spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour.*

birth before 37 weeks' gestation, perinatal mortality and admission to neonatal intensive care. Other maternal and perinatal outcomes are shown in *Table 29*.

COX inhibitors were significantly more effective than placebo in preventing birth within 48 hours (*Figure 216*), within 7 days of treatment (*Figure 220*), and before 37 weeks' gestation (*Figure 224*). They were significantly more effective than betamimetics in preventing birth within 48 hours of treatment (*Figure 217*, *Table 28*) or before 37 weeks' gestation (*Figure 224*, *Table 28*), but were not significantly different from magnesium sulphate on any primary outcome. COX inhibitors also caused significantly fewer maternal side effects than other tocolytic agents, both overall and those requiring cessation of treatment (*Table 29*). Rofecoxib given to asymptomatic women at high risk of spontaneous preterm birth increased the incidence of birth before 37 weeks' gestation (*Figure 226*) and was also associated with an increased occurrence of premature pre-labour rupture of membranes and a greatly increased occurrence of oligohydramnios (*Table 29*). Aspirin given to asymptomatic women was associated with increased occurrence of postpartum haemorrhage and other (non-vaginal or vomiting) bleeding during pregnancy (*Table 26*). Summary RRs (of studies vs placebo comparators) from the forest plots presented were used in the decision analyses.

## Ethanol as a tocolytic

Oxytocin is involved in the initiation and maintenance of uterine contractions in labour and alcohol appears to suppress the episodic release of oxytocin in term labour; the efficacy of ethanol in the treatment of threatened preterm labour has been credited to this mechanism of action. However, ethanol has been associated with a number of adverse events, such as respiratory depression, nausea and vomiting and urinary incontinence,[611] and has not been used in clinical practice for many years.



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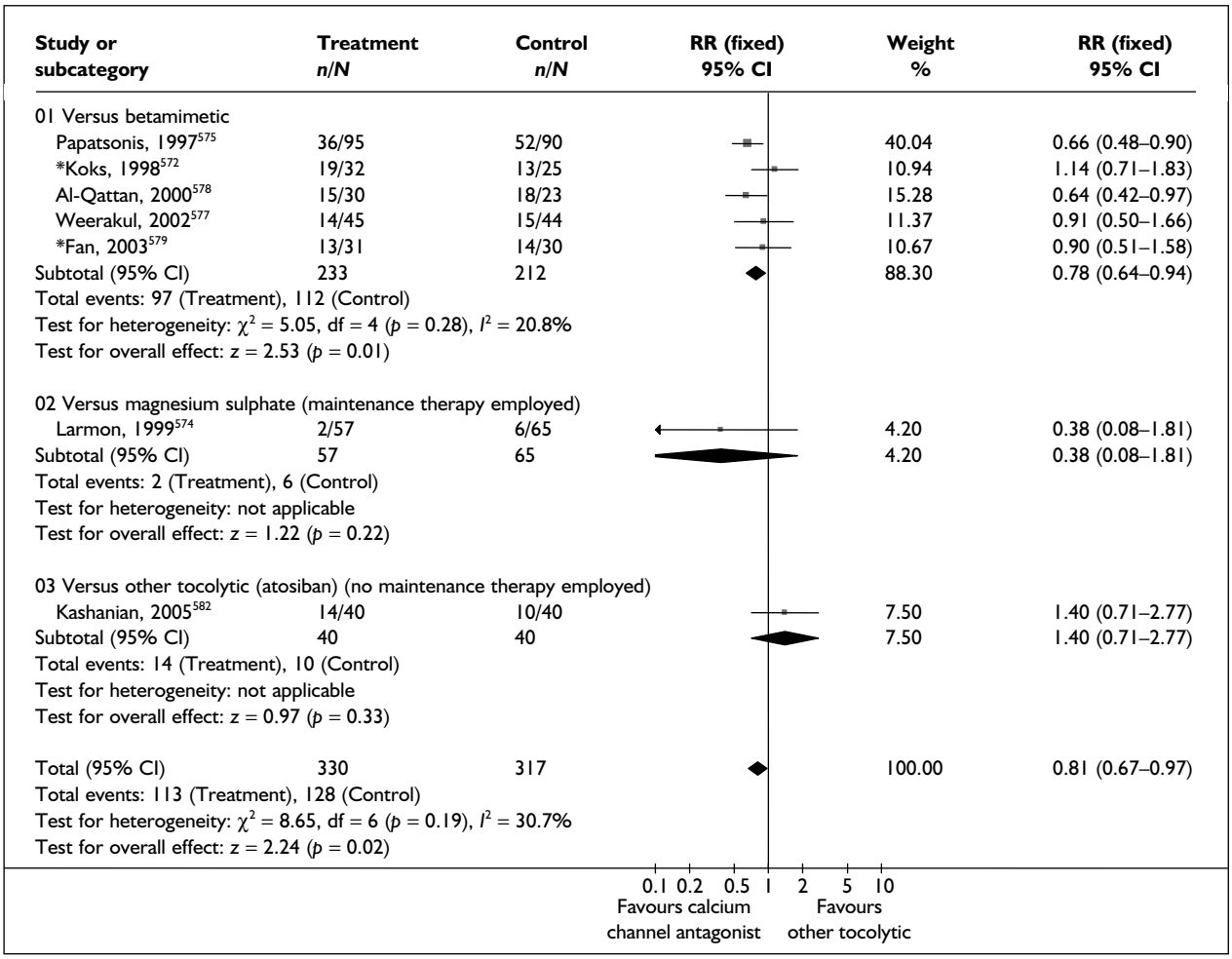


***FIGURE 197*** *Forest plot of the effects of calcium channel antagonists versus any other tocolytic for the prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour.*

The review of ethanol included three RCTs[612–614] and two quasi-RCTs[615,616] ($n = 446$). Further details of the studies can be found in Appendix 6, *Table 135*. The overall methodological quality of the studies was generally poor; the findings are shown in *Figure 236*. Ethanol was not found to reduce the risk of spontaneous preterm birth before 37 weeks' or 34 weeks' gestation when compared to betamimetics (*Figures 237* and *238*, respectively). Although no statistically significant difference was shown between ethanol and control groups for delivery within 24 and 48 hours after intervention administration (*Figures 239* and *240*, respectively), ethanol was shown to increase the risk of delivery within 7 days (*Figure 241*). Ethanol did not improve perinatal mortality when compared to betamimetics or other comparators (*Figure 242* and *Table 30*). A greater incidence of nausea, vomiting and loss of consciousness was shown in the ethanol group compared to controls (*Table 30*). There were, however, fewer cardiovascular changes (mean maternal and fetal heart acceleration, mean maternal systolic blood pressure increase, and mean fetal systolic blood pressure decrease) when compared with ritodrine (*Table 30*). The summary RRs were not used in the decision analyses. On the basis of the available poor-quality evidence, ethanol does not appear to be beneficial as a tocolytic in the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.

## Magnesium sulphate acute tocolysis

Magnesium sulphate is one of a number of tocolytic agents that are used in the management of threatened preterm labour. Magnesium sulphate acts on the central nervous system to block neuromuscular transmission. However, the

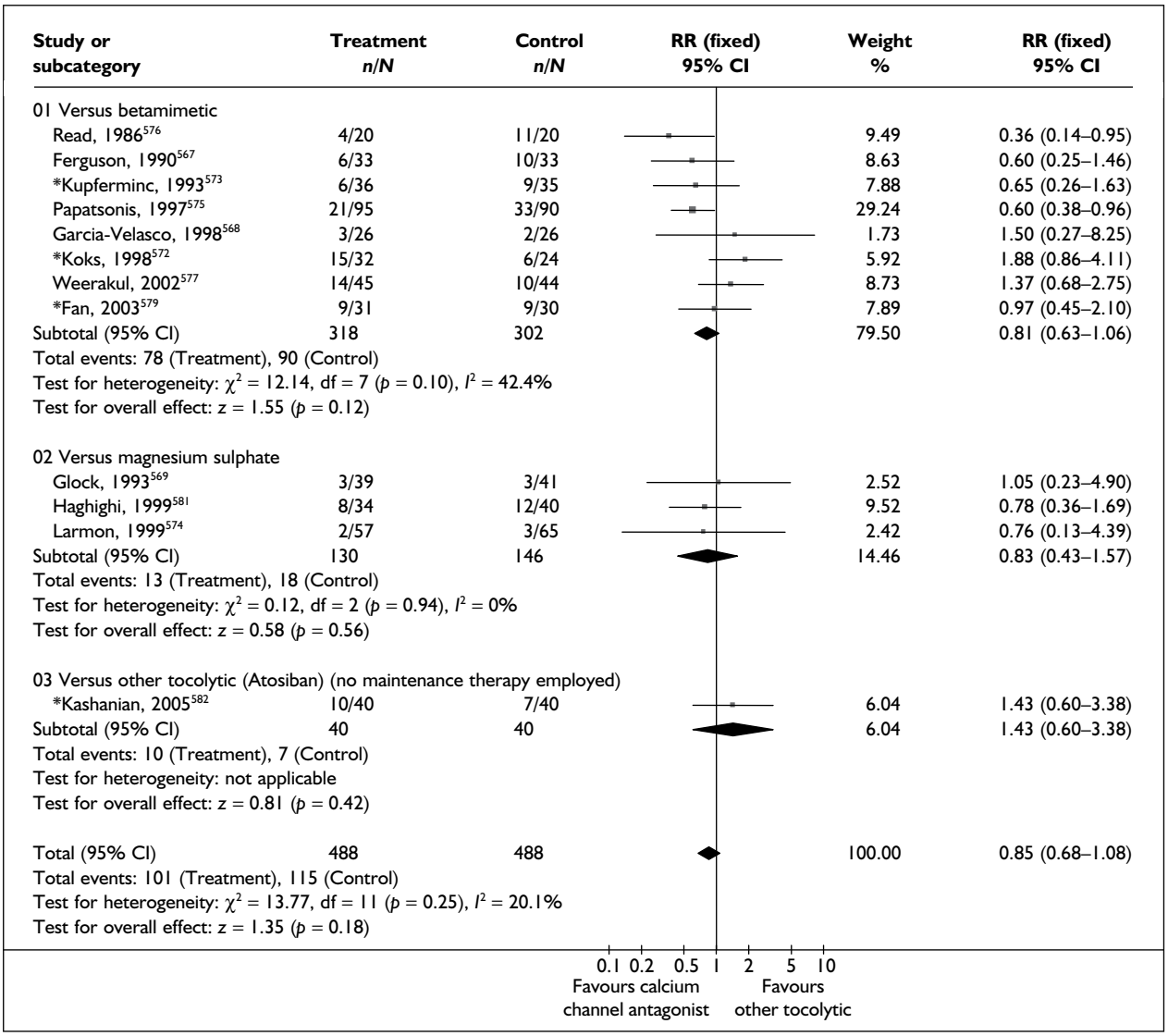


***FIGURE 198*** *Forest plot of the effects of calcium channel antagonists versus any other tocolytic for the prevention of spontaneous preterm birth within 48 hours of treatment in symptomatic women with threatened preterm labour.*

mechanism by which it inhibits uterine contractions is not fully understood, although it is thought to be related to calcium antagonist activity.

The review of magnesium sulphate for the prevention of spontaneous preterm birth included 22 RCTs[537,569,574,580,581,605,617–630] and two quasi-RCTs ($n$ = 2036);[600,631] one RCT[598] was added to the primary studies identified in an earlier systematic review.[632] Further details of the review and the additional study can be found in Appendix 6, *Table 136*. The quality of these studies is shown in *Figure 243*. The quality was often poor; less than half of the included studies reported adequate randomisation or allocation concealment. Magnesium sulphate was not found to significantly reduce the incidence of spontaneous preterm birth before 37 and 34 weeks' gestation, or admission to neonatal intensive care unit compared to other tocolytic agents, non-tocolytic therapy, or no treatment (*Figures 244, 245* and *247*, respectively). Similarly, when compared to other tocolytic agents, magnesium sulphate did not reduce the risk of delivery within 48 hours of treatment; however, when compared to non-tocolytic treatment a significant reduction in risk was shown (*Figure 246*). Relevant information relating to delivery within 24 hours or within 7 days of treatment, or perinatal mortality was not reported. A higher incidence of total infant mortality was found in mothers receiving magnesium sulphate compared with all comparators but this was not statistically significant



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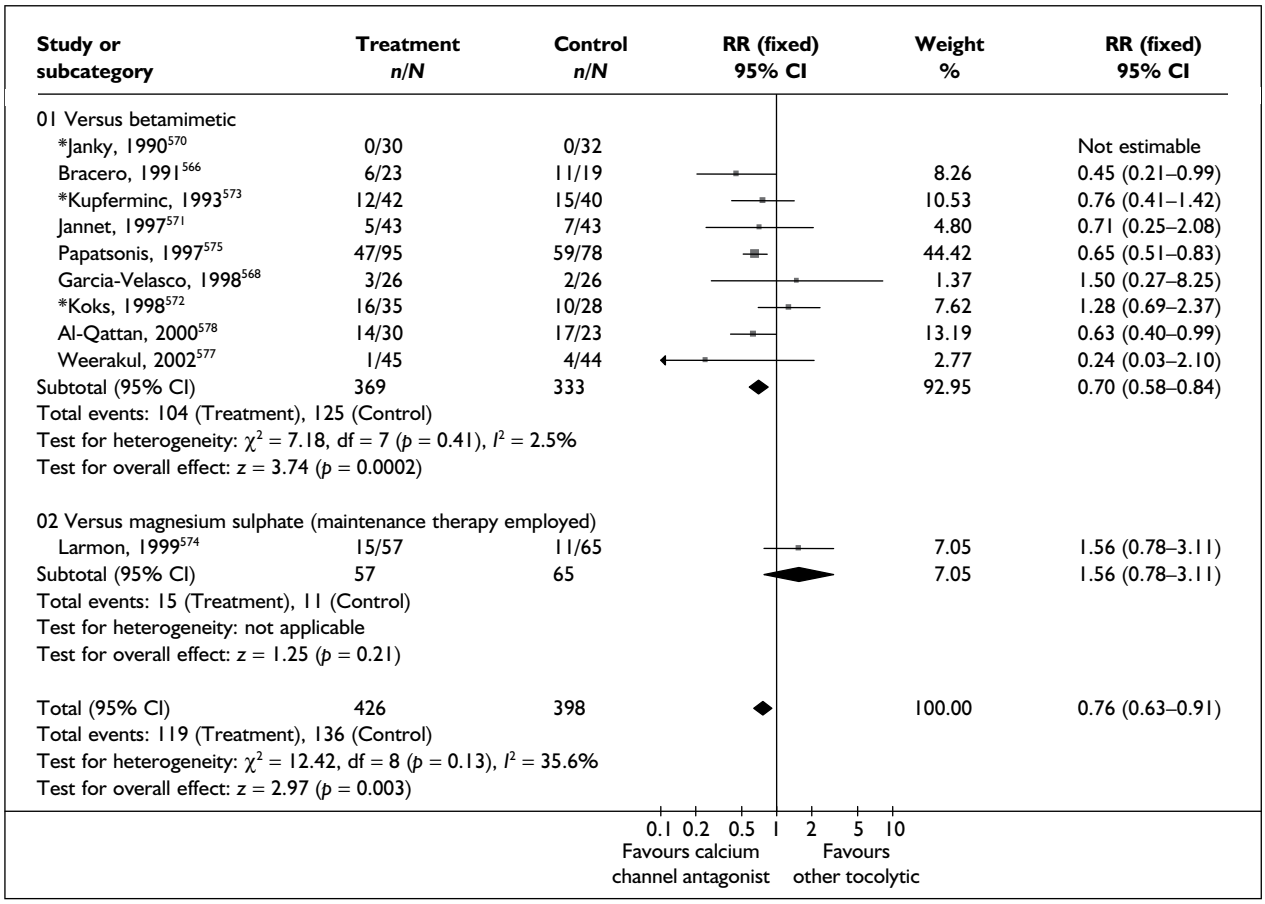


***FIGURE 199*** *Forest plot of the effects of calcium channel antagonists versus any other tocolytic for the prevention of admission to neonatal intensive care unit.*

(*Table 31*). Few significant differences were found for the other infant and maternal outcomes reported (*Table 31*); an exception was that women treated with magnesium sulphate reported fewer side effects leading to discontinuation of treatment compared to betamimetics. When data were analysed according to different dosing regimens (magnesium sulphate ≤ 2 g/hour versus > 2 g/hour), no statistically significant differences in the reported outcomes were demonstrated. It should be noted that only four of the included studies explicitly stated that only women with singleton pregnancies were included. Summary RRs from the forest plots presented (*Figures 244–247*) were used in the decision analysis for all primary outcomes. Overall, magnesium sulphate did not appear to significantly reduce the risk of spontaneous preterm birth before 37 weeks' gestation, and had no beneficial effect on perinatal or neonatal outcomes; however, the included studies were often of poor quality.

## Magnesium sulphate maintenance

Women who remain undelivered after their first course of tocolytic treatment for threatened preterm labour continue to be at increased risk of spontaneous preterm birth. Maintenance tocolysis may be given after successful treatment with acute tocolytic therapy to maintain uterine quiescence. Magnesium sulphate is one type of maintenance tocolytic therapy used after an episode of threatened preterm labour.

The review of magnesium maintenance therapy[633] for the prevention of spontaneous preterm birth included three randomised controlled trials ($n = 303$);[558–560] no further trials were identified. Further details of the review can be found in Appendix 6, *Table 136*. The quality of these studies is shown in *Figure 248* where overall one trial was of good quality and the other two were of questionable quality. No statistically significant difference in risk for spontaneous

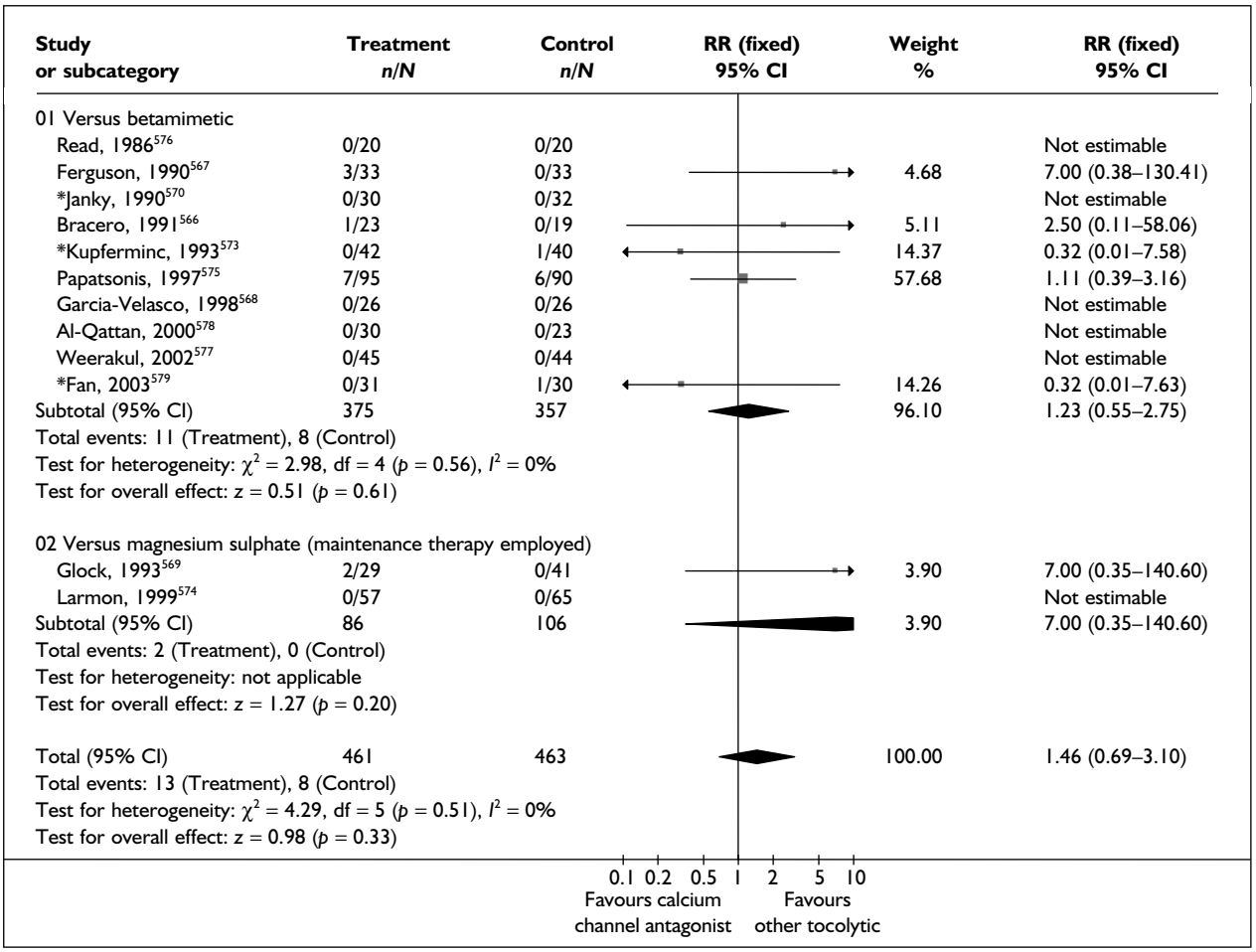


***FIGURE 200*** *Forest plot of the effects of calcium channel antagonists versus any other tocolytic for the prevention of perinatal mortality.*

preterm birth before 37 weeks' gestation (*Figure 249*), or admission to neonatal intensive care unit was shown between magnesium maintenance therapy and placebo or an alternative tocolytic maintenance therapy (*Figure 250*). Information relating to delivery before 34 weeks' gestation and perinatal mortality was not reported. Women receiving magnesium maintenance therapy were more likely to report experiencing side effects of therapy than women in the placebo/no treatment group; however, they were less likely to report side effects than women in the alternative tocolytic maintenance therapy group (*Table 32*). Specifically, women receiving magnesium maintenance therapy were more likely to report diarrhoea than women in either control group, but women receiving alternative tocolytic maintenance therapy were more likely to report palpitations or tachycardia than women receiving magnesium maintenance therapy. Summary RRs from the forest plots presented (*Figures 249* and *250*) were used in the decision analyses. The limited evidence available does not indicate that magnesium maintenance therapy is effective.

## Nitric oxide donors tocolysis

Nitric oxide, a gaseous free radical, has been shown to be involved in numerous aspects of female reproductive physiology. Various nitric oxide donors have been shown to inhibit myometrial contractability, probably by mimicking the action of nitric oxide. This mechanism of action appears to also affect several other organ systems, most notably the cardiovascular system.

The review of nitric oxide donors (glyceryl trinitrate; GTN) for the inhibition of threatened preterm labour included six trials ($n = 704$); one RCT[634] was added to the five primary studies[621,635–638] identified in an earlier review.[639] Further details of the review can be found in



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***TABLE 24*** *Effects of calcium channel blockers on primary outcomes: effect of the deployment of maintenance therapy*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Birth <37 weeks' gestation*** | | | |
| Versus betamimetic (6 studies, *n* = 531)[567,568,571,575,577,578] | 0.92 | 0.80–1.05 | 60.9% (0.03) |
| Maintenance therapy employed (5 studies, *n* = 442)[567,568,571,575,578] | 0.84 | 0.73–0.98 | 63.5% (0.03) |
| No maintenance therapy employed (1 study, *n* = 89)[577] | 1.14 | 0.80–1.62 | NA |
| ***Birth <34 weeks' gestation*** | | | |
| Versus betamimetic (5 studies, *n* = 531)[571,572,575,577,578] | 0.77 | 0.65–0.91 | 0% (0.79) |
| Maintenance therapy employed (4 studies, *n* = 442)[571,572,575,578] | 0.76 | 0.64–0.91 | 0% (0.64) |
| No maintenance therapy employed (1 study, *n* = 89)[577] | 0.81 | 0.45–1.43 | NA |
| ***Birth within 7 days of intervention*** | | | |
| Versus betamimetic (5 studies, *n* = 445)[572,575,577,578,579] | 0.78 | 0.64–0.94 | 20.8% (0.28) |
| Maintenance therapy employed (4 studies, *n* = 356)[572,575,578,579] | 0.76 | 0.61–0.93 | 36.1% (0.20) |
| No maintenance therapy employed (1 study, *n* = 89) [577] | 0.91 | 0.50–1.66 | NA |
| ***Birth within 48 h of intervention*** | | | |
| Versus betamimetic (8 studies, *n* = 620) [567,568,572,573,575–77,579] | 0.81 | 0.63–1.06 | 42.4% (0.10) |
| Maintenance therapy employed (6 studies, *n* = 491) [567,568,572,573,575,579] | 0.8 | 0.60–1.08 | 31.5% (0.20) |
| No maintenance therapy employed (2 studies, *n* = 129) [576,578] | 0.85 | 0.49–1.45 | 79.1% (0.03) |
| ***Birth within 48 h of intervention*** | | | |
| Versus magnesium sulphate: (3 studies, *n* = 276) [569,574,581] | 0.83 | 0.43–1.57 | 0% (0.94) |
| Maintenance therapy employed (2 studies, *n* = 202) [569,574] | 0.91 | 0.29–2.88 | 0% (0.79) |
| No maintenance therapy employed (1 study, *n* = 74)[581] | 0.78 | 0.36–1.69 | NA |
| ***Admission to neonatal intensive care unit*** | | | |
| Versus betamimetic (8 studies, *n* = 640)[566,568,571–573,575,577,578] | 0.7 | 0.58–0.84 | 2.5% (0.41) |
| Maintenance therapy employed (7 studies, *n* = 551)[566,568,571–573,575,578] | 0.71 | 0.59–0.86 | 5.5% (0.39) |
| No maintenance therapy employed (1 study, *n* = 89) [578] | 0.24 | 0.03–2.10 | NA |
| ***Perinatal mortality*** | | | |
| Versus betamimetic (10 studies, *n* = 732)[566–568,570,573,575–579] | 1.23 | 0.55–2.75 | 0% (0.56) |
| Maintenance therapy employed (7 studies, *n* = 541)[566–568,570,573,578,579] | 1.23 | 0.55–2.75 | 0% (0.56) |
| No maintenance therapy employed (3 studies, *n* = 191)[570,576,577] | Not estimable | Not estimable | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

***TABLE 25*** *Effects of calcium channel blockers on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Birth <35 weeks' gestation*** | | | |
| Versus betamimetic (maintenance therapy employed) (1 study, $n = 61$)[579] | 0.85 | 0.51–1.41 | NA |
| ***Perinatal mortality excluding congenital abnormality*** | | | |
| Versus any other tocolytic (10 studies, $n = 820$)[566–570,573–577] | 1.42 | 0.61–3.31 | 0% (0.48) |
| Versus betamimetic (8 studies, $n = 618$)[566–568,570,573,575–577] | 1.2 | 0.49–2.94 | 0% (0.70) |
| Versus magnesium sulphate (maintenance therapy employed) (2 studies, $n = 202$)[569,574] | 5.25 | 0.26–106.01 | NA |
| ***Fetal death*** | | | |
| Versus any other tocolytic (10 studies, $n = 820$)[566–570,573–578] | 3 | 0.13–71.07 | NA |
| Versus betamimetic (8 studies, $n = 618$)[566–568,570,573,575–577] | 3 | 0.13–71.07 | NA |
| ***Neonatal death*** | | | |
| Versus any other tocolytic (11 studies, $n = 883$)[566–570,572–577] | 1.58 | 0.74–3.39 | 0% (0.73) |
| Versus betamimetic (9 studies, $n = 671$)[566–568,570,572,573,575–578] | 1.4 | 0.63–3.12 | 0% (0.72) |
| Maintenance therapy employed (6 studies, $n = 480$)[566–568,572,573,575] | 1.4 | 0.63–3.12 | 0% (0.72) |
| Versus magnesium sulphate (maintenance therapy employed) (2 studies, $n = 202$)[569,574] | 5.25 | 0.26–106.01 | NA |
| ***Neonatal death excluding congenital abnormality*** | | | |
| Versus any other tocolytic (10 studies, $n = 820$)[566–570,573–578] | 1.42 | 0.61–3.31 | 0% (0.48) |
| Versus betamimetic (8 studies, $n = 618$)[566–568,570,573,575–577] | 1.2 | 0.49–2.94 | 0% (0.46) |
| Maintenance therapy employed (5 studies, $n = 539$)[566–568,573,575] | 1.2 | 0.49–2.94 | 0% (0.46) |
| Versus magnesium sulphate (maintenance therapy employed) (2 studies, $n = 202$)[569,574] | 5.25 | 0.26–106.01 | NA |
| ***Low birthweight <2500 g*** | | | |
| Versus any other tocolytic (2 studies, $n = 143$)[580,578] | 0.72 | 0.54–0.96 | 45.4% (0.18) |
| Versus betamimetic (maintenance therapy employed) (1 study, $n = 53$)[578] | 0.84 | 0.65–1.10 | NA |
| Versus magnesium sulphate (maintenance therapy employed) (1 study, $n = 90$)[580] | 0.59 | 0.34–1.02 | NA |
| ***Low birthweight <1500 g*** | | | |
| Versus any other tocolytic (2 studies, $n = 143$)[580,578] | 0.65 | 0.33–1.29 | 0% (0.42) |
| Versus betamimetic (maintenance therapy employed) (1 study, $n = 53$)[578] | 0.56 | 0.27–1.16 | NA |
| Versus magnesium sulphate (maintenance therapy employed) (1 study, $n = 90$)[578] | 1.2 | 0.21–6.84 | NA |
| ***Respiratory distress syndrome*** | | | |
| Versus any other tocolytic (12 studies, $n = 967$)[566–568,570,573–575,577–580] | 0.67 | 0.50–0.91 | 0% (0.80) |
| Versus betamimetic (10 studies, $n = 755$)[566–568,570,572,573,575,577,578,579] | 0.66 | 0.47–0.92 | 0% (0.68) |
| Maintenance therapy employed (8 studies, $n = 604$)[566–568,573,575,578,579] | 0.67 | 0.48–0.94 | 0% (0.59) |

*continued*



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***TABLE 25*** *Effects of calcium channel blockers on other perinatal and maternal outcomes (continued)*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| No maintenance therapy employed (2 studies, $n = 151$)[570,577] | 0.49 | 0.09–2.53 | NA |
| Versus magnesium sulphate (maintenance therapy employed) (2 studies, $n = 212$)[574,580] | 0.76 | 0.34–1.68 | 0% (0.58) |
| ***Neonatal jaundice*** | | | |
| Versus betamimetic (maintenance therapy employed) (2 studies, $n = 227$) [566,575] | 0.73 | 0.57–0.93 | 47.7% (0.17) |
| ***Neonatal sepsis*** | | | |
| Versus betamimetic (4 studies, $n = 378$)[566,570,575,577] | 0.73 | 0.46–1.16 | 0% (0.57) |
| ***Necrotising enterocolitis*** | | | |
| Versus betamimetic (3 studies, $n = 323$)[566,575,577] | 0.21 | 0.05–0.96 | 0% (0.97) |
| Maintenance therapy employed (2 studies, $n = 234$)[566,575] | 0.21 | 0.04–1.25 | 0% (0.82) |
| No maintenance therapy employed (1 study, $n = 89$)[577] | 0.2 | 0.01–3.96 | NA |
| ***Intraventricular haemorrhage: all grades*** | | | |
| Versus betamimetic (4 studies, $n = 393$)[567,575,577,578] | 0.59 | 0.36–0.98 | 0% (0.46) |
| Maintenance therapy employed (3 studies, $n = 304$)[467,575,578] | 0.61 | 0.31–1.01 | 0% (0.49) |
| No maintenance therapy employed (1 study, $n = 89$)[577] | 0.2 | 0.01–3.96 | NA |
| ***Intraventricular haemorrhage: grades 3 and 4*** | | | |
| Versus betamimetic (3 studies, $n = 340$)[467,575,577] | 0.5 | 0.16–1.55 | 0% (0.48) |
| ***Transient tachypnoea of newborn*** | | | |
| Versus magnesium sulphate (maintenance therapy employed) (1 study, $n = 90$)[580] | 0.16 | 0.01–3.26 | NA |
| ***Apgar score <7 at 5 min*** | | | |
| Versus any other tocolytic (5 studies, $n = 568$)[573–575,577,578] | 0.83 | 0.44,1.54 | 0% (0.65) |
| Versus betamimetic (3 studies, $n = 356$)[575,575,577] | 0.57 | 0.21–1.52 | 0% (0.54) |
| Maintenance therapy employed (2 studies, $n = 267$)[573,575] | 0.57 | 0.21–1.52 | 0% (0.54) |
| Versus magnesium sulphate (maintenance therapy employed) (2 studies, $n = 212$)[574,580] | 1.11 | 0.49–2.52 | 0% (0.59) |
| ***Maternal adverse drug reaction*** | | | |
| Versus any other tocolytic (12 studies, $n = 1022$)[566–569,571,574–577,579–582] | 0.47 | 0.38–0.58 | 79.0% (<0.00001) |
| Versus betamimetic (7 studies, $n = 576$)[566,567,571,575–577,579] | 0.36 | 0.28–0.46 | 81.0% (0.0001) |
| Maintenance therapy employed (5 studies, $n = 447$)[566,567,571,575,576] | 0.5 | 0.38–0.65 | 67.8% (0.01) |
| No maintenance therapy employed (2 studies, $n = 129$)[576,577] | 0.07 | 0.03–0.19 | 35.2% (0.21) |
| Versus magnesium sulphate (4 studies, $n = 366$)[569,574,580,581] | 0.62 | 0.37–1.03 | 65.4% (0.03) |
| Maintenance therapy employed (3 studies, $n = 292$)[569,574,580] | 0.4 | 0.21–0.73 | 0% (0.92) |
| No maintenance therapy employed (1 study, $n = 74$)[581] | 3.14 | 0.90–10.90 | NA |
| Versus atosiban (No maintenance therapy employed) (1 study, $n = 80$)[582] | 2.29 | 1.06–4.95 | NA |

***TABLE 25*** *Effects of calcium channel blockers on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Maternal adverse drug reaction requiring cessation of treatment*** | | | |
| Versus any other tocolytic (12 studies, $n = 1116$)[566–570,573–575,577,580,578,581] | 0.16 | 0.07–0.35 | 0% (0.62) |
| Versus betamimetic (9 studies, $n = 750$)[566–568,570,573,575,577,578,579] | 0.09 | 0.03–0.27 | 0% (0.97) |
| Maintenance therapy employed (8 studies, $n = 599$)[566–568,573,575,578,579] | 0.1 | 0.03–0.31 | 0% (0.94) |
| No maintenance therapy employed (2 studies, $n = 151$)[570,577] | 0.08 | 0.00–1.30 | NA |
| Versus magnesium sulphate (4 studies, $n = 366$)[569,574,580,581] | 0.47 | 0.15–1.54 | 16.7% (0.30) |
| Maintenance therapy employed (3 studies, $n = 292$)[569,574,580] | 0.47 | 0.15–1.54 | 16.7% (0.30) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

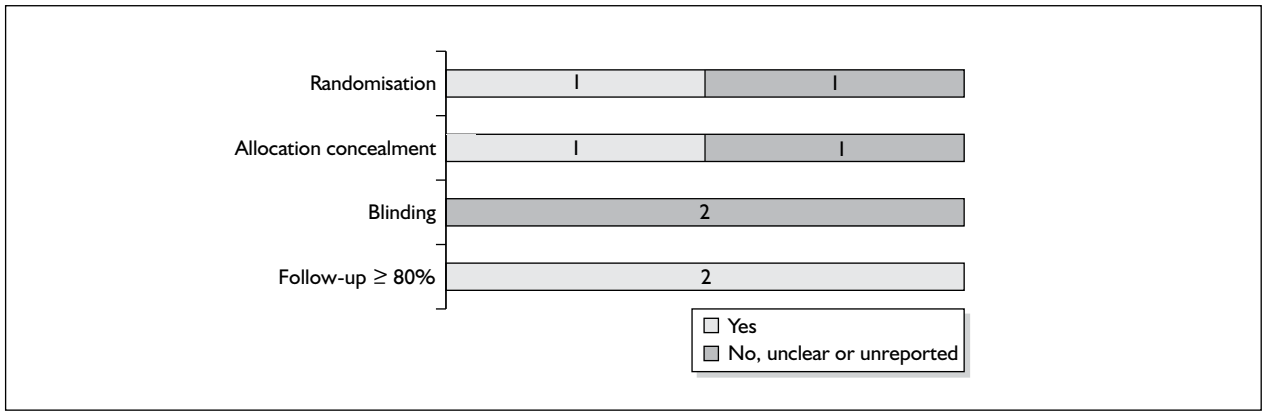


***FIGURE 201*** *Methodological quality of the included trials of nifedipine maintenance therapy for the prevention of spontaneous preterm birth following acute tocolytic therapy in symptomatic women with threatened preterm labour.*

Appendix 6, *Table 137*. The quality of the studies (*Figure 251*) was mixed with blinding in particular being poorly reported or not carried out. GTN was not found to reduce the risk of spontaneous preterm birth before 34 weeks' gestation when compared to any other tocolytic agent; however, a small but statistically significant reduction in risk of spontaneous preterm birth before 37 weeks' gestation was shown in favour of GTN (*Figures 252* and *253*). The groups did not differ significantly with regard to risk of spontaneous preterm birth within 24 or 48 hours, or 7 days of treatment administration, although a trend favouring the control group (other tocolytic agent) was observed (*Figures 254*, *255*, and *256*, respectively). There was no statistically significant difference in rate of perinatal mortality between GTN and other tocolytics (*Figure 257*). A greater number of cardiovascular changes (palpitations, tachycardia, shortness of breath and chest pain) was reported in the GTN group compared with other tocolytic agents (*Table 33*). RRs for subgroups using a placebo comparator were used in the decision analyses. The available evidence does not indicate that the efficacy of GTN is sufficient to recommend its use.

## Prophylactic corticosteroids for fetal lung maturation

Antenatal corticosteroid treatment of women expected to give birth preterm significantly reduced the incidence of respiratory distress syndrome (RDS) and mortality among neonates, as was first reported in 1972.[640] Since then the administration of corticosteroids to pregnant



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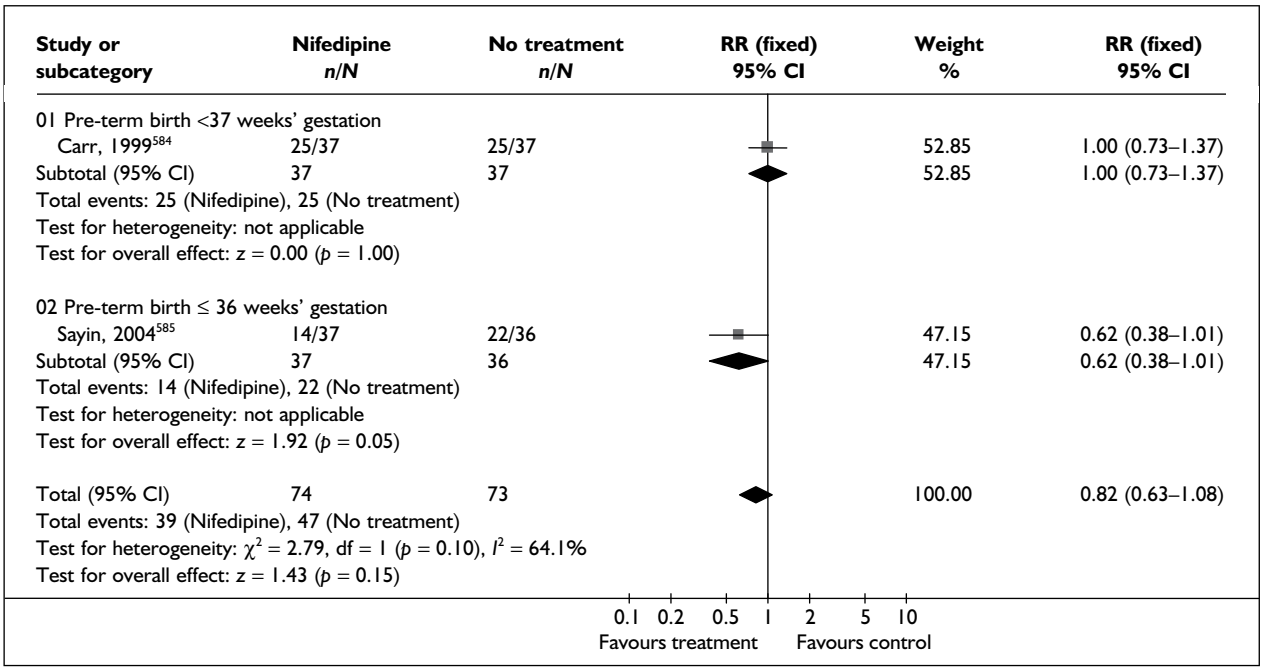


***FIGURE 202*** *Forest plot of the effects of maintenance nifedipine versus no treatment for the inhibition of spontaneous preterm birth before 37 weeks' gestation.*

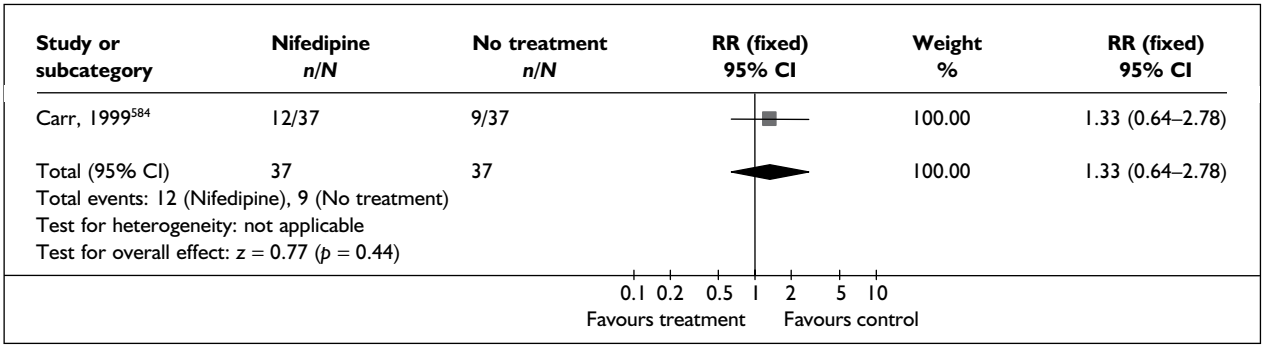


***FIGURE 203*** *Forest plot of the effects of maintenance nifedipine versus no treatment for the inhibition of spontaneous preterm birth before 34 weeks' gestation.*

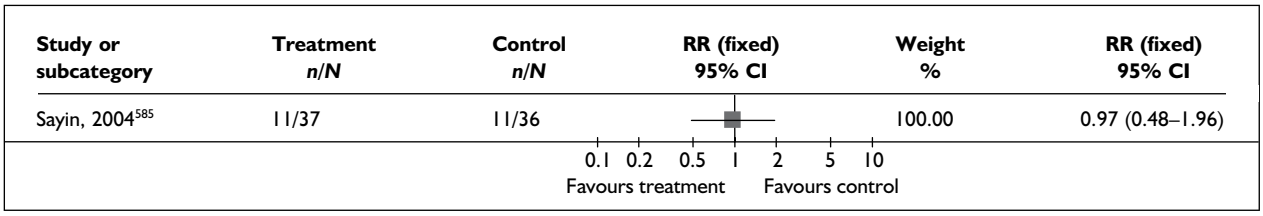


***FIGURE 204*** *Forest plot of the effects of nifedipine versus no treatment on admission to neonatal intensive care unit.*

***TABLE 26*** *Effects of maintenance nifedipine versus no treatment on other perinatal and maternal outcomes*

| Outcome (number of RCTs) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| Small for gestational age (1 study, $n = 73$) [585] | 1.5 | 0.27–8.46 | NA |
| Respiratory distress syndrome (1 study, $n = 73$)[585] | 1 | 0.22–4.64 | NA |
| Mechanical ventilation (1 study, $n = 73$)[585] | 1 | 0.22–4.64 | NA |
| Intraventricular haemorrhage (1 study, $n = 73$)[585] | 1 | 0.06–15.40 | NA |
| Necrotising enterocolitis (1 study, $n = 73$)[585] | 1 | 0.06–15.40 | NA |
| Bronchopulmonary dysplasia (1 study, $n = 73$)[585] | 0.32 | 0.01–7.71 | NA |
| Sepsis/meningitis (1 study, $n = 73$)[585] | 1.95 | 0.18–20.53 | NA |
| Pneumonia (1 study, $n = 73$)[585] | 1.46 | 0.26–8.23 | NA |
| Neonatal mortality (1 study, $n = 73$)[585] | 0.19 | 0.01–3.92 | NA |
| Neonatal jaundice (1 study, $n = 73$)[585] | 0.97 | 0.63–1.51 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

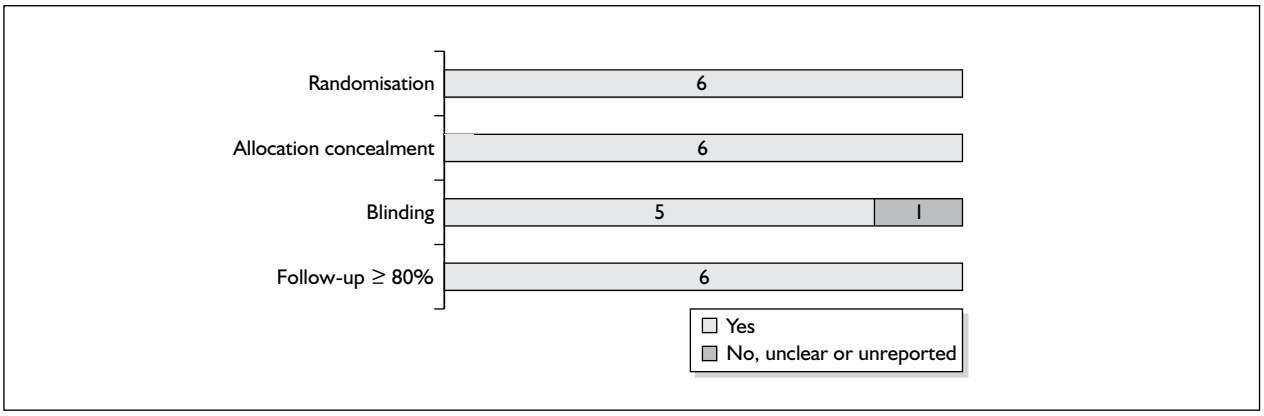


***FIGURE 205*** *Methodological quality of RCTs of oxytocin receptor antagonists for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*

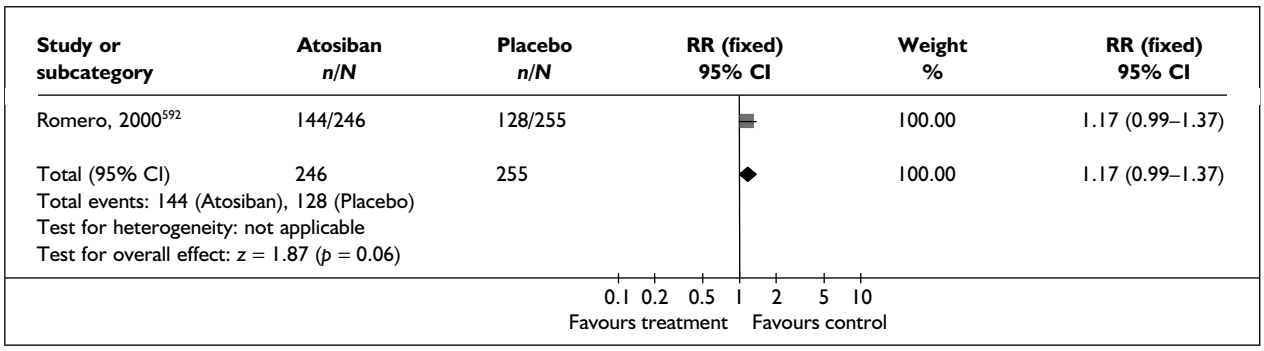


***FIGURE 206*** *Forest plot of the effects of atosiban versus placebo therapy on prevention of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*



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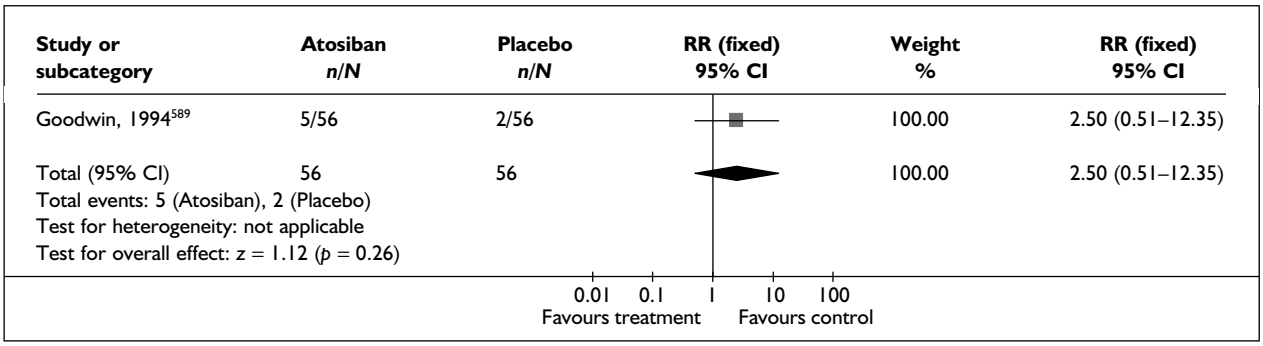


***FIGURE 207*** *Forest plot of the effects of atosiban versus placebo therapy on prevention of spontaneous preterm birth within 48 hours of initiation of treatment in symptomatic women with threatened preterm labour.*

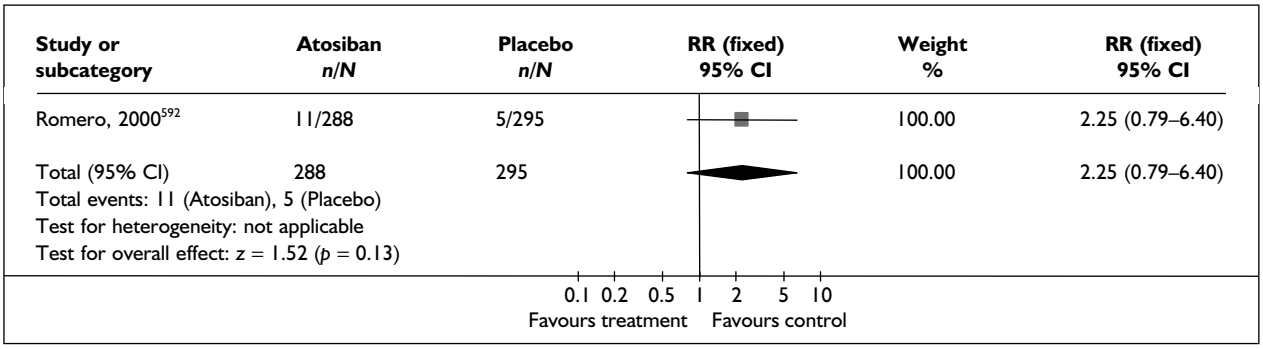


***FIGURE 208*** *Forest plot of the effects of atosiban versus placebo therapy on perinatal mortality.*

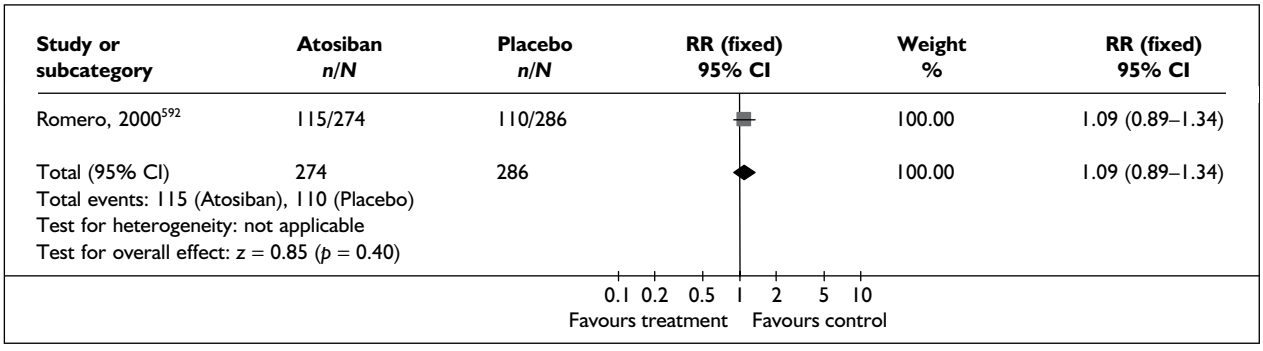


***FIGURE 209*** *Forest plot of the effects of atosiban versus placebo therapy on neonatal admission to intensive care unit.*

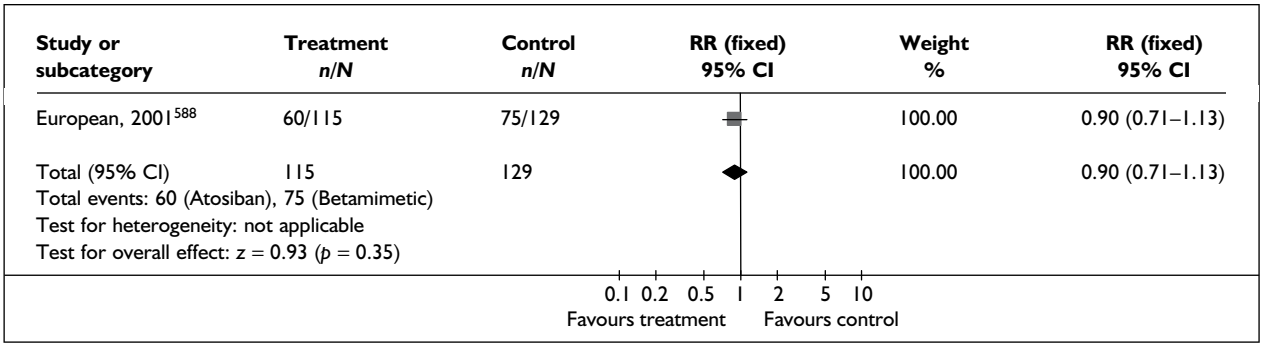


***FIGURE 210*** *Forest plot of the effects of atosiban versus betamimetic therapy on prevention of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*

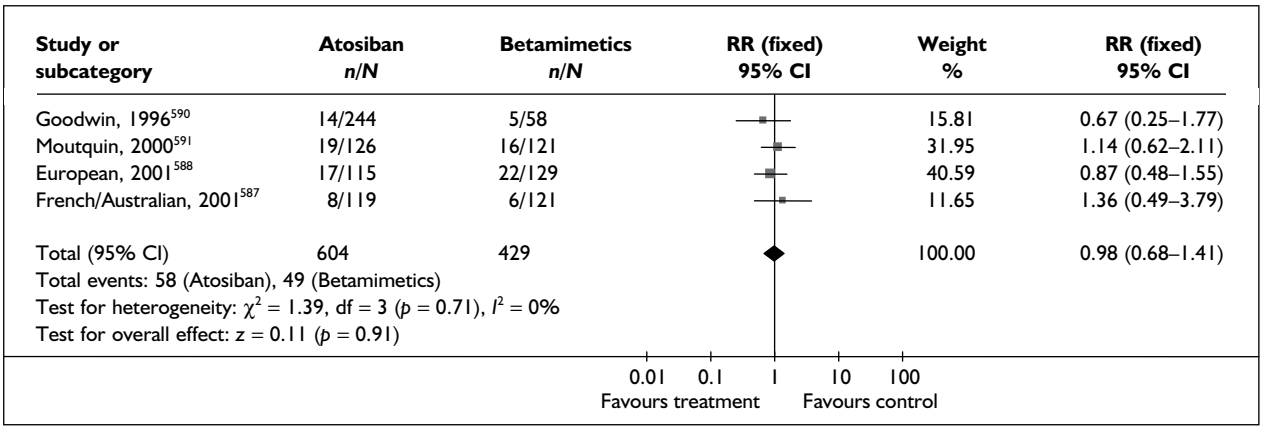


***FIGURE 211*** *Forest plot of the effects of atosiban versus betamimetic therapy on prevention of spontaneous preterm birth within 48 hours of initiation of treatment in symptomatic women with threatened preterm labour.*

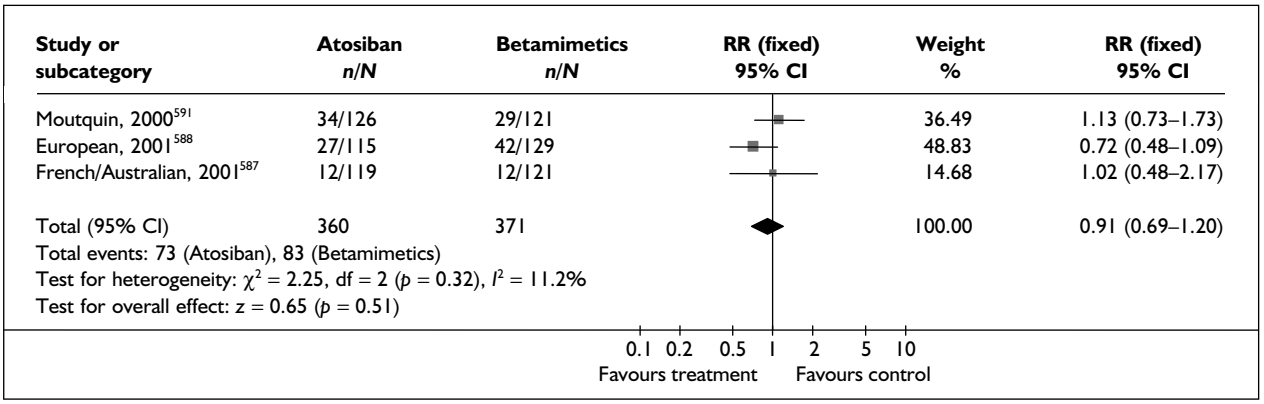


***FIGURE 212*** *Forest plot of the effects of atosiban versus betamimetic therapy on prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour.*

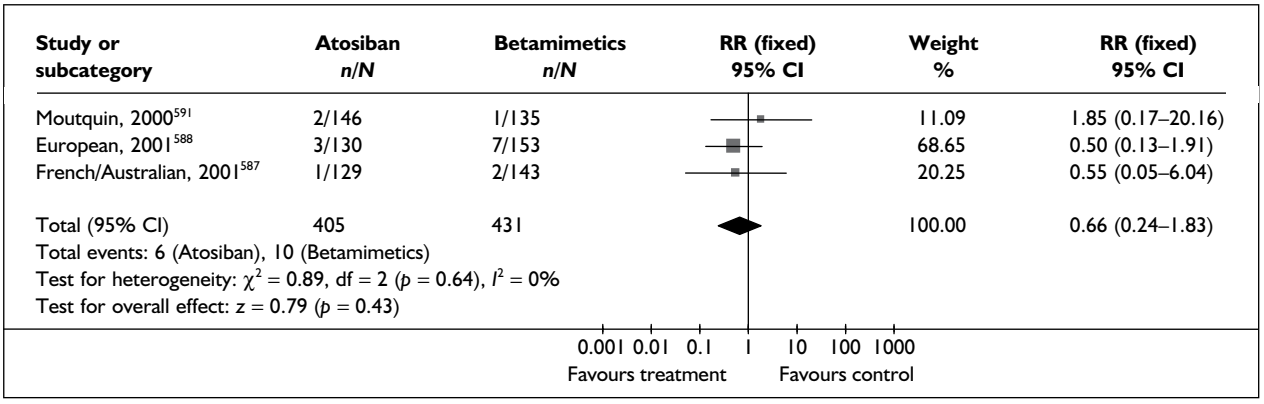


***FIGURE 213*** *Forest plot of the effects of atosiban versus betamimetic therapy on perinatal mortality.*



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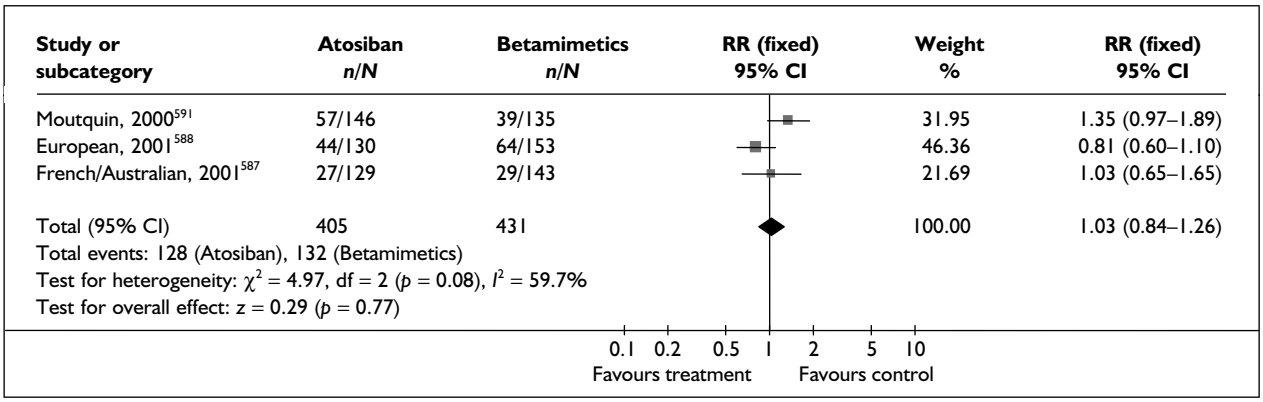


***FIGURE 214*** *Forest plot of the effects of atosiban versus betamimetics on neonatal admission to intensive care unit.*

***TABLE 27*** *Effects of oxytocyin receptor antagonists on other perinatal and maternal outcomes*

| Outcome (number of RCTs) | RR | 95% CI | $I^2$ and *p*-value |
|---|---|---|---|
| ***Preterm birth <28 weeks gestation*** | | | |
| Atosiban vs placebo (1 study, $n = 585$)[592] | 2.25 | 0.80–6.35 | NA |
| ***Fetal death*** | | | |
| Atosiban vs placebo (2 studies, $n = 585$)[592,589] | 1.02 | 0.21–5.03 | NA* |
| Atosiban vs betamimetics (3 studies, $n = 836$)[587,588,591] | 0.55 | 0.05–6.04 | NA* |
| ***Neonatal death (up to 28 days)*** | | | |
| Atosiban vs placebo (1 study, $n = 583$)[592] | 4.1 | 0.88–19.13 | NA |
| Atosiban vs betamimetics (4 studies, $n = 1130$)[587–589,591] | 0.7 | 0.27–1.81 | 0%, 0.57 |
| ***Respiratory distress syndrome*** | | | |
| Atosiban vs placebo (2 studies, $n = 689$)[589,592] | 1.28 | 0.93–1.76 | 26.2%, 0.24 |
| Atosiban vs betamimetics (4 studies, $n = 1129$)[587–589,591] | 0.99 | 0.76–1.29 | 55.2%, 0.08 |
| ***Intraventricular haemorrhage*** | | | |
| Atosiban vs placebo (1 study, $n = 489$)[592] | 0.85 | 0.45–1.62 | NA |
| ***Necrotising enterocolitis*** | | | |
| Atosiban vs placebo (1 study, $n = 575$)[592] | 0.21 | 0.02–1.76 | NA |
| Atosiban vs betamimetics (2 studies, $n = 576$)[588,590] | 0.48 | 0.12–1.98 | 0%, 0.58 |
| ***Hypoglycaemia*** | | | |
| Atosiban vs placebo (1 study, $n = 114$)[589] | 0.75 | 0.18–3.20 | NA |
| Atosiban vs betamimetics (3 studies, $n = 837$)[587,588,591] | 1.07 | 0.63–1.82 | 6%, 0.35 |
| ***Neonatal sepsis*** | | | |
| Atosiban vs betamimetics (4 studies, $n = 1129$)[587–589,591] | 0.91 | 0.56–1.46 | 0%, 0.63 |
| ***Patent duct arteriosus*** | | | |
| Atosiban vs placebo (2 studies, $n = 689$)[589,592] | 1.28 | 0.68–2.40 | 0%, 0.35 |
| Atosiban vs betamimetics (4 studies, $n = 1129$)[587–589,591] | 1.02 | 0.58–1.79 | 0%, 0.49 |
| ***Maternal adverse drug reaction requiring treatment cessation*** | | | |
| Atosiban vs placebo (2 studies, $n = 613$)[592,589] | 4.02 | 2.05–7.85 | NA* |
| Atosiban vs betamimetics (4 studies, $n = 1034$)[587–589,591] | 0.04 | 0.02–0.11 | 0%, 0.53 |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

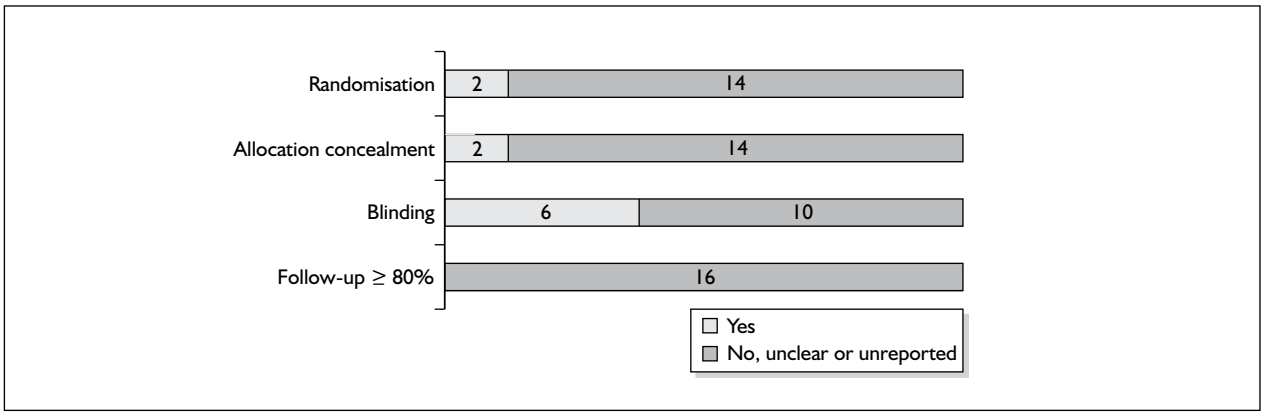


***FIGURE 215*** *Methodological quality of the included trials of non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*

| Study or subcategory | Treatment *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| Zuckerman, 1984[607] | 1/18 | 14/18 | | 65.03 | 0.07 (0.01–0.49) |
| Panter, 1999[602] | 3/16 | 8/18 | | 34.97 | 0.42 (0.13–1.32) |
| Total (95% CI) | 34 | 36 | | 100.00 | 0.19 (0.07–0.51) |
| Total events: 4 (Treatment), 22 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 2.81$, df = 1 ($p = 0.09$), $I^2 = 64.5\%$ | | | | | |
| Test for overall effect: $z = 3.35$ ($p = 0.0008$) | | | | | |

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

***FIGURE 216*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus placebo for the prevention of spontaneous preterm birth within 48 hours of initiation of treatment in symptomatic women with threatened preterm labour.*

| Study or subcategory | Treatment *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Versus betamimetic | | | | | |
| Besinger, 1991[595] | 2/22 | 3/18 | | 10.71 | 0.55 (0.10–2.92) |
| Kurki, 1991[597] | 1/30 | 7/30 | | 22.71 | 0.14 (0.02–1.09) |
| Subtotal (95% CI) | 52 | 48 | | 33.42 | 0.27 (0.08–0.96) |
| Total events: 3 (Treatment), 10 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 1.05$, df = 1 ($p = 0.31$), $I^2 = 4.5\%$ | | | | | |
| Test for overall effect: $z = 2.03$ ($p = 0.04$) | | | | | |
| 02 Versus magnesium sulphate | | | | | |
| Morales, 1993[600] | 5/49 | 8/52 | | 25.19 | 0.66 (0.23–1.89) |
| McWhorter, 2004[598] | 10/105 | 13/109 | | 41.39 | 0.80 (0.37–1.74) |
| Subtotal (95% CI) | 154 | 161 | | 66.58 | 0.75 (0.40–1.40) |
| Total events: 15 (Treatment), 21 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.08$, df = 1 ($p = 0.78$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.91$ ($p = 0.36$) | | | | | |
| Total (95% CI) | 206 | 209 | | 100.00 | 0.59 (0.34–1.02) |
| Total events: 18 (Treatment), 31 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 2.51$, df = 3 ($p = 0.47$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 1.89$ ($p = 0.06$) | | | | | |

0.1 0.2 0.5 1 2 5 10
Favours COX inhibitor Favours other tocolytic

***FIGURE 217*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus any other tocolytic for the prevention of spontaneous preterm birth within 48 hours of initiation of treatment in symptomatic women with threatened preterm labour.*



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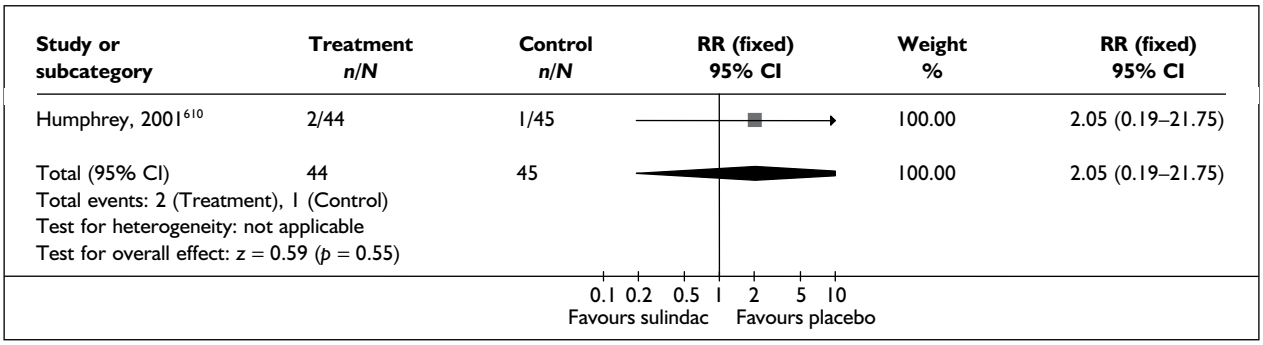


***FIGURE 218*** *Forest plot of the effects of sulindac versus placebo for the prevention of spontaneous preterm birth within 48 hours of treatment in symptomatic women with threatened preterm labour (maintenance therapy after arrest of preterm labour).*

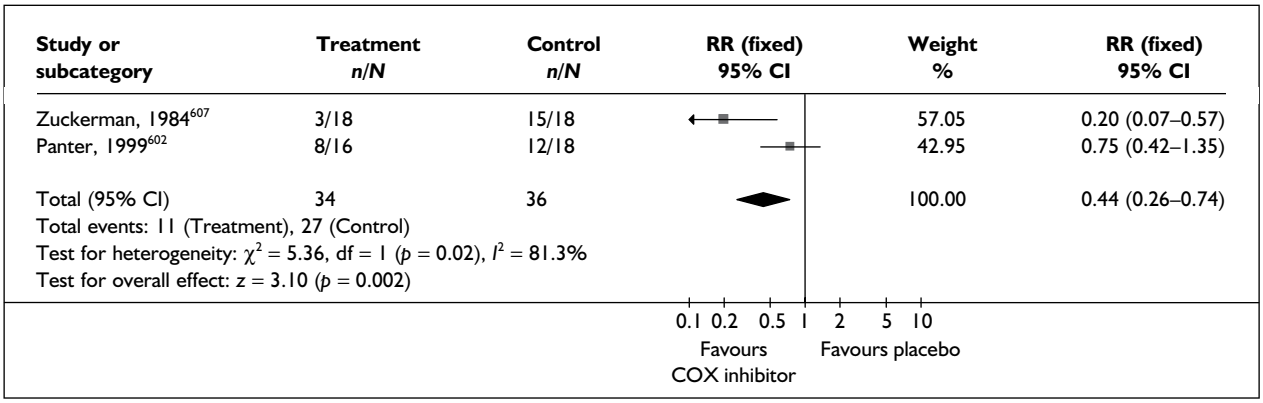


***FIGURE 219*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus placebo for the prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour.*

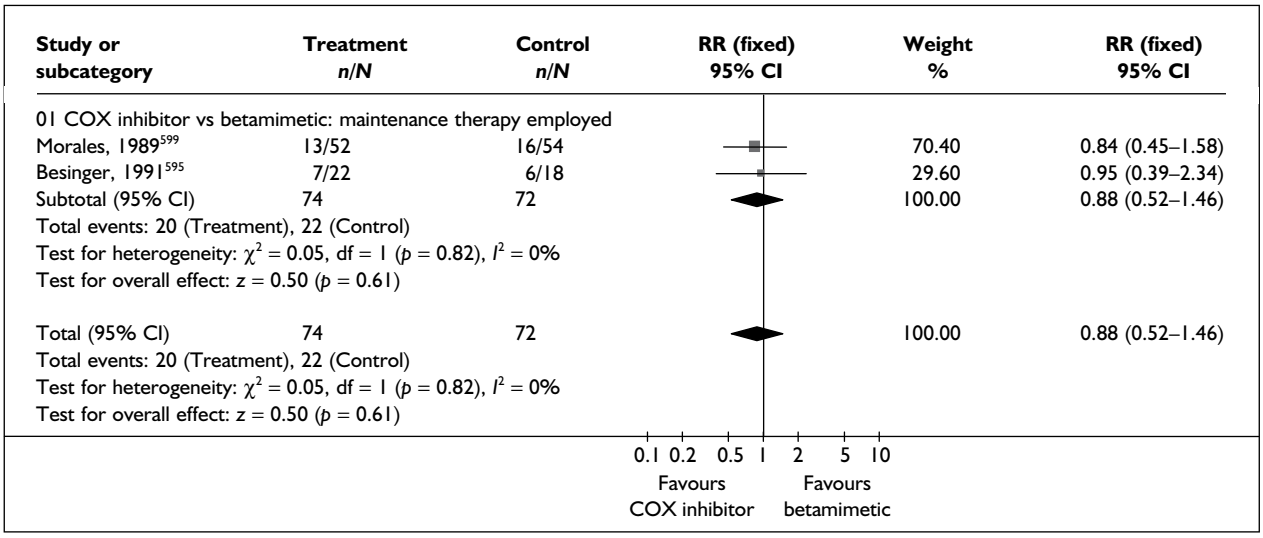


***FIGURE 220*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus betamimetic for the prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour.*

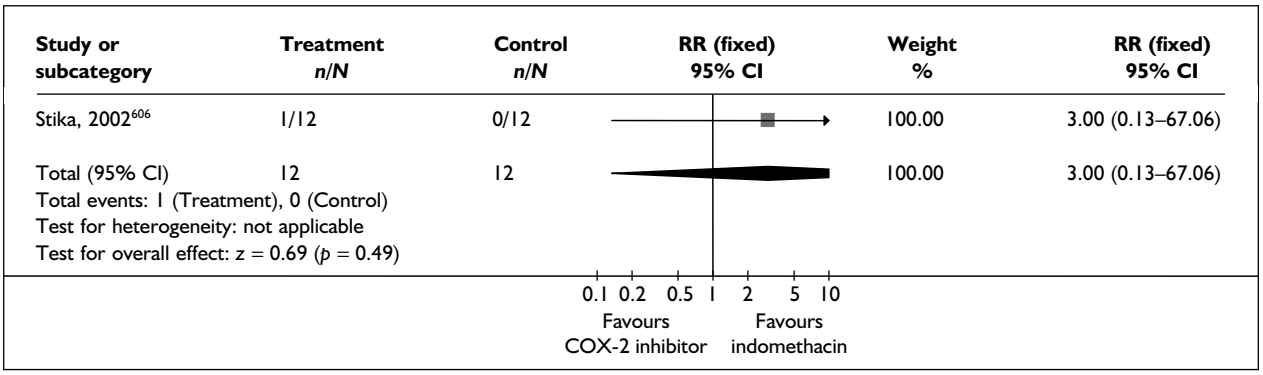


***FIGURE 221*** *Forest plot of the effects of indomethacin versus any cyclo-oxygenase 2 (COX-2) inhibitor for the prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour.*

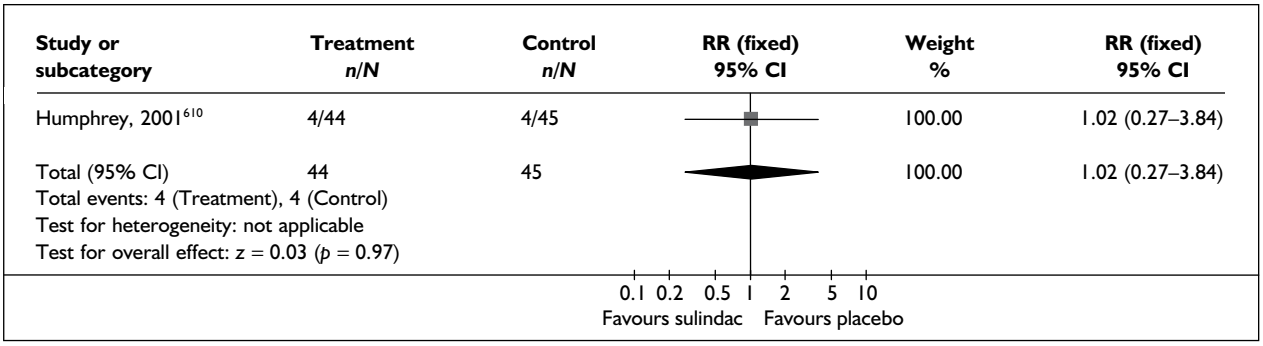


***FIGURE 222*** *Forest plot of the effects of sulindac versus placebo for the prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour (maintenance therapy after arrest of preterm labour).*

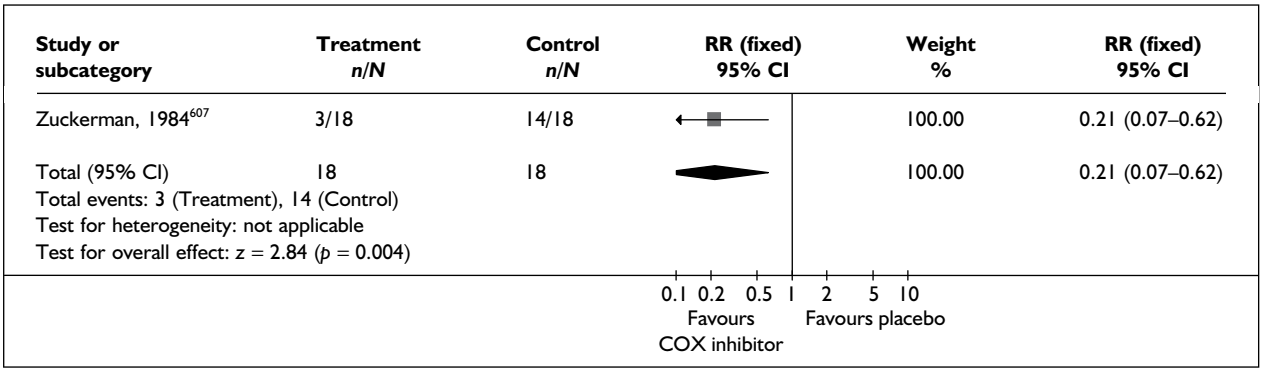


***FIGURE 223*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus placebo for the prevention of spontaneous preterm birth before 37 weeks' gestation.*



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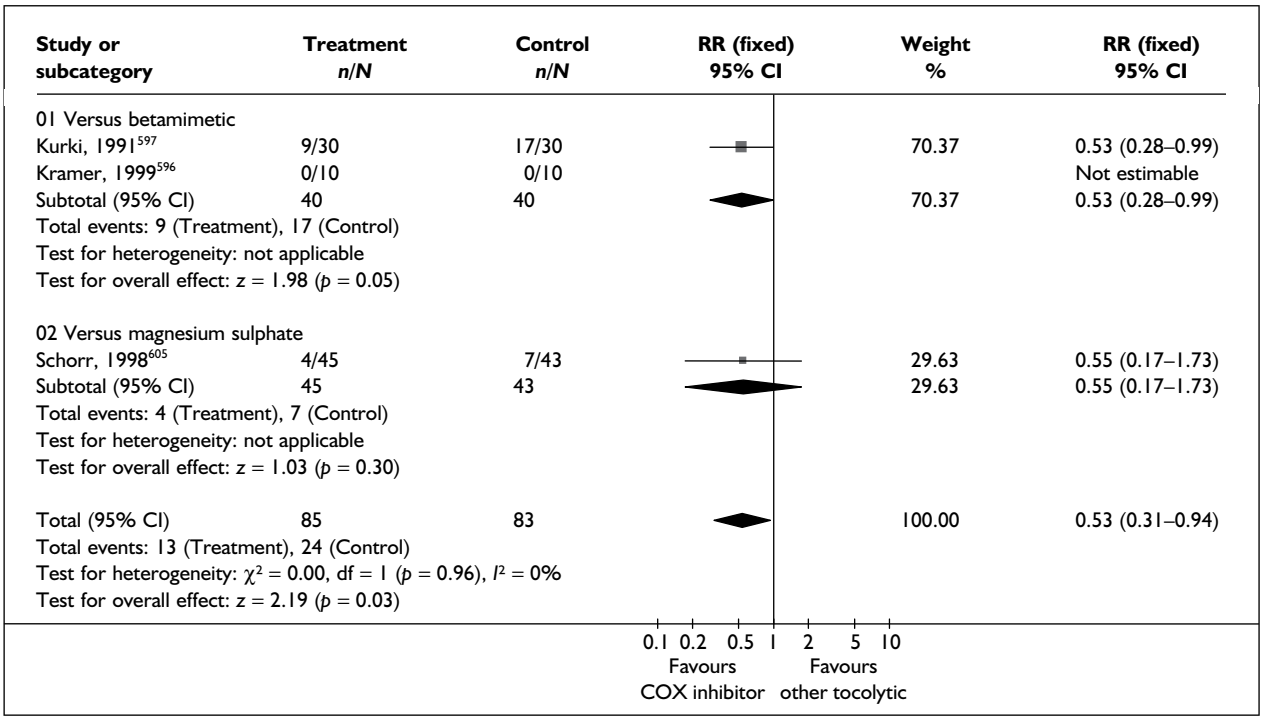


***FIGURE 224*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus any other tocolytic for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

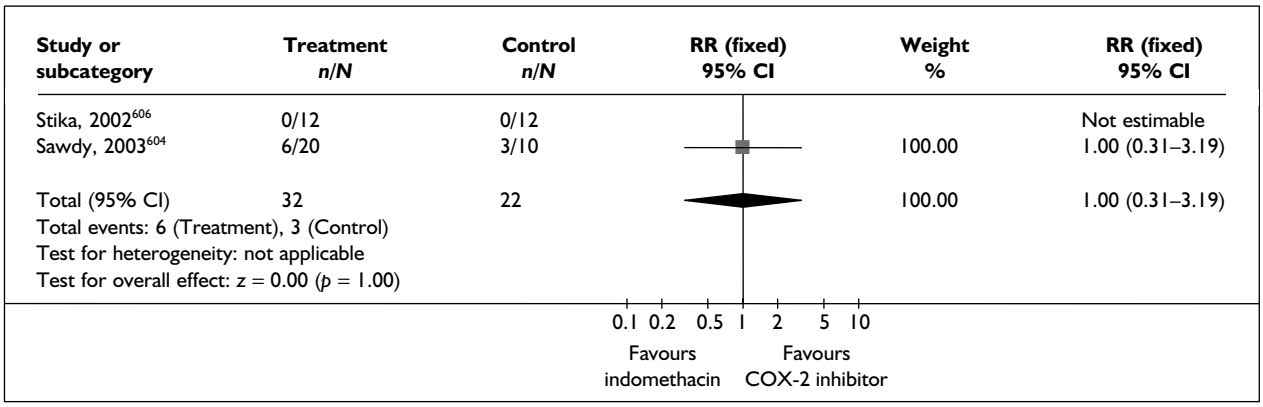


***FIGURE 225*** *Forest plot of the effects of indomethacin versus any cyclo-oxygenase 2 (COX-2) inhibitor for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

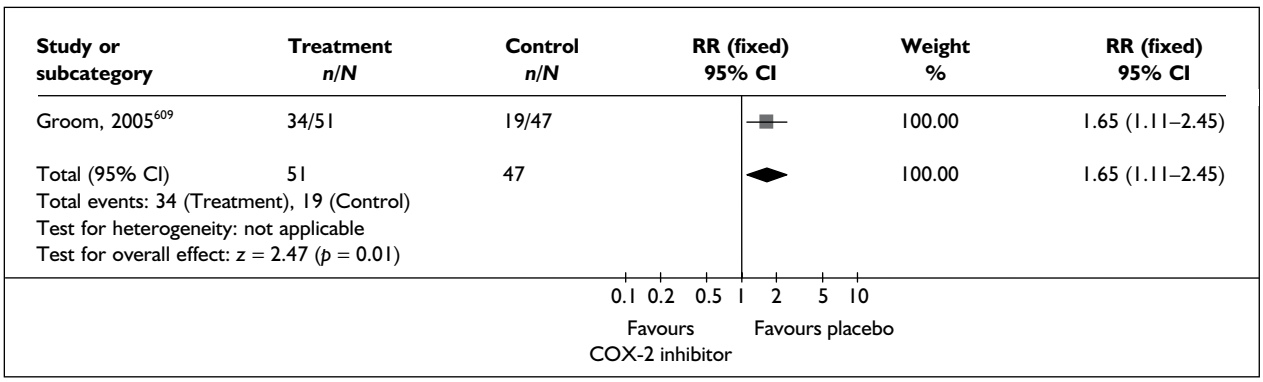


***FIGURE 226*** *Forest plot of the effects of prophylactic rofecoxib versus placebo for the prevention of spontaneous preterm birth before 37 weeks' gestation in high-risk women.*

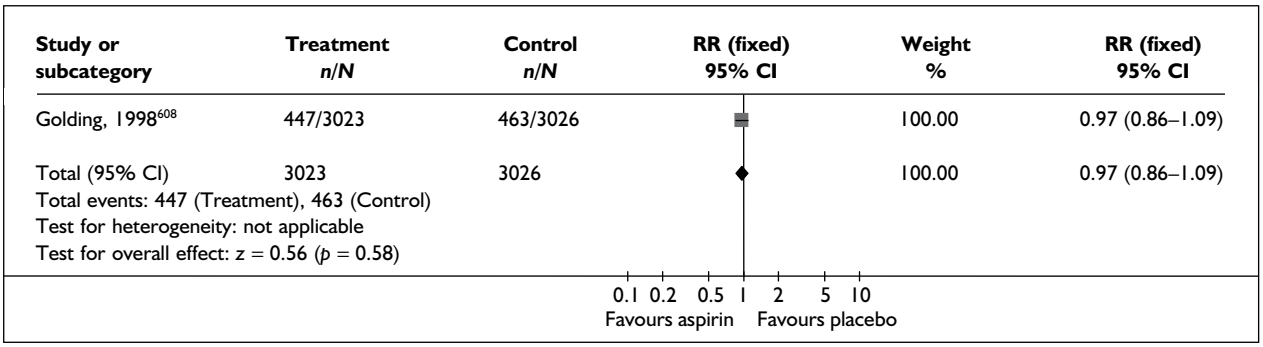


***FIGURE 227*** *Forest plot of the effects of prophylactic antenatal low-dose aspirin versus placebo for the prevention of spontaneous preterm birth before 37 weeks' gestation.*

women at risk of preterm birth to reduce the severity of neonatal RDS has become an established intervention. RDS occurring as a result of surfactant deficiency and immaturity of lung development is a serious complication of prematurity and a significant cause of perinatal and neonatal death.

The review of prophylactic antenatal corticosteroids to women symptomatic of threatened preterm labour[24] included 17 RCTs[640–657] and one quasi-RCT.[658] The latter trial was removed from the results because it did not meet the inclusion criteria for study design set out in the original review. Only corticosteroids capable of crossing the placenta were eligible for inclusion (betamethasone, dexamethasone and hydrocortisone). No additional RCTs were found when the searches were updated. Further details of the review can be found in Appendix 6, *Table 139*. The quality of the included studies was variable, as shown in *Figure 258*.

Antenatal corticosteroid given to women with expectant delivery has a beneficial effect on the incidence of RDS compared to placebo/no treatment (*Figure 259*). When subgrouped by type of corticosteroid used, betamethasone, dexamethasone and hydrocortisone all showed a reduction in the risk of RDS compared to placebo/no treatment, although this difference was not statistically significant for hydrocortisone. The effects are most clearly demonstrated after 28 weeks' and before 34 weeks' gestation, and in babies delivering 1–7 days after the intervention. (*Figures 260* and *261*, respectively). However, one trial did not show a statistically significant long-term reduction in neonatal chronic lung disease (*Figure 262*). In addition, one trial reported a significant reduction in the use of surfactant (*Figure 263*). No data on incidence of spontaneous preterm birth, perinatal mortality or requirement for neonatal intensive care unit admission was reported; however, a reduction in risk of neonatal mortality was shown in those receiving corticosteroid treatment (*Table 34*). However, antenatal corticosteroids increased the risk of maternal infection, and the likelihood of stillbirth in women with hypertension, compared to placebo/

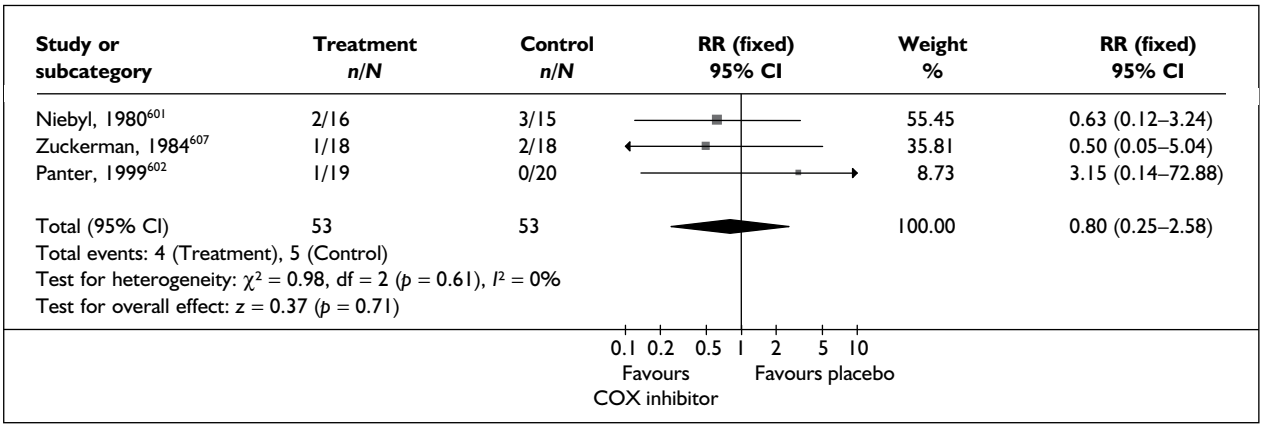


***FIGURE 228*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus placebo for the prevention of perinatal mortality related to spontaneous preterm birth.*



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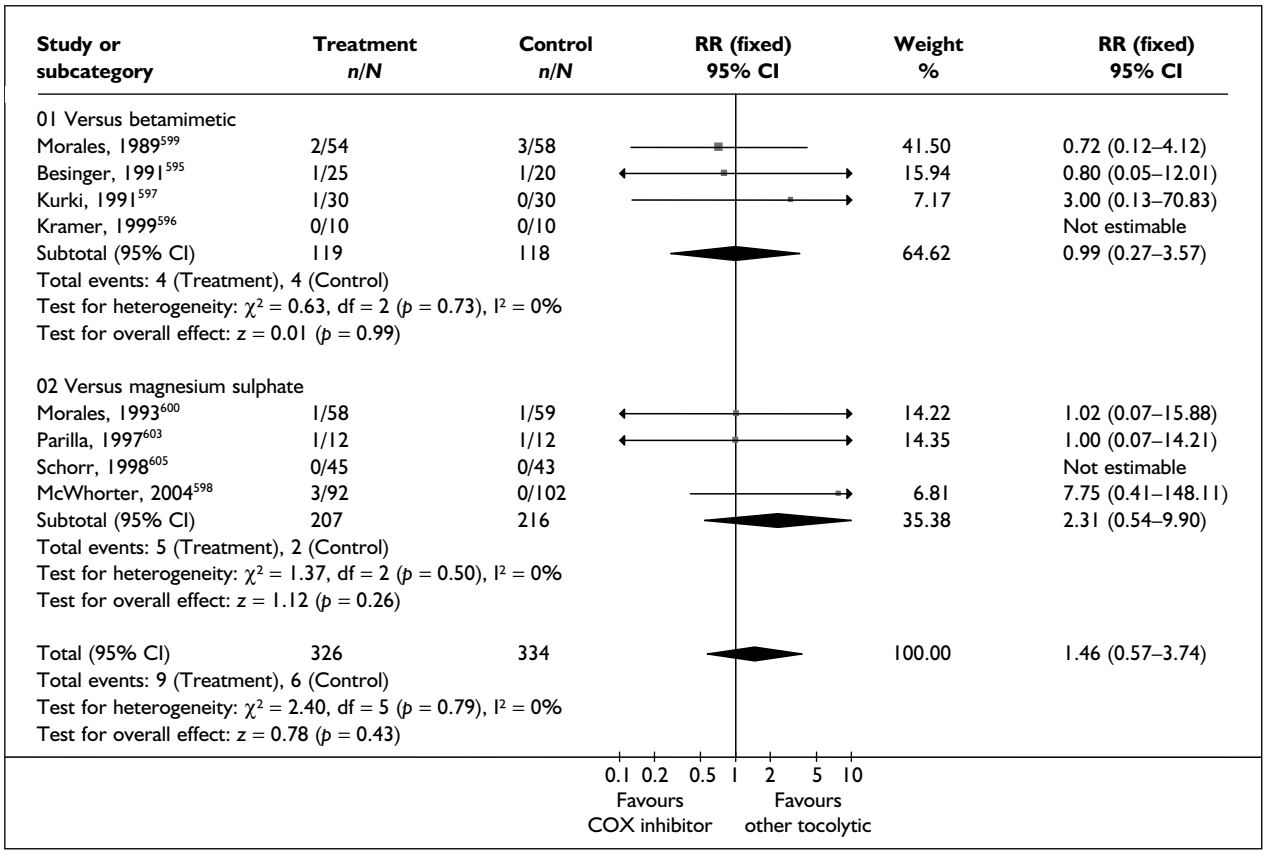


***FIGURE 229*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus any other tocolytic for the prevention of perinatal mortality related spontaneous preterm birth.*

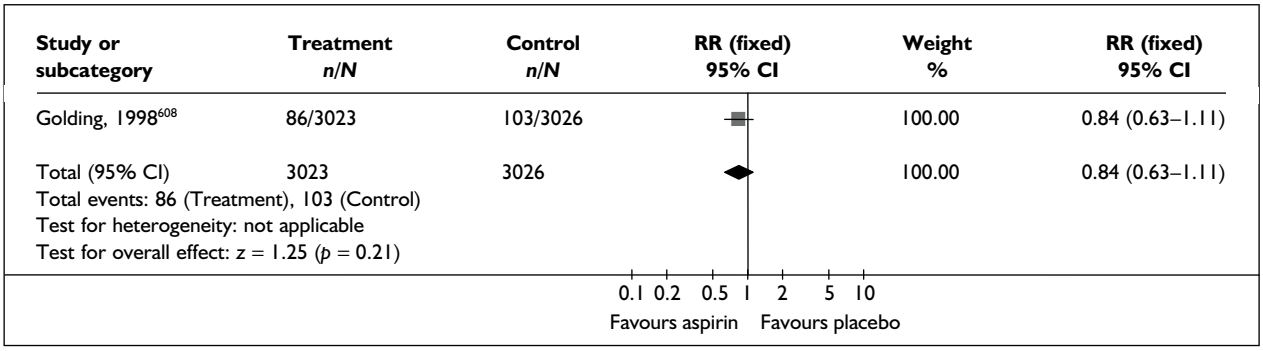


***FIGURE 230*** *Forest plot of the effects of prophylactic antenatal low-dose aspirin versus placebo for the prevention of perinatal mortality related to spontaneous preterm birth.*

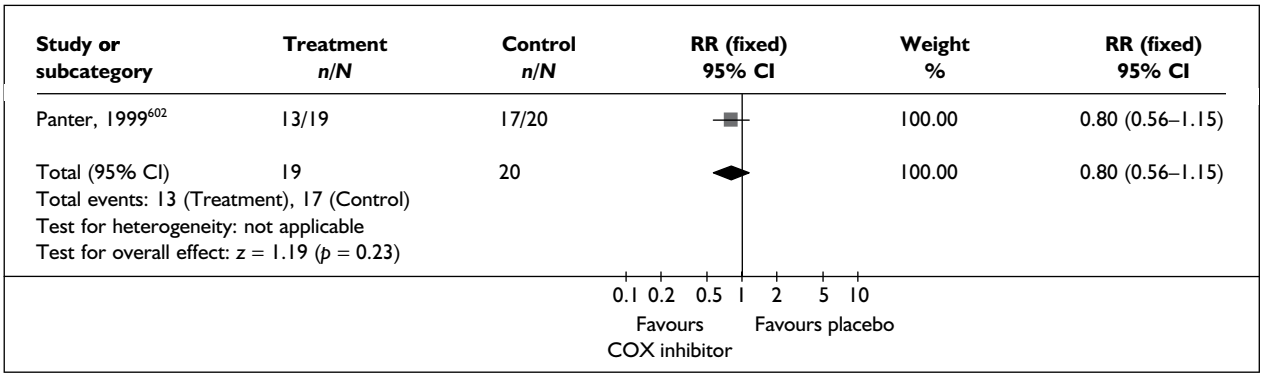


***FIGURE 231*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus placebo for the prevention of neonatal intensive care admission.*

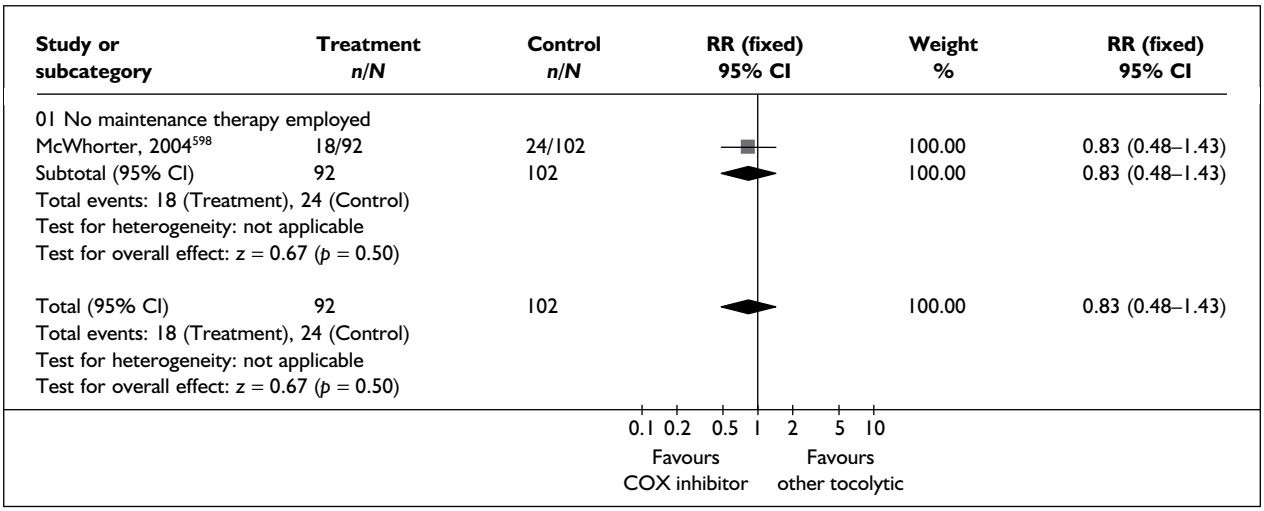


***FIGURE 232*** *Forest plot of the effects of any cyclo-oxygenase (COX) inhibitor versus magnesium sulphate for the prevention of neonatal intensive care admission.*

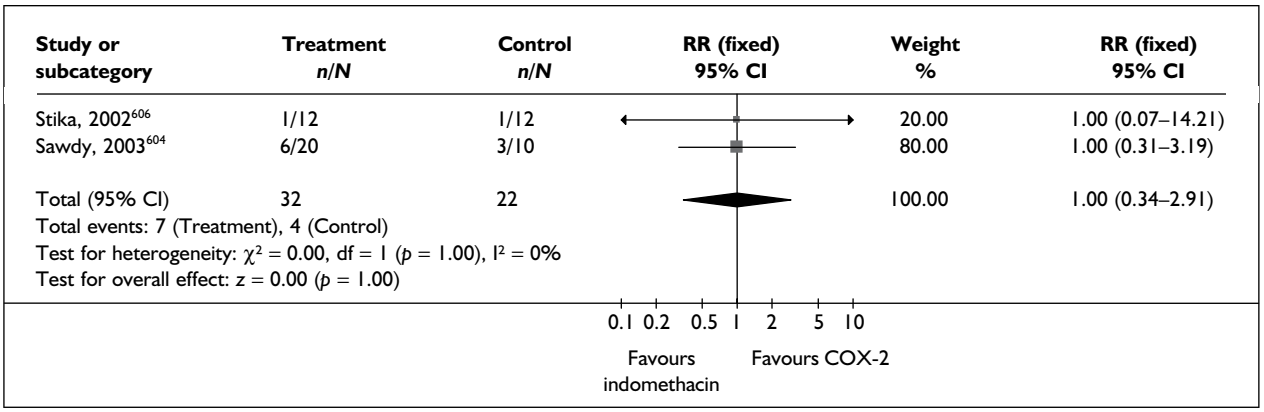


***FIGURE 233*** *Forest plot of the effects of indomethacin versus any cyclo-oxygenase 2 (COX-2) inhibitor for the prevention of neonatal intensive care admission.*

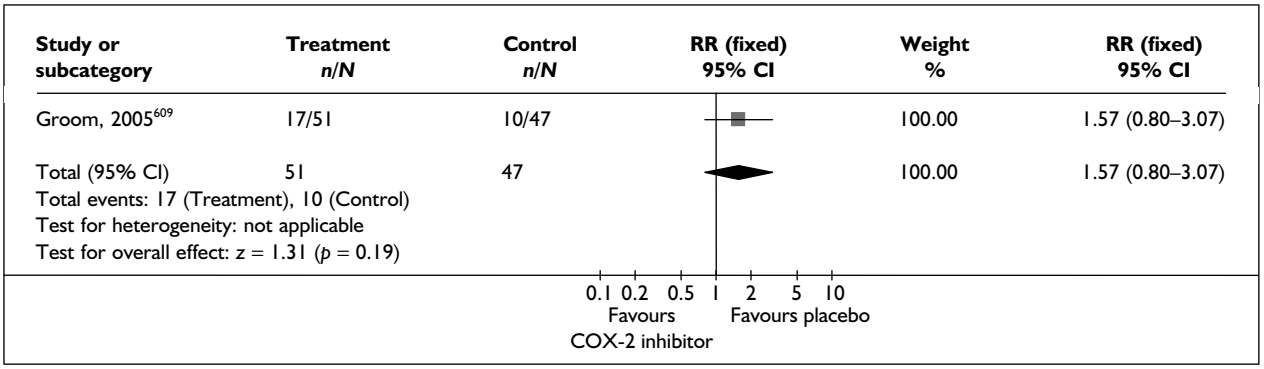


***FIGURE 234*** *Forest plot of the effects of prophylactic antenatal rofecoxib versus placebo for the prevention of neonatal intensive care admission in women at high risk of spontaneous preterm birth.*



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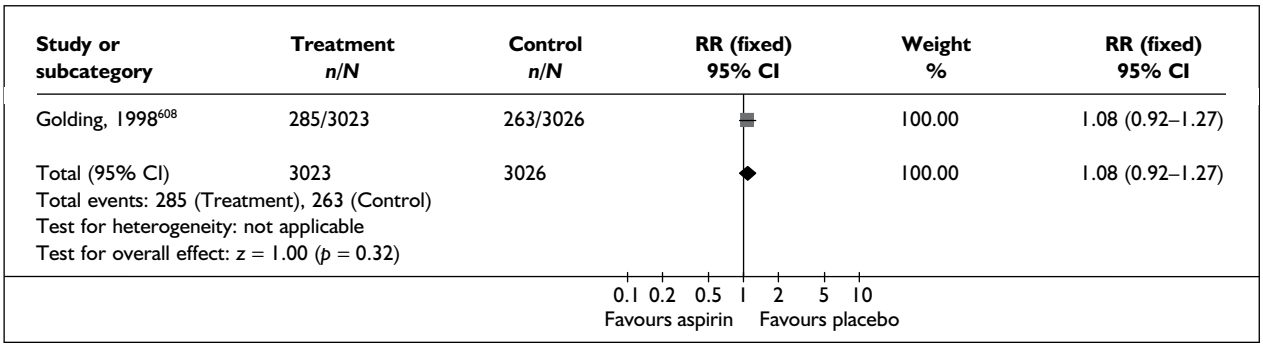


***FIGURE 235*** *Forest plot of the effects of prophylactic antenatal low-dose aspirin versus placebo for the prevention of neonatal intensive care admission.*

***TABLE 28*** *Effects of non-steroidal anti-inflammatory drugs (NSAIDs)/cyclo-oxygenase 2 (COX-2) inhibitors on primary outcomes: effect of whether maintenance therapy was employed*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Birth <37 weeks gestation*** | | | |
| Versus betamimetic (2 studies, $n = 80$) [596,597] | 0.53 | 0.28–0.99 | NA |
| Maintenance therapy employed (1 study, $n = 20$) [596] | Not estimable | Not estimable | NA |
| No maintenance therapy employed (1 study, $n = 60$) [597] | 0.53 | 0.28–0.99 | NA |
| ***Birth within 48 h of intervention*** | | | |
| Versus betamimetic (2 studies, $n = 620$) [595,597] | 0.27 | 0.08–0.96 | 4.5% (0.31) |
| Maintenance therapy employed (1 study, $n = 40$) [595] | 0.55 | 0.10–2.92 | NA |
| No maintenance therapy employed (1 study, $n = 60$) [597] | 0.14 | 0.02–1.09 | NA |
| Versus magnesium sulphate (2 studies, $n = 315$) [598,600] | 0.75 | 0.40–1.40 | 0% (0.78) |
| Maintenance therapy employed (1 study, $n = 101$) [600] | 0.66 | 0.23–1.89 | NA |
| No maintenance therapy employed (1 study, $n = 214$) [600] | 0.8 | 0.37–1.74 | NA |
| ***Perinatal mortality*** | | | |
| Versus betamimetic (4 studies, $n = 237$) [595–597,599] | 0.99 | 0.27–3.57 | 0% (0.73) |
| Maintenance therapy employed (3 studies, $n = 177$) [595,596,599] | 0.74 | 0.17–3.21 | 0% (0.95) |
| No maintenance therapy employed (1 study, $n = 60$) [597] | 3 | 0.13–70.83 | NA |
| Versus magnesium sulphate (4 studies, $n = 423$) [598,600,603,605] | 2.31 | 0.54–9.90 | 0% (0.50) |
| Maintenance therapy employed (2 studies, $n = 205$) [598,605] | 1.02 | 0.07–15.88 | NA |
| No maintenance therapy employed (2 studies, $n = 218$) [600,603] | 3.17 | 0.53–19.10 | 7.4% (0.30) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

***TABLE 29*** *Effects of non-steroidal anti-inflammatory drugs/cyclo-oxygenase 2 (NSAIDs/COX-2) inhibitors on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Birth within 48 h of intervention*** | | | |
| Indomethacin vs COX-2 inhibitor (1 study, $n = 24$)[606] | Not estimable | Not estimable | NA |
| Birth within 7 days of intervention | | | |
| Indomethacin vs COX-2 inhibitor (1 study, $n = 24$)[606] | Not estimable | Not estimable | NA |
| ***Perinatal mortality*** | | | |
| Indomethacin vs COX-2 inhibitor (2 studies, $n = 54$)[604,606] | Not estimable | Not estimable | NA |
| ***Low birthweight (< 2500 g)*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, $n = 6049$)[608] | 0.93 | 0.80–1.08 | NA |
| ***Respiratory distress syndrome*** | | | |
| COX inhibitor vs placebo (3 studies, $n = 106$)[601,602,607] | 1 | 0.40–2.49 | 26.2% (0.26) |
| COX inhibitor vs other tocolytic (6 studies, $n = 503$)[596–598,600,603,605] | 1.08 | 0.66–1.76 | 0% (0.98) |
| Indomethacin vs COX-2 inhibitor (1 study, $n = 24$)[606] | 1 | 0.07–14.21 | NA |
| Sulindac vs placebo (maintenance therapy) (1 study, $n = 89$)[610] | 1.53 | 0.27–8.74 | NA |
| ***Neonatal mechanical ventilation*** | | | |
| COX inhibitor vs other tocolytic (betamimetic, no maintenance therapy employed) (1 study, $n = 60$)[597] | 1.5 | 0.47–4.78 | NA |
| Indomethacin vs COX-2 inhibitor (1 study, $n = 24$)[606] | 1 | 0.07–14.21 | NA |
| Rofecoxib vs placebo (prophylaxis) (1 study, $n = 98$)[609] | 1.84 | 0.49–6.96 | NA |
| ***Intraventricular haemorrhage: all grades*** | | | |
| COX inhibitor vs other tocolytic (7 studies, $n = 548$)[595–598,600,603,605] | 1.18 | 0.66–2.11 | 0% (0.58) |
| Indomethacin vs COX-2 inhibitor (1 study, $n = 24$)[606] | 0.5 | 0.05–4.81 | NA |
| ***Intraventricular haemorrhage: grades 3 and 4*** | | | |
| COX inhibitor vs placebo (1 study, $n = 39$)[602] | 3.15 | 0.14–72.88 | NA |
| COX inhibitor vs other tocolytic (4 studies, $n = 249$)[596,600,603,605,] | 0.61 | 0.08–4.40 | 0% (0.60) |
| ***Intercranial haemorrhage*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, $n = 6049$)[608] | 3 | 0.12–73.69 | NA |
| ***Other neonatal bleeding*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, $n = 6049$)[608] | 1.5 | 0.25–8.98 | NA |
| ***Necrotising enterocolitis*** | | | |
| COX inhibitor vs placebo (2 studies, $n = 70$)[601,602] | 0.97 | 0.21–4.43 | 0% (0.94) |
| COX inhibitor vs other tocolytic (4 studies, $n = 298$)[596–598,603] | 3.82 | 0.65–22.51 | 0% (0.95) |
| Rofecoxib vs placebo (prophylaxis) (1 study, $n = 98$)[609] | 2.77 | 0.12–66.36 | NA |

*continued*



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***TABLE 29*** *Effects of non-steroidal anti-inflammatory drugs/cyclo-oxygenase 2 (NSAIDs/COX-2) inhibitors on other perinatal and maternal outcomes (continued)*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Chronic neonatal lung disease*** | | | |
| COX inhibitor vs placebo (2 studies, $n = 70$)[601,602] | 1.24 | 0.39–3.94 | 60.1% (0.11) |
| Rofecoxib vs placebo (prophylaxis) (1 study, $n = 98$)[609] | 0.92 | 0.20–4.34 | NA |
| ***Apgar score <7 at 5 min*** | | | |
| COX inhibitor vs placebo (1 study, $n = 39$)[602] | 0.53 | 0.05–5.34 | NA |
| COX inhibitor vs other tocolytic (2 studies, $n = 254$) [597,598] | 0.53 | 0.21–1.30 | 25.2% (0.25) |
| Indomethacin vs COX-2 inhibitor (1 study, $n = 24$)[606] | 3 | 0.13–67.06 | NA |
| ***Apgar score <5 at 5 min*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, $n = 6049$)[608] | 1.52 | 0.92–2.51 | NA |
| *Persistent pulmonary hypertension of newborn* | | | |
| COX inhibitor vs other tocolytic (5 studies, $n = 488$)[595,596,598–600] | 2.85 | 0.56–14.38 | 0% (0.72) |
| ***Neonatal sepsis*** | | | |
| COX inhibitor vs placebo (2 studies, $n = 70$)[601,602] | 0.31 | 0.01–7.15 | NA |
| COX inhibitor vs betamimetic (2 studies, $n = 80$)[596,597] | 1 | 0.07–15.26 | NA |
| Indomethacin vs COX-2 inhibitor (1 study, $n = 24$)[606] | 0.33 | 0.01–7.45 | NA |
| Sulindac vs placebo (maintenance therapy) (1 study, $n = 89$)[610] | 1.02 | 0.15–6.94 | NA |
| ***Neonate discharged alive and well*** | | | |
| Rofecoxib vs placebo (prophylaxis) (1 study, $n = 98$)[609] | 0.9 | 0.73–1.10 | NA |
| ***Maternal adverse drug reaction*** | | | |
| COX inhibitor vs placebo (3 studies, $n = 101$)[601,602,607] | 1.58 | 0.66–3.78 | 0% (0.87) |
| COX inhibitor vs other tocolytic | 0.22 | 0.15–0.33 | 65.8% (0.01) |
| Total (7 studies, $n = 629$)[595–600,603] | 0.1 | 0.05–0.20 | 5 |
| COX inhibitor vs betamimetic (4 studies, $n = 226$)[595–597,599] | 0.03 | 0.01–0.15 | 9.1% (0.06) |
| Maintenance therapy employed (3 studies, $n = 166$)[595,596,599] | 0.24 | 0.12–0.50 | 0% (0.56) |
| No maintenance therapy employed (1 study, $n = 60$)[597] | 0.41 | 0.26–0.66 | NA |
| COX inhibitor vs magnesium sulphate (3 studies, $n = 403$)[598,600,605] | 0.2 | 0.06–0.64 | 3.5% (0.14) |
| Maintenance therapy employed (2 studies, $n = 189$)[600,605] | 0.51 | 0.30–0.86 | NA |
| No maintenance therapy employed (1 study, $n = 214$)[598] | | | NA |
| ***Maternal adverse drug reaction requiring cessation of treatment*** | | | |
| COX inhibitor vs other tocolytic | 0.07 | 0.02–0.29 | 0% (0.81) |
| Total (5 studies, $n = 355$)[595,596,599,600,605] | 0.07 | 0.01–0.37 | 0% (0.63) |
| COX inhibitor vs betamimetic, maintenance therapy employed (3 studies, $n = 166$)[595,596,599] | 0.06 | 0.00–1.05 | NA |

***TABLE 29*** *Effects of non-steroidal anti-inflammatory drugs/cyclo-oxygenase 2 (NSAIDs/COX-2) inhibitors on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| COX inhibitor vs magnesium sulphate, maintenance therapy employed (2 studies, *n* = 189)[600,605] | 1 | 0.63–1.59 | NA |
| Aspirin vs placebo (prophylaxis) (1 study, *n* = 6049)[608] | | | |
| ***Treatment required to be stopped <32 weeks gestation*** | | | |
| Rofecoxib vs placebo (prophylaxis) (1 study, *n* = 98)[609] | 1.21 | 0.72–2.03 | na |
| ***Antepartum haemorrhage*** | | | |
| Indomethacin vs COX-2 inhibitor (1 study, *n* = 24)[606] | 0.33 | 0.01–7.45 | NA |
| ***Postpartum haemorrhage*** | | | |
| COX inhibitor vs placebo (1 study, *n* = 34)[602] | 3.94 | 0.95–16.29 | NA |
| Rofecoxib vs placebo (prophylaxis) (1 study, *n* = 98)[609] | 2.77 | 0.12–66.36 | NA |
| Aspirin vs placebo (prophylaxis) (1 study, *n* = 6049)[608] | 1.38 | 1.13–1.68 | NA |
| ***Chorioamnionitis or endometritis*** | | | |
| COX inhibitor vs placebo (2 studies, *n* = 64)[601,602] | 1.94 | 0.44–8.60 | 0% (0.39) |
| Indomethacin vs COX-2 inhibitor (1 study, *n* = 24)[606] | 2 | 0.21–19.23 | NA |
| ***Oligohydramnios*** | | | |
| COX inhibitor vs other tocolytic (3 studies, *n* = 295)[599,600,605] | 2.53 | 0.76–8.84 | 0% (0.57) |
| Indomethacin vs COX-2 inhibitor (1 study, *n* = 24)[606] | 4 | 0.52–30.76 | NA |
| Rofecoxib vs placebo (prophylaxis) (1 study, *n* = 98)[609] | 8.29 | 1.09–63.00 | NA |
| ***PPROM*** | | | |
| Rofecoxib vs placebo (prophylaxis) (1 study, *n* = 98)[609] | 2.46 | 1.28–4.73 | NA |
| ***Vaginal bleeding during pregnancy*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, *n* = 6049)[608] | 1.12 | 0.81–1.55 | NA |
| ***Vomiting blood during pregnancy*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, *n* = 6049)[608] | 0.88 | 0.44–1.77 | NA |
| ***Other maternal bleeding during pregnancy*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, *n* = 6049)[608] | 1.53 | 1.02–2.29 | NA |
| ***Antenatal admission*** | | | |
| Aspirin vs placebo (prophylaxis) (1 study, *n* = 6049)[608] | 1.07 | 0.96–1.20 | NA |

CI, confidence interval; NA, not available; PPROM, premature pre-labour rupture of membranes; RCT, randomised controlled trial; RR, relative risk.



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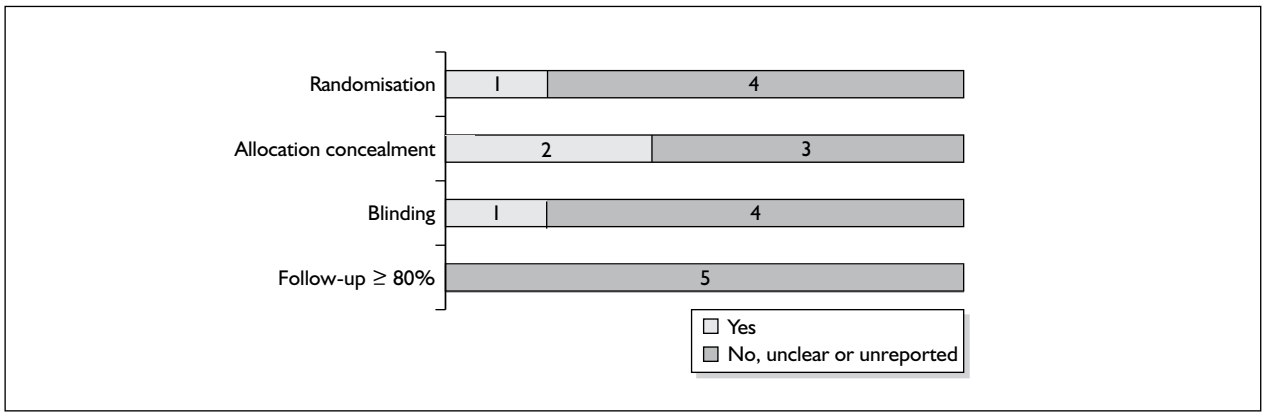


***FIGURE 236*** *Methodological quality of the included trials of ethanol for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*

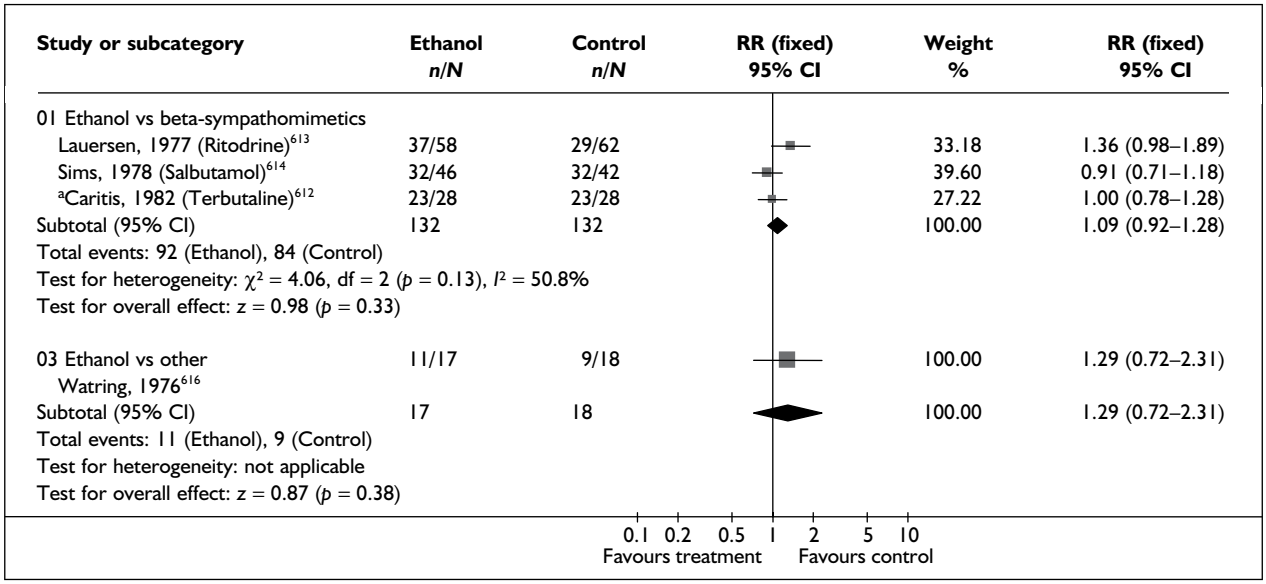


***FIGURE 237*** *Forest plot of the effects of ethanol versus beta-sympathomimetics for the prevention of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour. a, Women with intact membranes only.*

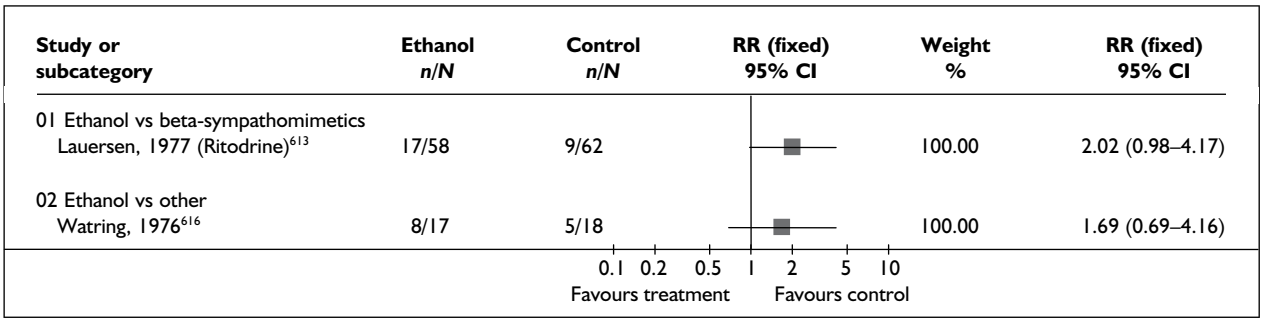


***FIGURE 238*** *Forest plot of the effects of ethanol versus beta-sympathomimetics for the prevention of spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour.*

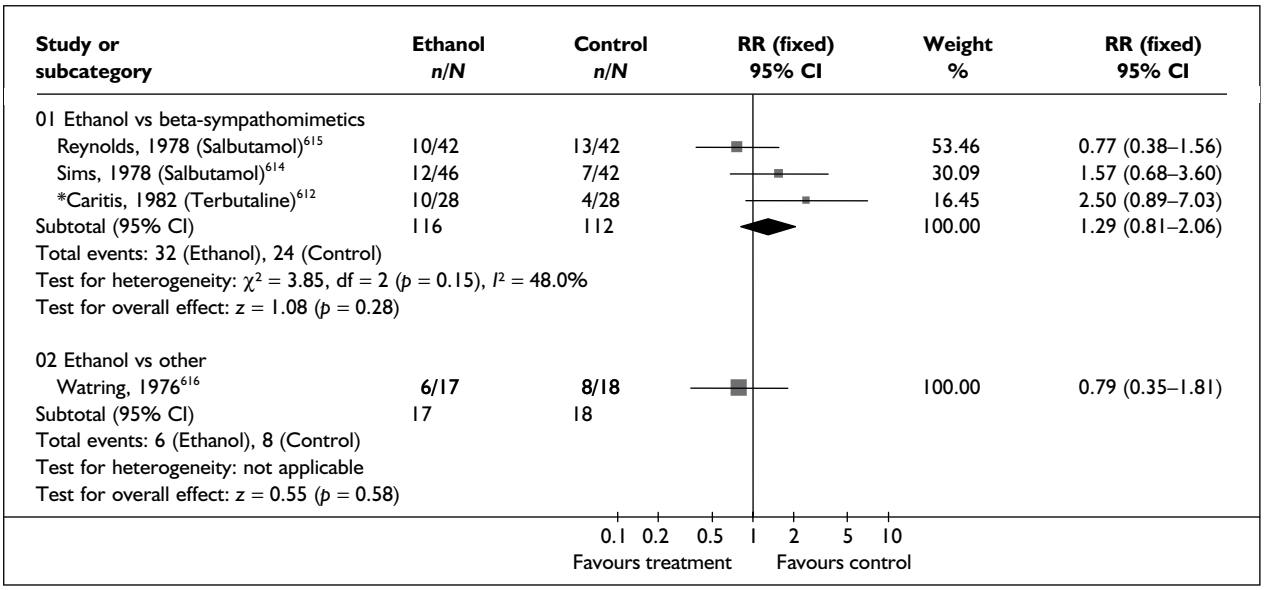


***FIGURE 239*** *Forest plot of the effects of ethanol versus beta-sympathomimetics for the prevention of spontaneous preterm birth within 24 hours of treatment in symptomatic women with threatened preterm labour. a, Women with intact membranes only.*

no treatment; but appeared to decrease the risk of intraventricular haemorrhage and demonstrated a trend in the reduction of necrotising enterocolitis in the premature neonates. Summary RRs for the primary outcomes of all infants assessed were used in the decision analyses. It should be noted that most of the trials included a mixed population, with infants from both singleton and multiple gestations included in the results. Overall, despite some evidence of adverse events, prophylactic corticosteroids are effective in reducing RDS in preterm babies and the current recommendation for their routine use appears justified.

## Repeat corticosteroid course(s)

For women at increased risk of spontaneous preterm birth, the benefits of a single course of antenatal corticosteroids are well established, including a reduction in neonatal RDS, intraventricular haemorrhage, neonatal mortality and the need for surfactant therapy. The normal thinning of the double capillary loops, to form the thin gas exchanging walls of alveoli, is accelerated, resulting in rapid alveolisation.[659] The maturation of surfactant producing type II pneumocytes is also accelerated.[660] Repeat courses of antenatal corticosteroids are less well studied.

The review of repeat antenatal corticosteroid course(s)[661] for the prevention of neonatal respiratory disease included three RCTs ($n = 551$);[662–664] no additional trials were found. Further details of the review can be found in Appendix 6, *Table 139*. The quality of these studies was good as shown in *Figure 264*. No statistically

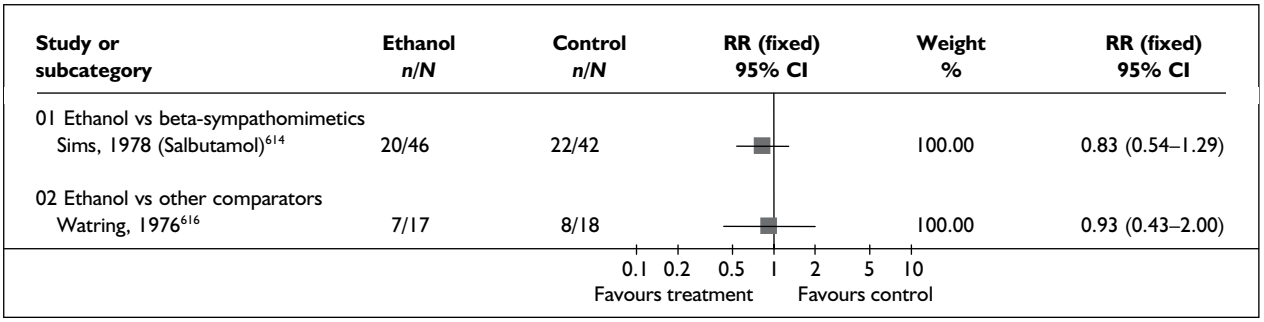


***FIGURE 240*** *Forest plot of the effects of ethanol versus beta-sympathomimetics for the prevention of spontaneous preterm birth within 48 hours of treatment in symptomatic women with threatened preterm labour.*



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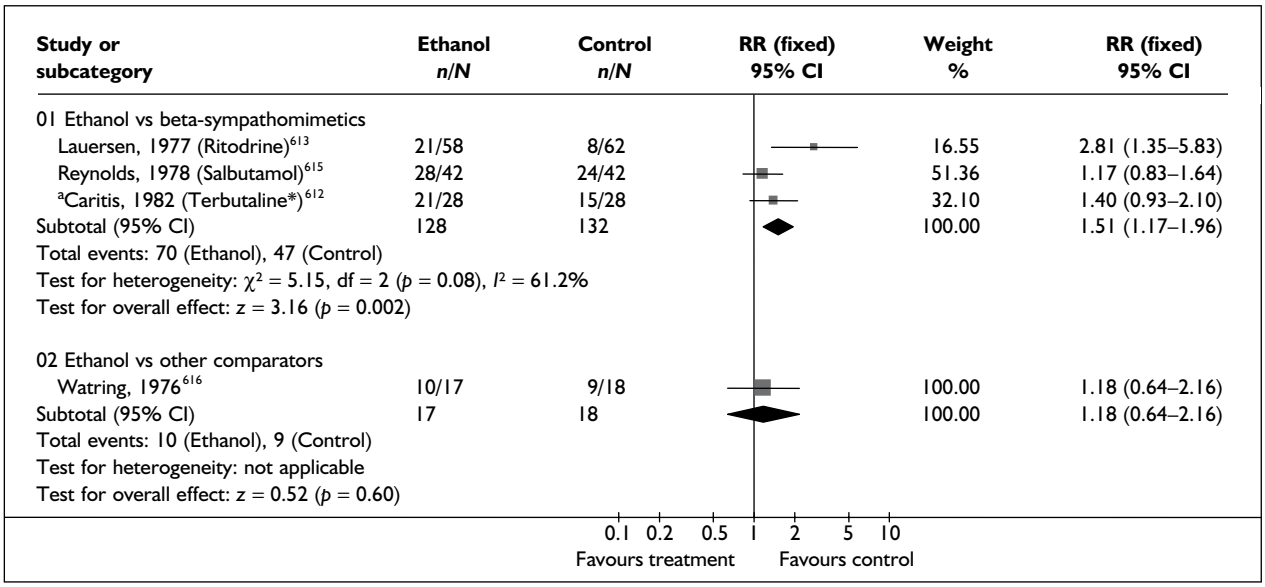


***FIGURE 241*** *Forest plot of the effects of ethanol versus beta-sympathomimetics for the prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour. a, Women with intact membranes only*

significant between-group differences were shown for any other infant or maternal outcome reported, including the risk of spontaneous preterm birth before 37 and 34 weeks' gestation (*Figures 265* and *266,* respectively, and *Table 35*). While the use of repeat course(s) did not reduce the risk of RDS or the risk of chronic lung disease (*Figures 267* and *268*), a small reduction in the severity of lung disease was shown in infants receiving repeat course(s) of corticosteroids compared to placebo, based on one trial (*Figure 269*). In addition, fewer infants receiving repeat corticosteroid course(s) required surfactant therapy compared to placebo (*Table 35*). None of these studies reported outcomes of perinatal mortality or admission to a neonatal intensive care unit. Two RCTs were published after the searches were completed.[665,666] These studies were not included in the review because neither reported separate data for women with singleton pregnancies. However, both studies suggested that repeat doses of corticosteroids may be beneficial to babies at continued risk of preterm birth following initial corticosteroid treatment. Summary RRs, comparing repeat doses of antenatal corticosteroids with a single prenatal corticosteroid dose, were used in the decision analyses for all primary end points. Overall, the current benefit and risk data are insufficient to support the routine use of repeat or rescue courses of antenatal corticosteroids in clinical practice.

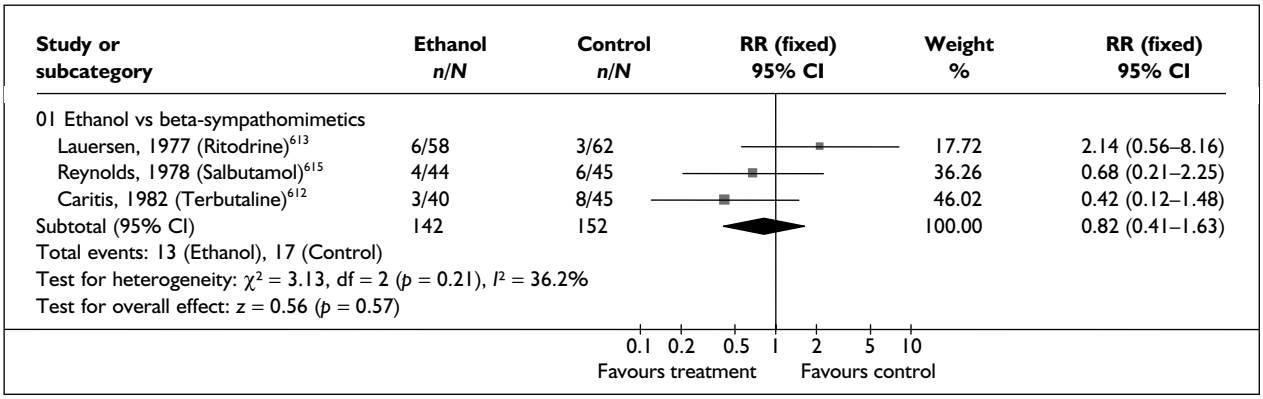


***FIGURE 242*** *Forest plot of the effects of ethanol versus beta-sympathomimetic tocolysis for the prevention of perinatal mortality related to spontaneous preterm birth.*

***TABLE 30*** *Effect of ethanol tocolysis on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Stillbirths*** | | | |
| Ethanol vs terbutaline (1 study, $n = 56$)[612] | 0.5 | 0.05–5.20 | NA |
| ***Neonatal death*** | ***0.33*** | ***0.07–1.51*** | ***NA*** |
| Ethanol vs terbutaline (1 study, $n = 56$)[612] | 2.45 | 0.67–9.04 | NA |
| Ethanol vs ritodrine (1 study, $n = 119$)[613] | 2.28 | 0.77–6.73 | NA |
| Ethanol vs salbutamol (1 study, $n = 88$)[614] | 1.41 | 0.37–5.40 | NA |
| Ethanol vs other comparators (1 study, $n = 35$)[616] | | | |
| ***Respiratory distress syndrome*** | | | |
| Ethanol vs ritodrine (1 study, $n = 149$)[613] | 2.4 | 0.99–5.85 | NA |
| Ethanol vs other comparators (1 study, $n = 35$)[616] | 0.85 | 0.27–2.64 | NA |
| ***Hyaline membrane disease*** | | | |
| Ethanol vs terbutaline (1 study, $n = 56$)[612] | 1 | 0.47–2.14 | NA |
| ***Birthweight*** | | | |
| Ethanol vs other comparators (1 study, $n = 35$)[616] | WMD –431.43 | –1038.63 to 175.77 | NA |
| *Birthweight <2500 g* | | | |
| Ethanol vs ritodrine (1 study, $n = 149$)[613] | *2.49* | *1.57–3.93* | *NA* |
| *Birthweight <1500 g* | | | |
| Ethanol vs ritodrine (1 study, $n = 149$)[613] | 1.76 | 0.69–4.51 | NA |
| ***Maternal chest pain and shortness of breath*** | | | |
| Ethanol vs terbutaline (1 study, $n = 85$)[613] | 0.1 | 0.01–1.79 | NA |
| ***Mean maternal heart acceleration (beats/min)*** | | | |
| Ethanol vs ritodrine (1 study, $n = 135$)[613] | WMD –22.20 | –26.74 to –7.66 | NA |
| ***Mean fetal heart acceleration (beats/min)*** | | | |
| Ethanol vs ritodrine (1 study, $n = 149$)[613] | WMD –10.40 | –14.83 to –5.97 | NA |
| ***Mean maternal systolic blood pressure increase (mmHg)*** | | | |
| Ethanol vs ritodrine (1 study, $n = 135$)[613] | WMD –9.20 | –12.73 to –5.67 | NA |
| ***Mean fetal systolic blood pressure decrease (mmHg)*** | | | |
| Ethanol vs ritodrine (1 study, $n = 149$)[613] | WMD –5.80 | –9.16 to –2.44 | NA |
| ***Cardiac arrhythmia*** | | | |
| Ethanol vs terbutaline (1 study, $n = 85$)[612] | 0.37 | 0.02–8.93 | NA |
| ***Maternal nausea and vomiting*** | | | |
| Ethanol vs terbutaline (1 study, $n = 85$)[612] | 10.33 | 3.42–31.21 | NA |
| Ethanol vs salbutamol (1 study, $n = 84$)[615] | 2.77 | 1.71–4.49 | NA |
| ***Loss of consciousness*** | | | |
| Ethanol vs terbutaline (1 study, $n = 85$)[612] | 21.23 | 1.28–354.96 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.



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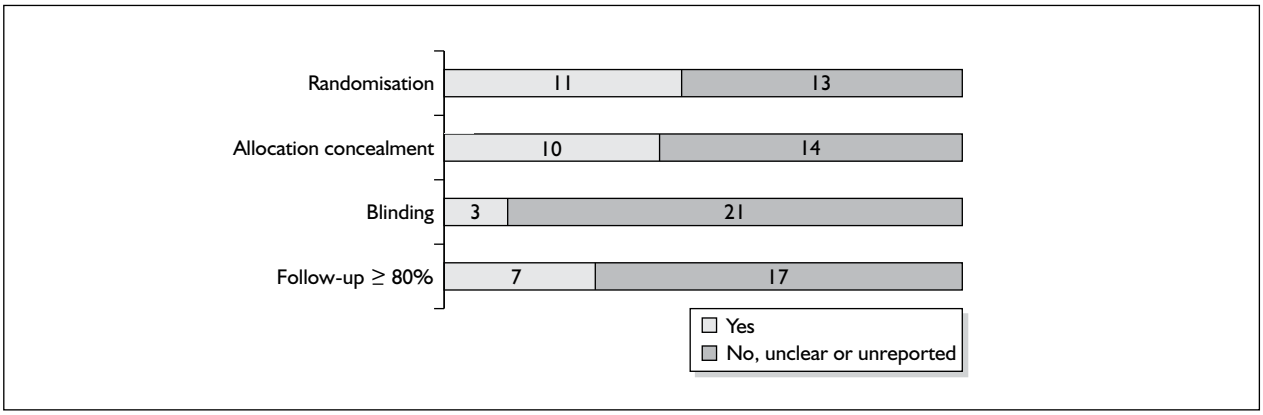


***FIGURE 243*** *Methodological quality of the included trials of magnesium sulphate tocolysis for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*

| Study or subcategory | Magnesium sulphate *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Betamimetics | | | | | |
| Wilkins, 1988[613] (Ritodrine) | 35/66 | 29/54 | | 49.32 | 0.99 (0.71–1.38) |
| Aramayo, 1990[617] (Terbutaline) | 11/15 | 9/14 | | 14.39 | 1.14 (0.69–1.87) |
| Chau, 1992[631] (Terbutaline) | 12/46 | 25/52 | | 36.29 | 0.54 (0.31–0.95) |
| Subtotal (95% CI) | 127 | 120 | | 100.00 | 0.85 (0.66–1.10) |
| Total events: 58 (Magnesium sulphate), 63 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 4.58$, df = 2 ($p = 0.10$), $I^2 = 56.4\%$ | | | | | |
| Test for overall effect: $z = 1.26$ ($p = 0.21$) | | | | | |
| 02 Calcium channel blockers | | | | | |
| Floyd, 1992[580] (Nifedipine) | 11/29 | 13/39 | | 31.99 | 1.14 (0.60–2.17) |
| Glock, 1993[569] (Nifedipine) | 24/41 | 23/39 | | 68.01 | 0.99 (0.69–1.43) |
| Subtotal (95% CI) | 70 | 78 | | 100.00 | 1.04 (0.75–1.44) |
| Total events: 35 (Magnesium sulphate), 36 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.14$, df = 1 ($p = 0.71$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.23$ ($p = 0.82$) | | | | | |
| 04 Other (no tocolytic agent) | | | | | |
| Ma, 1992[624] (Bed rest) | 6/14 | 7/15 | | 100.00 | 0.92 (0.41–2.07) |
| Subtotal (95% CI) | 14 | 15 | | 100.00 | 0.92 (0.41–2.07) |
| Total events: 6 (Magnesium sulphate), 7 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.21$ ($p = 0.84$) | | | | | |



***FIGURE 244*** *Forest plot of the effects of magnesium sulphate tocolysis for the prevention of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*

| Study or subcategory | Magnesium sulphate *n/N* | Control *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Calcium channel blockers | | | | | |
| Glock, 1993[569] | 13/41 | 15/39 | | 100.00 | 0.82 (0.45–1.50) |



***FIGURE 245*** *Forest plot of the effects of magnesium sulphate tocolysis for the prevention of spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour.*

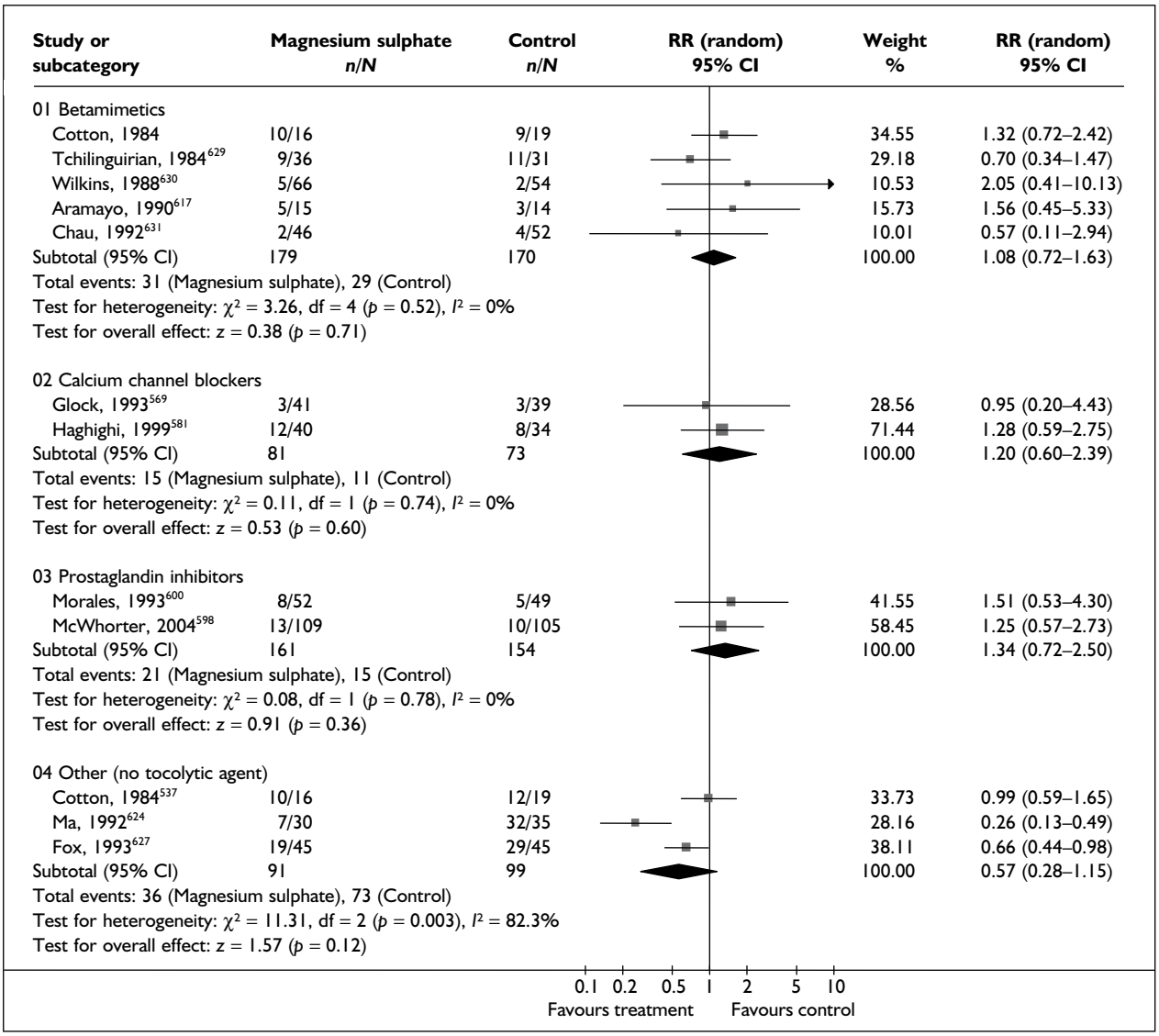


***FIGURE 246*** *Forest plot of the effects of magnesium sulphate tocolysis for the prevention of spontaneous preterm birth within 48 hours of treatment in symptomatic women with threatened preterm labour.*

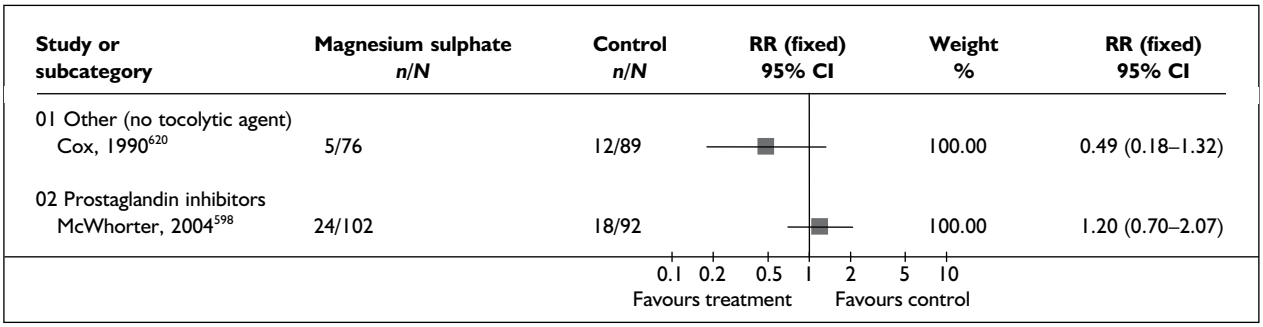


***FIGURE 247*** *Forest plot of the effects of magnesium sulphate tocolysis for the prevention of neonatal intensive care unit admission.*



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***TABLE 31*** *Effect of magnesium sulphate acute tocolytic therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Total deaths (fetal, neonatal and infant)*** | | | |
| Magnesium sulphate vs all comparators (8 studies, $n = 921$)[537,569,598,600,619,620,622,626] | 2.29 | 0.92–5.69 | 17.7% (0.30) |
| Magnesium sulphate vs betamimetics (2 studies, $n = 166$)[537,619] | 1.19 | 0.08–17.51 | NA |
| Magnesium sulphate vs calcium channel blockers (1 study, $n = 80$)[569] | 0.19 | 0.01–3.85 | NA |
| Magnesium sulphate vs prostaglandin inhibitors (2 studies, $n = 311$)[598,600] | 3.5 | 0.56–21.64 | 12.2% (0.29) |
| Magnesium sulphate vs other (3 studies, $n = 292$)[537,620,622] | 1.74 | 0.63–4.77 | 76.8% (0.04) |
| ***Respiratory distress syndrome*** | | | |
| Magnesium sulphate vs betamimetics (2 studies, $n = 65$)[537,625] | 1.79 | 0.73–4.41 | 0% (0.86) |
| Magnesium sulphate vs prostaglandin inhibitors (2 studies, $n = 311$)[598,600] | 0.96 | 0.57–1.61 | 0% (0.96) |
| Magnesium sulphate vs other (3 studies, $n = 471$)[537,620,622] | 1.09 | 0.98–1.22 | 0% (0.92) |
| ***Need for assisted ventilation*** | | | |
| Magnesium sulphate vs other (1 study, $n = 165$)[537] | 1.17 | 0.61–2.24 | NA |
| ***Cerebroventricular haemorrhage (all grades)*** | | | |
| Magnesium sulphate vs betamimetics (1 study, $n = 34$)[537] | 0.63 | 0.06–6.34 | NA |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 117$)[600] | 0.98 | 0.26–3.75 | NA |
| Magnesium sulphate vs other (3 studies, $n = 289$)[537,620,622] | 0.86 | 0.28–2.62 | 0% (0.43) |
| ***Severe cerebroventricular haemorrhage (grades 3 and 4) or periventricular leukomalacia*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 117$)[600] | 0.98 | 0.06–15.35 | NA |
| ***Necrotising enterocolitis*** | | | |
| Magnesium sulphate vs betamimetics (1 study, $n = 34$)[537] | 0.42 | 0.02–9.55 | NA |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[598] | 0.18 | 0.01–3.71 | NA |
| Magnesium sulphate vs other (3 studies, $n = 289$)[537,620,622] | 1.19 | 0.33–4.29 | NA |
| ***Neonatal infection*** | | | |
| Magnesium sulphate vs betamimetics (1 study, $n = 34$)[537] | 0.36 | 0.09–1.49 | NA |
| Magnesium sulphate vs other (1 study, $n = 34$)[537] | 6.25 | 0.32–121.14 | NA |
| ***Intraventricular haemorrhage*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[617] | 1.05 | 0.37–3.02 | NA |
| ***Cerebral palsy*** | | | |
| Magnesium sulphate vs other tocolytic (1 study, $n = 73$)[626] | 0.14 | 0.01–2.60 | NA |
| ***Pulmonary hypertension*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[617] | 0.9 | 0.06–14.21 | NA |
| ***Maternal respiratory arrest*** | | | |
| Magnesium sulphate vs other (1 study, $n = 156$)[620] | 3.16 | 0.13–76.30 | NA |
| ***Nausea*** | | | |
| Magnesium sulphate vs nitric oxide donor (1 study, $n = 30$)[621] | 1.47 | 0.75–2.90 | NA |
| ***Vomiting*** | | | |
| Magnesium sulphate vs nitric oxide donor (1 study, $n = 30$)[621] | 0.86 | 0.23–3.19 | NA |
| ***Hypotension*** | | | |
| Magnesium sulphate vs other (1 study, $n = 156$)[620] | 3.16 | 0.13–76.30 | NA |

***TABLE 31*** *Effect of magnesium sulphate acute tocolytic therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Tachycardia*** | | | |
| Magnesium sulphate vs betamimetics (2 studies, $n = 133$)[537,631] | 0.23 | 0.03–1.9 | NA |
| ***Headache*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[598] | 1.61 | 0.39–6.55 | NA |
| ***Shortness of breath*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[598] | 0.19 | 0.02–1.62 | NA |
| ***Lethargy*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[598] | 0.06 | 0.00–0.97 | NA |
| ***Flushing*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[598] | 0.24 | 0.05–1.11 | NA |
| ***Any side effect of treatment*** | | | |
| Magnesium sulphate vs prostaglandin inhibitors (1 study, $n = 194$)[598] | 0.51 | 0.30–0.86 | NA |
| ***Side effects leading to discontinuation of treatment*** | | | |
| Magnesium sulphate vs betamimetics (3 studies, $n = 264$)[537,619,631] | 0.07 | 0.02–0.31 | 0% (0.40) |
| Magnesium sulphate vs calcium channel blockers (1 study, $n = 80$)[569] | 8.57 | 0.48–154.15 | NA |
| Magnesium sulphate vs prostaglandin inhibitors (2 studies, $n = 189$)[598,600] | 16.04 | 0.95–270.65 | NA |
| Magnesium sulphate vs other (4 studies, $n = 310$)[537–620,622,624] | 1.59 | 0.57–4.41 | 84.9% (0.01) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

## Magnesium sulphate for neonatal neuroprotection

Infants born preterm have increased risks of death or neurosensory impairments and disabilities. A large retrospective case–control study suggested that the prophylactic antenatal administration of low-dose magnesium sulphate may act as a neuroprotective agent;[667] magnesium sulphate was associated with a lower risk of intraventricular haemorrhage, which predisposes to cerebral palsy. Subsequent trials have attempted to examine this neuroprotective 'magnesium hypothesis'.

The review of magnesium sulphate for neuroprotection included two RCTs ($n = 1119$).[668,669] However, after the searches were completed, two potentially relevant clinical trials were identified, but too late for inclusion in this review.[670,671] Further details of the review can be found in Appendix 6, *Table 140*. The quality of the included studies was good and is summarised in *Figure 270*. When compared to placebo, antenatal administration of magnesium sulphate was not found to reduce the risk of intraventricular haemorrhage or periventricular leukomalacia (*Figures 271 and 272*). Although a reduction in the incidence of cerebral palsy was found in the magnesium sulphate group, this was not statistically significant (*Figure 273*). Summary RRs, presented in the forest plots (*Figures 271–273*) , were used in the decision analysis. No information on perinatal mortality or admission to neonatal intensive care was reported. Results for other neonatal, infant and maternal variables are shown in *Table 36*. It should be noted that both the primary studies included twin gestations in their results; the proportion of multiple gestations ranged from 3.5% to 16.6%. The current evidence does not support the widespread use of magnesium sulphate for the protection of neurological morbidity in women with imminent spontaneous preterm birth; however, further randomised controlled trials are necessary before its clinical relevance can be determined.



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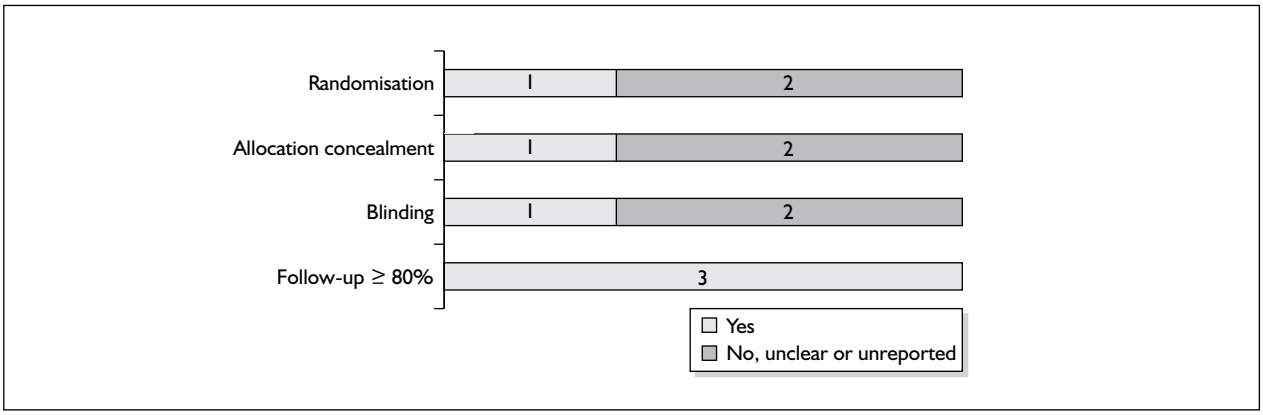


***FIGURE 248*** *Methodological quality of the included trials of magnesium sulphate maintenance following acute tocolytic therapy for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*

| Study or subcategory | Magnesium sulphate n/N | Control n/N | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Magnesium maintenance therapy vs placebo/no treatment | | | | | |
| **Ricci, 1991**[558] | 11/25 | 13/25 | | 100.00 | 0.85 (0.47–1.51) |
| Subtotal (95% CI) | 25 | 25 | | 100.00 | 0.85 (0.47–1.51) |
| Total events: 11 (Magnesium sulphate), 13 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.56$ ($p = 0.57$) | | | | | |
| 02 Magnesium maintenance therapy vs alternative tocolytic maintenance therapy | | | | | |
| Ridgeway, 1990[559] (Terbutaline) | 4/23 | 5/27 | | 29.49 | 0.94 (0.29–3.09) |
| **Ricci, 1991**[558] (Ritodrine) | 11/25 | 11/25 | | **70.51** | 1.00 (0.54–1.87) |
| Subtotal (95% CI) | 48 | 52 | | 100.00 | 0.98 (0.56–1.72) |
| Total events: 15 (Magnesium sulphate), 16 (Control) | | | | | |
| Test for heterogeneity: $\chi^2 = 0.01$, df = 1 ($p = 0.93$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $z = 0.06$ ($p = 0.95$) | | | | | |

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

***FIGURE 249*** *Forest plot of the effects of magnesium sulphate maintenance following acute tocolytic therapy for the prevention of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*

| Study or subcategory | Treatment n/N | Control n/N | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| 01 Magnesium maintenance therapy vs placebo/no treatment | | | | | |
| **Rust, 1996**[560] | 15/65 | 10/68 | | 100.00 | 1.57 (0.76–3.24) |
| Subtotal (95% CI) | 65 | 68 | | 100.00 | 1.57 (0.76–3.24) |
| Total events: 15 (Treatment), 10 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 1.22$ ($p = 0.22$) | | | | | |
| 02 Magnesium maintenance therapy vs alternative tocolytic maintenance therapy | | | | | |
| Rust, 1996[560] (Terbutaline) | 15/65 | 17/72 | | 100.00 | 0.98 (0.53–1.80) |
| Subtotal (95% CI) | 65 | 72 | | 100.00 | 0.98 (0.53–1.80) |
| Total events: 15 (Treatment), 17 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: $z = 0.07$ ($p = 0.94$) | | | | | |

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

***FIGURE 250*** *Forest plot of the effects of magnesium sulphate maintenance following acute tocolytic therapy for the prevention of neonatal intensive care unit admission.*

***TABLE 32*** *Effect of magnesium maintenance therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Infant death before hospital discharge*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 50$)[558] | 5 | 0.25–99.16 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (1 study, $n = 50$)[558] | 5 | 0.25–99.16 | NA |
| ***Respiratory distress syndrome*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 50$)[558] | 3 | 0.13–70.30 | NA |
| ***Periventricular haemorrhage*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 50$)[558] | 3 | 0.13–70.30 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (1 study, $n = 50$)[558] | 1 | 0.07–15.12 | NA |
| ***Any maternal side effects*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 133$)[560] | 1.88 | 1.11–3.20 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (3 studies, $n = 237$)[558–560] | 0.69 | 0.52–0.91 | 32.8% (0.23) |
| ***Nausea*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 133$)[560] | 0.73 | 0.30–1.81 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (3 studies, $n = 237$)[558–560] | 0.94 | 0.50–1.75 | 0% (0.75) |
| ***Vomiting*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 133$)[560] | 0.42 | 0.08–2.08 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (3 studies, $n = 237$)[558–560] | 0.92 | 0.39–2.17 | 61.0% (0.11) |
| ***Diarrhoea*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 133$)[560] | 7.67 | 2.41–24.41 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (3 studies, $n = 237$)[558–560] | 10.67 | 3.35–33.99 | 46.6% (0.15) |
| ***Palpitations/tachycardia*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 133$)[560] | 1.05 | 0.15–7.21 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (3 studies, $n = 237$)[558–560] | 0.22 | 0.11–0.44 | 0% (0.41) |
| ***Maternal re-admission for threatened preterm labour*** | | | |
| Magnesium maintenance vs placebo/no treatment (1 study, $n = 50$)[558] | 0.79 | 0.45–1.38 | NA |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (2 studies, $n = 100$)[558,559] | 1.01 | 0.63–1.65 | NA |

*continued*



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***TABLE 32*** *Effect of magnesium maintenance therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Discontinued therapy*** | | | |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (2 studies, $n = 100$)[558,559] | 1.11 | 0.29–4.23 | 0% (0.52) |
| ***Length of neonatal stay (days)*** | | | |
| Magnesium maintenance vs placebo/no treatment (2 studies, $n = 180$)[558,560] | WMD 1.18 | −0.43–2.82 | 0% (0.39) |
| Magnesium maintenance vs alternative tocolytic maintenance therapy (2 studies, $n = 180$)[558,560] | WMD −2.63 | −5.70–0.43 | 24.9% (0.25) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

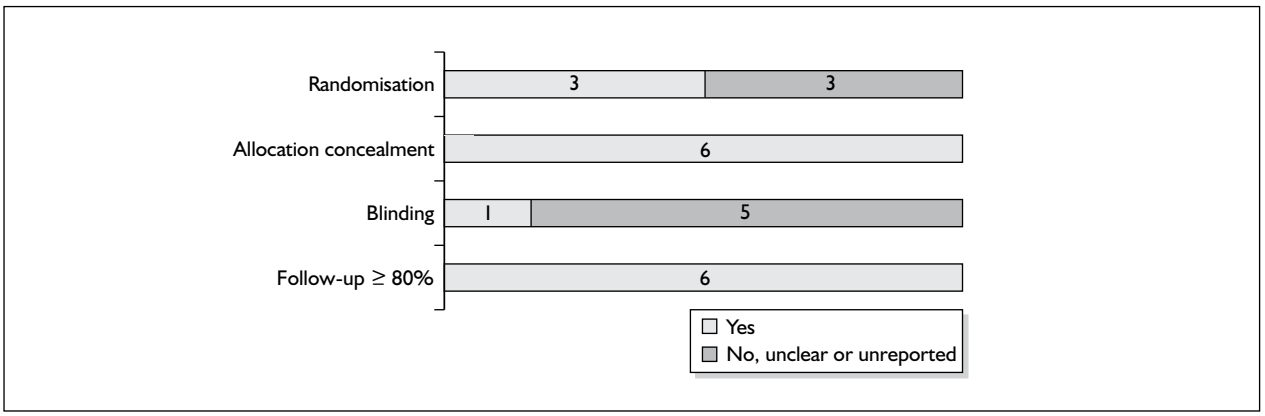


***FIGURE 251*** *Methodological quality of the included trials of nitric oxide tocolytic therapy for the prevention of spontaneous preterm birth in symptomatic women with threatened preterm labour.*

## Vitamin K before preterm birth for neuroprotection

Infants have no reserves of vitamin K at birth, and lack of this vitamin can cause potentially serious bleeding complications. Administration of vitamin K to the mother before imminent preterm birth may help to reduce the incidence of haemorrhagic disease of the newborn through improved coagulation.

The review of vitamin K[672] included five RCTs and quasi-RCTs ($n = 642$).[673–677] Further details of the review can be found in Appendix 6, *Table 141*. The quality of the included studies was mixed and is presented in *Figure 274*. When compared to placebo or no treatment, antenatal administration of vitamin K was found to reduce the incidence of perinatal mortality (*Figure 275*), although this was not statistically significant; the exclusion of poorer quality trials did not change this finding. A non-significant trend for a reduction in neurological morbidity, as measured by the incidence of periventricular haemorrhage, was shown for infants receiving antenatal vitamin K compared to infants receiving placebo/no treatment (*Figures 276* and *277*); however, when only the higher quality trial is considered this trend disappears.[676] No information on neurodevelopment or admission to neonatal intensive care was provided. The pooled RRs presented in *Figure 275* for perinatal mortality and RR 0.84 (95% CI 0.67–1.06) for the prevention of periventricular haemorrhage were used in the decision analysis. Results for other perinatal and maternal variables are shown in *Table 37*. It should be noted that it is unclear whether the primary studies have included multiple gestations in their results. Overall, the current evidence does not support the antenatal use of vitamin K for the prevention of neurological morbidity in preterm infants.

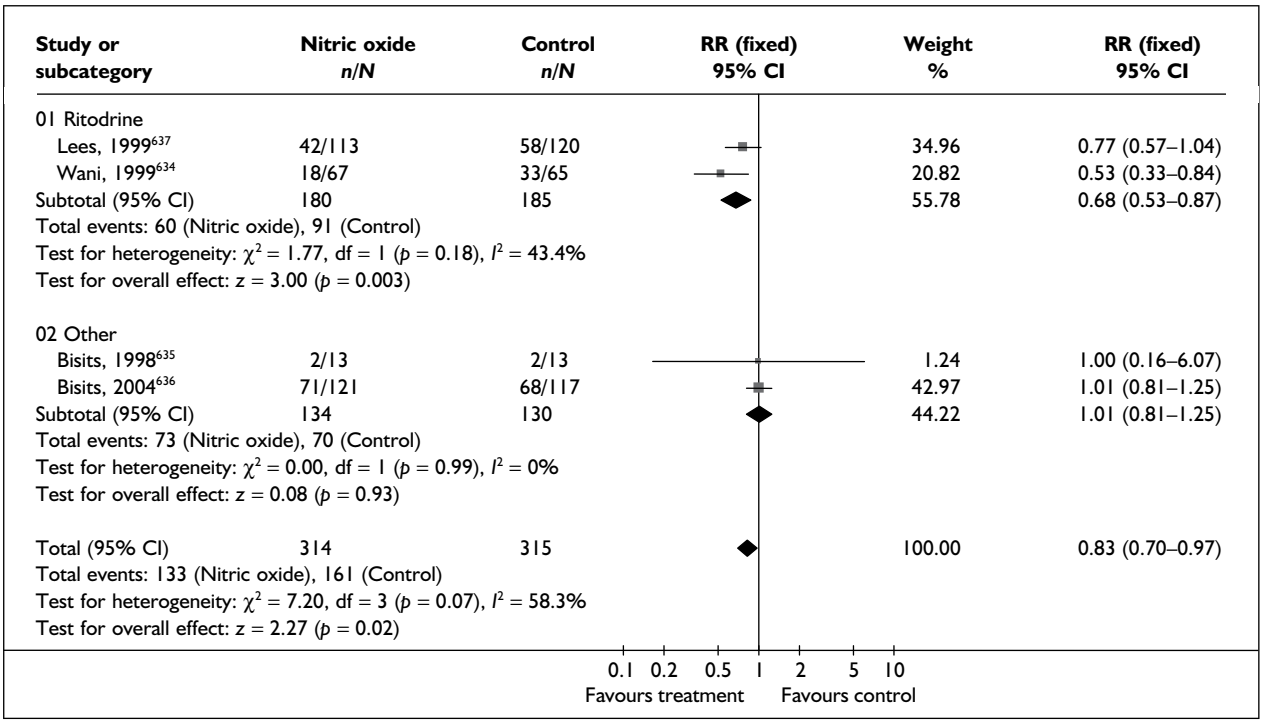


***FIGURE 252*** *Forest plot of the effects of nitric oxide donors versus any other tocolytic agent for the prevention of spontaneous preterm birth before 37 weeks' gestation in symptomatic women with threatened preterm labour.*

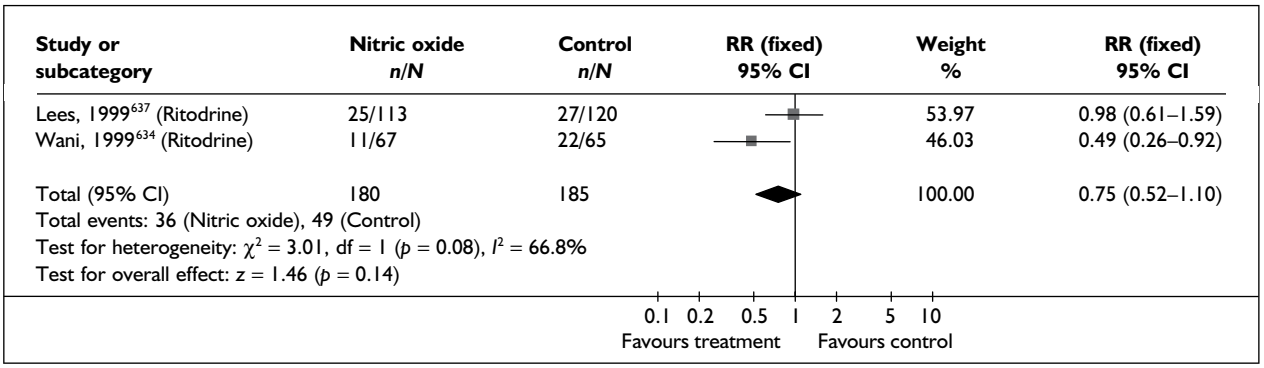


***FIGURE 253*** *Forest plot of the effects of nitric oxide donors versus any other tocolytic agent for the prevention of spontaneous preterm birth before 34 weeks' gestation in symptomatic women with threatened preterm labour.*

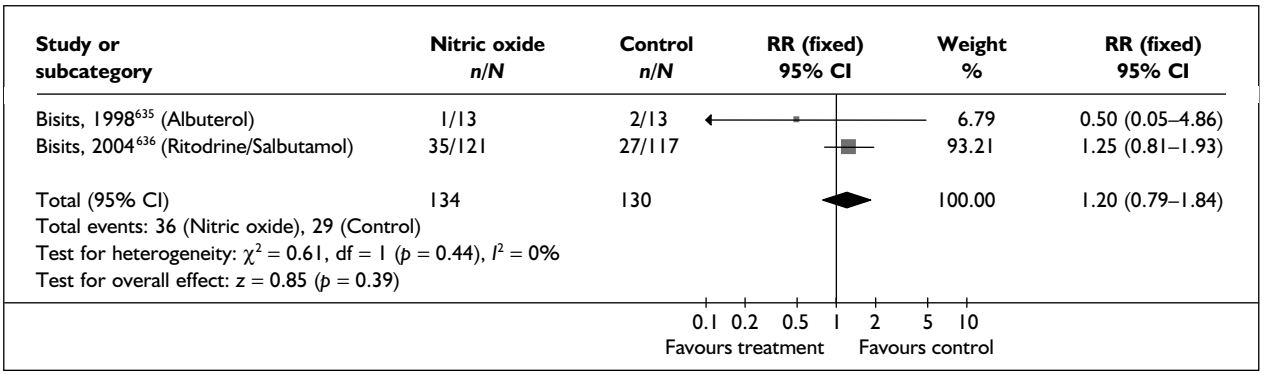


***FIGURE 254*** *Forest plot of the effects of nitric oxide donors versus any other tocolytic agent for the prevention of spontaneous preterm birth within 24 hours of treatment in symptomatic women with threatened preterm labour.*



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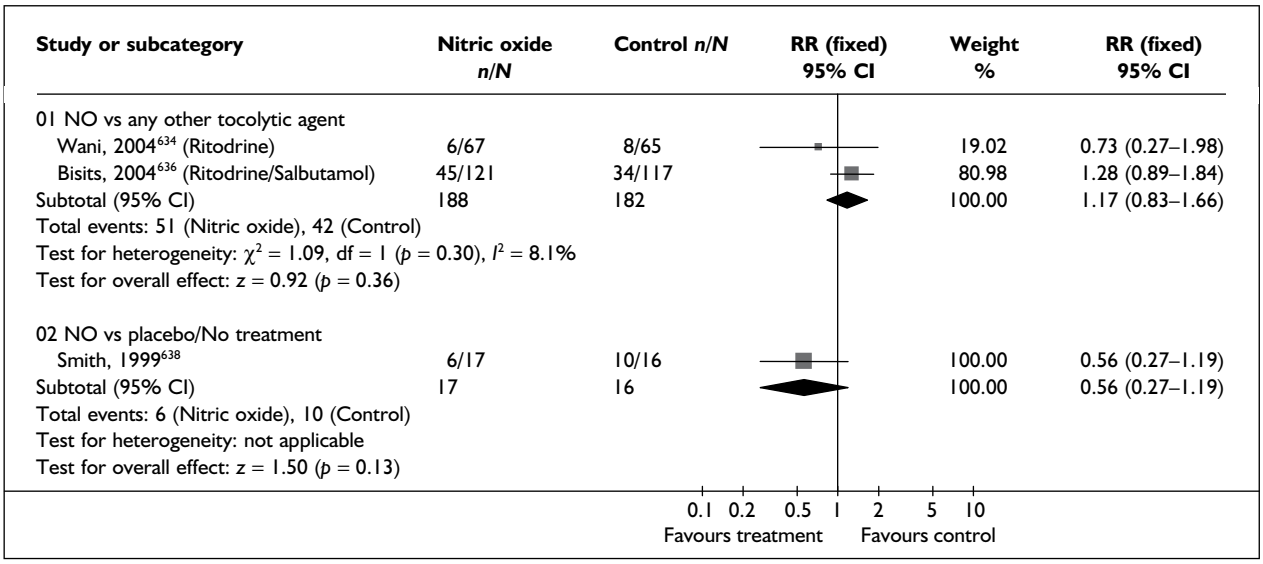


***FIGURE 255*** *Forest plot of the effects of nitric oxide donors versus any other tocolytic agent for the prevention of spontaneous preterm birth within 48 hours of treatment in symptomatic women with threatened preterm labour.*

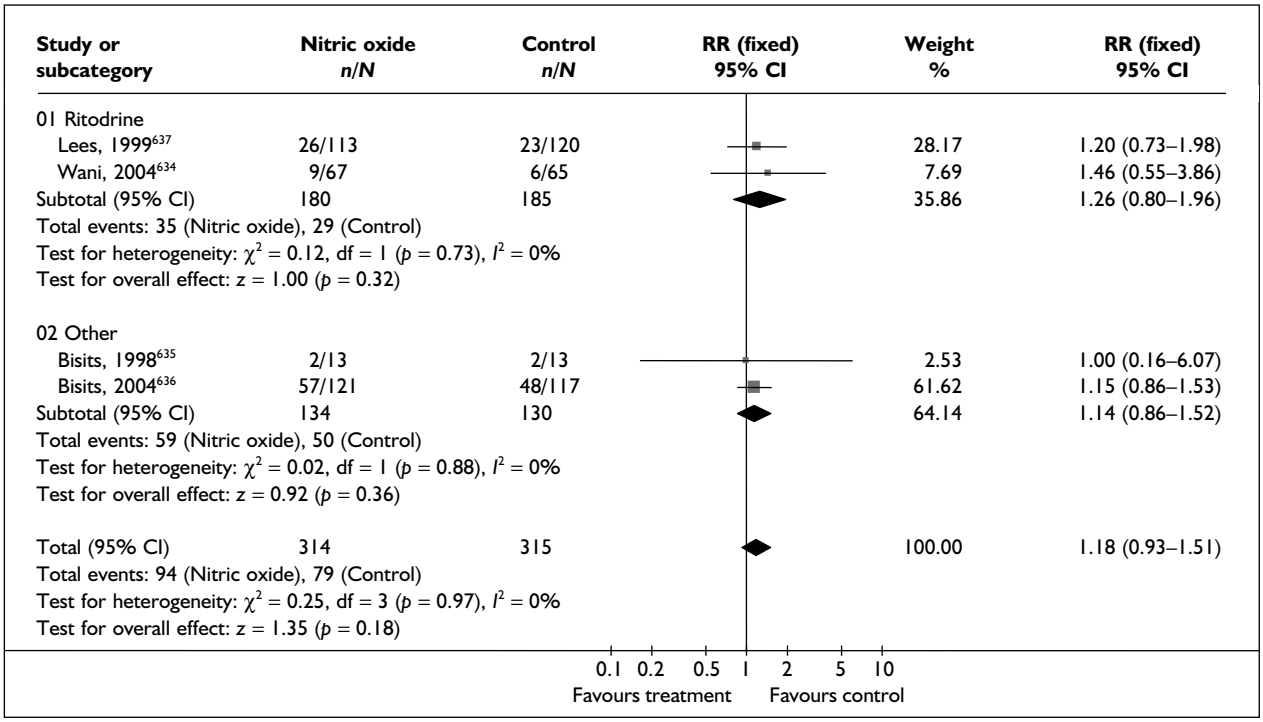


***FIGURE 256*** *Forest plot of the effects of nitric oxide donors versus any other tocolytic agent for the prevention of spontaneous preterm birth within 7 days of treatment in symptomatic women with threatened preterm labour.*

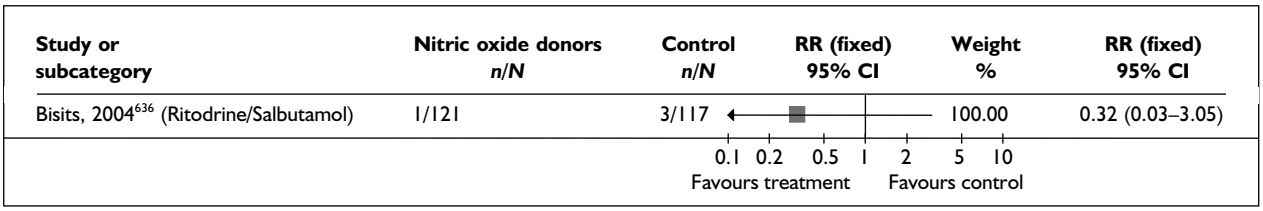


***FIGURE 257*** *Forest plot of the effects of nitric oxide donors versus any other tocolytic agent on perinatal mortality related to spontaneous preterm birth.*

***TABLE 33*** *Effect of nitric oxide donors on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| Neonatal death unrelated to congenital abnormalities (1 study, $n = 33$)[638] | 0.94 | 0.06–13.82 | NA |
| Chronic lung disease (1 study, $n = 238$)[636] | 0.97 | 0.40–2.35 | NA |
| Necrotising enterocolitis (1 study, $n = 238$)[636] | 0.97 | 0.42–2.24 | NA |
| Patent duct arteriosus (1 study, $n = 238$)[636] | 0.26 | 0.08–0.92 | NA |
| Intracerebral haemorrhage (1 study, $n = 238$)[636] | 0.24 | 0.05–1.11 | NA |
| Cardiovascular effects | | | |
| Palpitations (3 studies, $n = 353$)[621,634,637] | 0.09 | 0.02–0.32 | 10.3% (0.33) |
| Hypotension (1 study, $n = 30$)[621] | 7.94 | 0.46–135.65 | NA |
| Tachycardia (2 studies, $n = 323$)[634,637] | 0.03 | 0.01–0.10 | 0% (0.64) |
| Shortness of breath (2 studies, $n = 217$)[635,637] | 0.09 | 0.02–0.46 | 0% (0.89) |
| Chest pain/tightness (2 studies, $n = 323$)[634,637] | 0.12 | 0.02–0.64 | 0% (0.69) |
| Headache (4 studies, $n = 379$)[621,634,635,637] | 4.14 | 2.44–7.04 | 62.0% (0.05) |
| Nausea (3 studies, $n = 227$)[634,637] | 0.38 | 0.09–1.55 | 0% (0.89) |
| Dizziness (2 studies, $n = 221$)[621,637] | 2.34 | 0.76–6.89 | 0% (0.55) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk.

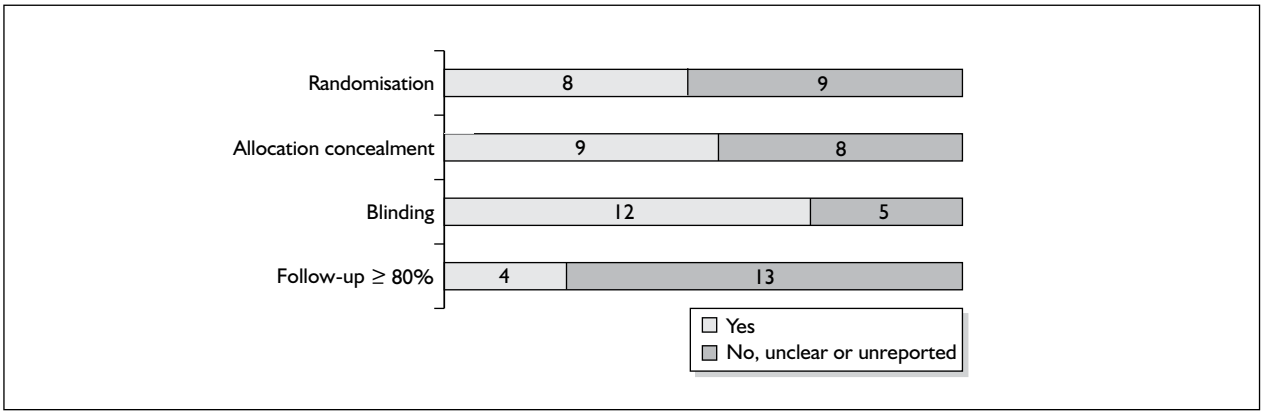


***FIGURE 258*** *Methodological quality of the included trials of prophylactic corticosteroid therapy in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome.*



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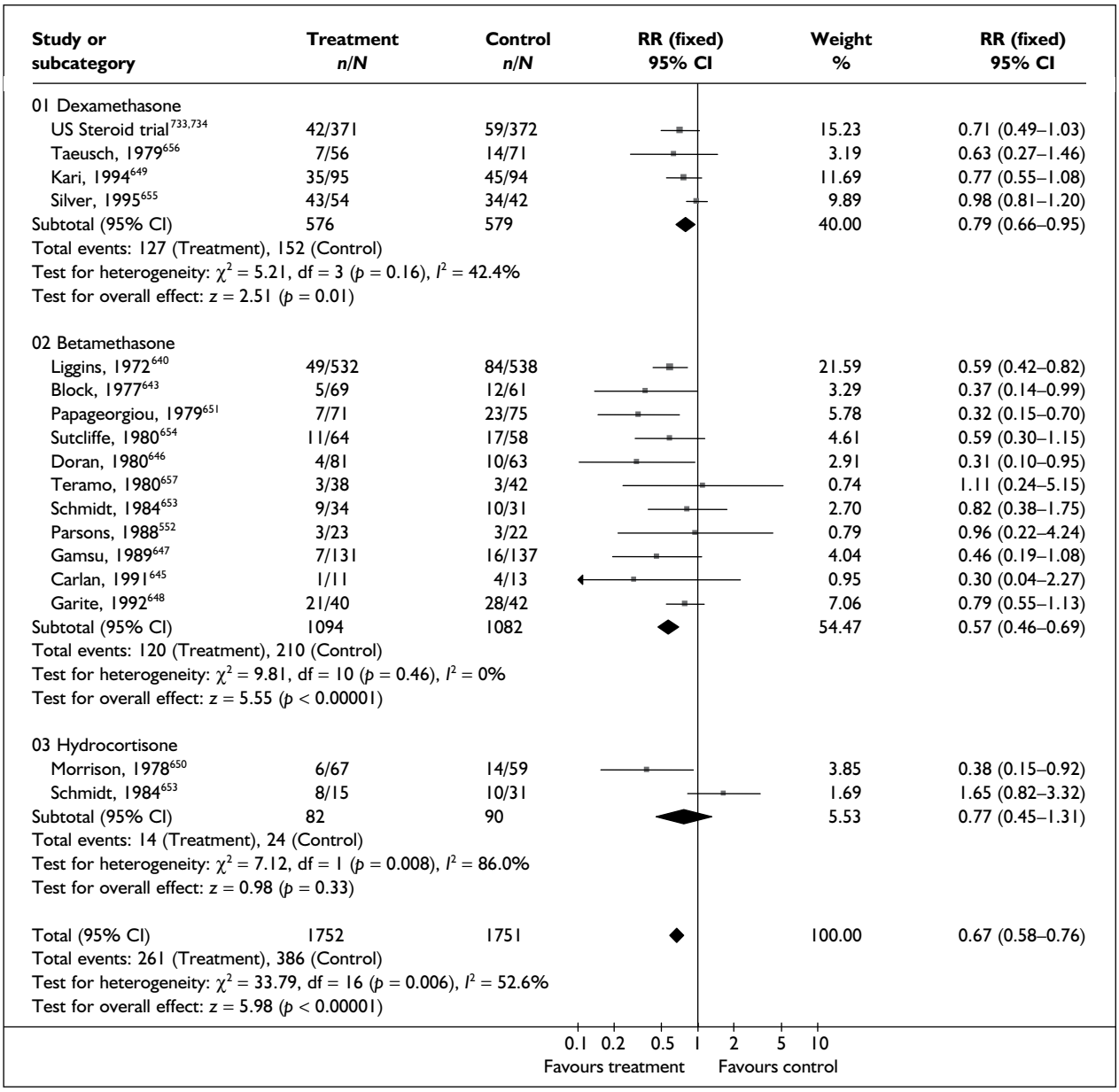


***FIGURE 259*** *Forest plot of the effects of prophylactic corticosteroid therapy versus placebo/no treatment in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome.*

# Summary of effectiveness reviews

## Summary of results of review of interventions

The evidence-based review assessed 40 interventions aimed at preventing preterm birth and its consequences. Previously published systematic reviews were identified for 33 of these topic areas. New rapid reviews were carried out for five topic areas: ethanol, home uterine monitoring, periodontal disease, fish oil and magnesium sulphate for neuroprotection. No systematic reviews or relevant RCTs were identified for two topic areas: in utero transfer and hypnotism.

*Figures 279–281* indicate that most interventions which seemed to show a beneficial effect in terms of their ability to reduce the incidence of spontaneous preterm birth were aimed at treating women at high risk of spontaneous preterm birth or with symptoms of threatened preterm labour. In general, prophylactic treatment of low-risk, asymptomatic women did not appear to reduce the incidence of spontaneous preterm birth.

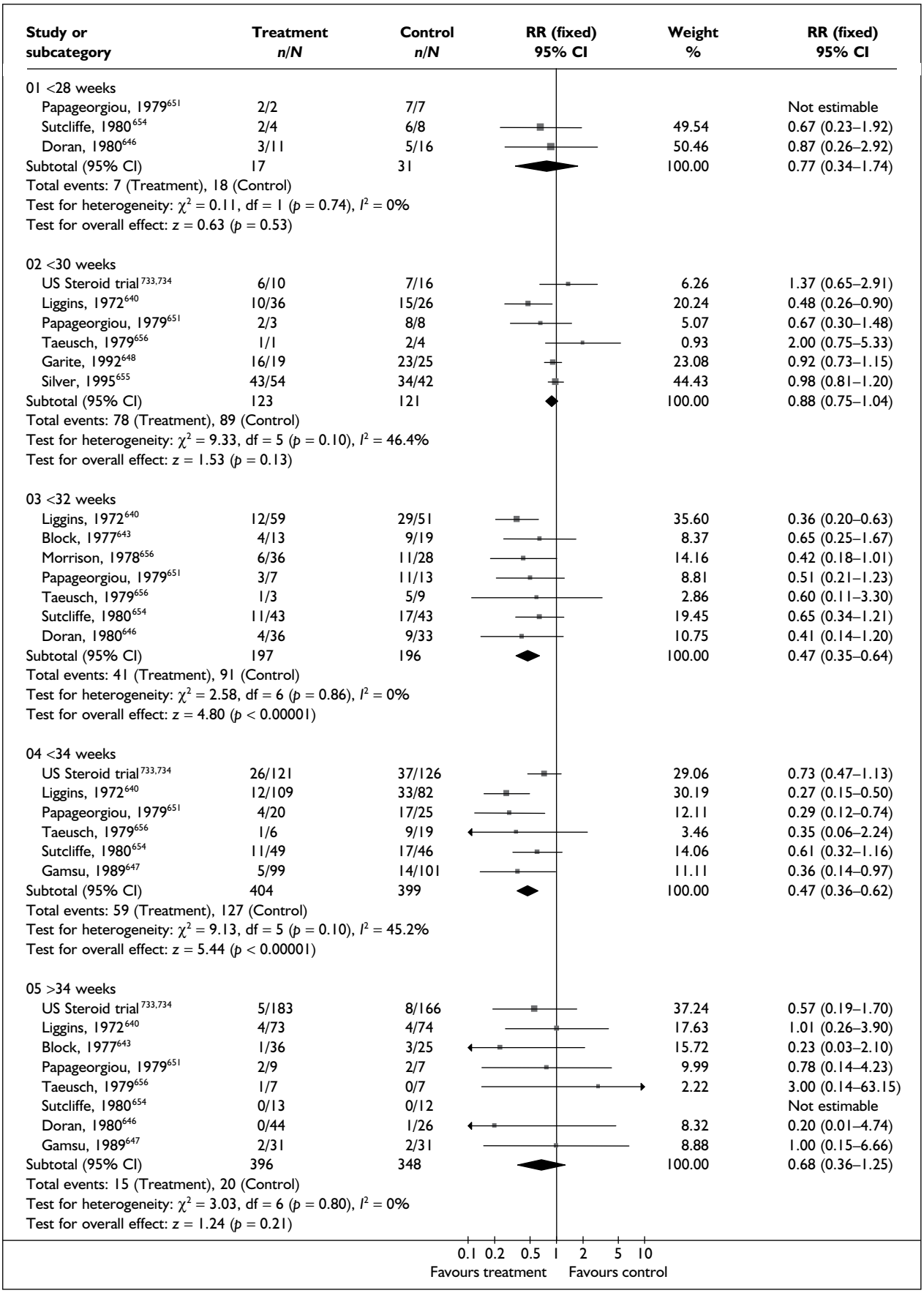


***FIGURE 260*** *Forest plot of the effects of prophylactic corticosteroid therapy versus placebo/no treatment in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome subgrouped by gestational age.*



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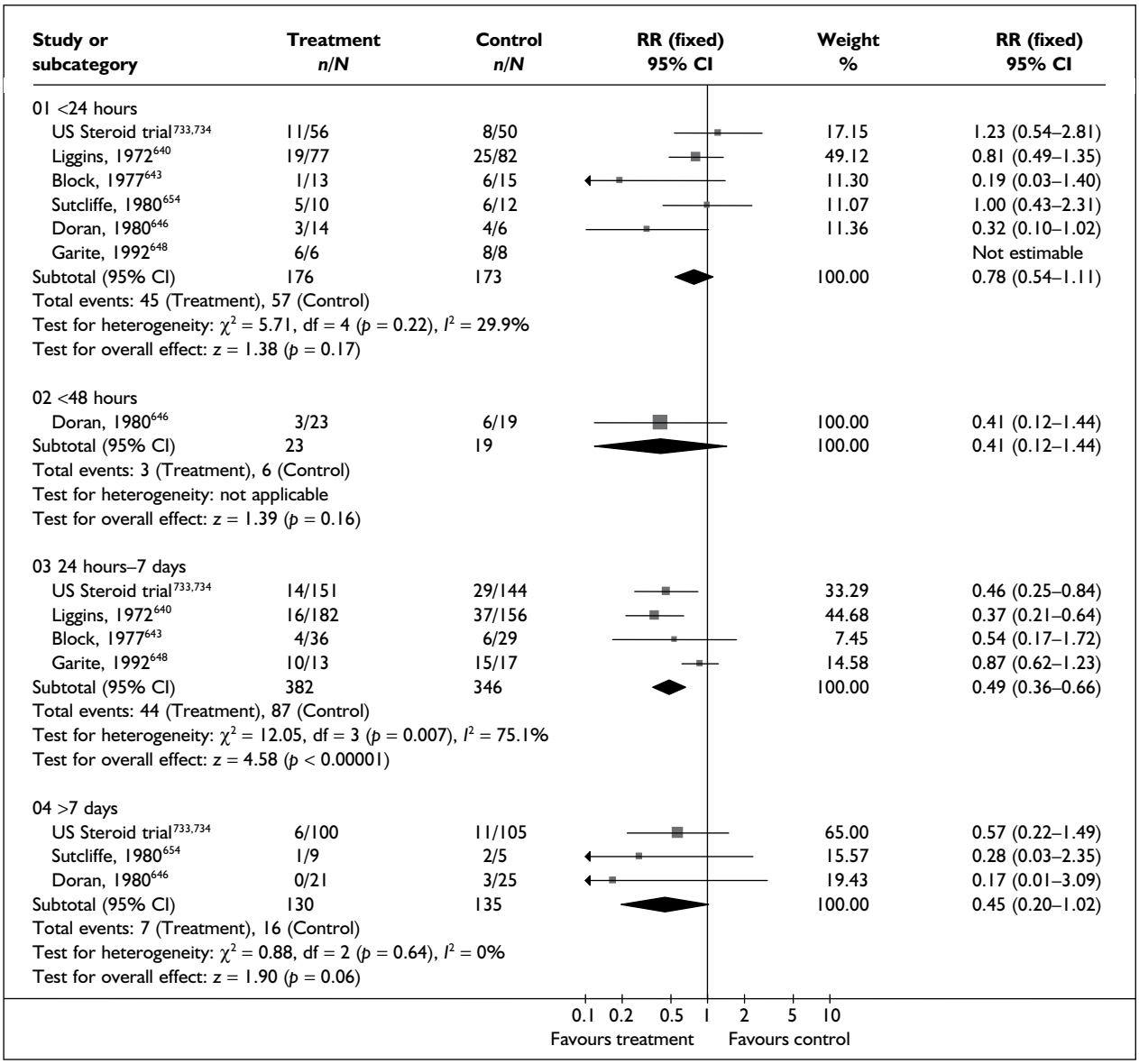


***FIGURE 261*** *Forest plot of the effects of prophylactic corticosteroid therapy versus placebo/no treatment in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome subgrouped by time of delivery after first dose.*

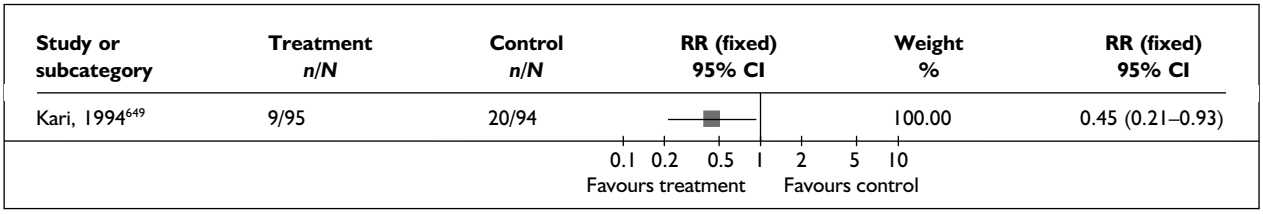


***FIGURE 262*** *Forest plot of the effects of prophylactic corticosteroid therapy versus placebo/no treatment in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome for the requirement of surfactant therapy.*

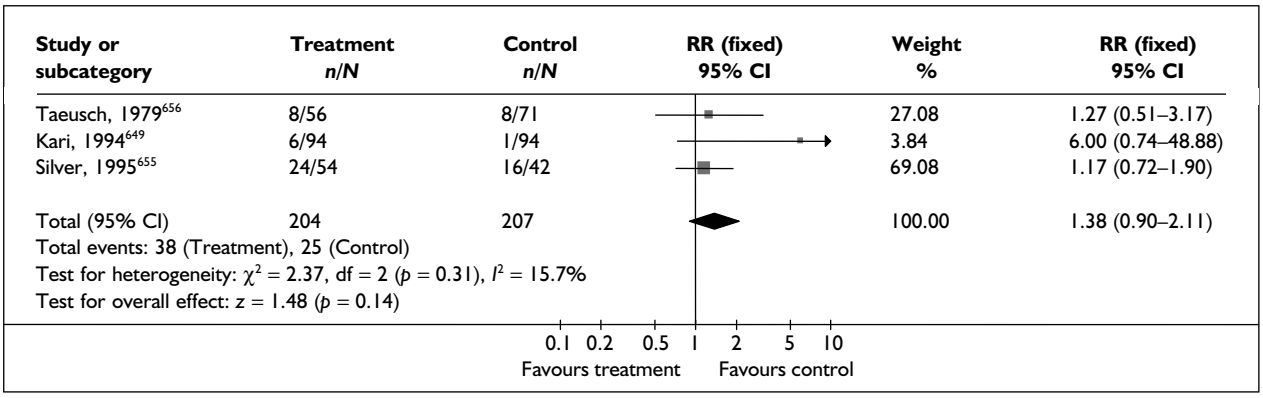


***FIGURE 263*** *Forest plot of the effects of prophylactic corticosteroid therapy versus placebo/no treatment in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome on the incidence of chronic lung disease in the neonate.*

The main results of the methodological quality assessment as summarised in *Figure 278* indicate that the quality of the included studies was often poor. Poor reporting also frequently made quality assessment difficult. Areas of concern included poor randomisation and allocation concealment, small sample sizes and lack of blinding. In addition, the number of studies per intervention area was frequently small; median number was five (range 0 to 24). Although a few interventions appeared to show some benefit towards preventing or delaying spontaneous preterm birth, the evidence base for a number of these interventions was severely limited by the quantity and/or quality of the included trials.

For most of the interventions evaluated, results were pooled using a fixed effect model. However, where only a single RCT contributed to the outcome(s), as in the case of bed rest, treatment for periodontal disease and ureaplasma; or where meta-analysis was not considered appropriate because of clinical variation, as in the case of zinc supplementation and home uterine monitoring, individual studies were considered. The forest plots presented here (*Figures 279–281*) highlight the primary outcomes for spontaneous preterm birth in asymptomatic and symptomatic women. The forest plots include both data that have been put forward for use in the decision analysis (highlighted in bold) and data that have not. This results section relates to clinical effectiveness. Clinical trials measure health-care outcomes to determine the efficacy or effectiveness of specific interventions. If infinite resources were available, effectiveness alone would be sufficient to determine a course of treatment. However, this is not the case; resources are finite. There is therefore a need to establish the relative cost effectiveness of interventions. Economic evaluations incorporate both costs and outcomes, and as a result the findings may differ from the results of the effectiveness review.

## Summary of effectiveness findings

This review has sought to cover a vast area of research within a rapidly evolving field, which has been problematic given the limited resources and time available. We have employed rigorous methods but as with all systematic reviews, our findings should be interpreted in light of the restrictions imposed by both the methodology and the primary data.

The overall quality of studies across the different interventions was often poor, although whether this was because of poor reporting or poor methodology was sometimes difficult to assess. Particular areas of concern include poor randomisation and allocation concealment, lack of blinding (where appropriate), and small sample sizes. In some cases only quasi-RCTs were available (e.g. periodontal therapy), and for other interventions, assessments were based only on a limited number of small trials with fewer than 100 participants (e.g. fish oil and hydration). Sample size calculations were often not performed and so it was not possible to determine whether the lack of significant findings was the result of a true lack of effectiveness or of an inadequate sample size.

Small sample sizes also led to problems for some perinatal outcomes such as mortality, where the small number of participants often resulted in zero event rates. This often led to data being excluded from the original reviews. Consequently



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***TABLE 34*** *Effects of prophylactic corticosteroid therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| ***Neonatal mortality*** | | | |
| All infants (13 studies, $n = 3272$)[640,641,643,646–648,650–654,656] | 0.63 | 0.51–0.79 | 13.4% (0.31) |
| Treated ≤ 1980 (8 studies, $n = 258$)[640,643–646,647,650,651,654,656] | 0.53 | 0.40–0.70 | 25.8% (0.22) |
| Treated > 1980 (5 studies, $n = 1139$)[641,648,649,652,653] | 0.86 | 0.60–1.22 | 0% (0.93) |
| ***Stillbirth*** | | | |
| All infants (11 studies, $n = 3061$)[1,3,4,7–10,12,13,17,19,640,641,643,646–648,650,651,654,656] | 0.84 | 0.59–1.21 | 0% (0.54) |
| Women with hypertension (4 studies, $n = 239$)[641,647,649,654] | 3.66 | 1.11–12.10 | NA |
| ***Intraventricular haemorrhage*** | | | |
| All infants (7 studies, $n = 1214$)[640,646–649,655,656] | 0.55 | 0.38–0.78 | 58.1% (0.03) |
| Diagnosed after autopsy (4 studies, $n = 863$)[640,646,647,656] | 0.3 | 0.14–0.66 | 0% (0.86) |
| Diagnosed during ultrasound (3 studies, $n = 351$)[648,649,655] | 0.68 | 0.46–1.01 | 76.4% (0.01) |
| ***Necrotising enterocoloitis*** | | | |
| All infants (4 studies, $n = 1154$) [641,649,650,655] | 0.6 | 0.33–1.09 | 58.4% (0.07) |
| ***Long-term neurological abnormality*** | | | |
| All infants (3 studies, 778)[640,641,654] | 0.65 | 0.39–1.08 | 0% (0.94) |
| ***Fetal and neonatal infection*** | | | |
| All infants (14 studies, $n = 2430$)[641,643–649,651–656] | 0.8 | 0.55–1.16 | 2.9% (0.42) |
| After PROM > 24 h before delivery (2 studies, $n = 163$) [651,656] | 2.16 | 0.77–6.12 | 0% (0.96) |
| PROM at trial entry (3 studies, $n = 84$)[644,645,652] | 1.21 | 0.34–4.23 | 46.7% (0.15) |
| ***Maternal infection*** | | | |
| All infants (10 studies, $n = 1864$)[641,645,647–651,653,654,656] | 1.44 | 1.13–1.82 | 4.7% (0.40) |
| After PROM >24 h before delivery (1 study, $n = 42$)[656] | 4.84 | 1.16–20.14 | NA |
| PROM at trial entry (2 studies, $n = 75$)[645,653] | 1.78 | 0.89–3.58 | 32.2% (0.22) |

CI, confidence interval; NA, not available; PROM, pre-labour rupture of membranes; RCT, randomised controlled trial; RR, relative risk.

relative risks were in some cases based on very few trials and events, increasing the error limits and reducing the statistical power.

Reviews included in our report were restricted, where possible, to RCTs in women with singleton gestations and uncomplicated pregnancies. However, quasi-RCTs were included in a number of existing reviews, potentially diluting the quality of the included studies. Similarly, existing reviews and primary studies may have included women with multiple pregnancies, assisted pregnancies or pregnancies with maternal or fetal complications. This may limit the applicability of the findings to the general population of women's risk of spontaneous preterm birth, as these factors are considered to increase the risk of spontaneous preterm birth[678,679]. In some cases, where studies were carried out in particular populations such as rural Gambian women or women with severe nutritional deficits, the degree to which the data could be generalised to the general UK population was also unclear.

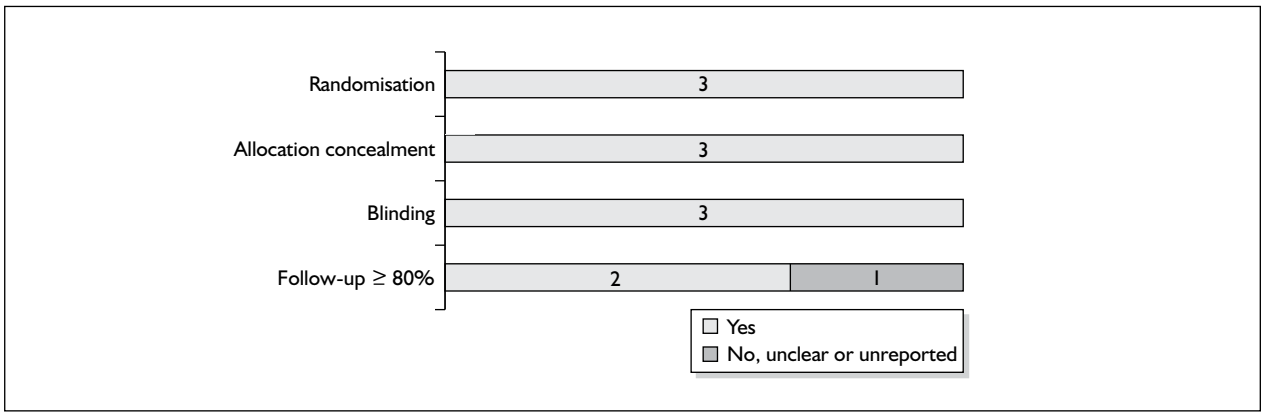


***FIGURE 264*** *Methodological quality of the included trials of repeat antenatal corticosteroid courses in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome.*

| Study or subcategory | Repeat dose *n/N* | Single dose *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| Aghajafari, 2002[662] | 6/6 | 3/6 | | 33.94 | 2.00 (0.90–4.45) |
| McEvoy, 2002[664] | 5/18 | 6/19 | | 66.06 | 0.88 (0.32–2.38) |
| Total (95% CI) | 24 | 25 | | 100.00 | 1.26 (0.66–2.41) |

Total events: 11 (Repeat dose), 9 (Single dose)
Test for heterogeneity: $\chi^2 = 1.78$, df = 1 ($p = 0.18$), $I^2 = 43.8\%$
Test for overall effect: $z = 0.70$ ($p = 0.48$)

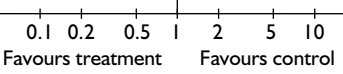


***FIGURE 265*** *Forest plot of the effects of repeat course(s) versus single course of antenatal corticosteroid therapy in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome on spontaneous preterm birth before 37 weeks' gestation.*

| Study or subcategory | Repeat dose *n/N* | Single dose *n/N* | RR (fixed) 95% CI | Weight % | RR (fixed) 95% CI |
|---|---|---|---|---|---|
| Aghajafari, 2002[662] | 4/6 | 3/6 | | 1.97 | 1.33 (0.50–3.55) |
| Guinn, 2001[663] | 167/251 | 145/237 | | 98.03 | 1.09 (0.95–1.24) |
| Total (95% CI) | 257 | 243 | | 100.00 | 1.09 (0.96–1.25) |

Total events: 171 (Repeat dose), 148 (Single dose)
Test for heterogeneity: $\chi^2 = 0.16$, df = 1 ($p = 0.69$), $I^2 = 0\%$
Test for overall effect: $z = 1.30$ ($p = 0.19$)

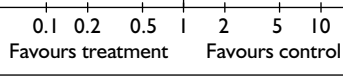


***FIGURE 266*** *Forest plot of the effects of repeat course(s) versus single course of antenatal corticosteroid therapy in symptomatic women with threatened preterm labour for the prevention of neonatal respiratory distress syndrome on spontaneous preterm birth before 34 weeks' gestation.*



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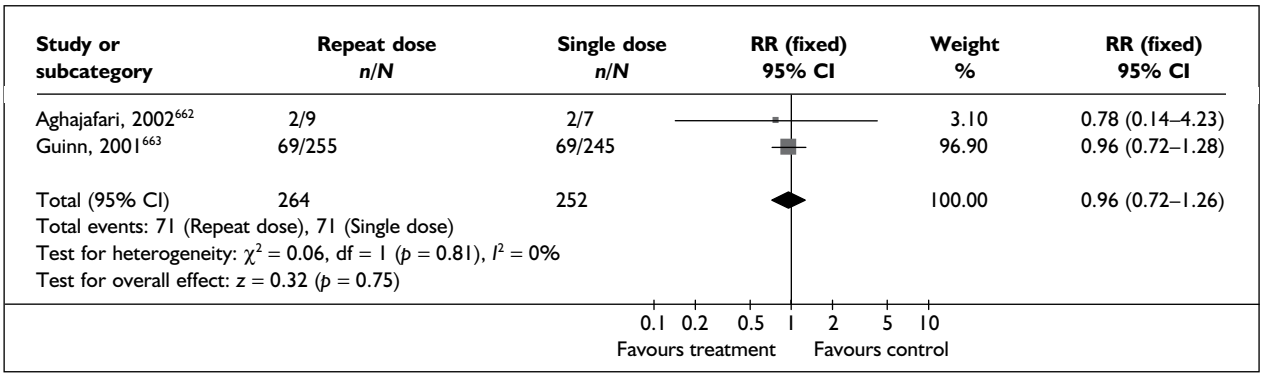


***FIGURE 267*** *Forest plot of the effects of repeat course(s) versus single course of antenatal corticosteroid therapy in symptomatic women with threatened preterm labour on the incidence of neonatal respiratory distress syndrome.*

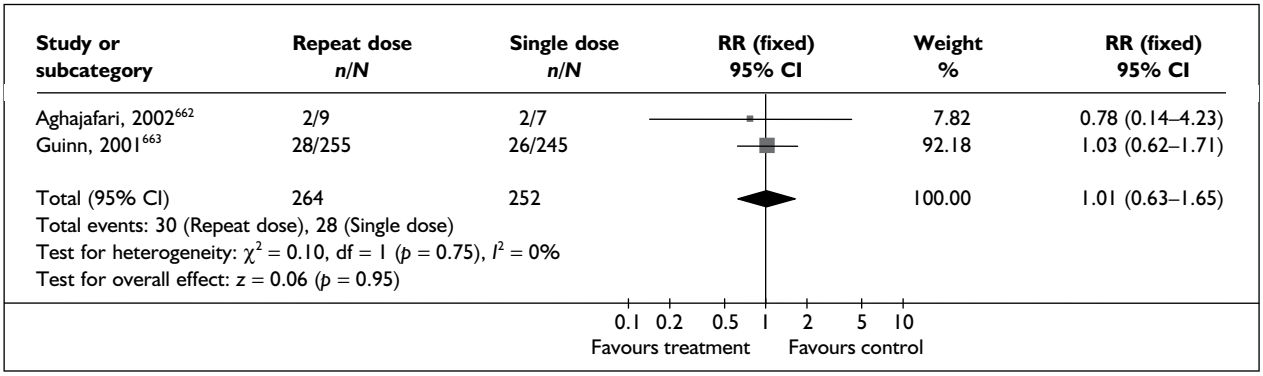


***FIGURE 268*** *Forest plot of the effects of repeat course(s) versus single course of antenatal corticosteroid therapy in symptomatic women with threatened preterm labour on the incidence of neonatal chronic lung diease.*

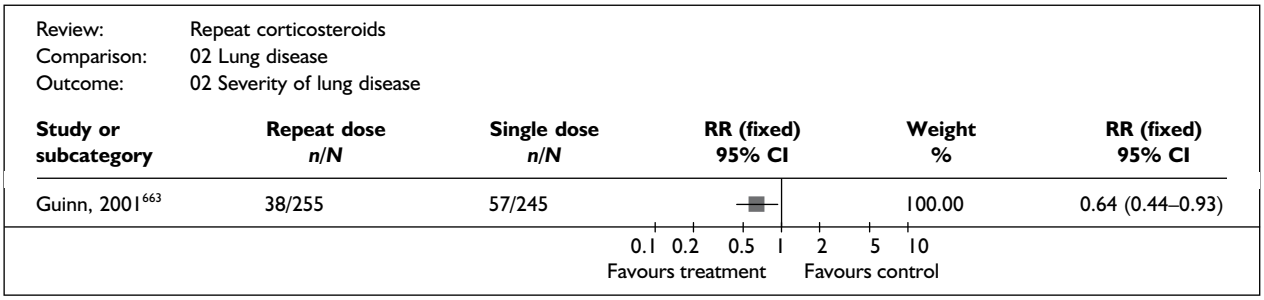


***FIGURE 269*** *Forest plot of the effects of repeat course(s) versus single course of antenatal corticosteroid therapy in symptomatic women with threatened preterm labour on the severity of neonatal lung disease from respiratory distress.*

***TABLE 35*** *Effect of repeat course(s) of antenatal corticosteroid therapy on other perinatal and maternal outcomes*

| Outcome (RCT) | RR | 95% CI | % Heterogeneity (*p*-value) |
|---|---|---|---|
| Fetal, neonatal and infant mortality (2 studies, $n = 518$)[662,663] | 0.53 | 0.18–1.57 | NA* |
| Periventricular haemorrhage | | | |
| All grades (1 study, $n = 500$)[663] | 1.15 | 0.70–1.90 | NA* |
| Grades 3 and 4 (2 studies, $n = 516$)[662,663] | 2.50 | 0.76–8.22 | 60.8% (0.11) |
| Periventricular leukomalacia (2 studies, $n = 516$)[662,663] | 0.64 | 0.11–3.80 | NA* |
| Chorioamnionitis (2 studies, $n = 497$)[662,663] | 1.35 | 0.95–1.92 | NA* |
| Puerperal sepsis (2 studies, $n = 497$)[662,663] | 0.88 | 0.42–1.83 | NA* |
| Preterm birth < 28 weeks gestation (1 study, $n = 488$)[663] | 1.08 | 0.67–1.74 | NA |
| Necrotising enterocolitis (2 studies, $n = 516$)[662,663] | 1.07 | 0.44–2.58 | NA* |
| Infection while in neonatal intensive care unit (2 studies, $n = 516$)[662,663] | 1.09 | 0.52–2.30 | 0% (0.33) |
| Patent ductus arteriosus requiring treatment (1 study, $n = 16$)[662] | 0.78 | 0.17–13.87 | NA |
| Retinopathy of prematurity (1 study, $n = 16$)[662] | 0.78 | 0.22–2.74 | NA |
| Postpartum haemorrhage (1 study, $n = 485$)[663] | 0.60 | 0.33–1.07 | NA |
| Composite serious morbidity (2 studies, $n = 518$)[662,663] | 0.80 | 0.60–1.07 | 0% (0.56) |
| Birthweight (2 studies, $n = 539$)[663,664] | WMD –137.67 | –281.53 to 6.20 | 0% (0.75) |
| Duration of oxygen supplementation, days (1 study, $n = 37$)[664] | WMD 3.30 | –2.31 to 8.91 | NA |
| Duration of respiratory support, days (1 study, $n = 37$)[664] | WMD 0.30 | –0.90 to 1.50 | NA |
| Duration of postnatal hospital stay (1 study, $n = 485$)[663] | WMD 0.00 | –0.22 to 0.22 | NA |
| Use of surfactant (2 studies, $n = 537$)[663,664] | 0.65 | 0.46–0.92 | 0% (0.97) |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.

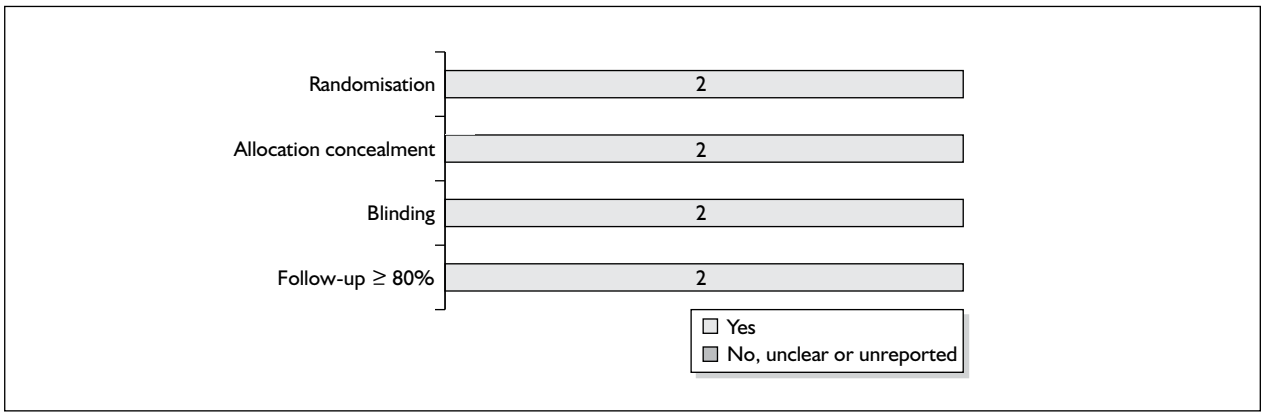


***FIGURE 270*** *Methodological quality of the included trials of maternal magnesium sulphate therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour.*



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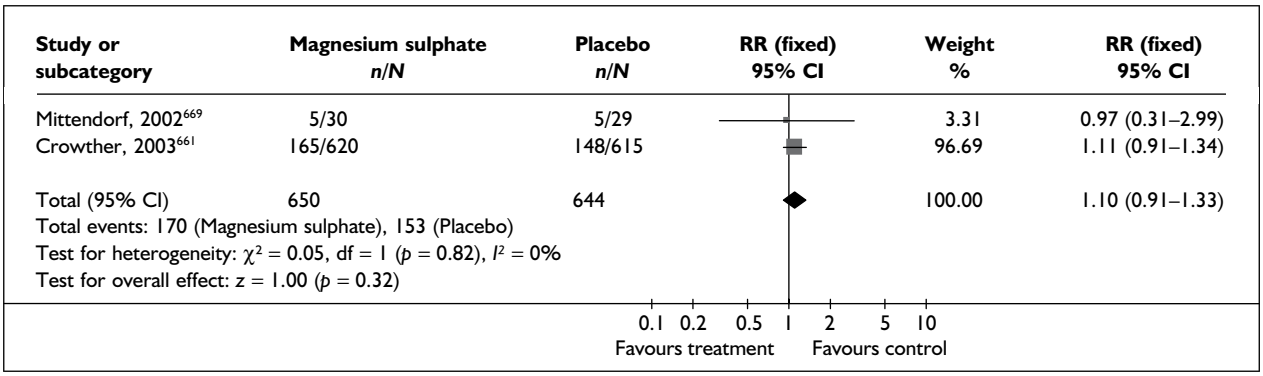


***FIGURE 271*** *Forest plot of the effect of maternal magnesium sulphate therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour on the incidence of intraventricular haemorrhage (all grades) in the premature neonates.*

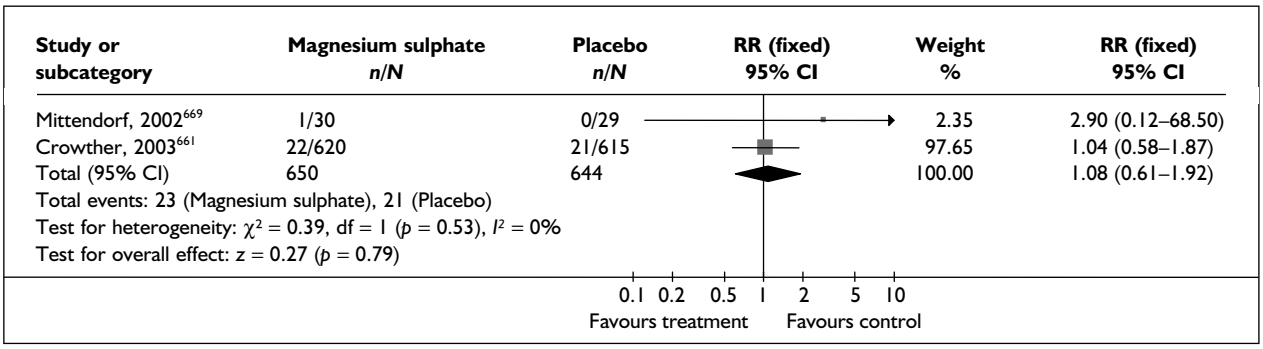


***FIGURE 272*** *Forest plot of the effect of maternal magnesium sulphate therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour on the incidence of serious periventricular leukomalacia in the premature neonates.*

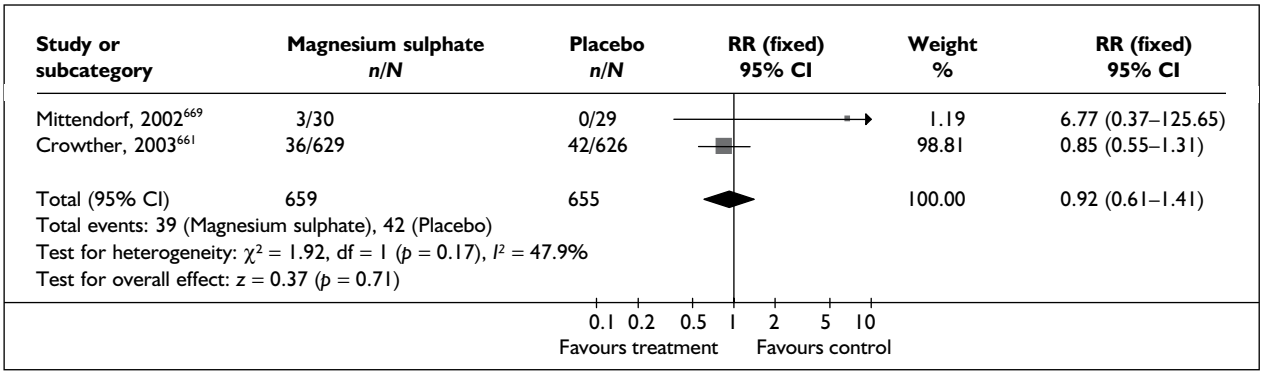


***FIGURE 273*** *Forest plot of the effect of maternal magnesium sulphate therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour on the incidence of cerebral palsy.*

***TABLE 36*** *Perinatal and maternal effects of magnesium sulphate*

| Outcome (number of RCTs) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| Total deaths: fetal, neonatal and postnatal (2 studies, *n* = 1314)[668,669] | 0.82 | 0.63–1.06 | 0%, 0.47 |
| Substantial gross motor dysfunction (1 study,[a] *n* = 1047) | 0.53 | 0.30–0.92 | NA |
| Neurosensory disability (1 study,[a] *n* = 1047) | 1.00 | 0.85–1.17 | NA |
| Bayley PDI (1 study,[a] *n* = 943): WMD | –1.30 | –3.66 to 1.06 | NA |
| Bayley MDI (1 study,[a] *n* = 949): WMD | –1.40 | –3.77 to 0.97 | NA |
| Delayed development (1 study,[a] *n* = 1047) | 1.00 | 0.84–1.19 | NA |
| Blindness (1 study,[a] *n* = 1047) | 0.96 | 0.06–15.38 | NA |
| Deafness (1 study,[a] *n* = 1047) | 1.10 | 0.40–3.02 | NA |
| Chronic lung disease (1 study,[a] *n* = 1235) | 1.07 | 0.94–1.21 | NA |
| Necrotising enterocolitis (1 study,[a] *n* = 1235) | 0.96 | 0.59–1.57 | NA |
| Mechanical ventilation (1 study,[a] *n* = 1235) | 1.02 | 0.99–1.05 | NA |
| Maternal infusion stopped due to adverse effects (1 study,[a] *n* = 1062) | 2.74 | 1.81–4.15 | NA |
| Any maternal adverse effects (1 study,[a] *n* = 1062) | 2.36 | 2.10–2.64 | NA |

CI, confidence interval; NA, not available; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference.
a Crowther *et al.*[668,669]

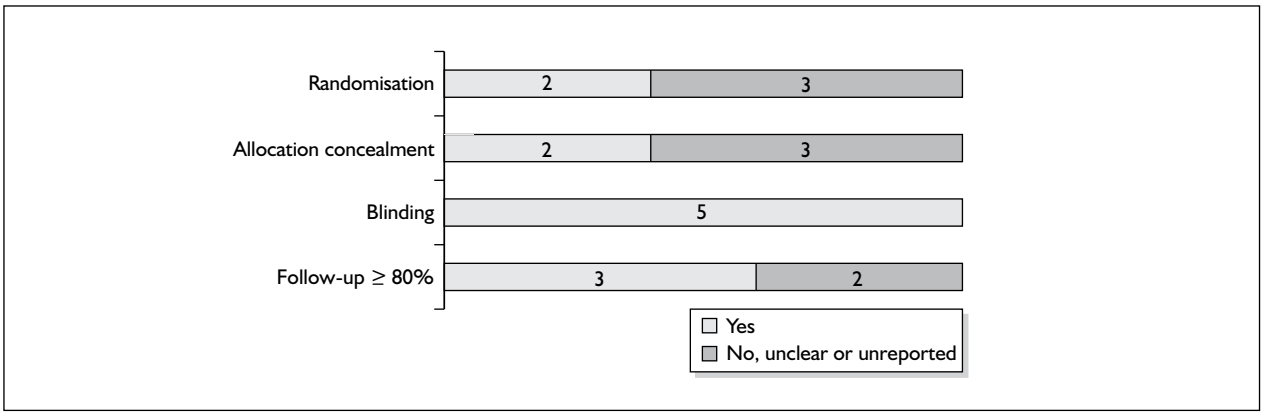


***FIGURE 274*** *Methodological quality of the included trials of maternal vitamin K therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour.*

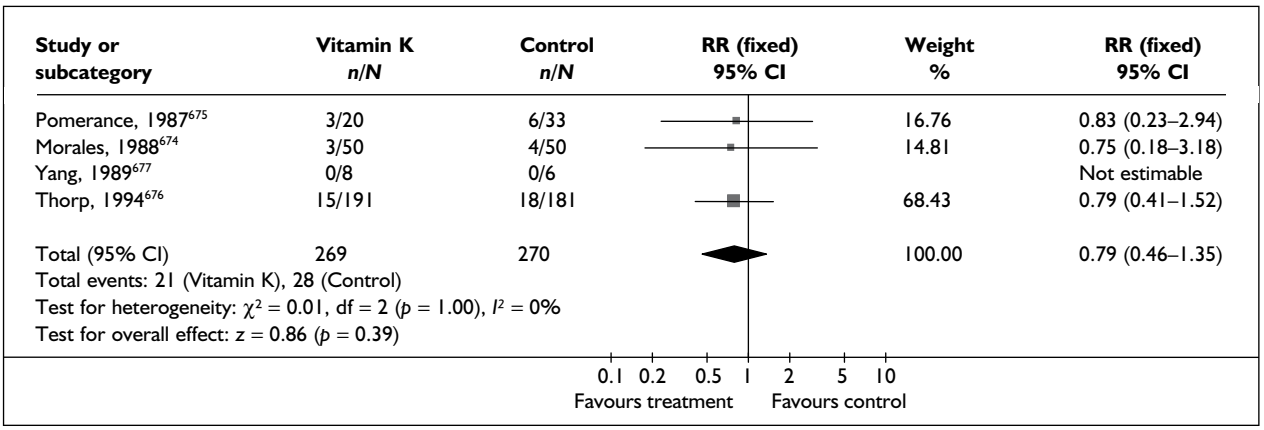


***FIGURE 275*** *Forest plot of the effect of maternal vitamin K therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour on the incidence of early neonatal mortality.*



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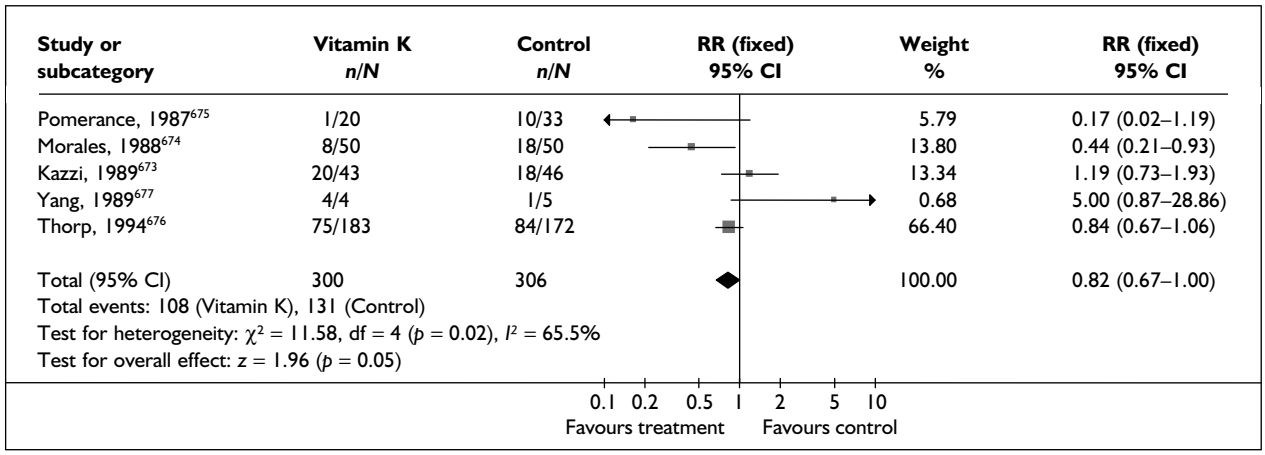


***FIGURE 276*** *Forest plot of the effect of maternal vitamin K therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour on the incidence of neonatal periventricular haemorrhage (all grades).*

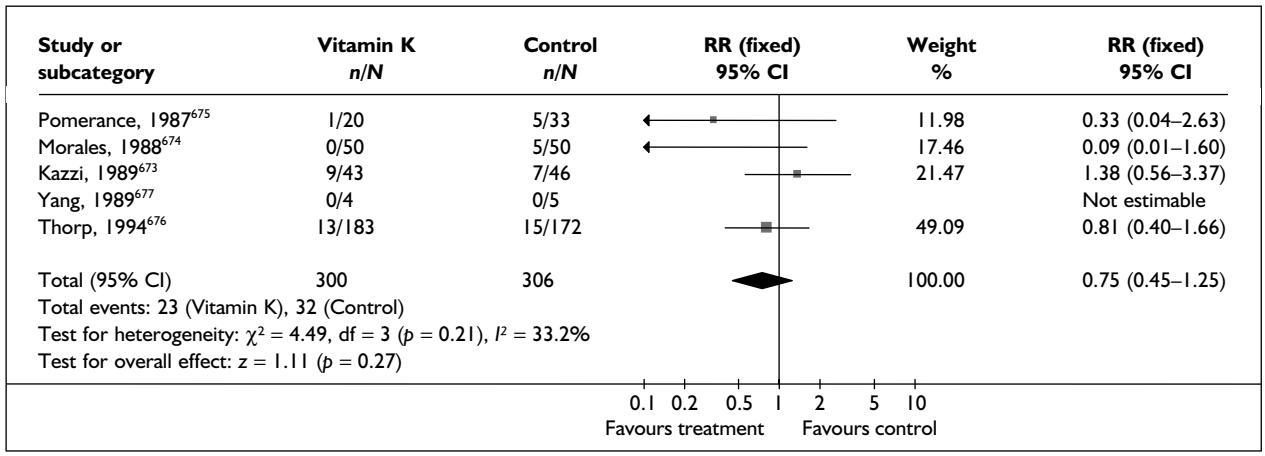


***FIGURE 277*** *Forest plot of the effect of maternal vitamin K therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour on the incidence of serious neonatal periventricular haemorrhage (grades 3 and 4).*

***TABLE 37*** *Perinatal and maternal effects of maternal vitamin K therapy for protection against neonatal neurological morbidity in symptomatic women with threatened preterm labour*

| Outcome (number of RCTs) | RR | 95% CI | $I^2$, *p*-value |
|---|---|---|---|
| Use of mechanical ventilation (5 studies, $n = 642$)[673–677] | 0.96 | 0.84–1.10 | 0%, 0.65 |
| Low Apgar score at 5 minutes (2 studies, $n = 475$)[673,676] | 0.99 | 0.63–1.57 | 0%, 0.53 |
| Respiratory distress syndrome (3 studies, $n = 167$)[674,675,677] | 1.02 | 0.76–1.37 | 0%, 0.53 |
| Pulmonary air leak (2 studies, $n = 475$)[673,676] | 1.74 | 0.59–5.10 | 0%, 0.56 |
| Patent ductus arteriosus (3 studies, $n = 528$)[673,676,677] | 0.96 | 0.57–1.63 | 0%, 0.61 |
| Any maternal side effects (4 studies, $n = 474$)[673,675–677] | 3.78 | 0.41–35.07 | 0%, 0.83 |

CI, confidence interval; RCT, randomised controlled trial; RR, relative risk.

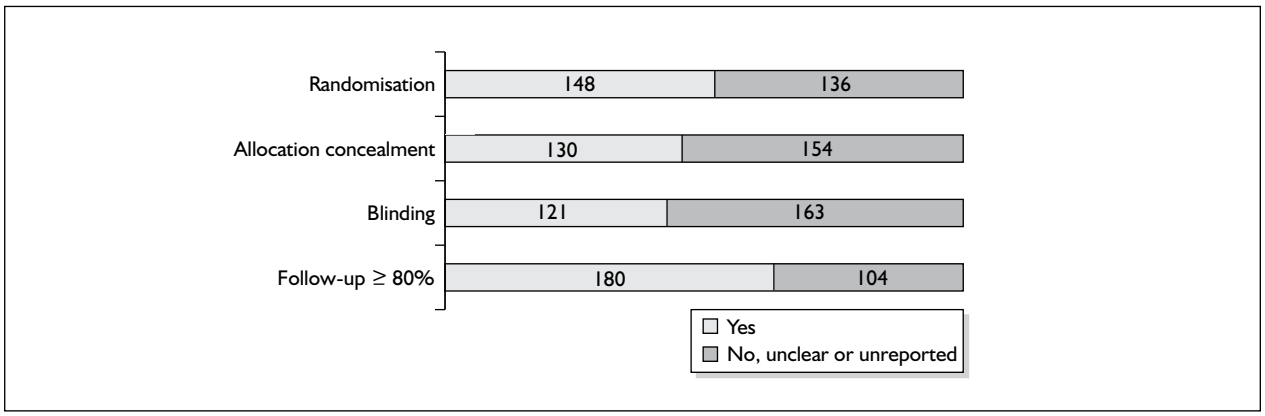


***FIGURE 278*** *Overall methodological quality of studies included in the reviews of interventions in prevention of spontaneous preterm birth. Note: (a) Some studies are included in more than one review; however, they have not been counted twice for this figure. (b) The three studies included in the reviews considering antibiotic treatment for ureaplasma and gonorrhoea were not included in this figure because they did not contribute to any of the primary outcomes sought.*

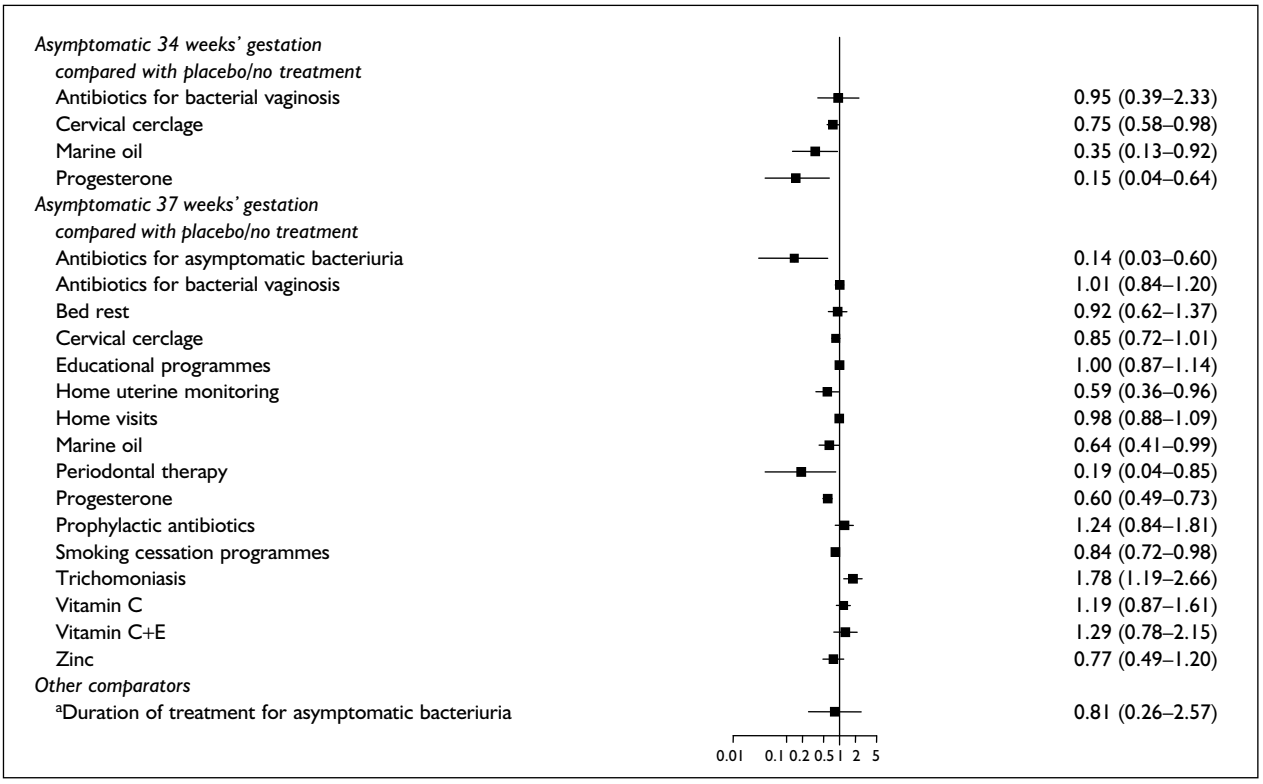


***FIGURE 279*** *Summary forest plots of relative risks of various interventions for prevention of spontaneous preterm birth before 34 and 37 weeks' gestation in asymptomatic women. a, Single dose vs short course.*



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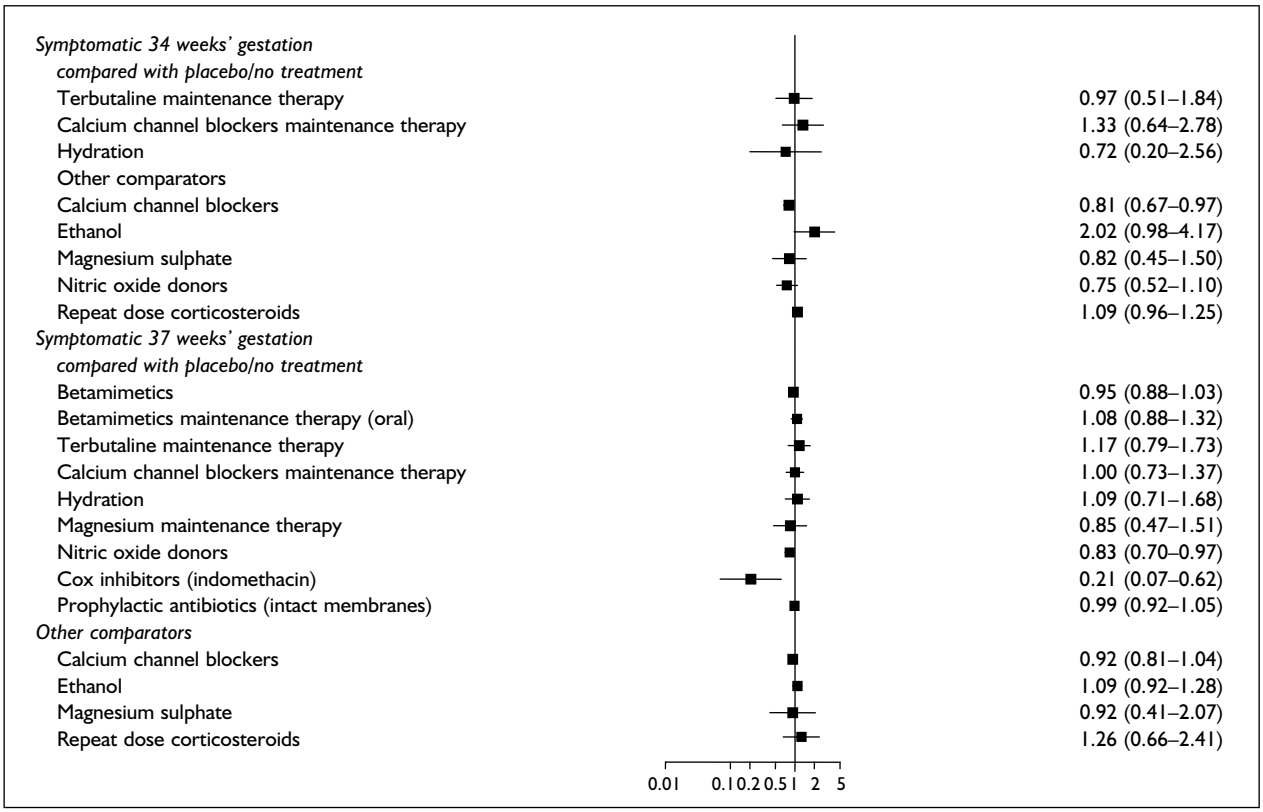


***FIGURE 280*** *Summary forest plots of relative risks of various interventions for prevention of spontaneous preterm birth before 34 and 37 weeks' gestation in symptomatic women.*

## Provisos/limitations arising from problems with primary data

Overall, advances in perinatal care over recent years have resulted in improvements in perinatal outcomes, yet studies included in the reviews were in some cases published over a period spanning more than three decades. This introduces problems when comparing and interpreting data because both research and clinical practice have evolved over time. These factors, in addition to heterogeneity in the outcomes, length of follow-up, dose regimens and population characteristics, hindered the interpretation of the data. For example, low birthweight was used as a proxy measure of gestational age in some earlier studies, particularly in the review of asymptomatic bacteriuria. While some concordance does exist, low birthweight and gestational age are not interchangeable; indeed, on the basis of an accumulation of epidemiological data, the World Health Organization recommended in 1961 that low birthweight no longer be used as the official definition of prematurity.[680] This appears to be supported by the results of the review of asymptomatic bacteriuria, as relative risks supported treatment for true spontaneous preterm birth but not for low birthweight. For the purposes of effectiveness, low birthweight was not considered an acceptable surrogate marker for spontaneous preterm birth.

Definitions for high-risk and low-risk women varied between studies. Women with a history of spontaneous preterm birth or threatened preterm labour, or women at risk of pre-eclampsia or diagnosed with a urogenital tract infection were largely, but not in all cases, defined as 'high risk'. In some cases women were only considered at high risk if they had two or more second trimester miscarriages before 30 weeks' gestation or cervical changes requiring cerclage within the current pregnancy.[609] Consequently, whether women were considered to be at low or high risk was not necessarily consistently defined across the various reviews or across studies within a review.

Threatened preterm labour was also not consistently defined across studies. Currently accepted hallmarks of threatened preterm labour include uterine contractions and concomitant changes in cervical dilatation or effacement before full-term gestation. Definitions that do not include cervical changes may inappropriately classify women as showing signs of threatened preterm

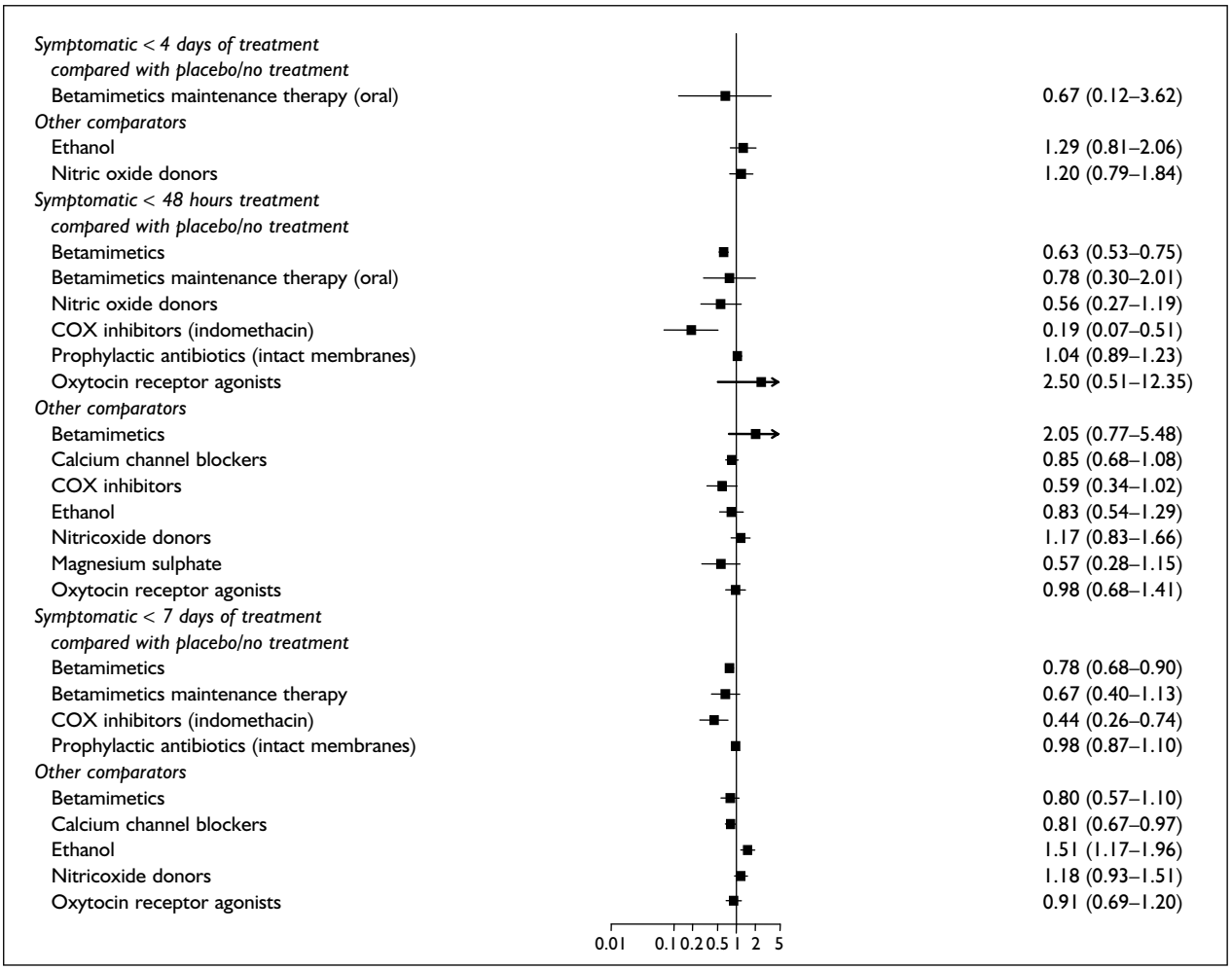


***FIGURE 281*** *Summary forest plots of relative risks of various interventions for prevention of spontaneous preterm birth within 24 hours 48 hours, and 7 days of initiating treatment in symptomatic women with threatened preterm labour.*

labour when in fact they would subsequently deliver at term without treatment. However, in such cases waiting to confirm progressive cervical dilatation may result in the treatment being initiated too late to have any effect.

In addition a number of studies reported admission of infants to 'special care' or 'neonatal care' and, while this definition was accepted as referring to intensive care, it may in some instances refer to the lower-dependency units sometimes referred to as special care baby units, rather than to neonatal intensive care.

## Provisos/limitations arising from review methods

Given the large number of potential interventions and the short timescale available it has been necessary to limit our review. Largely, this has been driven by the demands of the economic model which is the focus of the report. For instance, included interventions were chosen for their relevance according to the consensus opinions of a panel of experts. Time constraints also meant it was not feasible to carry out new reviews in each area. Indeed, in many cases this would have duplicated work already carried out by other researchers, in particular the Cochrane Pregnancy and Childbirth Review Group. The Cochrane Collaboration is an internationally recognised source of regularly updated, rigorous systematic reviews. Therefore we have used previously published good quality reviews and updated this work where required. Where no such review exists it has been necessary to carry out a rapid review for a small number of interventions (e.g. fish and marine oils, magnesium sulphate for neuroprotection, ethanol, home uterine monitoring and periodontal disease). Again the methodology used has been tailored to fit the demands of the economic model.



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Our report focuses on seven key outcome measures: (1) spontaneous preterm birth before 34 weeks' gestation, (2) spontaneous preterm birth before 37 weeks' gestation, (3) birth within 24 hours of intervention, (4) birth within 48 hours of intervention, (5) birth within 7 days of intervention, (6) admission to neonatal intensive care unit, and (7) perinatal mortality. These were chosen as key outcomes for the economic model as identified by consensus opinion. Trials should evaluate outcomes that are important to infants and their families as well as to health practitioners and the health service. Broadly, outcomes improve with gestational age, and the outcomes for preterm infants born at or after 34 weeks' gestation are similar to those for term infants, although minor morbidities, which often lengthen hospitalisation, remain for neonates born between 34 and 37 weeks' gestation. Any advantages on prolonging pregnancy in terms of morbidity and mortality may not be apparent from summary estimates of the incidence of spontaneous preterm birth before 37 weeks' gestation; however, few studies reported on spontaneous preterm birth rates before 34 weeks' gestation. Our review therefore has focused on short-term outcomes, largely relating to birth and the perinatal period. However, longer-term neurological effects, such as cerebral palsy, are also important to consider. In addition, the limitation of the review to RCTs may mean that relevant data on adverse events, often investigated using other study designs, may not have been included in the review. Postnatal administration of corticosteroids has been associated with improved respiratory outcomes in the short term but also a greater risk of adverse neurological effects in the longer term.[681] However, longer-term outcome data are not always available as the evaluation and follow-up of large trial cohorts can be expensive and difficult.

Given our reliance on existing reviews, it follows that the accuracy of the data presented in this report is very much dependent on that reported in the original reviews/trials. For instance, where a review required updating, searches were only carried out from the last search date reported by the original researchers. Consequently, any studies omitted from the original review are likely to remain undetected. Furthermore, data synthesis was reliant on the information reported by the original review authors or in the case of new rapid reviews, those reported by the original trial authors. Given the time and resources available attempts were only made to contact authors of newly identified primary studies where issues relating to relevance and quality were unclear. However, our success rate was low, which is not surprising given the age of some of the publications.

## Provisos/limitations arising from things not done (omissions)

The prevention of spontaneous preterm birth appears to be a rapidly evolving field. This is apparent from our report as a number of new trials were published after our searches were completed but before the report was submitted for publication. Given more time it may have been possible to identify and obtain pre-publication data for inclusion in the report, but because of the aforementioned constraints this was not possible. We have referred to such studies where possible, but this does suggest that future updates of this report should be carried out relatively frequently.

There are a small number of other omissions in the report given the time limitations and the necessity to assign deadlines for the completion of each stage of the project. This has in most cases been because of difficulties in obtaining copies of original trial reports. On completion of the report only two publications remained unobtainable but a number of others did not arrive in time for assessment. However, this has been highlighted where applicable. In particular the original review of educational interventions did not provide sufficient details of the individual studies to enable figures for study quality and forest plots to be constructed. Delays in obtaining copies of the original trial reports resulted in these figures being omitted from this section of the report. In the case of interventions to treat bacterial vaginosis, delays in completing the review resulted in the relevant data missing the deadline for entry into the economic model. Again this has been made clear in the report.

## Findings in the light of limitations

The interventions included in the review can broadly be divided into four categories: prevention, treatment of acute threatened preterm labour symptoms (e.g. tocolysis), maintenance therapy and interventions aimed at improving the health of the neonate (e.g. neuroprotection, reduction of RDS, and other neonatal morbidity).

Interventions given to asymptomatic women (i.e. women not experiencing symptoms of threatened preterm labour) at low risk of spontaneous preterm birth, such as prophylactic antibiotics, are aimed

at preventing the occurrence of threatened preterm labour and spontaneous preterm birth. Our review suggests that there is little evidence that this approach avoids spontaneous preterm birth, and the practice of administering antibiotics to low-risk, asymptomatic women for the sole purpose of preventing spontaneous preterm birth is not supported. It may be that prophylactic administration is useful against early-onset infection, but potential harms would need to be weighed against any benefits. There is some evidence that prophylactic antibiotics given to women at high risk of spontaneous preterm birth are effective in reducing low birthweight and maternal infection rates. Similarly, antibiotic treatment for bacterial vaginosis significantly reduced the incidence of spontaneous preterm birth in women with a diagnosis of intermediate vaginal flora. No effective test was available; however, this does not impact on the effectiveness of the intervention. Should a more accurate test become available then the overall effectiveness is likely to increase. Antibiotics given to women with asymptomatic bacteriuria also significantly reduced the incidence of spontaneous preterm birth, although this was based on the results of a very small study of questionable quality. Conversely, antibiotics given for the treatment of trichomoniasis increased the risk of spontaneous preterm birth.

In many cases, non-pharmacological interventions to prevent spontaneous preterm birth in asymptomatic women who are at high risk of spontaneous preterm birth did not demonstrate a clear benefit for prevention of spontaneous preterm birth or other maternal or perinatal outcomes when compared to placebo or no intervention. Where reported, bed rest, education, home visits and antioxidants did not significantly reduce the risk of spontaneous preterm birth or infant mortality; however, existing studies were generally not of high quality or were of unclear methodology, making it difficult to confidently evaluate the findings. The results do, however, raise the question of whether asymptomatic women without current urogenital infection should be treated purely on the basis of their previous history.

One possible exception to the apparent ineffectiveness of prophylactic interventions was periodontal therapy, which showed potential in terms of a reduction in spontaneous preterm birth before 37 weeks' gestation. However, this was based on one poor-quality quasi-RCT and other relevant outcomes were not reported.

Progesterone, fish oil, home uterine activity monitoring and dietary advice also appeared to be promising interventions. Intramuscular progesterone reduced the incidence of spontaneous preterm birth before 34 and 37 weeks' gestation, although evidence to support a reduction in perinatal mortality and morbidity was less convincing. Further research is needed regarding the use of vaginal progesterone in the prevention of spontaneous preterm birth, although the one available study showed a benefit. Fish or marine oil, given for the prevention of spontaneous preterm birth in asymptomatic women at high risk of spontaneous preterm birth, demonstrated a reduction in spontaneous preterm birth, but as data were limited to two studies of different oils and regimens, further investigation is required. Home uterine activity monitoring appeared to reduce the risk of spontaneous preterm birth; however, results were based on a single (adequately conducted) study with limited evidence of neonatal safety. Additional research is therefore required to determine support for the use of home monitoring. Dietary advice, specifically aimed at women to increase energy and protein intake, also appeared to reduce the risk of spontaneous preterm birth. However, the results are dominated by one study undertaken in rural Greece, with questionable relevance to UK practice. Interventions designed to deal with a specific problem, such as smoking or infection, known to increase spontaneous preterm birth, appeared to be beneficial whereas interventions targeted at lower-risk women to improve general health, such as antioxidants, appeared not to be. This may be a consequence of participants' absolute risk from the cause or deficiency targeted being relatively low to start with.

Smoking cessation interventions appeared to show some benefit in reducing spontaneous preterm birth and low birthweight (<2500 g) compared to usual care, but the quality of the studies was poor. Although no direct assessment of verified smoking cessation and spontaneous preterm birth was employed, smoking during pregnancy is one of the most clearly identifiable causes of spontaneous preterm birth, so this finding is perhaps not surprising. Future research might wish to consider the most appropriate methods of persuading pregnant women or those planning a pregnancy to stop smoking, looking at what level of intervention may become counterproductive, and whether programmes can be transferred to other areas of addiction, such as alcohol or recreational drugs. It was not possible to identify the specific aspects



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of these interventions that might increase the likelihood of success.

Cervical cerclage, which is aimed at asymptomatic women who are at high risk of spontaneous preterm birth, was also suggested to have some benefit in preventing spontaneous preterm birth, but this needs to be considered in light of the limited evidence concerning neonatal and maternal adverse effects. Similarly, progesterone given to asymptomatic women at high risk of spontaneous preterm birth demonstrated a reduction in the risk of spontaneous preterm birth, and perinatal mortality; however, other infant and maternal outcomes were less well reported, with many outcomes taken from a single study. A recent systematic review, which also conducted a review of adverse events, concluded that progestational agents did not show any evidence of harm.[498]

Tocolytic agents are aimed at controlling the symptoms of threatened preterm labour in symptomatic women, thereby delaying spontaneous preterm birth. There was reasonable evidence to determine the effectiveness of the different tocolytic agents in the majority of cases, with the exception of ethanol, which only had one high-quality study. Evidence to support the use of hydration in symptomatic women was limited by the size of the trials. When compared with placebo, most other tocolytic classes, except ethanol, appeared effective in prolonging pregnancy. A reduced risk of spontaneous preterm birth in comparison with placebo was, however, only shown for NSAIDs (including COX inhibitors) and progesterone. NSAIDs also showed a reduced risk of spontaneous preterm birth in comparison with betamimetics and magnesium sulphate. The RCOG guidelines [Clinical guideline No. 1(B), 2002] currently recommend that if a tocolytic is used, nifedipine, a calcium channel blocker, or atosiban, an oxytocin receptor agonist, should be preferred. However, this was not supported by the data from direct comparisons in this review. Atosiban did not appear superior to placebo or betamimetics for any of the outcomes considered, although in some cases this was only based on a very limited number of small trials. However, an indirect comparison carried out during the economic modelling suggested a benefit to atosiban use. Direct comparisons were not available for calcium channel blockers versus placebo, but they were superior to betamimetics, and for some outcomes to other tocolytic agents. Indirect comparisons suggested that calcium channel blockers were more effective than placebo in preventing preterm birth up to 7 days following intervention. An indirect comparison of atosiban and calcium channel blockers was also performed and a favourable effect for admission to neonatal intensive care unit was found for calcium channel blockers (Appendix 7). This is in line with results from a meta-analysis with indirect comparisons of randomised trials.[682] Notably, rescue tocolysis was employed in a substantial number of the tocolytic studies, particularly within the reviews for NSAIDs, oxytocin receptor antagonists and magnesium sulphate. This practice may have diluted or inflated the results obtained, particularly as it was not always clear how many participants this applied to within a given trial. In addition, evidence regarding the effectiveness of the acute administration of tocolytic agents versus the effect of including a maintenance regimen was difficult to interpret because data for acute administration was often contaminated by the inclusion of maintenance regimens. Although attempts were made to separate data where information allowed, this was not always possible. Furthermore, studies often included different regimens (e.g. dose and/or route of administration); this was particularly noticeable in the reviews of calcium channel blockers. Greater standardisation in treatment regimens would be useful for future research. Differences in effect between different classes of tocolytic drug do appear to exist, but are difficult to assess because of inconsistencies across studies; therefore further research is needed.

Despite the prolongation of pregnancy and a reduction in spontaneous preterm birth, no clear evidence of a beneficial effect on perinatal mortality, or on serious morbidity as evidenced by admission to neonatal care units, was found for tocolytics in general. This may be because the trials included too many women who were so advanced in their gestation that any further prolongation would have little potential benefit, or it may be that many of the earlier studies were undertaken before the use of antenatal steroids, and therefore delay of birth may not have been used to optimum benefit. Furthermore, few RCTs comparing the effect of tocolytic agents with placebo or no treatment for these outcomes were identified, and the results are largely based on single studies with small datasets.

Overall, an increase in adverse events was observed for all tocolytic agents compared with placebo. In particular, treatment with betamimetics was found to be associated with a greater number of adverse events leading to cessation of treatment. Betamimetics are known to be potent

cardiovascular stimulants, and the increased cardiovascular changes shown in this review are likely to have contributed to this finding. In consequence the review supports current clinical opinion that betamimetics are not an appropriate treatment for women with threatened preterm labour. NSAIDs compared favourably with alternative tocolytics in terms of maternal adverse events. However, the RCOG currently recommends that NSAIDs should not be used for tocolysis, this is principally because of concerns over the fetal adverse event profile. Calcium channel blockers appeared to have a good maternal and fetal safety profile. This is in line with the RCOG guidelines [Clinical guideline No. 1(B), 2002] that if a tocolytic is used, nifedipine, a calcium channel blocker, or atosiban, an oxytocin receptor antagonist, may be preferable because they have fewer adverse side effects. However, many RCTs will not detect rare, long-term effects, largely as a consequence of short-term follow-ups, or because they are not powered to detect significant differences in adverse events. There is a clear need for well-conducted studies that specifically consider the safety aspects of treatment. This is particularly important for repeated acute tocolytic therapy in women with recurring symptoms, although this was not assessed in this review.

Maintenance therapy refers to continued tocolytic treatment in women who have successfully been treated with acute tocolysis after presenting with threatened preterm labour. Prolonged oral, subcutaneous or intravenous tocolytic treatment was not associated with greater maternal or fetal benefits compared to placebo or no intervention, and in some trials a negative response to treatment was reported. Betamimetics and magnesium sulphate demonstrated greater adverse events when compared to placebo, although women receiving magnesium sulphate were less likely to report side effects than women receiving alternative tocolytics. In contrast, two trials comparing the efficacy of calcium channel blockers for acute treatment of threatened preterm labour with magnesium sulphate (both employing maintenance regimens of the same tocolytic agent used for the acute treatment) found that women receiving calcium channel blockers demonstrated significantly fewer adverse effects compared with magnesium sulphate.

In addition to interventions aimed at preventing or treating threatened preterm labour, and so delaying spontaneous preterm birth, a number of interventions included in this review were aimed at preparing the fetus for spontaneous preterm birth and trying to reduce associated neonatal morbidity. Such interventions included antenatal administration of magnesium sulphate and vitamin K for neuroprotection, neither of which demonstrated any clear beneficial effect; and prophylactic corticosteroids to prevent RDS. Antenatal corticosteroids were found to have a beneficial effect on the incidence of RDS, the risk of intraventricular haemorrhage, and may also reduce necrotising enterocolitis when compared to placebo or no treatment. The effects were most clearly demonstrated after 28 weeks' and before 34 weeks' gestation, and in babies delivering 1–7 days after the intervention. Whether it is beneficial to administer repeat doses of corticosteroids is currently unknown because insufficient evidence was available regarding the risks or benefits of repeat or rescue courses of antenatal corticosteroids to support their routine use in clinical practice.

Our report highlights a number of evidence gaps related to the prevention of spontaneous preterm birth. Most notable are the assessments of in utero transfer and antibiotics for urogenital infections. One of the primary aims of first-line tocolysis is to delay birth to allow transfer to a unit with more specialised facilities for premature babies. However, no RCTs were identified that assessed the efficacy and safety of in utero compared to extrauterine transfer. Few studies and fewer relevant outcomes were found by reviews of treatments for syphilis and gonorrhoea, limiting our ability to adequately assess the effectiveness of these interventions. While placebo-controlled trials would not be ethical, some research on the best therapy is required, particularly given the rising incidence of these conditions often in conjunction with HIV/AIDS. In addition, the review of ureaplasma found only one trial, which did not report any relevant primary outcomes, and no systematic reviews or relevant RCTs were identified for hypnosis, indicating a need for further research in these areas.

## Recommendations for the economic model

In a number of instances, the aforementioned limitations had implications for the data entered into the economic model. Data were only entered into the model if it was in comparison with placebo and if the relative risk was favourable. Delays in



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completing the review of interventions for bacterial vaginosis prevented the inclusion of these data in the economic model. However, the intervention only appeared beneficial in a subgroup of women with a diagnosis of intermediate vaginal flora. In addition, no placebo comparison was available for a number of the interventions. This can in some circumstances be resolved by the inclusion of data from indirect comparisons. However, for a number of the interventions, most notably antibiotic treatments, leaving infections untreated poses ethical dilemmas and so this was not considered appropriate. Our health economists did however calculate and use an indirect comparison for calcium channel blockers versus placebo.

A further indirect comparison was used for atosiban versus placebo. A direct comparison was available but this was mainly based on one small trial of 112 participants and the data favoured placebo over atosiban. Where data are limited indirect comparisons may also offer additional information. In this case data from the direct comparison (favours placebo) and the indirect comparison (favours atosiban) are conflicting. It is important therefore to consider the internal validity and similarity of the included trials used in the indirect comparisons when interpreting the findings (Appendix 7). Direct and indirect comparisons often agree, but can, as in this circumstance, produce opposing results. This may be the result of random errors between the two estimates or deficiencies in the trials used in the direct, indirect or both comparisons.[683]

The decision to use the indirect comparison in the economic model was based on the fact that atosiban is used so widely in clinical practice and indeed is favoured by the RCOG guidelines [Clinical guideline No. 1(B), 2002]. We felt it is important to consider both the direct and indirect comparisons using them as 'worst case' and 'best case' scenarios, respectively. Using the 'worst case' scenario (i.e. the direct comparison) the intervention would not have been effective enough to be entered into the economic model. The 'best case' scenario (i.e. the indirect comparison) allows the data to be entered into the model so that it can be compared with the other interventions commonly used in practice. However, the findings from the economic model need to be interpreted in light of the limitations and caveats accompanying the use of indirect comparisons, particularly when they are in conflict with evidence from direct comparisons. This also highlights the urgent need for further trials directly comparing atosiban with placebo and other relevant comparators.

Other data entered into the model also need to be considered in light of the quantity and quality of the trials included in the various reviews. For instance, the hydration review data was only based on two small trials of 228 women in total. The data for fish oil was mainly based on only two trials involving only around 250 women. The quality of the trials included in the asymptomatic bacteriuria review and smoking cessation reviews was in the main poor or questionable. The review of periodontal therapy included only one poor quality quasi-RCT ($n = 351$). The data for nutritional advice were mainly based on two studies of questionable quality, one of which was very small ($n = 20$), and neither of which defined spontaneous preterm birth. Finally, the energy/protein supplementation data were based on four trials, only one of which was considered to be of adequate quality.

In addition to problems with the internal validity of the trials, there are also issues with the external validity of certain trials. This calls into question the applicability of the findings to the UK setting. For instance the trial dominating the assessment of nutritional advice is based in a rural population of Greek women ($n = 429$) many of whom had nutritional problems. Similarly one of the four trials included in the assessment of energy/protein supplementation was based in a group of rural Gambian women with chronically marginal nutrition, and another looked at women in a Bogota slum.

## Recommendations for practice

- Tocolysis should be used in women symptomatic with threatened preterm labour to prevent or delay spontaneous preterm birth.
- NSAIDs and calcium channel blockers appear to be favourable interventions to delay spontaneous preterm birth in women with symptoms of threatened preterm labour. However, evidence of contrasting maternal and fetal adverse event profiles should be taken into consideration, particularly in the light of the RCOG guideline recommendation that NSAIDs should not be used.
- There is insufficient direct evidence to support the routine use of oxytocin receptor antagonists such as atosiban.
- Antenatal corticosteroids are the most favourable interventions to treat symptomatic women in terms of preventing complications of prematurity in the newborn.

- Progesterone appears to be the most favourable intervention to treat asymptomatic antenatal women in terms of preventing spontaneous preterm birth.
- Cervical cerclage may be effective in preventing preterm birth in asymptomatic women known to be at increased risk of spontaneous preterm birth.

## Recommendations for further research

Large randomised controlled trials are required for the following interventions and comparators. These should be reported according to the standards of the CONSORT statement and should carry out separate subgroup analysis for multiple pregnancies, complicated pregnancies and IVF pregnancies. Treatment regimens should be standardised; clearly defined populations and outcomes for spontaneous preterm birth before a specific stated gestation should be reported (ideally before 34 weeks' gestation or even earlier). Additionally, spontaneous preterm birth within 24 to 48 hours of treatment (but certainly within 7 days), perinatal mortality, admission to neonatal intensive care, adverse events and longer-term neurological morbidity should also be reported.

### *Asymptomatic antenatal women*

- Periodontal therapy
- Antibiotics for urogenital infections
- Antibiotics for intermediate flora bacterial vaginosis
- Antibiotics for asymptomatic bacteriuria
- Fish oils
- Progestational agents
- Dietary advice
- Smoking cessation interventions versus no intervention, specifically aimed at exploring which individual components of smoking cessation programmes are effective
- Cervical cerclage versus no cerclage.

### *Symptomatic women with threatened preterm labour*

- In utero transfer versus extrauterine transfer
- A systematic review should be conducted to investigate the adverse fetal events associated with NSAIDs; in case insufficient evidence is available for such a review, high-quality randomised trials should be conducted to assess adverse outcomes
- Oxytocin antagonists versus other tocolytics (e.g. NSAIDs, calcium channel blockers)
- Hydration versus placebo.

## Conclusions of reviews of interventions

The overall quantity and quality of many of the trials was often poor or unclear because of poor reporting. No data were found to assess the effects of in utero transfer, antibiotics for urogenital infections (i.e. syphilis, gonorrhoea and ureaplasma) or hypnosis. Treatments aimed at preventing spontaneous preterm birth in asymptomatic women were generally less promising than those aimed at delaying birth in women displaying symptoms of threatened preterm labour (i.e. symptomatic women). Antibiotics were generally not beneficial with the exception of those used to treat bacterial vaginosis (only in women with intermediate flora) and asymptomatic bacteriuria. Trials of non-pharmacological interventions (i.e. bed rest, education, home visits and antioxidants) in asymptomatic women were generally of poor quality and did not show any reduction in spontaneous preterm birth. Smoking cessation interventions, progesterone, home uterine activity monitoring and cervical cerclage did suggest some benefit in terms of preventing spontaneous preterm birth; and the use of fish oil, dietary advice to increase energy/protein intake and periodontal therapy also appeared promising, but findings from all of these reviews were based on limited and sometimes poor quality data. An individual patient data meta-analysis of cerclage in women with a short cervix[684] currently exists, the results of which suggest that cerclage may be of benefit in women with singleton gestations, particularly those with prior preterm birth or prior second trimester miscarriage.

Most tocolytic therapies aimed at delaying spontaneous preterm birth in symptomatic women appeared to show some beneficial effects with the exception of ethanol. However, there was insufficient good-quality evidence to assess the use of tocolytic maintenance therapy. The available evidence suggested that NSAIDs appeared to be the most effective treatments in terms of reducing spontaneous preterm birth and prolonging pregnancy, although evidence to support a reduction in perinatal mortality and morbidity was less convincing. However, only one placebo-controlled trial, published over 20 years ago, was available, and some caution is required in interpreting the data based on comparisons



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with other tocolytics. This is particularly the case because there is some evidence, from one non-randomised study and a review of largely non-randomised studies (not included in this review), which indicates that indomethacin may increase the incidence of neonatal complications, including the likelihood of the infant requiring surfactant treatment[685] and an increased probability of neonatal pulmonary hypertension.[686] No data comparing calcium channel blockers with placebo was available. However, comparisons between calcium channel blockers and other tocolytics showed that calcium channel antagonists were clearly superior to betamimetics, and may be superior to other tocolytics. There appeared to be little direct evidence to support the use of oxytocin receptor antagonists in comparison with placebo or betamimetics. What evidence was available was often limited and/or of questionable quality. However, data from an indirect comparison did not support the findings from these direct comparisons, and it is therefore difficult to form definitive conclusions as to the efficacy of these interventions. Similarly, evidence to support the use of hydration in symptomatic women was limited.

Antenatal corticosteroids were found to have a beneficial effect on the incidence of RDS and the risk of intraventricular haemorrhage (between 28 and 34 weeks' gestation), but the effects of repeat courses of corticosteroids were unclear because of insufficient data. Subsequent to the searches being completed two RCTs evaluating repeated doses of corticosteroids appeared.[665,666] These studies included some women with multiple gestations, but their results provide some support for the practice of giving repeat courses of corticosteroids to women who remain undelivered following initial therapy. However, these studies have not been fully evaluated, nor did they meet the inclusion criteria for this review. Therefore, no conclusions as to the efficacy of repeated therapy can be drawn. Additionally, there is some evidence from animal studies[662] that fetal brain function and growth may be adversely affected, although caution should be exercised when extrapolating such evidence to humans.[687] There was no clear beneficial effect to support the use of antenatal magnesium sulphate or vitamin K for fetal neuroprotection.

# Chapter 6

# Results of decision analyses

## Systematic review of economics and costs studies

### Introduction

We undertook this systematic review to assess the evidence for the cost-effectiveness of different approaches for detecting risk factors and providing treatment for preterm labour. More specifically, this review aimed to assess the appropriateness of the models used and the data requirements for an economic model, and to identify areas of uncertainty that should be explored in the model-based economic evaluation of tests to identify at-risk women and interventions for prevention or delay of spontaneous preterm birth. The review formed part of a wider project: a multidisciplinary series of reviews and modelling that examined the available evidence.

### Methods

Systematic reviewing and meta-analysis of clinical studies, particularly of randomised controlled trials (RCTs), is a well-established research method. The same approach to economic and cost studies is also increasingly being applied, but with marked heterogeneity typical in economic studies, data synthesis and meta-analysis are rarely possible. Usually the most appropriate method for reviewing economic studies is to use a more qualitative approach. This review followed an established method used to systematically review economic studies.[688–691]

The objective of this section of the report is to describe the review of the costs and cost-effectiveness of tests and interventions aiming to predict and prevent spontaneous preterm birth, based on systematic review of the economic literature. The aim was to include all information relating to costs of all aspects of routine tests and interventions in threatened preterm labour. The cost of a spontaneous preterm birth including its calculation can be found in Appendix 8.

### Inclusion criteria

To be included in this study, papers had to meet the following criteria:

- Participants: pregnant women, singleton gestation and preterm labour
- Tests: those included in Appendix 2 of the accuracy review
- Interventions: those included in Appendix 3 of the effectiveness review
- Studies: formal economic evaluations and cost studies; cost studies include studies reporting primary research on the costs and use of care, and studies that discuss economic aspects of care and contain useful primary or secondary cost or use data.

The 'cost-generating' events or knock-on costs influenced by threatened preterm labour were also considered. These include delivery and postnatal care for women and baby/neonatal intensive care unit. Studies were identified using the search strategy described by York CRD, University of York (Appendix 1).

### Exclusion criteria

Premature pre-labour rupture of the membranes may lead to threatened preterm labour and spontaneous preterm birth but it is not the focus of this study so these papers were excluded.

### Selection of papers for review

#### *Stage I and II – initial categorisation of studies*

Each study was categorised on the basis of its title, Medical Subject Heading (MeSH) and abstract when available, by one investigator (A.T.) and the results were independently assessed by a different investigator (T.R.). Where there was disagreement it was resolved by consensus. A two-stage reviewing approach was used as described in detail elsewhere.[690] In the first stage, each study was categorised on the basis of title and abstract and classified as either an economic evaluation (coded A) or a cost study (coded B) or another category deemed irrelevant to the review. In the second stage, studies were retrieved and reviewed in full, and if the initial classification was confirmed, the final classification was A1 or B1. After review, studies that were initially classified as economic evaluations but with further scrutiny were found



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to be cost studies were finally classified as A2. The converse occurred for cost studies that after review were found to be economic evaluations. Studies that, after full review, were confirmed to be either economic evaluations or cost studies were included in the quality assessment section of the review. Foreign language papers were included if relevant. All other papers and studies that did not fall into one of the relevant categories were rejected.

### *Stage III – quality criteria*

The quality of the economic evaluations was assessed according to the criteria used elsewhere,[690] which are presented in Appendix 4.

If the studies fulfilled all the necessary criteria they were considered for data extraction in Stage IV. Some studies that just missed fulfilling all the quality criteria, but which nevertheless contained information that might be relevant and might be the only such available data, were not rejected but were marked with a query (?).

### *Stage IV – data extraction*

An example of a data extraction sheet is presented in Appendix 4. Cost data were then inflated to 2006 prices using the National Health Service (NHS) Executive Hospital and Community Health Services Pay and Prices inflation index.[692]

## Results

A total of 1157 papers were identified by the literature search. The initial and subsequent classifications of these studies, together with the result of the quality assessment, are shown in *Figure 282*.

In the final classification, 15 studies were confirmed as economic evaluations (ten were categorised as A1, five as B1) and there was one additional paper which was a published review. Overall the quality was not good with only one study passing all the quality criteria.[693] Eight other studies, excluding the review, were marked with a query.[56,57,694–700] The studies marked with a query were not excluded from the review and the summary data for these studies are presented in *Table 38*. Six studies categorised as economic evaluations failed to meet the required quality criteria and were excluded.[701–706] A summary of the excluded studies is presented in *Table 39*. The quality criteria were

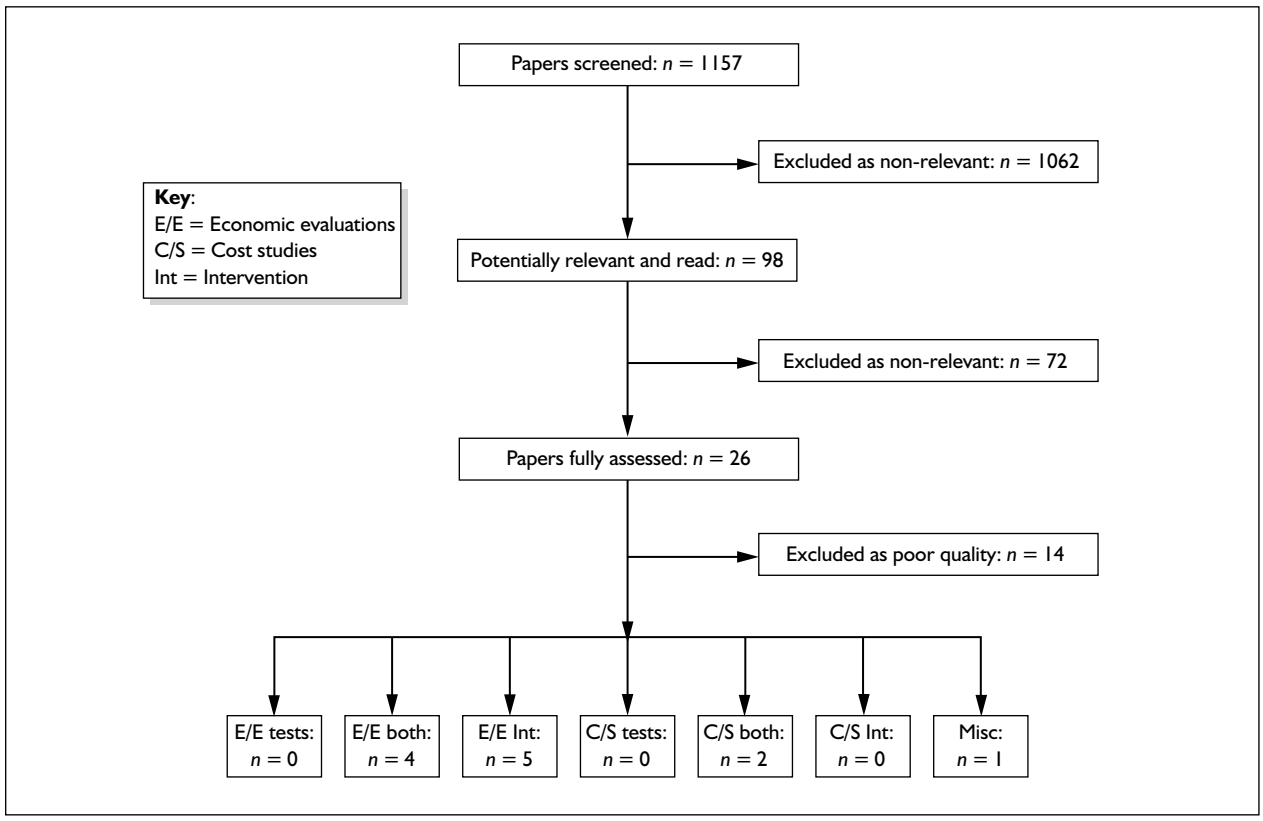


***FIGURE 282*** *Literature search results.*

not applicable to a review,[700] which was therefore not graded but discussed separately below.

Only two studies were confirmed as cost studies, but their quality was dubious and they were both marked with a query.[123,707]

Of the nine economic evaluations that remained in the final stage of the current review, five (including the review) were carried out in the USA. The remaining four studies were European; none were from the UK.

### *Bacterial vaginosis and antibiotic interventions*

The only study to pass the required quality criteria was from Finland. [693] The authors used a decision tree to conduct an economic evaluation of screening and treatment of bacterial vaginosis (BV). The analysis was a cost-effectiveness analysis conducted from the perspective of the Finnish Health-Care System. The study population was asymptomatic women in early pregnancy at low risk for spontaneous preterm birth. Screening was carried out by detection using Gram-stain of the vaginal discharge. For treatment, two scenarios were assessed: scenario 1 was treatment with metronidazole 400 mg twice daily for 7 days and scenario 2 was treatment with clindamycin. The evaluation found that the probability of spontaneous preterm birth predicted by the model was 2.8% [95% confidence intervals (CI) 1.7–4.2] in the screening strategy and 2.7% in the no-screening strategy. Given the statistical uncertainty around point estimates, the authors' conclusion was that there was no difference between the strategies. The authors concluded with implications for practice, which suggested that screening and treatment of BV in early pregnancy among low-risk women might not reduce costs compared to no screening.

*Comment:* Given that this paper passed all the quality criteria and was considered by the review team to be well carried out, there are no reasons to doubt these results from an economic perspective. The results provide no economic support for screening and treatment of BV in early pregnancy.

Muller *et al.*[57] also carried out an evaluation to estimate the economic impact of screening for, and treatment of, BV during early pregnancy. The results of the study suggested that $168 could be saved per delivery when women were screened in the early second trimester and, if the diagnosis was positive, treated for BV. The authors concluded that the current practice in Germany of not screening or treating positive cases should be re-evaluated.

*Comment:* This paper was marked with a query because it did not meet the required quality criteria. One reason for this was that the paper included a decision tree that was not used in the analysis. The authors present data on costs and effectiveness, but they do not combine them. Because of these concerns the conclusion from this study should be treated with caution.

From these two studies on BV, there is currently no clear economic evidence to support screening and treatment of BV in pregnancy to prevent spontaneous preterm birth.

### *Tocolytic interventions*

The papers by Mozurkewich *et al.,* Ambrose *et al.,* Ferriols *et al.*, Korenbrot *et al.*, Lam *et al.* and Myers *et al.* [56,694,696–699] all focused on evaluating tocolytic interventions. The study by Mozurkewich *et al.*[56] combined the evaluation with some tests, which included the rapid fetal fibronectin test and measurement of cervical length. The study by Myers *et al.*[699] combined the evaluation with an amniocentesis test.

#### Test and tocolytic interventions

Mozurkewich *et al.*[56] compared the cost-effectiveness of nine strategies for the management of threatened preterm labour based on a decision tree analysis from the perspective of the third-party payer. The study population was patients diagnosed with threatened preterm labour (defined as regular uterine contractions) between 24 and 34 weeks, intact membranes, and without advanced cervical dilatation (≥3 cm). The paper examined a traditional fetal fibronectin test, rapid fetal fibronectin test and cervical length measurement; and treatment with corticosteroids or tocolytics. The main results of the study were that 'Rapid fetal fibronectin testing', 'cervical length assessment', 'rapid fetal fibronectin plus cervical length', and 'treat none' strategies were 'dominated' in the analysis of incremental cost-effectiveness, being both more costly and less effective than the next least expensive strategy which was the assessment of risk for spontaneous preterm birth with fetal fibronectin testing or cervical length assessment. They found that this assessment could result in significant cost savings relative to the current policy of treating all women who present with threatened premature onset of labour. The addition of corticosteroids to either rapid risk assessment strategy may further lower costs by reducing



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***TABLE 38*** *Economic study characteristics*

| Study details, including quality | Type of economic evaluation/ Study population | Viewpoint | Effectiveness data sources | Cost data; year and currency | Model used | Test |
|---|---|---|---|---|---|---|
| Ambrose *et al*. 2004[694]<br>USA<br>B(1)<br>Query | Cost consequences analysis<br>Symptomatic Women | Not reported, it appears to be that of the third-party payer | Own primary study | US$, cost year was not reported | None | None |
| Egberts 1992[695]<br>The Netherlands<br>B(1)<br>Query | Cost-effectiveness analysis<br>Preterm infants (< 30 weeks) | Not reported, it appears to be of the health-care provider | Literature | The Netherlands Dfl, 1990 | None | None |
| Ferriols *et al*. 2005[696]<br>Spain<br>A(1)<br>Query | Cost-effectiveness analysis<br>Symptomatic women | Health-care system | Literature | Euro €, cost year was not reported | Decision tree | None |
| Kekki *et al*. 2004[693]<br>Finland<br>A(1)<br>Pass | Cost-effectiveness analysis<br>Asymptomatic women (early pregnancy) | Health-care system | Two own primary studies. Published perinatal statistics | Euro €, 2000 | Decision tree | Gram-stain of the vaginal discharge |
| Korenbrot *et al*. 1984[697]<br>USA<br>A(1)<br>Query | Cost consequences analysis<br>General population | Not stated, it seems to be that of the hospital | Hospital resources | US$, 1981 | None | None |
| Lam *et al*. 2003[698]<br>USA<br>A(1)<br>Query | Cost consequences analysis<br>Symptomatic women | Not stated, it seems to be that of the health-service provider | Own primary study | US$, cost year was not reported | None | None |

| Intervention | Primary outcome | Results | Comments |
|---|---|---|---|
| Inpatient vs outpatient tocolysis with continuous subcutaneous terbutaline (SQT) | Costs and outcomes were not synthesised. Primary outcomes were 'cost of total pregnancy', 'rate of preterm delivery' | Inpatient tocolysis costs $56,089 and has a preterm birth rate of 86.7%. and outpatient tocolysis costs $25,540 with a preterm birth rate of 74.4%. Therefore, outpatient management is cheaper and gives a lower preterm birth rate, and thus could be introduced | Appeared to be comprehensive with some shortcomings. Reported unit costs are incomplete. No sensitivity analysis was carried out, therefore results should be viewed with caution |
| Corticosteroids; surfactant (prophylactic and therapeutic) | Cost per survivor, cost per extra survivor | Prenatal corticosteroid administration had the lowest cost per survivor of 66.3). Corticosteroids and prophylactic surfactant was the most cost-effective strategy at 63.7 (× Dfl 1000) per survivor, and gave the lowest intensive- and high-dependency-care days in hospital | There were study shortcomings. Interventions were not defined thoroughly. Results were very unclear and sensitivity analysis was not carried out. Data available to calculate ICERs but they were not calculated |
| Ritodrine vs atosiban | Cost per preterm birth (PTB) avoided within 48 hours | The ICER for ritodrine was $194/PTB avoided and for atosiban: was$632/PTB avoided (within 48 h). Therefore it was reported that ritodrine should be the first choice agent and atosiban a rescue drug | Clear definitions of interventions and a well-defined model. However, presentation of ICER is incorrect therefore results based upon it are incorrect and misleading |
| Metronidazole, clindamycin | Cost per pregnant woman | The probability of PTB was 2.8% for screening and 2.7% for no screening. The no screening strategy was marginally less costly, therefore dominated all screening strategies. Authors stated statistical uncertainty may suggest no difference between strategies, and screening and treatment may provide more health benefits | Passed all quality criteria and appears to be sound. Tests and interventions are defined thoroughly. PSA is presented in full detail. One disadvantage is the assumption of a normal distribution for the cost variables |
| Terbutaline or isoxsuprine (β-adrenergic drugs) vs no intervention | Costs and outcomes were not synthesised. Primary outcomes were 'expected maternal and neonatal charges per survivor', 'extension of gestation' and 'perinatal survival rate' | Cost-effectiveness of treatment dependent on gestational age at onset of first PTL. Treatment between 26 and 33 weeks of gestation was cost-effective, resulting in expected savings of $11,240 per birth. Treatment at 20–25 weeks cost-effective if chance of survival taken into account. Little difference in costs for treatment or no treatment over 33 weeks. β-Adrenergic tocolytic intervention should be used to prevent PTL | Comprehensive but not meeting all quality criteria. Parameters used in the statistical analysis are extensive, but no sensitivity analysis is performed. Therefore results should be viewed with caution. Final recommendations not clear |
| Oral tocolysis versus subcutaneous terbutaline infusion | Costs and outcomes were not synthesised. Primary outcomes were 'overall cost per pregnancy' and 'antepartum hospitalisation charges per patient' | Overall cost per pregnancy of subcutaneous terbutaline (SQT) infusion was $5286 less than oral tocolysis. Also there was greater pregnancy prolongation with SQT and better neonatal outcomes. Therefore SQT was cost-effective | Generally well carried out and reported, with both interventions defined thoroughly. Cost year and perspective not reported. Estimation of final costs unclear. Results should be viewed with caution because of this |

*continued*



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***TABLE 38*** *Economic study characteristics (continued)*

| Study details, including quality | Type of economic evaluation/ Study population | Viewpoint | Effectiveness data sources | Cost data; year and currency | Model used | Test |
|---|---|---|---|---|---|---|
| Mozurkewich *et al*. 2000[56]<br>USA<br>A(1)<br>Query | Cost-effectiveness analysis<br>Symptomatic women | Third-party payer | Literature | US$, 1999 | Decision tree | Traditional/rapid fetal fibronectin test<br>Cervical length measurement |
| Muller *et al*. 1999[57]<br>Germany<br>A(1)<br>Query | Cost minimisation analysis<br>Asymptomatic women | Third-party payer | Own primary study and standard German sources | US$, 1996 | Decision tree | Screening for bacterial vaginosis (clue cell diagnosis) |
| Myers *et al*. 1997[699]<br>USA<br>A(1)<br>Query | Cost-effectiveness analysis<br>Symptomatic women | Hospital-based | Literature and hospital resources | US$, 1996 | Markov model | Amniocentesis (test all) |
| [a]Rushing and Ment 2004[700]<br>USA<br>A(1)<br>Quality criteria not applicable | NA | NA | NA | NA | None | None |

NA, not applicable; PTL, preterm labour; QALY, quality-adjusted life years; RDS, respiratory distress syndrome; SQT, subcutaneous terbutaline.
a This paper is a review of economic evaluations and cost studies.

morbidity among infants born to mothers with false-negative results.

*Comment:* This paper was marked with a query because it did not meet the required quality. Although there was some useful information on costs, it was quite unclear how the authors actually calculated incremental cost-effectiveness ratios (ICERs). As a result we have to view the results with some caution although the shortcomings may be a result of poor reporting as opposed to poor analysis.

Myers *et al.*[699] carried out a study to determine the incremental cost-effectiveness of two strategies for preventing respiratory distress syndrome resulting from spontaneous preterm birth, from a hospital-based perspective using a Markov model. Women with preterm labour were followed over a 7-day period. Three options were compared: (1) treat all with tocolysis with betamimetic agonists and corticosteroids (TREATALL) without testing, (2) amniocentesis and testing for fetal lung maturity, with treatment based on test results (TESTALL), and (3) no treatment. Based on the model, the

| Intervention | Primary outcome | Results | Comments |
|---|---|---|---|
| Corticosteroids, tocolytic agents | Incremental costs per additional case of RDS or neonatal death prevented by the next most effective strategy | Five strategies were dominated. Fetal fibronectin testing or cervical length assessment may be cost saving relative to treating all women. Adding corticosteroids to either rapid risk assessment strategy may lower costs by reducing morbidity among infants born to mothers with false-negative results | Costs are defined thoroughly, giving useful information Calculation of ICERs and sensitivity analysis are quite unclear. Results should be viewed with caution because of this |
| Clindamycin 2% vaginal cream; *Lactobacillus* preparation | Costs and outcomes were not synthesised. Primary outcomes were total cost and net savings | No screening or treatment was most expensive at $534,926. Screening and treatment with clindamycin was cheapest at $493,159. Screening and treatment with lactobacillus was $497,619. $168 can be saved per delivery if women are screened and treated | The decision tree is not used in the estimation of costs. Sensitivity analysis is carried out on prevalence and charges, but on a limited range. Costs were hospital charges for insurance funds. Cost and effectiveness could be synthesised, but no ICER was calculated |
| Tocolysis with β-mimetic antagonists and corticosteroids (treat all) | Cost per case of RDS prevented | Tocolysis and corticosteroids strategy was most cost-effective at before 34 weeks. Amniocentesis and fetal lung maturity testing strategy was most cost-effective at 34–36 weeks and no treatment strategy after 36 weeks. Cost per case of RDS prevented for Treat all strategy ranged from $10,500 to $1 million dependent on prevalence of RDS (2–17%) | 'Test all' strategies were not defined thoroughly. Estimation of 'cost of RDS' and 'cost of preterm delivery' are not sound and may be underestimated. Overall, the paper would have benefited from reporting methods more fully. |
| Antenatal steroids, surfactant, indomethacin, dexamethasone (postnatal) | Cost per additional survivor, additional cost per additional life year gained, additional cost per additional QALY gained | Results vary. Antenatal steroids decrease costs per additional survivor. Surfactant has decreased treatment costs and is more beneficial when given prenatally. Indomethacin results in cost savings in survivors | Criteria for including papers were unclear. Overall the conclusions were variable. Papers included in review were not subjected to critical scrutiny. No confidence in results |

available literature and current costs, empirical tocolysis and corticosteroid administration before 34 weeks' gestation was considered the most cost-effective strategy. Amniocentesis and fetal lung maturity testing appeared to be the most cost-effective strategy in this specific clinical setting within the limited time frame of 34–36 weeks' gestation. No treatment was the most cost-effective option after 36 weeks.

*Comment:* Overall this was considered a relatively good paper but with some limitations, so it did not meet all of the predetermined quality criteria and was marked with a query. The reasons for this include the underestimation of costs, for example the outpatient costs for prenatal visits were omitted with the justification that these costs are small relative to hospital costs. Furthermore, the TESTALL strategy included a single or a series of tests for lung maturity, but these were not further defined or described. These items may be the result of a failure in reporting and so the results should be viewed with some limited caution but should not be rejected entirely. The use of a Markov model in this analysis was appropriate and will be discussed further.



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***TABLE 39*** *Summary of the excluded studies*

| Study details, incliding quality | Type of economic evaluation/Study population | Viewpoint | Effectiveness data sources | Cost data; year and currency | Model used | Test |
|---|---|---|---|---|---|---|
| Abenhaim *et al.* 2005[701]<br>Canada<br>B(1)<br>Fail | Cost consequences analysis<br>Symptomatic women | Not stated, it seems to be that of the health-care provider | Hospital databases | US$, cost year was not reported | None | Fetal fibronectin test vs no intervention |
| Harrison *et al.* 2001[702]<br>Canada<br>B(1)<br>Fail | Cost consequences analysis<br>Symptomatic women | Not stated | Hospital databases | Canadian $, cost year was not reported | None | Home uterine activity monitoring |
| Morrison *et al.* 2001[703]<br>USA<br>A(1)<br>Fail | Cost consequences analysis<br>Symptomatic women | Not stated, it seems to be that of the third-party payer | Hospital databases | US$, cost year was not reported | None | Home uterine activity monitoring, telephone nursing contact |
| Moya and Goldenberg 2002[704]<br>USA<br>A(1)<br>Fail | Cost-effectiveness analysis, cost utility analysis<br>Preterm infants (not defined further) | Societal perspective | Literature and clinical expertise | US$, cost year was not reported | Decision tree | None |
| Oswald and Mark 1996[705]<br>USA<br>B(1)<br>Fail | Cost-effectiveness analysis, cost analysis<br>High-risk women | Not stated, it seems to be that of the third-party payer | Hospital databases | US$, 1989 | None | Previous history of preterm birth (PTB) |
| Ross *et al.* 1994[706]<br>USA<br>A(1)<br>Fail | Cost-effectiveness analysis<br>High-risk women | Not stated, it seems to be of the health-service provider | Own primary study and hospital databases | US$, 1992–1993 | None | None |

ICER, incremental cost-effectiveness ratio; PRT, preterm birth; QALY, quality-adjusted life years.

### Tocolytic interventions only

Four papers evaluated various tocolytic approaches only, without evaluating a test.[694,696–698] Only one study used a decision tree model.[696]

Ferriols *et al.*[696] evaluated the relative cost-effectiveness of two tocolytic agents, ritodrine and atosiban. They used a decision tree model and adopted the perspective of the health service. The authors concluded that a tocolysis protocol using ritodrine as first-choice agent and atosiban as a rescue drug was the most efficient option based on available evidence.

*Comment:* Again, this paper was marked with a query. The strengths of the paper are that it presented clear definitions of the interventions with a well-defined model and clear information on the sources of costs and outcomes. However, the effectiveness data were not clearly defined and

| Intervention | Primary outcome | Results | Comments |
|---|---|---|---|
| None | Mean cost per patient with preterm labour | Mean cost per patient with preterm labour: $581 (study group), $3666 (baseline group) | Authors acknowledge underestimation of costs, by excluding radiological and laboratory costs. Cost year is not reported. Sensitivity analysis is not carried out. Results unhelpful to this study |
| Education, home care, nutrition | Total cost, total cost per woman | *In-home care group: t*otal cost $16,556<br><br>*In-hospital care group: t*otal cost $22,891<br><br>No significant difference for total cost per woman | The perspective is unclear. The cost year is not reported. Sensitivity analysis is not carried out. Total cost per woman is not presented for the two groups |
| Education, smoking cessation, nutrition, exercise | Costs and outcomes were not synthesised. Primary outcome was 'cost per pregnancy' | Total mean cost per pregnancy: $7,225 (telemedicine group), $21,684 (control group) average savings: $14,459 | No formal incremental analysis. Unit costs are not reported separately. Sensitivity analysis is not carried out. |
| Prophylactic indomethacin vs standard treatment | Cost per life expectancy, cost per QALY | Cost per life expectancy: $7142 (prophylactic group), $7727 (standard treatment group)<br><br>Cost per QALY: $9168 (prophylactic group), $8443 (standard treatment) | Sensitivity analysis is not applied on all relevant parameters and no reason for this is given. The ICER presented is misleading. Cost per life expectancy and Cost per QALY of each alternative are estimated and then are wrongly subtracted |
| Education | Average cost per case of PTB avoided | Average cost per case of PTB avoided: $10,662 (control group); $28,903 (comparison group) | The PTB prevention programme evaluated is not defined thoroughly. Hence, the exclusion of its cost from the analysis is not sound. Sensitivity analysis is not carried out. No ICER is calculated. Conclusions are based on the cost analysis and net savings between groups |
| Five interventions (not further defined) | Average cost per patient | Average cost per patient: $294 (prenatal care group) | The five interventions of the prenatal care group are treated as one and are compared versus no intervention. No individual information is given on the costs and benefits of the interventions. Sensitivity analysis is not carried out. No ICER is calculated. Conclusions are based on the cost analysis |

crucially an ICER was not presented. Instead the authors presented two effectiveness values for each agent and divided them (instead of subtracting them) to draw a comparison. This is inappropriate and consequently, the results from this study are incorrect.

Korenbrot *et al.*[697] compared the effectiveness and costs of care with beta-adrenergic drug treatment (terbutaline or isoxsuprine) with the expected costs in the absence of such treatment. The perspective was not clear but appeared to be that of the health-care provider. Preterm labour was defined as the occurrence of contractions leading to cervical change or premature rupture of the membranes (or both) between the 20th and 37th weeks of gestation. The authors found that: at 20–25 weeks treatment is cost-effective if the improved chances of survival of the baby are considered; at 26–33 weeks of gestation, treatment was clearly



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cost-effective; and after 33 weeks, expected costs with tocolytic treatment were not significantly different from costs without treatment, with or without consideration of costs per survivor. The authors conclude therefore that the beta-adrenergic tocolytic intervention should be used in the prevention of spontaneous preterm birth.

*Comment:* Despite being old, this paper was considered to be fairly comprehensive although it did not meet all the predetermined quality criteria and so it was marked with a query. Clinical outcomes and costs are presented for various gestational groups, but the final recommendation, in terms of appropriate gestation, was not clear.

Ambrose *et al.*[694] compared pregnancy and economic outcomes in women receiving inpatient with those in women receiving outpatient tocolysis with continuous subcutaneous terbutaline (SQT).

Although the perspective of the analysis was not reported it appeared to be that of the third-party payer. The study population was women hospitalised for stabilisation of an acute episode of preterm labour and thereafter prescribed continuous SQT therapy between 24.0 and 33.9 weeks' gestation. The authors concluded that outpatient management resulted in improved pregnancy outcomes at a cost less than that of inpatient management and they suggested that outpatient management could be introduced to pregnant women.

*Comment:* Although this paper was marked with a query because it did not meet the predetermined quality criteria, overall it appeared to be a comprehensive evaluation. One disadvantage was that the year for the unit costs was not reported; some costs were also omitted, such as physician charges. More critically, no sensitivity analysis was performed and so we view these results with some limited caution.

In a similar analysis to that carried out by Ambrose *et al.*[694], Lam *et al.*[698] compared the clinical benefit and cost-effectiveness of using SQT and oral tocolytics following recurrent preterm labour. Again the perspective was not reported but it appeared to be that of the health-service provider. The results suggested that in this population, SQT infusion was both a clinically beneficial and a cost-effective treatment following recurrent preterm labour. Women treated with SQT infusion had greater pregnancy prolongation with better neonatal outcomes than women who were treated with oral tocolytics.

*Comment:* This study did not meet the predetermined quality criteria, principally because the cost year and the perspective were not reported. However, the study was otherwise considered to be generally quite well carried out and explained.

#### *Other drug-related interventions, e.g. steroids, surfactant*

The remaining paper evaluated the cost-effectiveness of corticosteroid interventions.[695] Egberts *et al.*[695] compared the costs and effectiveness of prenatal administration of corticosteroids and prenatal and postnatal administration of surfactant. The perspective of the analysis was not clear but appeared to be that of the health-care provider because all cost estimations were based on the number of hospitalisation days. The result showed that the estimated costs per extra survivor were the lowest for prenatal corticosteroid administration. The authors concluded that the combination of prenatal corticosteroid and postnatal prophylactic surfactant was the most cost-effective option because it produced the greater number of survivors and the lowest number of intensive and high dependency care days in hospital.

*Comment:* In general this cost-effectiveness study was found to have a number of omissions and so it failed to meet the predetermined quality criteria and therefore was marked with a query. In particular, no sensitivity analysis was presented; the ICERs, which could have been calculated, were not; and as a result the overall results were very unclear.

#### *Review of economic evaluations*

The published review by Rushing *et al.*[700] called itself a cost–benefit analysis but basically presented a summary of information from a number of studies that covered the entire perinatal period. It included summary information that applied to different points in the perinatal period including postnatal treatments. The criteria for selecting or maintaining papers in the review were not made explicit. Furthermore the papers discussed and their results were subjected to very little critical scrutiny. Given the lack of rigorous appraisal of the results it is consequently not possible either to have any faith in the results or to provide any support for the conclusions from this paper.

## Discussion

In general the overall quality of the studies reviewed was poor and therefore a clear case for a test or treatment has not been supported by the results of this review of economic evaluations. All but one of the studies failed to meet all the predetermined quality criteria. However, where only one or two of the criteria were unfulfilled the paper was not excluded because it was considered that it might have some useful information and so it was marked with a query.

The main findings are summarised as follows:

- There is no evidence to suggest that screening for and treatment of BV is a cost-effective strategy.[57,693]
- Evaluation of testing for the risk of preterm labour with either the fetal fibronectin test or cervical length measurement test found both to be cost-effective strategies.[56]
- The use of terbutaline was found to be a potentially cost-effective intervention and this result was supported by three studies although the quality of all three was defined as equivocal.[694,697,698]
- Prenatal steroids and postnatal surfactant were found to be cost-effective in reducing perinatal mortality.[695]
- The use of a Markov model by Myers *et al.*,[699] was noted. The authors used this model structure appropriately to model repeat doses of tocolytics in their 7-day model as women who give birth before 7 days leave the model and there is no risk of overestimating the costs of the treatment.

# Methods for evaluating the relative cost-effectiveness of tests and interventions

## Introduction

The objective of the economic evaluation in this study was to collate the data from the reviews on the accuracy of the tests with the data on the effectiveness of the interventions and to explore the relative cost-effectiveness of a range of different testing and treatment options. Recommendations made in previous chapters on the basis of clinical effectiveness of some of the interventions may not necessarily be reiterated on this chapter because of the introduction of cost to the analysis. All data identified from the reviews may not be included in the model. The data had to meet certain threshold criteria either in terms of the accuracy data for the tests or the effectiveness data for the interventions to be included. The final output of the modelling exercise is in terms of the dominating strategies (those achieving greater effectiveness at reduced cost) and the relative ICER for the better test and treatment options. For the symptomatic cases the results are in terms of cost per case of spontaneous preterm birth avoided and cost per perinatal death avoided as appropriate for the model. For the asymptomatic analysis the results are in terms of cost per symptom avoided and cost per perinatal death avoided as appropriate for the model. The perspective adopted for the economic evaluation was that of the NHS. Private out-of-pocket costs to women are not included in the analysis.

## Methods

### *General*

This section provides further detail about the economic modelling summarised in Chapter 3.

#### *Model structure*

The appropriate model structure for use in this study was a decision tree. The analysis for this study required nine different cases to be evaluated. This mirrored the different target populations and outcomes discussed in detail in Chapter 1, Delineation of the problem.

Symptomatic analysis:

- Case 1 – women delivering within 24 h of being treated for symptoms of preterm labour
- Case 2 – women delivering within 48 h of being treated for symptoms of preterm labour
- Case 3 – women delivering within 7 days of being treated for symptoms of preterm labour
- Case 4 – women before 34 weeks' gestation who experience symptoms of preterm labour
- Case 5 – women before 37 weeks' gestation who experience symptoms of preterm labour
- Case 6 – women experiencing symptoms of preterm labour who are at risk of perinatal mortality

Asymptomatic analysis:

- Case 7 – Asymptomatic women before 34 weeks' gestation who risk preterm labour
- Case 8 – Asymptomatic women before 37 weeks' gestation who risk preterm labour
- Case 9 – Asymptomatic women who are at risk of perinatal mortality



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The models were constructed in DATA TREEAGE. Space constraints do not allow all illustrations of the model structure to be presented. To illustrate the approach for each test/treatment pairing we present a subset of the model (*Figure 283*), used in the symptomatic analysis of women at 37 weeks' gestation who experience symptoms of preterm labour. The subset of the model presents one test (fetal fibronectin) and one intervention (indomethacin).

In *Figure 283* each branch to the right of the chance node (square symbol) indicates one way in which the test under consideration (fetal fibronectin) and treatment (indomethacin) can be brought together. All the ways in which test and treatment could in theory be used together are considered for completeness, although not all of these may have direct clinical relevance (see below for further explanation). The model considers for each test and treatment combination the number of cases of spontaneous preterm birth and the associated cost for:

1. No test and no intervention ['No test/no treatment']
2. Intervention, indomethacin, given to all with no preceding testing ['No test/indomethacin_ all']
3. Test, fetal fibronectin, applied to all, but no subsequent intervention ['Fetal fibronectin/no treatment']
4. Test, fetal fibronectin, applied to all, followed by the intervention, indomethacin, being just given to those testing positive (having the characteristic indicated or a test value above a stated value) ['Fetal fibronectin/indomethacin_ positive']
5. Test, fetal Fibronectin, applied to all followed by the intervention, indomethacin to all (regardless of test result) ['Fetal fibronectin/ indomethacin all']

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

Branches 2 and 4 represent the chief clinically relevant alternative strategies for test and treatment pairings. Branch 2 considers the benefits and costs of treating all mothers, an important scenario to investigate if there is doubt about the accuracy of the available tests. Branch 4 considers the approach that attempts to focus the intervention on those indicated by the test to be at highest risk, and so avoid any adverse effects of the intervention in those thought unlikely to gain benefit, because their risk of developing spontaneous preterm birth is so low.

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

In *Figure 283*, the right hand side of the diagram indicates the outcomes considered in measuring which of branches 1 to 5 in this and other modules is optimal. As already indicated, the main outcome for the symptomatic models (excluding the outcome of perinatal mortality) is cases of spontaneous preterm birth relative to cases without. In branches where a test result is obtained, the model considers separately the number of cases of spontaneous preterm birth occurring in those testing positive and those testing negative. Although this is shown as being a feature of the way the model works in branches 3 to 5, it is only strictly necessary in branch 4 because this is the only option where treatment is truly contingent on the test result. The box beneath the population of interest, symptomatic women, on the far left of the diagram, indicates the model parameters being used. Thus 'c indomethacin =1646.01' indicates that the cost of indomethacin over the course of pregnancy is £1646.01, 'mLR_Neg_ Fibronectin=0.128' indicates that the likelihood ratio of a negative fetal fibronectin test result estimate being used in this module of the model is 0.128 and 'mLR_Pos_Fibronectin=7.791' indicates

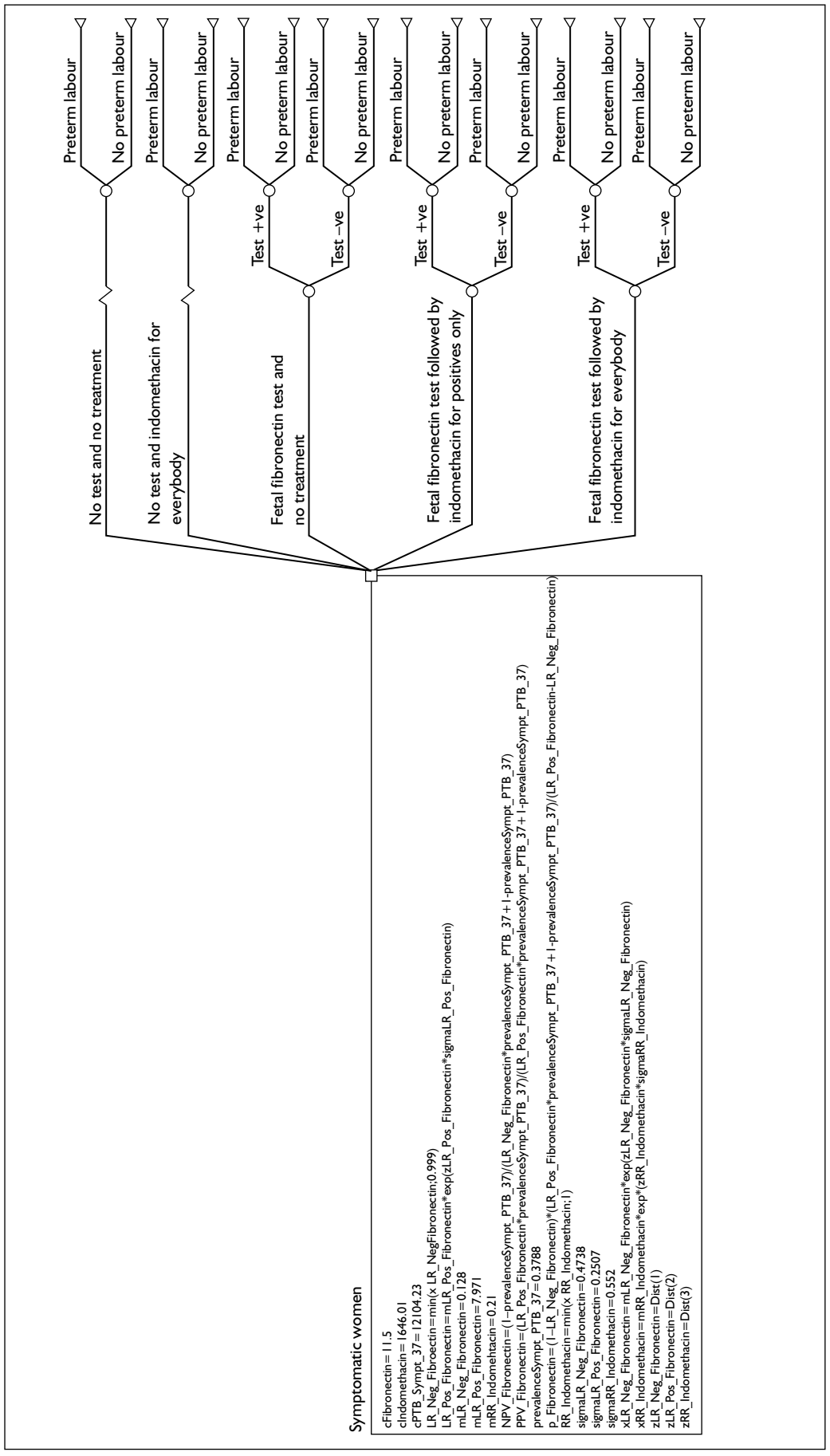


***FIGURE 283*** *Decision tree.*



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that the positive likelihood ratio is 7.791. These parameters will differ depending on the module.

***Test accuracy and effectiveness data***

The data from the systematic reviews assessing the accuracy of all the tests reviewed as part of this project, reported in Chapter 4, were the source of the likelihood ratio model parameters. The actual values used were generally based on either pooled likelihood ratios for positive (LR+) and negative (LR–) tests or the largest highest quality individual study result, as described in the review methods section (Chapter 3). These values and their associated 95% CI are tabulated in *Table 40* for asymptomatic women and *Table 41* for symptomatic women. Similarly, the data from the systematic reviews of the effectiveness, reported in Chapter 5, were the source of model parameters concerning the effect of various treatments on the number of cases of spontaneous preterm birth and perinatal mortality. The values used, generally the summary relative risks (RR) from the meta-analyses, along with their 95% CI, are summarised in *Table 42* for asymptomatic women and *Table 43* for symptomatic women.

There are two main groups of treatments differentiated because they are dealt with slightly differently by the models (see below). In group 1, the 95% CI for the RR do not include values >1.0, indicating that a true value of the RR compatible with increased numbers of spontaneous preterm birth or perinatal mortality cases (i.e. worsened outcome) is unlikely. These are typically the only data for interventions that will be used in the probabilistic sensitivity analysis (PSA) – described in more detail in the next section. Conversely in group 2, the 95% CI for RR do include values >1.0, i.e. a possible worsened outcome. *Table 41* also gives values for the RR (group 3) obtained from indirect comparisons, where the intervention was compared with another intervention and not with placebo. In those cases the RR values were computed by combining the relevant values to obtain the intervention versus placebo RR. When relevant, data from group 3 are also included in the PSA. Typically, data on interventions from groups 1, 2 and 3 are all used in the deterministic analysis.

**Test accuracy cost data**

The cost estimates for each test are described in more detail (*Table 44*). All costs are presented in UK£ at 2005 prices. Cost data for the tests came from two main sources, the literature and the Birmingham Women's Hospital, Birmingham, UK. The literature estimates of cost for a particular test were primarily identified from studies known to the health economics and modelling team from their work on similar topics in the past.

A cost estimate for the amniotic fluid interleukin-6 (IL-6), amniotic fluid interleukin-8 (IL-8) and amniotic fluid C-reactive protein (CRP) was obtained by Wald *et al*.[708] This was inflated to 2005 prices using the hospital and community health services (HCHS) pay and price inflation index.

Cost estimates for the absence of fetal breathing movements and measurement of cervical length were obtained by Bricker *et al*.[709] We used a proxy cost based on a detailed scan which was again inflated to 2005 prices (£69.47).

For the cost of abdominal palpation we used the unit cost per hour of client contact by a practice nurse (£28/hour) as a proxy for midwife.[692]

A cost estimate for the serum CRP was obtained by the Birmingham Women's Hospital (BWH) (£7.50 inclusive of reagents, equipment and technician's time). The cost of the health-care assistant's time (unit cost per hour spent with a patient, £20/hour),[692] was used as a proxy for the cost of the time of the phlebotomist who performs the test. The estimated total cost was £9.50 and this was used as a proxy for all venous blood tests performed by a phlebotomist which then requires further analysis in a laboratory (e.g. serum IL-6, serum β-human chorioic gonadotrophin, serum α-fetoprotein, serum estriol, serum corticotrophin-releasing hormone, serum relaxin and plasma MMP-9 tests).

A cost estimate for 'Cervical Digital Examination' was not available in the literature. We used the cost of CRP (£7.50) for the laboratory technician's time and the laboratory analysis; then added the cost of the doctor's time (unit cost per hour on duty by a specialist registrar doctor, £23/hour). The estimated total cost was £11.50 and this was used as a proxy for all cervical vaginal secretion/mucus specimen tests performed by the doctor that then required further analysis in the laboratory. Such tests included: cervicovaginal IL-6, cervical IL-8, cervicovaginal β-human chorionic gonadotrophin, cervicovaginal fetal fibronectin, phIGFBP-1 and CV-Prolactin.

The cost of 'previous history of either spontaneous preterm birth' was assumed to be zero because this test is part of a process followed for all women

during their routine antenatal care, and as a test, this precedes all other tests in the analysis.

A cost estimate for salivary estriol was not available in the literature. We used the cost of CRP (£7.50) as a proxy for the technician's time and the laboratory analysis for this test; then added the cost of a practice nurse's time (unit cost per hour of client contact, £28/hour) as a proxy for midwife time. The estimated total cost was £12.50.

No cost estimates for the urine tests (e.g. MMP-9, midstream urine culture) were available in the literature for the urine tests. We assumed self-collection for both. The cost of CRP was again used as a proxy for the cost of the MMP-9 test. The cost of midstream urine culture was obtained by BWH (£4.02) without the laboratory technician's time and laboratory analysis. We added the cost of CRP (£7.50) as a proxy for the latter. This resulted in an estimated total cost of £11.52 for midstream urine culture.

The cost of detection of bacterial vaginosis was obtained by BWH (£11.52 – including wet preparation, Gram-stained culture plates and technician time). We added the unit cost per hour on duty by a specialist registrar doctor (£23/hour) to include the time of the doctor who performs the test. The estimated total cost was £15.35.

The cost of periodontal screening was obtained by the 'Dental & Implant Centre' of the University of Birmingham. We used the NHS charge of £15.50 for a 'General examination and cleaning'.

No cost data was available for uterine activity monitoring. An attempt was made to contact the manufacturer (Tokos Medical Corp) without success. An estimate for 'Ambulatory monitoring costs' was available in the literature at $60/day in 1988 values.[707] The cost of the device for the 12 weeks of its use translated to £7308 in UK sterling in 2005 values. Concerned about the uncertainty associated with this cost, we actually used £250 as the cost of the test.

A cost estimate for Rheobase was not available in the literature. We used the cost of an anomaly scan (£15.46) from the literature as a proxy for the cost of the rheobase measuring equipment.[709]

A cost estimate for the mammary stimulation test was not available. We used the unit cost per hour of a home visit by a practice nurse (£35/hour) as a proxy for a midwife, to estimate the midwife's time; and we used the cost of an anomaly scan (£15.46)[709] as a proxy for the cost of the cardiotocography machine. The estimated total cost for the mammary stimulation test was £26.66.

**Intervention cost data**

The systematic reviews of intervention effectiveness indicated the dose and duration of treatment used in the included RCTs. Where no dose or duration was available, those used in the *British National Formulary* (BNF) were used (after consensus with C.R.D., K.S.K. and H.H.). These are summarised in *Table 45*. Where a dose range was presented, the costs of the upper and lower limits of the dose were used. The treatment dose (if appropriate) and duration were applied to the treatment unit costs to give the total cost. For drugs the unit costs were taken from the BNF (Vol. 51, March 2006). The unit costs for the vitamin or herbal supplements such as fish oils were obtained from the Holland and Barrett website (a commercial health food shop) (http://www.hollandandbarrett.com/).

For all symptomatic women we assumed that they are hospitalised for a minimum of 5 days (based on consultation with the clinicians in the project team). This assumed hospitalisation 1 day before administration of the intervention and at least 2 days after delivery. Cost of the first day was assumed to be £532 based on HRG data 'Admissions not Related to Delivery Event = £532 – Non-elective inpatient TNELIP sheet' (link: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4133221). [Source: Department of Health (2006), NHS Reference Costs 2005, NHS Trusts and Primary Care Trusts combined.] and for each of the following days the cost was assumed to be £278 based on 'Admissions not Related to Delivery Event = £278 – Non-elective inpatient excess days TNELIPXS sheet' (link: (http://www.dh.gov.uk/assetRoot/04/13/32/28/04133228.xls). [Source: Department of Health (2006), NHS Reference Costs 2005, NHS Trusts and Primary Care Trusts Combined.]

Hence, the total cost of hospitalisation was estimated to be £1644 based on 5 days hospitalisation for the following models: Delivery within 48 hours of intervention, delivery up to 34 weeks' gestation, delivery up to 37 weeks' gestation, and perinatal mortality. Finally, the total cost of hospitalisation was estimated to be £2478 based on 8 days hospitalisation, which applied to the 7-day model.



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***TABLE 40*** *Asymptomatic women, likelihood ratio positive (LR+) and likelihood ratio negative (LR–) for each test provided by this project's systematic reviews of test accuracy*

| | Detecting PTL during the first 34 weeks of gestation | | | | Detecting PTL during the first 37 weeks of gestation | | | |
|---|---|---|---|---|---|---|---|---|
| **Test** | **LR+** | **95% CI** | **LR–** | **95% CI** | **LR+** | **95% CI** | **LR–** | **95% CI** |
| Previous history of either spontaneous or iatrogenic preterm birth | 4.624 | (3.278–6.251) | 0.677 | (0.56–0.817) | 2.259 | (1.86–2.74) | 0.715 | (0.635–0.805) |
| Digital examination | 9.247 | (3.914–21.847) | 0.457 | (0.194–1.08) | 1.15457 | (0.86–1.53) | 0.89 | (0.68 – 1.16) |
| Cervicovaginal interleukin-6 (serial testing) | – | – | – | – | 3.342 | (1.96–5.70) | 0.588 | (0.417–0.829) |
| Cervicovaginal interleukin-6 (single testing)[a] | – | – | – | – | 0.564 | (0.0799–3.973) | 1.0839 | (0.873–1.346) |
| Amniotic fluid interleukin-6 | 2.65 | (1.37–5.14) | 0.91 | (0.84–0.98) | 1.913 | (0.997–3.672) | 0.95 | (0.9–1.002) |
| Cervical mucus interleukin-8 (360 ng/ml) | 2.228 | (1.455–3.412) | 0.694 | (0.495–0.973) | 1.377 | (1.043–1.818) | 0.907 | (0.818–1.005) |
| Fetal fibronectin | 10.181 | (6.562–15.798) | 0.689 | (0.56–0.847) | 26.375 | (1.726–402.986) | 0.939 | (0.828–1.066) |
| Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) | – | – | – | – | 4.167 | (2.436–7.127) | 0.208 | (0.084–0.514) |
| CV-Prolactin | 19 | (1.76–205.15) | 0.51 | (0.13–2.06) | 3.15 | (1.62–6.12) | 0.23 | (0.04–1.37) |
| Serum α-fetoprotein (threshold 2.0 MoM) | – | – | – | – | 1.63 | (0.812–3.273) | 0.957 | (0.886–1.034) |
| Serum α-fetoprotein (threshold 2.5 MoM) | 4.99 | (3.97–6.28) | 0.95 | (0.94–0.97) | 2.63 | (1.35–5.096) | 0.987 | (0.974–1.0) |
| Maternal serum β-human chorionic gonadotrophin | – | – | – | – | 2.77 | (2.07–3.69) | 0.984 | (0.98–0.99) |
| Salivary estriol (threshold 2.1 ng/ml – single) | – | – | – | – | 2.55 | (1.73–3.77) | 0.56 | (0.35–0.89) |
| Salivary estriol (threshold 2.1 ng/ml – repeat) | – | – | – | – | 5.46 | (3.18–9.40) | 0.61 | (0.43–0.88) |
| Serum estriol (threshold ≤0.5 MoM)[a] | – | – | – | – | 0.764 | (0.581–1.004) | 1.018 | (1.002–1.035) |
| Serum estriol (threshold ≤0.75 MoM) | – | – | – | – | 1.188 | (0.577–2.444) | 0.98 | (0.893–1.075) |
| Serum corticotrophin-releasing hormone | 3.36 | (2.298–4.918) | 0.348 | (0.133–0.914) | 1.428 | (0.863–2.362) | 0.891 | (0.735–1.082) |
| Relaxin (serum) | 1.598 | (1.241–2.059) | 0.839 | (0.74–0.952) | 1.207 | (0.725–2.1) | 0.744 | (0.285–1.947) |
| C-reactive protein | – | – | – | – | 2.061 | (1.29–3.293) | 0.767 | (0.646–0.91) |
| Amniotic fluid C-reactive protein | 2.63 | (1.85–3.75) | 0.29 | (0.08–0.99) | 4.37 | (3.03–6.29) | 0.09 | (0.01–0.60) |
| Detection of bacterial vaginosis Nugent's (single)[a] | – | – | – | – | 0.804 | (0.376–1.716) | 1.04 | (0.921–1.174) |

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| | Detecting PTL during the first 34 weeks of gestation | | | | Detecting PTL during the first 37 weeks of gestation | | | |
|---|---|---|---|---|---|---|---|---|
| **Test** | **LR+** | **95% CI** | **LR–** | **95% CI** | **LR+** | **95% CI** | **LR–** | **95% CI** |
| Detection of bacterial vaginosis Nugent's (serial) | – | – | – | – | 1.924 | (0.625–5.918) | 0.933 | (0.794–1.095) |
| Detection of bacterial vaginosis Amsel's (single) | – | – | – | – | 1.617 | (0.443–5.907) | 0.901 | (0.632–1.287) |
| Periodontal evaluation | – | – | – | – | 2.262 | (1.349–3.792) | 0.791 | (0.655–0.956) |
| Midstream urine culture | – | – | – | – | 2.63 | (1.54–4.50) | 0.96 | (0.92–0.99) |
| Uterine activity monitoring | 2.413 | (0.758–7.678) | 0.947 | (0.863–1.04) | 4.9 | (2.988–8.035) | 0.152 | (0.041–0.558) |
| Mammary stimulation test | 4.62 | (2.953–7.252) | 0.267 | (0.0786–0.908) | 3.3 | (1.537–7.084) | 0.489 | (0.166–1.433) |
| Measurement of cervical length – 15 mm (14–20 weeks' gestation) | 142.856 | (3.575–5709) | 0.888 | (0.816–0.966) | – | – | – | – |
| Measurement of cervical length – 20 mm (14–20 weeks' gestation) | 35.356 | (4.315–289.676) | 0.901 | (0.829–0.978) | – | – | – | – |
| Measurement of cervical length – 25 mm (14–20 weeks' gestation) | 13.379 | (6.896–25.957 | 0.798 | (0.711–0.895) | – | – | – | – |
| Measurement of cervical length – 30 mm (14–20 weeks' gestation) | 2.48 | (1.186–5.189) | 0.81 | (0.679–0.966) | – | – | – | – |
| Measurement of cervical length – 20 mm (20–24 weeks' gestation) | 7.642 | (5.213–11.203) | 0.794 | (0.721–0.873) | – | – | – | – |
| Measurement of cervical length – 22 mm (20–24 weeks' gestation) | 4.513 | (1.155–17.637) | 0.743 | (0.513–1.077) | – | – | – | – |
| Measurement of cervical length – 25 mm (20–24 weeks' gestation) | 4.682 | (3.638–6.027) | 0.681 | (0.599–0.775) | – | – | – | – |
| Measurement of cervical length – 30 mm (20–24 weeks' gestation) | 2.277 | (1.913–2.711) | 0.603 | (0.499–0.73) | – | – | – | – |
| Measurement of cervical length – 32.5 mm (20–24 weeks' gestation) | – | – | – | – | 3.99 | (2.84–5.62) | 0.33 | (0.17–0.66) |
| Presence of funnelling (16–20 weeks' gestation) | 5.026 | (2.534–9.968) | 0.744 | (0.559–0.992) | – | – | – | – |
| Presence of funnelling (20–24 weeks' gestation) | 4.63 | (3.306–6.482) | 0.789 | (0.713–0.874) | – | – | – | – |

CI, confidence interval; LR+, likelihood ratio positive; LR–, likelihood ratio negative; PTL, preterm labour.
a These tests were not included in the analysis because LR–>LR+

***TABLE 41*** *Symptomatic women, likelihood ratio positive (LR+) and likelihood ratio negative (LR–) for each test provided by this project's systematic reviews of test accuracy*

| | | Delivery within 48 h[b] | | | | Delivery within 7 days[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Test** | **24 h[a]** | **LR+** | **95% CI** | **LR–** | **95% CI** | **LR+** | **95% CI** | **LR–** | **95% CI** |
| Digital examination | – | – | – | – | – | – | – | – | – |
| Serum interleukin-6 | – | 2.05 | (0.852–4.93) | 0.661 | (0.324–1.351) | 3.34 | (1.485–7.526) | 0.442 | (0.297–0.659) |
| Cervicovaginal interleukin-6 | – | 1.902 | (1.083–3.342) | 0.231 | (0.017–3.173) | 4.009 | (2.018–7.964) | 0.658 | (0.51–0.849) |
| Amniotic fluid interleukin-6 | – | 3.758 | (2.135–6.614) | 0.11 | (0.0167–0.726) | 7.013 | (2.75–17.987) | 0.171 | (0.06–0.488) |
| Interleukin-8 (15 ng/ml amniotic fluid) | – | 36 | (2.296–564.5) | 0.103 | (0.008–1.424) | 28.5 | (1.779–456.57) | 0.257 | (0.064–1.028) |
| Interleukin-8 (7.7 ng/ml cervical swab) | – | – | – | – | – | 2.34 | (1.42–3.84) | 0.52 | (0.32–0.84) |
| β-human chorionic gonadotrophin | – | – | – | – | – | 6.07 | (3.07–11.99) | 0.04 | (0.01–0.16) |
| Fetal fibronectin | – | – | – | – | – | 3.516 | (2.364–5.227) | 0.237 | (0.067–0.832) |
| Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) | – | 1.73 | (0.92–3.252) | 0.593 | (0.242–1.451) | 2.83 | (1.571–5.092) | 0.371 | (0.133–1.038) |
| CV-Prolactin | – | – | – | – | – | 1.48 | (0.81–2.7) | 0.61 | (0.23–1.62) |
| Serum corticotrophin-releasing hormone | – | – | – | – | – | 3.12 | (1.42–6.84) | 0.63 | (0.38–1.05) |
| C-reactive protein (12.5 ng/ml) | – | – | – | – | – | 34.364 | (4.858–243.09) | 0.186 | (0.053–0.653) |
| Absence of fetal breathing movements | – | 16.077 | (5.216–49.55) | 0.162 | (0.045–0.581) | 4 | (0.73–21.84) | 0.67 | (0.32–1.38) |
| Measurement of cervical length (15 mm) | – | 6.43 | (5.17–8) | 0.027 | (0.0017–0.42) | 8.61 | (6.65–11.14) | 0.026 | (0.004–0.182) |
| | | **Detecting PTL during the first 34 weeks of gestation** | | | | **Detecting PTL during the first 37 weeks of gestation** | | | |
| | | **LR+** | **95% CI** | **LR–** | **95% CI** | **LR+** | **LR–** | **LR–** | **95% CI** |
| Digital examination | | – | – | – | – | 2.38 | 0.47 | 0.47 | (0.29–0.79) |
| Serum interleukin-6 | | 1.437 | (0.856–2.412) | 0.585 | (0.216–1.582) | 1.125 | 0.917 | 0.917 | (0.537–1.564) |
| Cervicovaginal interleukin-6 | | 4.923 | (1.801–13.46) | 0.738 | (0.629–0.867) | 1.833 | 0.688 | 0.688 | (0.396–1.195) |
| Amniotic fluid interleukin -6 | | 7.44 | (2.01–27.52) | 0.14 | (0.056–0.36) | 28.62 | 0.659 | 0.659 | (0.54–0.81) |

| Test | 24 h[a] | Delivery within 48 h[b] | | | | Delivery within 7 days[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | LR+ | 95% CI | LR– | 95% CI | LR+ | 95% CI | LR– | 95% CI |
| Interleukin-8 (3.739 ng/ml cervical swab) | | – | – | – | – | 1.4 | (0.83–2.35) | 0.67 | (0.3–1.5) |
| β-human chorionic gonadotrophin | | – | – | – | – | 2.11 | (1.61–2.77) | 0.45 | (0.31–0.66) |
| Fetal fibronectin | | (2.729–5.803) | 0.332 | 0.332 | (0.19–0.582) | 7.971 | (4.875–13.03) | 0.128 | (0.51–0.324) |
| Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) | | (1.438–11.99) | 0.305 | 0.305 | (0.027–3.381) | 3.868 | (1.539–9.724) | 0.325 | (0.149–0.709) |
| CV-Prolactin | | (1.809–11.97) | 0.489 | 0.489 | (0.207–1.156) | 2.5 | (0.88–7.1) | 0.79 | (0.55–1.11) |
| Salivary estriol (threshold 2.1 ng/ml – single) | | – | – | – | – | 2.31 | (1.64–3.24) | 0.398 | (0.199–0.794) |
| Serum corticotrophin-releasing hormone | | – | – | – | – | 4.06 | (1.68–9.81) | 0.68 | (0.51–0.91) |
| Relaxin (serum) | | (0.262–8.31) | 0.861 | 0.861 | (0.378–1.96) | 0.8[#] | (0.193–3.31) | 1.07[#] | (0.72–1.57) |
| C-reactive protein (12.5 ng/ml) | | – | – | – | – | 2.316 | (1.426–3.762) | 0.468 | (0.251–0.874) |
| C-reactive protein (15 ng/ml) | | (1.34–34) | 0.66 | 0.66 | (0.38–1.14) | – | – | – | – |
| Matrix metalloprotease-9 | | – | – | – | – | 7.33 | (1.07–50.27) | 0.37 | (0.14–0.94) |
| Detection of bacterial vaginosis Nugent's (single) [c] | | – | – | – | – | 0.995 | (0.359–2.756) | 1.0005 | (0.884–1.134) |
| Rheobase (2.8 mA) | | – | – | – | – | 2.29 | (1.5–3.52) | 0.6 | (0.41–0.88) |
| Rheobase (3.4 mA) | | – | – | – | – | 2.36 | (1.74–3.20) | 0.36 | (0.19–0.66) |
| Measurement of cervical length (18 mm) | | – | – | – | – | 3.36 | (1.73–6.54) | 0.35 | (0.17–0.7) |
| Measurement of cervical length (30 mm) | | (1.363–2.589) | 0.3 | 0.3 | (0.0834–1.072) | 2.29 | (1.68–3.12) | 0.29 | (0.15–0.58) |
| Presence of funnelling | | (1.90–11.66) | 0.61 | 0.61 | (0.34–1.1) | 2.53 | (1.02–6.25) | 0.86 | (0.71–1.03) |

CI, confidence interval; LR+, Likelihood Ratio positive; LR–, Likelihood Ratio negative; PTL, preterm labour.
a No data were available from the accuracy reviews on tests for risk factors of delivery within 24 hours from testing and giving treatment
b From testing and giving treatment
c These tests were not included in the analysis because LR–>LR+.

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***TABLE 42*** *Asymptomatic women, relative risk of preterm labour for each intervention provided by this project's systematic reviews of effectiveness*

| | | PTL before 34 weeks' gestation | | PTL before 37 weeks' gestation | | Perinatal mortality | |
|---|---|---|---|---|---|---|---|
| **Group** | **Test** | **RR[a]** | **95% CI** | **RR[a]** | **95% CI** | **RR[a]** | **95% CI** |
| Group 1[b] | Home uterine activity monitoring | – | – | 0.59 | (0.37–0.95) | – | – |
| | Asymptomatic bacteriuria | – | – | 0.14 | (0.04–0.52) | – | – |
| | Periodontal therapy | – | – | 0.19 | (0.04–0.85) | – | – |
| | Cervical cerclage | 0.75 | (0.58–0.98) | – | – | – | – |
| | Progestational agents | 0.15 | (0.04–0.64) | 0.6 | (0.49–0.73) | – | – |
| | Fish oil | 0.35 | (0.13–0.92) | 0.64 | (0.41–0.99) | – | – |
| | Nutritional advice | – | – | 0.46 | (0.21–0.98) | – | – |
| | Energy/protein supplementation | – | – | – | – | 0.55 | (0.31–0.97) |
| | Smoking cessation | – | – | 0.84 | (0.72–0.98) | – | – |
| Group 2[c] | Home visits | – | – | 0.98 | (0.88–1.10) | – | – |
| | Bed rest (home or hospital) | – | – | 0.92 | (0.62–1.37) | – | – |
| | Antibiotics (intra amniotic infections) | – | – | – | – | 0.53 | (0.13–2.18) |
| | Cervical cerclage | – | – | 0.85 | (0.72–1.01) | 0.66 | (0.66–1.37) |
| | Progestational agents | – | – | – | – | 0.55 | (0.29–1.06) |
| | Vitamin C | – | – | – | – | 0.51 | (0.05–5.54) |
| | Zinc | – | – | 0.77 | (0.49–1.20) | – | – |
| | Nutritional advice | – | – | – | – | 0.37 | (0.07–1.90) |
| | Energy/protein supplementation | – | – | 0.83 | (0.65–1.06) | – | – |
| | Energy/protein restriction | – | – | 0.5 | (0.09–2.66) | – | – |

CI, confidence interval; PTL, preterm labour.
a Relative risks (RRs) based on subgroup analyses, defined in detail in the text, and used as parameters in sensitivity analyses.
b Group 1 are those treatments with an RR whose upper 95% CI is < 1.0.
c Group 2 are those treatments with an RR whose 95% CI include a value compatible with worsened outcome.

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***TABLE 43*** *Symptomatic women, relative risk of spontaneous preterm birth for each intervention provided by the project's systematic reviews of effectiveness*

| | | Delivery within 24 hours[a] | | Delivery within 48 hours[a] | | Delivery within 7 days[a] | |
|---|---|---|---|---|---|---|---|
| **Group** | **Test** | **RR[b]** | **95% CI** | **RR[b]** | **95% CI** | **RR[b]** | **95% CI** |
| Group 1[c] | Indomethacin | – | – | 0.19 | (0.07–0.51) | 0.44 | (0.26–0.74) |
| | Terbutaline (intravenously) | – | – | 0.45 | (0.25–0.81) | 0.59 | (0.40–0.87) |
| Group 2[d] | Nitric oxide donors | – | – | 0.56 | (0.27–1.51) | – | – |
| | Magnesium Sulphate | – | – | 0.57 | (0.28–1.15) | – | – |
| | Terbutaline (orally) | 0.67 | (0.12–3.62) | 0.78 | (0.30–2.01) | 0.67 | (0.40–1.13) |
| | Antibiotics (intact membranes) | – | – | – | – | 0.98 | (0.87–1.10) |
| Group 3[e] | Calcium channel blockers | – | – | 0.44[d] | (0.16–(1.26) | 0.46[c] | (0.30–0.70) |
| | Atosiban | – | – | 0.44[c] | (0.22–0.88) | 0.54[c] | (0.33–0.86) |
| | | **PTL before 34 weeks' gestation** | | **PTL before 37 weeks' gestation** | | **Perinatal mortality** | |
| | **Effectiveness** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** |
| Group 1[c] | Indomethacin | – | – | 0.21 | (0.07–0.62) | – | – |
| | Terbutaline (intravenously) | – | – | 0.64 | (0.45–0.91) | – | – |
| Group 2[d] | Indomethacin | – | – | – | – | 0.80 | (0.25–2.58) |
| | Terbutaline pump maintenance | 0.97 | (0.51–1.84) | – | – | – | – |
| | Magnesium sulphate | – | – | 0.92 | (0.41–2.07) | – | – |
| | Antibiotics (intact membranes) | – | – | 0.99 | (0.92–1.05) | – | – |
| | Hydration | 0.72 | (0.20–2.56) | – | – | – | – |
| | Vitamin K (for neuroprotection) | – | – | – | – | 0.79 | (0.46–1.35) |
| | Prophylactic corticosteroids | – | – | – | – | 0.63 | (0.51 –0.79) |
| Group 3[e] | Calcium channel blockers | 0.74[d] | (0.38–1.43) | 0.98[d] | (0.65–1.50) | – | – |
| | Atosiban | – | – | 0.57[c] | (0.38–0.88) | – | – |
| | Feneterol[f] | – | – | – | – | 0.10 | (0–1.89) |

CI, confidence interval; PTL, preterm labour.
a From testing and giving treatment.
b Relative risks (RRs) based on subgroup analyses, defined in detail in the text, and used as parameters in sensitivity analyses
c Group 1 are those treatments with an RR whose upper 95% CI is <1.0
d Group 2 are those treatments with an RR whose 95% CI include a value compatible with worsened outcome
e Group 3 are those treatments whose RR and 95% CI were estimated through indirect comparisons
f Feneterol looks promising (RR=0.1), but there is a lot of uncertainty around it, so it was decided to exclude it from the analysis

***TABLE 44*** *Estimated costs for tests that predict spontaneous preterm birth*

| Test | Description/nature of test | Duration/when is the test performed |
|---|---|---|
| Previous history of either spontaneous or iatrogenic (including reason) preterm birth[a] | *History*<br>The midwife performs the test | 10 minutes<br>Pre-pregnancy (at the women's home or GP practice) or at antenatal booking (early in pregnancy) |
| Abdominal palpation[b] | *Examination*<br>The midwife performs the test. | 37.5 minutes (35–40 minutes) |
| CDE[a,b] | *Examination*<br>The doctor performs the test<br>Cervical mucus sample is taken during speculum examination with a normal swab<br>Lab technician is required to do the analysis using ELISA reagent | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>26–30 weeks' gestation and at 28 weeks (asymptomatic women)<br>24–36 weeks' gestation (symptomatic women) |
| Serum IL-6[b] | *Venous blood test*<br>The phlebotomist performs the test<br>Lab technician is required to do an analysis using ELISA | 5 minutes by the phlebotomist<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation |
| Cervicovaginal IL-6 (single testing)[a,b] | *Cervical vaginal secretion/mucus specimen*<br>The doctor performs the test<br>Lab technician is required to do an analysis using ELISA | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation (symptomatic women)<br>10–20 weeks' gestation (asymptomatic women) |
| Cervicovaginal IL-6 (serial testing) [a] | *Cervical vaginal secretion/mucus specimen*<br>The doctor performs the test<br>Lab technician is required to do an analysis using ELISA | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>10–20 weeks' gestation |
| Amniotic fluid IL-6 [a,b] | *Amniocentesis*<br>The doctor performs the test<br>Ultrasound scan guidance is required to avoid injury of the fetus<br>Lab technician is required to do an analysis using ELISA | 30 minutes by the doctor<br>24–36 weeks' gestation (symptomatic women)<br>14–20 weeks' gestation (asymptomatic women) |
| Amniotic fluid IL-8 [a,b] | *Amniocentesis*<br>The doctor performs the test<br>Ultrasound scan guidance is required to avoid injury of the fetus<br>Lab technician is required to do an analysis using ELISA | 30 minutes by the doctor<br>24–36 weeks' gestation (symptomatic women)<br>14–20 weeks' gestation (asymptomatic women) |
| Cervical IL-8 [a] | *Cervical vaginal secretion/mucus specimen*<br>The doctor performs the test.<br>Lab technician is required to do an analysis using ELISA | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>20–28 weeks' gestation (asymptomatic women) |
| Serum β-human chorionic gonadotrophin[a] | *Venous blood test*<br>The phlebotomist performs the test<br>Lab technician is required to do an analysis using ELISA | 5 minutes by the phlebotomist, 1 hour approx. by the lab technician (part of a batch)<br>10 – 20 weeks' gestation (asymptomatic women) |

| Unit cost | Source | Comments |
|---|---|---|
| None | Curtis and Netten[692] | This test is part of the process followed when a woman is admitted to the hospital with symptoms. We set the cost equal to zero because this test precedes all other tests below |
| £17.50 | Curtis and Netten[692] | We used the unit cost per hour of client contact by a practice nurse (£28/hour) as a proxy for midwife |
| £11.50 | Curtis and Netten[692] | Estimate not available for the cost of the test. We used a proxy (£7.50) based on serum CRP for the lab technician's time and lab analysis; then added the cost of the doctor's time (unit cost per hour on duty by a specialist registrar doctor, £23/hour) |
| £9.50 | Curtis and Netten[692] | Estimate not available for the cost of the test. We used a proxy (£7.50) based on Serum CRP for the lab technician's time and lab analysis; then added the cost of the health-care assistant's time (unit cost per hour spent with a patient, £20/hour) as a proxy for the phlebotomist |
| £11.50 | Curtis and Netten[692] | Proxy based on cost of CDE |
| £57.50 | Curtis and Netten[692] | Proxy based on cost of CDE<br>No information was available on how many times the test was performed, so it was assumed that it was done five times |
| £216.70 | Wald *et al.*[708] | The cost of amniocentesis was obtained by Wald *et al*. and then inflated to 2004/05 values using Curtis and Netten's inflation indices |
| £216.70 | Wald *et al*.[708] | The cost of amniocentesis was obtained by Wald *et al*. and then inflated to 2004/05 values using Curtis and Netten's inflation indices |
| £11.50 | Curtis and Netten[692] | Proxy based on cost of CDE |
| £9.50 | Curtis and Netten[692] | Proxy based on cost of serum IL-6 |

*continued*



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***TABLE 44*** *Estimated costs for tests that predict spontaneous preterm birth (continued)*

| Test | Description/nature of test | Duration/when is the test performed |
|---|---|---|
| Cervicovaginal β-human chorionic gonadotrophin[b] | *Cervical vaginal secretion/mucus specimen*<br>The doctor performs the test<br>Lab technician is required to do an analysis using ELISA | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation (symptomatic women) |
| Cervicovaginal fetal fibronectin[a,b] | *Cervical vaginal secretion/mucus specimen*<br>The doctor performs the test<br>Lab technician is required to do an analysis using ELISA | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation (symptomatic women)<br>16–24 weeks' gestation (asymptomatic women) |
| Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1)[a,b] | *Cervical vaginal secretion/mucus specimen*<br>The doctor performs the test<br>Lab technician is required to do an analysis using ELISA | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation (symptomatic women)<br>(16–24 weeks' gestation (asymptomatic women) |
| CV-Prolactin[a,b] | *Cervical vaginal secretion/mucus specimen*<br>The doctor performs the test<br>Lab technician is required to do an analysis using ELISA | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>24–32 weeks' gestation (both asymptomatic and symptomatic women) |
| Serum α-fetoprotein[a] | *Venous blood test*<br>The phlebotomist performs the test<br>Lab technician is required to do an analysis using ELISA | 5 minutes by the phlebotomist<br>1 hour approx. by the lab technician (part of a batch)<br>12–20 weeks' gestation |
| Salivary estriol[a,b] | *Salivary test*<br>The midwife performs the test, by collecting saliva specimen<br>Lab technician is required to do the analysis using the appropriate commercial assay (SalEst; Biex Inc, Dublin, CA) | 10 minutes by the midwife<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation (symptomatic women)<br>14–20 weeks' gestation (asymptomatic women) |
| Serum estriol[a] | *Venous blood test*<br>The phlebotomist performs the test<br>Lab technician is required to do an analysis using ELISA | 5 minutes by the phlebotomist<br>1 hour approx. by the lab technician (part of a batch)<br>14–20 weeks' gestation |
| Serum CRH[a,b] | *Venous blood test*<br>The phlebotomist performs the test<br>Lab technician is required to do an analysis using ELISA | 5 minutes by the phlebotomist<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation (symptomatic women)<br>12–20 weeks' gestation (asymptomatic women) |
| Relaxin (serum)[a,b] | *Venous blood test*<br>The phlebotomist performs the test<br>Lab technician is required to do an analysis using ELISA | 5 minutes by the phlebotomist 1 hour approx. by the lab technician (part of a batch)<br>24–34 weeks' gestation (symptomatic women) |

| Unit cost | Source | Comments |
|---|---|---|
| £11.50 | Curtis and Netten[692] | Proxy based on cost of CDE |
| £11.50 | Curtis and Netten[692] | Proxy based on cost of CDE |
| £11.50 | Curtis and Netten[692] | Proxy based on cost of CDE |
| £11.50 | Curtis and Netten[692] | Proxy based on cost of CDE |
| £9.50 | Curtis and Netten[692] | Proxy based on cost of serum IL-6 |
| £12.50 | Curtis and Netten[692] | Estimate not available for the cost of the test. We used a proxy (£7.50) based on serum CRP for the lab technician's time and lab analysis; then added the cost of the practice nurse's time (unit cost per hour of client contact, £28/hour) as a proxy for midwife |
| £9.50 | Curtis and Netten[692] | Proxy based on cost of serum IL-6 |
| £9.50 | Curtis and Netten[692] | Proxy based on cost of serum IL-6 |
| £9.50 | Curtis and Netten[692] | Proxy based on cost of serum IL-6 |

*continued*



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***TABLE 44*** *Estimated costs for tests that predict spontaneous preterm birth (continued)*

| Test | Description/nature of test | Duration/when is the test performed |
|---|---|---|
| Serum CRP[a,b] | *Venous blood test*<br>The phlebotomist performs the test<br>Lab technician is required to do an analysis using ELISA (or other necessary materials to measure serum CRP level) | 5 minutes by the phlebotomist<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation (symptomatic women)<br>14–20 weeks' gestation (asymptomatic women) |
| Amniotic fluid CRP[a,b] | *Amniocentesis*<br>The doctor performs the test<br>Ultrasound scan guidance is required to avoid injury of the fetus<br>Lab technician is required to do an analysis using ELISA | 30 minutes by the doctor<br>24–36 weeks' gestation (symptomatic women)<br>14–20 weeks' gestation (asymptomatic women) |
| MMP-9[b]<br>(urine) | *Urine test*<br>Assumed self-collection by woman<br>Lab technician is required to do the analysis using the enzyme immuno-assay for MMP-9 test kit (MediCorp, Montreal, Canada) | 1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation |
| MMP-9[b]<br>(plasma) | *Venous blood test.*<br>The phlebotomist performs the test<br>Lab technician is required to do the analysis using the enzyme immuno-assay for MMP-9 test kit (MediCorp, Montreal, Canada) | 5 minutes by the phlebotomist<br>1 hour approx. by the lab technician (part of a batch)<br>24–36 weeks' gestation |
| Detection of bacterial vaginosis[a] | *Cervical swab collection*<br>The doctor performs the test<br>Lab technician is required to do the analysis using the necessary equipment | 10 minutes by the doctor<br>1 hour approx. by the lab technician (part of a batch)<br>8–24 weeks' gestation (asymptomatic women) |
| Periodontal screening[a] | Dental hygienists or dentists perform the periodontal assessment | 30–60 minutes<br>8–20 weeks' gestation (asymptomatic women) |
| Midstream urine culture[a] | *Urine test*<br>Assumed self-collection by woman<br>Lab technician is required to do the standard microbiology culture | 1 hour approx. by the lab technician (part of a batch)<br>Before 16 weeks' gestation |
| Uterine activity monitoring[a] | *Uterine monitoring system*<br>Women are placed in the Term Guard (Tokos Medical Corp., Santa Ana, CA) uterine monitoring system for at least one hour per day<br>It was assumed that this is done at home and for 12 weeks in total | 1 hour per day<br>24–36 weeks' gestation |
| Rheobase[b] | The midwife performs the test using the rheobase measuring equipment | 30 minutes by the midwife<br>20–36 weeks' gestation (symptomatic women) |

| Unit cost | Source | Comments |
|---|---|---|
| £9.50 | BWH<br>Curtis and Netten[692] | Cost of serum CRP (£7.50, inclusive of reagents, equipment and technician time) was obtained by BWH<br>Cost of the health-care assistant's time (unit cost per hour spent with a patient, £20/hour) was used as a proxy for the phlebotomist |
| £216.70 | Wald *et al*.[708] | The cost of amniocentesis was obtained by Wald *et al*. and then inflated to 2004/05 values by Curtis and Netten's inflation indices |
| £7.50 | BWH | Estimate not available for the cost of the test. We used a proxy (£7.50) based on serum CRP for the lab technician's time and lab analysis |
| £9.50 | Curtis and Netten[692] | Proxy based on cost of serum IL-6 |
| £15.35 | BWH<br>Curtis and Netten[692] | We used the unit cost per hour on duty by a specialist registrar doctor (£23/hour). Cost of Detection of bacterial vaginosis (£11.52 – includes wet prep., Gram stain culture plates and technician time) was obtained by BWH |
| £15.50 | Dental & Implant Centre, UoB | We used the NHS charge of £15.50 for a 'general examination and cleaning' (obtained from the 'Dental & Implant Centre' of the University of Birmingham). |
| £11.52 | BWH | Cost of midstream urine culture (£4.02) was obtained by BWH<br>We used a proxy (£7.50) based on serum C-reactive protein for the lab technician's time and lab analysis |
| £250 | Kosasa *et al*.[707]<br>Curtis and Netten[692] | Estimate not available for the cost of the test. We have contacted Tokos Medical Corp but received no answer. Available from the literature were the 'Ambulatory monitoring costs $60/per day' in 1988 values. We used the 1990 Dollar to Pound conversion rate (0.62) because that was the closest to 1988 available (http://www.x-rates.com/). We used the inflation index from Curtis and Netten (234.2) to inflate the cost to 2004/05 values. This resulted in a cost of £87/day. The cost of the test was £7308 for the 12 weeks of the use of the machine. This value was considered not pragmatic. We used £250 as the cost of the test |
| £20.86 | Curtis and Netten[692]<br>Bricker *et al*.[709] | Estimate of the cost of the test was not available. We used a proxy based on an inflated anomaly scan (£15.46) for the cost of the rheobase measuring equipment |

*continued*



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***TABLE 44*** *Estimated costs for tests that predict spontaneous preterm birth (continued)*

| Test | Description/nature of test | Duration/when is the test performed |
|---|---|---|
| Mammary stimulation test[a] | The midwife performs the test | 10 minutes by the midwife |
| | Cardiotocogram (CTG) machine is required to monitor uterine contractions | 30 minutes monitor for uterine contractions in the CTG |
| Absence of fetal breathing movements[b] | *Ultrasound scan* | 45 minutes of ultrasound scanning |
| | The midwife performs the test | 24–36 weeks' gestation for symptomatic women |
| | A standard high-resolution machine is used. An image recorder may be required to record the observation | 14–20 weeks' gestation for asymptomatic women |
| Measurement of cervical length[a,b] | *Ultrasound scan* | 30 minutes of ultrasound scanning |
| | The midwife performs the test | 14–24 weeks' gestation for symptomatic women |
| | A standard high-resolution machine is used. An image recorder may be required to record the observation | 24–36 weeks' gestation for asymptomatic women |

CTG, cardiotocogram
a Test applied on asymptomatic women.
b Test applied on symptomatic women.

The costs of spontaneous preterm birth are required for all symptomatic models. These are estimated using a combination of data including the average birthweight by gestational age and the number of survivors by gestational age to calculate weight ranges for survivors that correspond with the costs estimated by Petrou *et al.* for low-birthweight infants.[60] The results of the calculations and derivation of costs are summarised in *Table 46*.

The methods for the estimation of prevalence required for the model are described in detail in Appendix 9. *Table 47* presents the summary of the prevalence results required for each model.

**Analysis**

The main objective of testing asymptomatic women for their risk of having a preterm labour and then treating them accordingly, is to prevent them from developing symptoms of preterm labour. Women who develop the symptoms of threatened preterm labour may be at risk of imminent spontaneous preterm birth. The main objective of testing women with symptoms is therefore to confirm their risk and to provide treatment to prevent or delay spontaneous preterm birth where indicated.

The main outcome of the symptomatic models is in terms of cost per spontaneous preterm birth avoided whereas the main outcome of the asymptomatic models is in terms of cost per threatened preterm labour avoided.

The cost of an asymptomatic individual becoming symptomatic is the cost associated with testing and treatment once they become symptomatic. Once symptomatic, we must assume that labour itself can be postponed by a maximum of 48 h. The results in terms of average cost per women tested and treated, which is estimated in the symptomatic model for 48 h, are required in the comparator arm of the asymptomatic model. It is this cost that the testing and treatment of asymptomatic women is attempting to avoid. It is necessary to estimate the results of the most cost-effective test and treatment in the symptomatic model for 48 h and use the average cost of the most cost-effective test and treatment combination in the asymptomatic model. This explains why analysis of symptomatic mothers, though somewhat counterintuitive, precedes the analysis of the asymptomatic scenarios.

For each model, a deterministic analysis was carried out.[710] In such an analysis, the point estimates of the probability parameters and the cost estimates for each test and each intervention relevant to the model were used. Where no effectiveness data comparing intervention with 'placebo/no treatment' were available from trials, the economics team estimated this from an adjusted indirect comparison. In the absence of direct data (or where

| Unit cost | Source | Comments |
|---|---|---|
| £26.66 | Curtis and Netten[692]<br>Roberts *et al.*[690] | Estimate of the cost of the test was not available. We used the unit cost per hour of home visit by a practice nurse (£35/hour) as a proxy for midwife and a proxy based on an inflated anomaly scan (£15.46) for the CTG machine |
| £69.47 | Curtis and Netten[692]<br>Bricker *et al.*[709] | Estimate of the cost of the test was not available. We used a proxy based on an inflated detailed scan (£51.47) |
| £69.47 | Curtis and Netten[692]<br>Bricker *et al.*[709] | Estimate of the cost of the test was not available. We used a proxy based on an inflated detailed scan (£51.47) |

direct data are limited), indirect data can provide an indication of the relative effectiveness; however, the internal validity and similarity of all of the trials involved in the indirect comparison should always be carefully examined.

The model estimated the cost-effectiveness relative to 'no test/no treatment' of each alternative combination of test and treatment pairing. The results, are presented in terms of the ICER, expressed as the additional cost per additional case of preterm birth avoided as a result of each test and treat combination.

In addition, for each model where possible a probabilistic sensitivity analysis was carried out to explore the effects on the ICERs of the uncertainty in accuracy of tests and effectiveness of interventions, such as implied by the 95% CI of the probability parameters.[710] In the probabilistic sensitivity analysis required for each model it was appropriate to include the interventions for which the 95% CI of the relative risk was <1 to avoid including interventions that could be deemed harmful. Each model parameter is assigned a distribution reflecting the amount and pattern of its variation. Cost-effectiveness results are calculated by simultaneously selecting random values from each distribution. The process is repeated many times in a Monte Carlo simulation of the model to give an indication of how variation in the model parameters leads to variation in the ICERs for a given test and treatment pairing.[711]

The appropriate distribution for the data on test accuracy (positive or negative likelihood ratios) was a log normal distribution. The assumption that log normal distributions are appropriate for likelihood ratios is itself an approximation and fails when the sampled value approaches 1. It is logically impossible that both likelihood ratios should be over 1, but sampling the ratios independently gives a ratio greater than 1 for a very small proportion of the samples. Since this is an artefact of the sampling, rather than a realistic extreme of the distribution, we have in such cases restricted any sampled value of the LR– (negative) to a maximum value of 0.999 and the corresponding LR+ (positive) to a minimum value of 1.001.

The appropriate distribution for data on intervention effectiveness (RR of developing spontaneous preterm birth) was a log normal distribution. A similar restriction was also applied to the relative risk of the interventions to avoid them exceeding 1 during the simulations.

A range of possible tests were identified in the literature as potentially relevant for detecting risk factors for spontaneous preterm birth, among both the symptomatic and asymptomatic women for the majority of models. The reviews provided these



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***TABLE 45*** *Costs of interventions (continued)*

| Intervention | Description/nature/dose of intervention | Duration | Total cost |
|---|---|---|---|
| ***Asymptomatic women*** | | | |
| Home visits | Weekly home visits of 1 hour length by the midwife. It was assumed that home visits last for 1 month | 4 weeks | £140 |
| Bed rest (home) | | | None |
| Home uterine activity monitoring | Women are placed in the Term Guard (Tokos Medical Corp., Santa Ana, CA) uterine monitoring system, twice daily (morning and evening) for 1 hour. The minimum care scheduled was a visit every 4 weeks until 30 weeks gestation, at least every 2 weeks between 30 and 36 weeks, at least weekly thereafter. Monitoring begun no earlier than 24 weeks gestation | 24–36 weeks | £250 |
| Antibiotics for asymptomatic bacteriuria | Cefalexin 500 mg, 3 times a day | 7 days | £3.29 |
| Antibiotics for treating intra-amniotic infections | Metronidazole 400 mg, 3 times a day<br>Erythromycin 500 mg, 4 times a day | 14 days | £12.93 |
| Periodontal therapy | | | £81.50 |
| Cervical cerclage | Cervical cerclage placement. Requires surgery under full anaesthesia | 1 day | £1219 |
| Nutritional advice to increase energy and protein intake | | | None |
| Vitamin C | Vitamin C 100 mg, once a day from the 20th week of gestation until the 37th week | 17 weeks | £1.08 |
| Zinc | One tablet in water, twice daily | 17 weeks | £34.56 |
| Fish oil | One capsule per day | 24 weeks | £16.99 |
| Balanced energy/protein supplementation | Multivitamin preparations: vitamins: ascorbic acid 15 mg, nicotinamide 7.5 mg, riboflavin 500 $\mu$g, thiamine hydrochloride 1 mg, vitamin A 2500 units, vitamin D 300 units<br>1 capsule per day | 17 weeks | £1.32 |
| Energy/protein restriction | | | None |

| Comments | Source of unit cost | Relevant model |
|---|---|---|
| We used the unit cost per hour of home visit by a practice nurse (£35/hour) as a proxy for midwife | Curtis and Netten[692] | Delivery up to 37 weeks |
| Bed rest at home incurs no direct cost to the NHS | | Delivery up to 37 weeks |
| Estimate not available for the cost of the intervention. We used £250 as the cost of the intervention (see *Table 44* for more information) | Kosasa *et al*.[707]<br>Curtis and Netten[692] | Delivery up to 37 weeks |
| Cefalexin 500 mg (21-cap pack) @ £3.29 (one pack required) | BNF | Delivery up to 37 weeks |
| Metronidazole 400 mg (21-tab pack) @ £1.41 (one pack required) | BNF | Delivery up to 37 weeks |
| Erythromycin 250 mg (20 tablets) @ £1.92 (six packs required) | | Perinatal mortality |
| We used the inflated 6-monthly manual and non-fluoridated dental check | Davenport *et al*.[716] | Delivery up to 37 weeks |
| We used the 'lower genital tract intermediate procedures' cost, non-elective inpatient data (TNELIP) | Department of Health (2006), NHS reference costs 2005, NHS trusts and primary care trusts combined | Delivery up to 34 weeks<br>Delivery up to 37 weeks<br>Perinatal mortality |
| Nutritional advice incurs no direct cost to the NHS | | Delivery up to 37 weeks<br>Perinatal mortality |
| Vitamin C 100 mg (20 tablets) @ 18p (six packs required) | BNF | Perinatal mortality |
| Solvazinc tablets (zinc sulphate monohydrate 125–45 mg zinc) (30-tablet pack) @ £4.32 (eight packs required) | BNF | Delivery up to 37 weeks |
| 250 capsules @ £16.99 | Holland and Barrett | Delivery up to 34 weeks<br>Delivery up to 37 weeks |
| Multivitamin preparations, 20-cap pack @ 22p (six packs required) | BNF | Delivery up to 37 weeks<br>Perinatal mortality |
| Energy/protein restriction incurs no direct cost to the NHS | | Delivery up to 37 weeks |

*continued*



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***TABLE 45*** *Costs of interventions (continued)*

| Intervention | Description/nature/dose of intervention | Duration | Total cost |
|---|---|---|---|
| Progestational agents | Weekly intramuscular injection of 250 $\mu$g 17-hydroxyprogesterone caproate | 15 weeks from 16–20 weeks | £923.55 |
| Smoking cessation | Bupropion: Start 1–2 weeks before target stop date, initially 150 mg daily for 6 days then 150 mg twice daily; max period of treatment 7–9 weeks | Bupropion: 9 weeks | £79.70 – £154.19 |
| | Nicotine patches: 15 mg/16 h for 8 weeks; then 10 mg/16 h for 3 weeks | Nicotine patches: 11 weeks | |
| ***Symptomatic women*** | | | |
| Prophylactic antibiotics (intact membranes) | Metronidazole 400 mg, 3 times per day | | £1645.41 (48 hours/37 weeks) |
| | | | £2479.41 (7 days) |
| Nitric oxide donors | GTN patch 9.6 mg/24 h for 48 hours | 48 hours | £1656.87 |
| Indomethacin | Indomethacin: loading dose of 50–100 mg (rectal administration) followed by 25–50 mg orally every 6 h for 24–48 hours | 48 hours | £1646.01 (48 hours/37 weeks/ perinatal mortality) |
| | | | £2480.01 (7 days) |
| Calcium channel blockers | Nifedipine capsules 10 mg orally, repeat every 30 minutes up to a maximum of 40 mg in 2 hours; then maintenance of nifedipine (Tensipine) MR 20 mg TDS for 48 h maximum | 48 hours | £1652.97 (48 hours/34 weeks/37 weeks) |
| | | | £2486.97 (7 days) |
| Magnesium sulphate | Initial treatment 4 g over 15–30 min; then maintenance 2.5 g/h continued for 48 hours | 48 hours | £1678.95 |
| Terbutaline (intravenously) | By intravenous infusion, 5 $\mu$g/min for 20 min, increased every 20 min in steps of 2.5 $\mu$g/min until contractions have ceased, continue for 1 hour; then decrease every 20 min in steps of 2.5 $\mu$g/min to lowest dose that maintains suppression, continue at this level for 12 hours; then by mouth, 5 mg every 8 hours for as long as is desirable to prolong pregnancy | 48 hours | £1647.62 (48 hours/37 weeks) |
| | | | £2480.22 (7 days) |

| Comments | Source of unit cost | Relevant model |
|---|---|---|
| 15 injections @ 57p each | BNF | Delivery up to 34 weeks |
| We used the 'other expectant mothers ante-natal follow up outpatients' cost (£61), available in the DoH, NHS reference costs, to include the cost of the visit (either GP or hospital) to get the injection. We used the outpatient adult follow up attendance data (TOPS FUA) | Department of Health (2006), NHS reference costs 2005, NHS trusts and primary care trusts combined | Delivery up to 37 weeks<br>Perinatal mortality |
| Bupropion, 60-tab pack @ £39.85 (two packs required) | BNF | Delivery up to 37 weeks |
| Nicotine patches<br>15 mg: 7 @ £9.07 (12 packs required)<br>10 mg: 7 @ £9.07 (five packs required) | | |
| Metronidazole, 400 mg, 21-pack @ £1.41 (one pack required) | BNF | Delivery within 48 hours<br>Delivery within 7 days<br>Delivery up to 37 weeks |
| 10 mg patch, 30 @ £12.87 (one pack required) | BNF | Delivery within 48 hours |
| Suppositories 100 mg, 10-pack @ £1.20 (one pack required)<br>Capsules 50 mg, 20-pack @ 81p (one pack required) | BNF | Delivery within 48 hours<br>Delivery within 7 days<br>Delivery up to 37 weeks<br>Perinatal mortality |
| Nifedipine 10 mg, 84-cap pack @ £3.72 (one pack required)<br>Tensipide MR 20 mg, 56-tab pack @ £5.25 (one pack required) | BNF | Delivery within 48 hours<br>Delivery within 7 days<br>Delivery up to 34 weeks<br>Delivery up to 37 weeks |
| Initial treatment, 10-ml (5-g) prefilled syringe @ £4.95 (one syringe required)<br>Maintenance, 5-ml (2.5-g) amp @ £2.50 (12 amps required) | BNF | Delivery within 48 hours<br>Delivery up to 37 weeks |
| Intravenous injections. 5-ml amp @ £1.40 (two injections required)<br>Bricanyl, tablets, terbutaline sulphate 5mg, 20 @ 82p (one pack required) | BNF | Delivery within 48 hours<br>Delivery within 7 days<br>Delivery up to 37 weeks |

*continued*



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***TABLE 45*** *Costs of interventions (continued)*

| Intervention | Description/nature/dose of intervention | Duration | Total cost |
|---|---|---|---|
| Terbutaline pump maintenance | 1 mg of terbutaline at 0.05 ml/hour with 0.25 bolus injections every 6 hours | 5 days | £1651 |
| Atosiban | By intravenous injection, initially 6.75 mg over 1 min, then by intravenous infusion 18 mg/h for 3 hours, then 6 mg/h for up to 45 hours; max duration of treatment 48 hours | 48 hours | £2555.4 (48 hours/37 weeks)<br>£3389.4 (7 days) |
| Terbutaline (orally) | Terbutaline 20 mg/day | 24 hours<br>48 hours<br>7 days | £1644.82 (24/48 hours)<br>£2479.64 (7 days) |
| Hydration | Intravenous hydration with 500 ml crystalloids over 20 min, followed by 200 ml/hour | 48 hours | £1645 |
| Vitamin K for neuroprotection | Vitamin K, 10 mg intramuscularly once and then after 5 days | 48 hours | £1646 |
| Prophylactic corticosteroids | Betamethasone, two injections, 12 mg each with 24-hour interval | 48 hours | £1651.32 |

data in terms of likelihood ratios. The likelihood ratios were converted to their corresponding sensitivities and specificities and ranked according to their sensitivity. Starting with the test with the highest sensitivity, each test was tried in turn in the relevant model, which included all appropriate interventions for the case in question, to ensure that they would be worth including in that model. The conversion to sensitivity and specificity was for ranking only. In the actual model it was the likelihood ratios, as provided by the reviews, that were used. If tests with accuracy below a certain threshold were included in that model they risked being overlooked in favour of a strategy that would recommend 'treating all without a preceding test' or simply being dominated by one of the other tests, and this would not show in the results. It was only worth including tests that had a chance of providing an option where the test was recommended and so only those testing positive were treated. Use of this threshold analysis had the advantage of avoiding creating an overly large structured model with unnecessary branches.

*Table 48* presents a summary on the analyses that were carried out.

# Results of the decision analyses

## Symptomatic analysis

### *Case 1 – Symptomatic women giving birth 24 hours after testing and treatment*

*Tables 41* and *43* present the available data from the reviews of accuracy and effectiveness of tests and interventions respectively. There were no available data for tests used to confirm diagnosis of preterm

***TABLE 46*** *Cost of spontaneous preterm birth*

| Costs during the neonatal period | Birthweight | | | | |
|---|---|---|---|---|---|
| | < 1000 g | 1000–1499 g | ≥ 1500 g | Total cost | Total cost – 2005 values |
| Cost up to 34 weeks | £1873.59 | £4107.27 | £6103.90 | £12,084.76 | £15,688.75[a] |
| Cost up to 37 weeks | £75.96 | £166.51 | £9081.20 | £9323.67 | £12,104.23 |

a Also used in the 48 hours, 7 days, perinatal mortality models.

| Comments | Source of unit cost | Relevant model |
|---|---|---|
| Injection, terbutaline sulphate 500 $\mu$g/ml; 5-ml amp @ £140 (five injections required) | BNF | Delivery up to 34 weeks |
| Injection, atosiban 7.5 mg/ml, 0.9-ml (6.75-mg) vial @ £18.60 (49 vials required) | BNF | Delivery within 48 hours<br>Delivery within 7 days<br>Delivery up to 37 weeks |
| Terbutaline sulphate 5 mg, 20-tab pack @ 82p (one pack required – 24/48 hours)<br>(two packs required – 7 days) | BNF | Delivery within 24 hours<br>Delivery within 48 hours<br>Delivery within 7 days |
| | No cost available for crystalloids: £1 assumed | Delivery up to 34 weeks |
| Konakion MM Paediatric, phytomenadione 10 mg/ml, 0.2-ml amp, £1.00 | BNF | Perinatal mortality |
| Injection, betamethasone 4 mg/ml, net price 1-ml amp £1.22 (six amps required) | BNF | Perinatal mortality |

labour at 24 h and there were data available for only one intervention, namely terbutaline (orally). Therefore it was not possible to carry out an economic analysis of tests and treatments for this case.

### *Case 2 – Symptomatic women giving birth 48 hours after testing and treatment*

The results presented in *Table 49* show that five tests met the necessary criteria for inclusion in the model.

*Table 50* presents the results of the deterministic model where all the included tests were combined with the full range of relevant interventions for 48 h as presented in *Table 43*. The results are presented incrementally compared to the previous best option. The results show that the least costly test and treat option is 'Absence of fetal breathing movement test/Indomethacin_positive' but this is not the most cost-effective option. The strategy of providing 'Cervical length measurement (15 mm) test/Indomethacin_positive' is the most cost-effective strategy. This means test everyone with the 'cervical length measurement (15 mm)' test and provide indomethacin to all the women who tested positive. This strategy has an average cost of £669 per woman treated (this value is also incorporated into the asymptomatic models at 34 and 37 weeks described later) and the strategy

***TABLE 47*** *Table of prevalence*

| | Within 24 hours | Within 48 hours | Within 7 days | Up to 34 weeks | Up to 37 weeks | Perinatal mortality |
|---|---|---|---|---|---|---|
| Overall prevalence of asymptomatic women having preterm birth | N/A | N/A | N/A | 3.46% (3.25–3.67) | 7.56% (7.40–7.73) | 18.37% (14.21–22.53) |
| Overall prevalence of symptomatic women having preterm birth | – | 7.55% (5.65–9.45) | 20.56% (18.26–22.85) | 24.25% (21.34–27.16) | 37.88% (36.42–39.34) | 18.37% (14.21–22.53) |
| Overall prevalence of asymptomatic women becoming symptomatic | N/A | N/A | N/A | 14.27% (14.04–14.50) | 19.97% (19.18–20.76) | N/A |



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***TABLE 48*** *Summary of analyses*

| | | |
|---|---|---|
| ***Symptomatic analysis*** | | |
| Case 1 | 24 hours | No model (no data) |
| Case 2 | 48 hours | Full model with PSA (all tests – atosiban, indomethacin, terbutaline) |
| Case 3 | 7 days | Full model with PSA (all tests – atosiban, indomethacin, calcium channel blockers, terbutaline, prophylactic antibiotics) |
| Case 4 | 34 weeks | Deterministic model on ALL tests and ALL interventions. No interventions available for the PSA – used the most effective intervention from Symptomatic 37 weeks, i.e. indomethacin (for the PSA only) |
| Case 5 | 37 weeks | Full model with PSA (one test – atosiban, indomethacin, terbutaline) |
| Case 6 | Perinatal mortality | Cost consequence only – no model |
| ***Asymptomatic analysis*** | | |
| Case 7 | 34 weeks | Full model with PSA (one test – all interventions) |
| Case 8 | 37 weeks | Full model with PSA (one test – huam, antibiotics for asymptomatic bacteriuria, periodontal therapy, progestational agents, fish oil, nutritional advice, smoking cessation) |
| Case 9 | Perinatal mortality | Cost consequence only – no model |

PSA, probabilistic sensitivity analysis.

saves nearly eight cases of preterm labour per 1000 women, a number needed to treat (NNT) of 125. There is an additional cost of £5268 per case of preterm labour averted. The next preferred strategy is 'No test/Indomethacin_all'. Given that the results are presented incrementally compared to the previous best option, 'No test/Indomethacin_all' avoids just over one more case of preterm labour in 1000 women than 'Cervical length measurement (15 mm)/Indomethacin_positive', but costs approximately £1202 more, giving an ICER of £858,334 of additional test and treatment cost per additional case of preterm labour averted. It should be noted that calcium channel blockers are one of only two treatments recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines. This option was included for evaluation in the deterministic analysis, but is dominated by the options presented in *Table 50*.

***TABLE 49*** *Case 2: Symptomatic women – 48 h. Threshold analysis based on test characteristics to determine which tests should be considered in the model*

| Test | Sensitivity | Specificity | Cost of test | Cost limit[a] | Comment[b] |
|---|---|---|---|---|---|
| Measurement of cervical length (15 mm) | 0.98 | 0.85 | £69.47 | £1230 | Included |
| Amniotic fluid IL-6 | 0.92 | 0.76 | £216.70 | £929 | Included |
| IL-8 (15 ng/ml amniotic fluid) | 0.90 | 0.98 | £216.70 | £1216 | Included |
| Cervicovaginal IL-6 | 0.88 | 0.54 | £11.50 | £489 | Included |
| Absence of fetal breathing movements | 0.76 | 0.90 | £69.47 | £1032 | Included |
| phIGFBP-1 | 0.62 | 0.64 | £11.50 | £0 | Not included |
| Serum IL-6 | 0.50 | 0.76 | The combined criteria of this test did not meet the required threshold | | |

a For the given test accuracy characteristics the cost of the test is required to be below this limit for the test to be worth considering in the modelling analysis.
b 'Included' refers to the test being considered in the modelling analysis.

***TABLE 50*** *Case 2: Symptomatic women – 48 h. Costs, effects and incremental cost-effectiveness ratios for most cost-effective combinations of test and treatment*

| Test/treatment combination | Mean cost per woman (UK £ 2005) | Difference in costs (UK £ 2005) | Effectiveness[a] | Absolute risk reduction | ICER[b] | NNT |
|---|---|---|---|---|---|---|
| Absence of fetal breathing movements test/ Indomethacin_+ve[c] | £627.10 | | 0.9763 | | | |
| Cervical length measurement (15 mm) test/Indomethacin_+ve | £669.20 | £42.1 | 0.9843 | 0.008 | £5268 | 125 |
| No test/Indomethacin_All | £1871.10 | £1201.9 | 0.9857 | 0.0014 | £858,334 | 714 |
| Cervicovaginal interleukin-6/ Indomethacin_All | £1882.60 | £11.5 | 0.9857 | 0 | (Undefined) | |

ICER, incremental cost-effectiveness ratio; NNT, number needed to treat.
a Effectiveness is defined as the proportion of women avoiding spontaneous preterm birth. Therefore the difference in effectiveness between two strategies is the absolute risk reduction.
b Incremental cost-effectiveness ratio expressed as the additional cost per additional case of preterm labour avoided.
c This represents the least costly option and is the baseline with which subsequent options are compared, but it is not the most cost-effective option.

In *Figure 284* the results of the deterministic analysis are presented diagrammatically alongside all the cost-effectiveness estimates produced by case 2. The majority of the points represent dominated options, where greater effectiveness can be achieved at lower cost by an alternative. The most cost-effective option from this analysis is shown to be 'Cervical length measurement (15mm)/ Indomethacin_positive' which is at the bottom right corner (low cost/high effect) of the diagram.

In *Table 51* the results of PSA for case 2 are presented. The interventions that are included in the PSA are those for which the 95% CI for the relative risks are < 1 as shown in *Table 43* and so they include only indomethacin, terbutaline (intravenously) and atosiban. The latter was estimated by an indirect comparison (Appendix 7) because the available data for atosiban from a placebo-controlled trial was based on only a small number of participants. The direct estimate was also not eligible for inclusion in the model because it did not suggest a favourable outcome for atosiban. However, atosiban is an important intervention in clinical practice so it was decided to enter the more favourable indirect estimate, which was eligible for inclusion in the model, and to use this as a 'best-case scenario'. The results from the model reaffirm that 'Cervical length measurement (15 mm)/Indomethacin_positive' is the dominant option at all values of willingness to pay after £30,000.

For example, at a given threshold of say £30,000, which means that a policy-maker would be willing to pay £30,000 per case of spontaneous preterm birth avoided, there is a 53% chance that 'Cervical length measurement (15 mm)/ Indomethacin_positive' is the preferred option with respect to its cost-effectiveness (*Figure 285*). At the same threshold there is only a 19% chance that an alternative option of 'Amniotic interleukin-8/ Indomethacin_positive' is the preferred option and less than a 1% chance of preference for other options such as 'Cervical length measurement (15 mm)/Atosiban_positive'. If the willingness to pay threshold is increased to £100,000 per case of spontaneous preterm birth avoided then there is now a 60% chance that 'Cervical length measurement (15 mm)/Indomethacin_positive' is the preferred option.

### *Case 3 – Symptomatic women who experience preterm labour within 7 days of testing and treatment*

The results presented in the *Table 52* show that six tests met the necessary criteria for inclusion in the model.

*Table 53* presents the results of the deterministic model in which all the included tests were combined with the full range of relevant interventions for the 7-day model. The results show that the least costly test and treat option is



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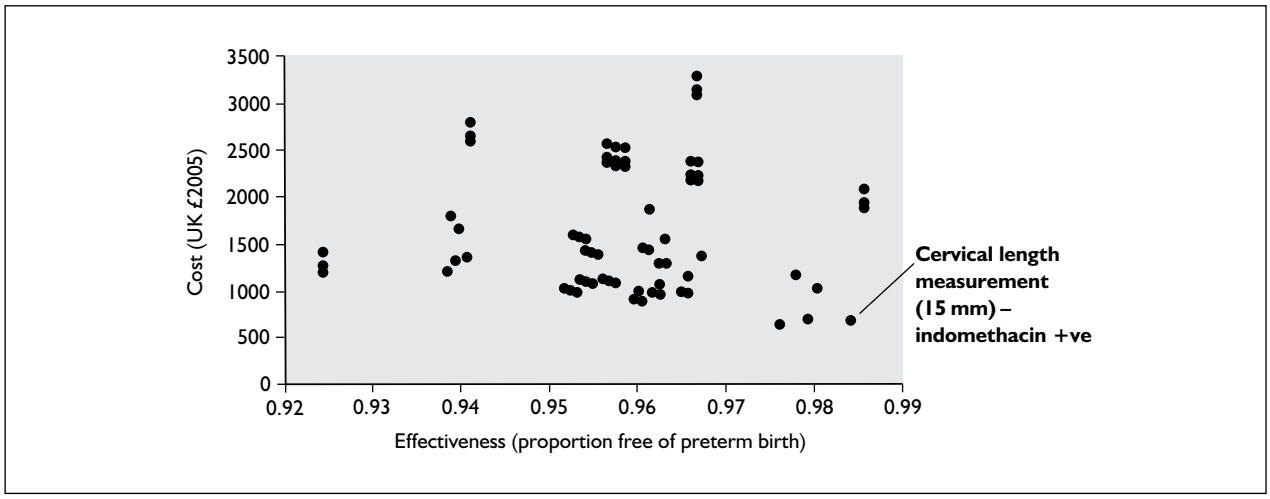


***FIGURE 284*** *Case 2: Symptomatic women – 48 h. Results: costs, effects and incremental cost-effectiveness ratios on cost-effectiveness plane for all combinations of test and treatment pairs.*

***TABLE 51*** *Case 2: Symptomatic women – 48 h. Probabilistic sensitivity analysis of case 2, results. Probability that stated options are the most cost-effective at different levels of willingness to pay for a case of spontaneous preterm birth avoided*

| | Willingness to pay (UK £ 2005/6)[a] | | | | | |
|---|---|---|---|---|---|---|
| **Test/Treatment option** | **0** | **10,000** | **30,000** | **50,000** | **80,000** | **100,000** |
| Cervical length measurement (15 mm)/ Indomethacin +ve | 0.2247 | 0.3919 | 0.5315 | 0.5777 | 0.6008 | 0.605 |
| Amniotic interleukin-8/Indomethacin +ve | 0.1783 | 0.1991 | 0.1971 | 0.1885 | 0.1774 | 0.1724 |
| Absence of fetal breathing movements/ Indomethacin +ve | 0.5118 | 0.3149 | 0.1613 | 0.1092 | 0.0763 | 0.0656 |
| Cervical length measurement (15 mm)/Atosiban +ve | 0.0007 | 0.0035 | 0.015 | 0.0232 | 0.0323 | 0.0363 |
| Cervical length measurement (15 mm)/Terbutaline +ve | 0.0106 | 0.0226 | 0.0331 | 0.0373 | 0.0382 | 0.0376 |
| Amniotic interleukin-6/Indomethacin +ve | 0 | 0.001 | 0.0069 | 0.0129 | 0.0239 | 0.0306 |
| Amniotic interleukin-8/Atosiban +ve | 0.008 | 0.0131 | 0.0165 | 0.0178 | 0.0171 | 0.0164 |
| Amniotic interleukin-8/Terbutaline +ve | 0.0092 | 0.0105 | 0.0106 | 0.0102 | 0.0099 | 0.0097 |
| Cervicovaginal interleukin-6/Indomethacin +ve | 0.0003 | 0.0006 | 0.0019 | 0.005 | 0.0096 | 0.0118 |
| Absence of fetal breathing movements/Atosiban +ve | 0.0141 | 0.0172 | 0.0132 | 0.0096 | 0.0064 | 0.0049 |
| Absence of fetal breathing movements/Terbutaline +ve | 0.0422 | 0.0256 | 0.0124 | 0.0073 | 0.005 | 0.0044 |

a Per case of preterm labour avoided.

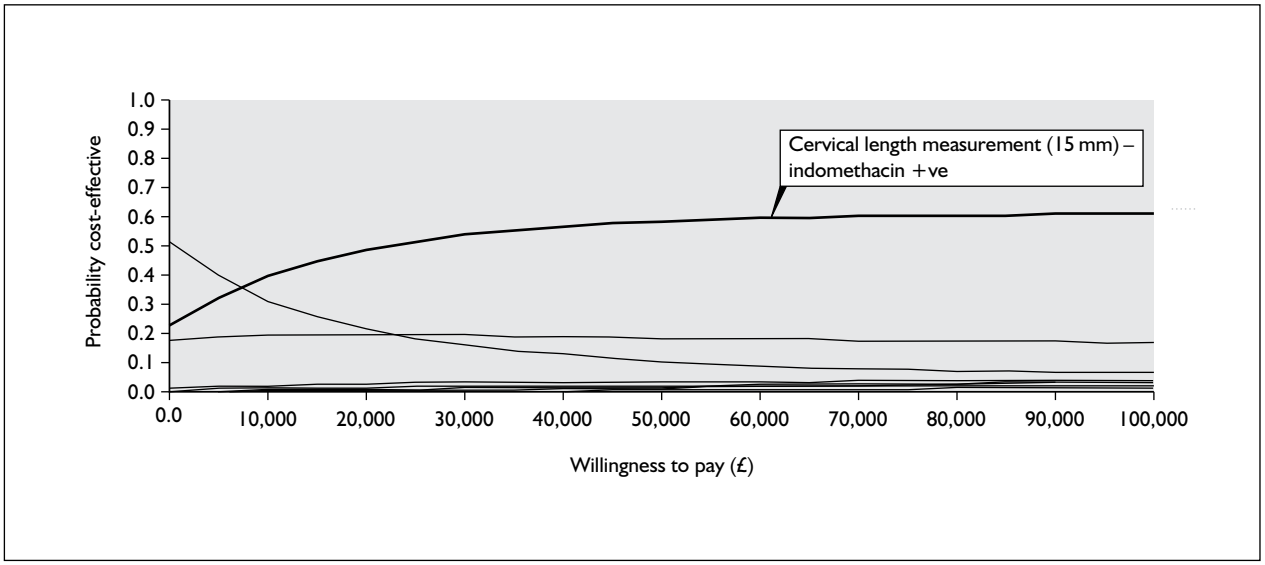


***FIGURE 285*** *Case 2: Symptomatic women – 48 h. Cost-effectiveness acceptability curves.*

***TABLE 52*** *Case 3: Symptomatic women – 7 days. Threshold analysis based on test characteristics to determine which tests should be considered in the model*

| Test | Sensitivity | Specificity | Cost of test | Cost limit[a] | Comment[b] |
|---|---|---|---|---|---|
| Measurement of cervical length (15 mm) | 0.98 | 0.89 | £69.47 | £1638 | Included |
| β-human chorionic gonadotrophin | 0.97 | 0.84 | £11.50 | £2298 | Included |
| Amniotic fluid IL-6 | 0.85 | 0.88 | £216.70 | | Included |
| Serum CRP | 0.82 | 0.98 | £9.50 | | Included |
| Fetal fibronectin | 0.82 | 0.77 | £11.50 | £648 | Included |
| IL-8 (15 ng/ml amniotic fluid) | 0.75 | 0.97 | £216.70 | £1020 | Included |
| phIGFBP-1 | 0.72 | 0.74 | £11.50 | £0 | Not included because it did not meet criteria |
| CV-Prolactin | 0.66 | 0.55 | The combined criteria of these tests did not meet the required threshold | | |
| Serum IL-6 | 0.64 | 0.81 | | | |
| IL-8 (7.7 ng/ml in cervical swab) | 0.62 | 0.74 | | | |
| Serum CRH | 0.46 | 0.85 | | | |
| Cervicovaginal IL-6 | 0.41 | 0.90 | | | |
| Absence of fetal breathing movements | 0.40 | 0.90 | | | |

a For the given test accuracy characteristics the cost of the test is required to be below this limit for the test to be worth considering in the modelling analysis.
b Included' refers to the test being considered in the modelling analysis.



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***TABLE 53*** *Case 3: Symptomatic women – 7 days. Costs, effects and incremental cost-effectiveness ratios for most cost-effective combinations of test and treatment*

| Test/treatment combination | Mean cost per woman (UK£ 2005) | Difference in costs (UK£ 2005) | Effectiveness[a] | Absolute risk reduction | ICER[b] | NNT |
|---|---|---|---|---|---|---|
| CRP/Indomethacin_+ve[c] | £2221.00 | | 0.889 | | | |
| Measurement of cervical length (15 mm)/Indomethacin_+ve | £2252.10 | £31.10 | 0.907 | 0.018 | £1703 | 55 |
| No test/Indomethacin | £3899.30 | £1647.20 | 0.910 | 0.003 | £620,688 | 333 |
| β-Human chorionic gonadotrophin/ Indomethacin_all | £3910.80 | £11.50 | 0.910 | 0.000 | (Undefined) | |
| Fetal fibronectin/Indomethacin_all | £3910.80 | £0.0 | 0.910 | 0.000 | (Undefined) | |

ICER, incremental cost-effectiveness ratio; NNT, number needed to treat.
a Effectiveness is defined as the proportion of women avoiding spontaneous preterm birth. Therefore the difference in effectiveness between two strategies is the absolute risk reduction.
b Incremental cost-effectiveness ratio expressed as the additional cost per additional case of spontaneous preterm birth avoided.
c This represents the least costly option and is the baseline with which subsequent options are compared, but it is not the most cost-effective option.

'CRP test/Indomethacin_positive' but this is not the most cost-effective option. The strategy of providing 'Cervical length measurement (15 mm)/ Indomethacin_positive' is, like the 48-h model, the most cost-effective strategy. This strategy has an average cost of £2252 per woman treated, costs only £31 more than the least costly strategy of 'CRP test/Indomethacin_positive' and avoided 18 cases of spontaneous preterm birth per 1000 women, an NNT of 55. There is an additional cost of £1703 per additional case of spontaneous preterm birth averted with this strategy. The next strategy is 'No test/Indomethacin_all' which is marginally more effective than 'Cervical length measurement (15 mm)/Indomethacin_positive' but costs approximately £1647 more, giving an ICER of £620,688 of additional test and treatment cost per additional case of spontaneous preterm birth averted, which would not be deemed cost-effective.

*Figure 286* shows the results of deterministic analysis, presented diagrammatically alongside all the cost-effectiveness estimates produced by case 3. Most of the points represent dominated options, where greater effectiveness can be achieved at lower cost using an alternative. It showed that the most cost-effective option from this analysis was 'Cervical length measurement (15 mm)/Indomethacin_ positive', which is at the bottom right hand corner (low cost/high effect) of the diagram.

In *Table 54* the results of the probabilistic sensitivity analysis for case 3 are presented. Again the PSA combines all the relevant tests with only the interventions for which the 95% CI for the relative risks was < 1, as shown in *Table 43*, and so includes only indomethacin, terbutaline (intravenously), calcium channel blockers (nifedipine) and atosiban. Again, appropriate data for nifedipine and atosiban were available through indirect comparison. The results reaffirm that 'Cervical length measurement (15 mm)/Indomethacin_positive' is the dominant option at all values of willingness to pay but the probability of it being the preferred option at the £30,000 threshold is only just over 23% (*Figure 287*). There are competing options for it being the most cost-effective option at all levels of willingness to pay particularly from 'β-Human chorionic gonadotrophin test/Indomethacin_positive', 'Cervical length measurement (15 mm)/Calcium channel blockers_positive' and 'β-Human chorionic gonadotrophin test/Calcium channel blockers_ positive' test/treatment pairings.

### *Case 4 – Symptomatic women at 34 weeks*

All the tests that met the necessary criteria were included in the model and these are presented in *Table 55*.

*Figure 288* shows the results of the deterministic analysis, presented diagrammatically alongside all the cost-effectiveness estimates produced by case 4. The majority of the points represent dominated options, where greater effectiveness can be achieved at lower cost by an alternative. The most cost-effective option from this analysis is shown

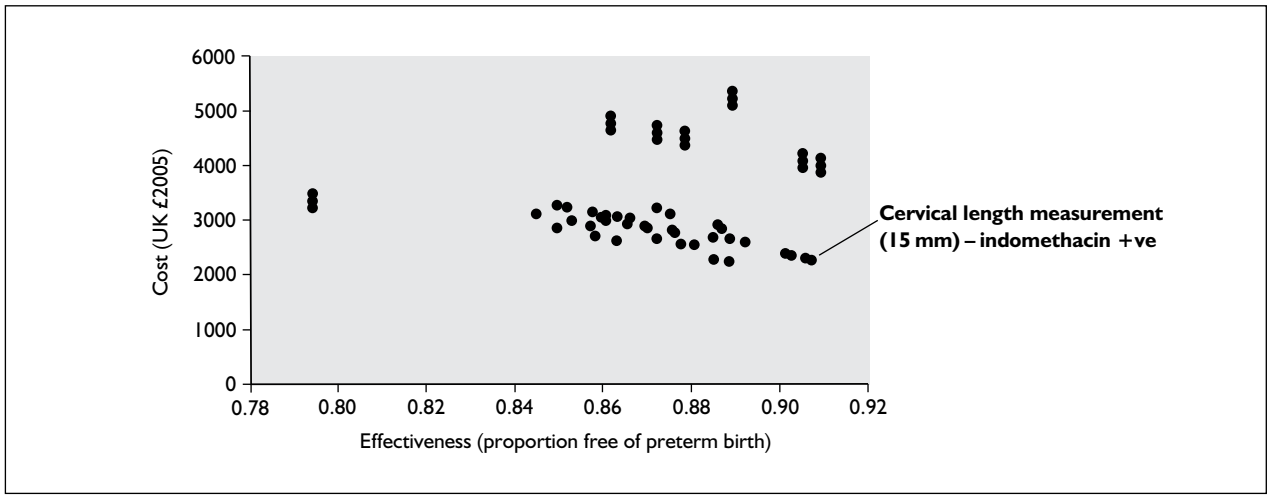


***FIGURE 286*** *Case 3: Symptomatic women – 7 days. Results: costs, effects and incremental cost-effectiveness ratios on cost-effectiveness plane for all combinations of test and treatments pairs.*

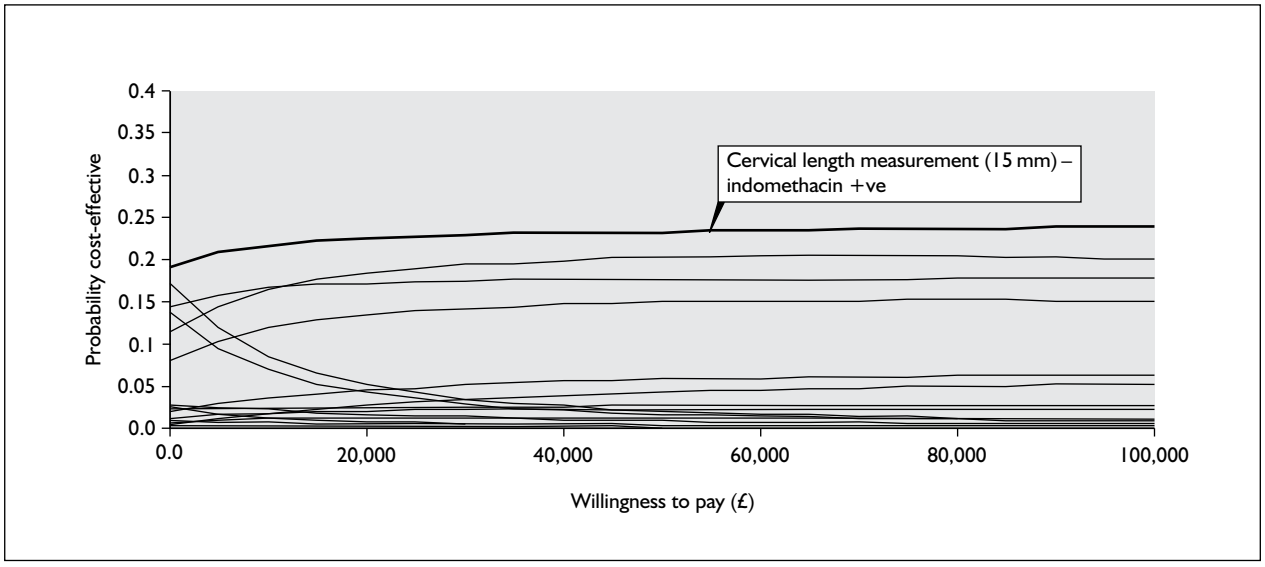


***FIGURE 287*** *Case 3: Symptomatic women – 7 days. Cost-effectiveness acceptability curves.*

to be 'Amniotic Fluid interleukin-6/Hydration_ positive', which is at the bottom right corner (low cost/high effect) of the diagram. *Table 56* presents the results of the deterministic model where all the included tests are combined with the full range of relevant interventions for 34 weeks. The results show that the least costly test and treat option is the 'Phosphorylated insulin-like growth factor binding protein-1 test/Hydration_positive' option but this is not the most cost-effective option. The strategy of providing 'Amniotic fluid interleukin-6 test/Hydration_positive' is the most cost-effective strategy. This test and intervention have an average cost of £3584 per woman treated and the strategy saves over eight cases of spontaneous preterm birth per 1000 women, an NNT of 116. There is an additional cost of £4976 per case of preterm labour averted. The next most effective option after 'Amniotic fluid interleukin-6 test/ Hydration_positive' is the 'No test/Hydration_all'. This option 'No test/Hydration_all' (which implies treat everyone with hydration without a preceding test) avoids almost eight more cases of spontaneous preterm birth in 1000 women than 'Amniotic fluid interleukin-6 test/Hydration_positive', but costs £800 more, giving an ICER of £95,430 of additional test and treatment cost per additional case of preterm labour avoided.

The interventions that are typically included in the PSA are those for which the 95% CI for the relative risks is < 1. However, as shown in *Table 43*, none



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***TABLE 54*** *Case 3: Symptomatic women – 7 days. Probabilistic sensitivity analysis results. Probability that stated options are the most cost-effective at different levels of willingness to pay for a case of spontaneous preterm birth avoided*

| | Willingness to pay (UK £ 2005/6)[a] | | | | | |
|---|---|---|---|---|---|---|
| **Test/treatment option** | **0** | **10,000** | **30,000** | **50,000** | **80,000** | **100,000** |
| Measurement of cervical length (15 mm)/ Indomethacin +ve | 0.1938 | 0.2201 | 0.2316 | 0.2322 | 0.2358 | 0.2376 |
| β-Human chorionic gonadotrophin/Indomethacin +ve | 0.1006 | 0.1517 | 0.1842 | 0.1947 | 0.1951 | 0.194 |
| Measurement of cervical length (15 mm)/Calcium channel blockers +ve | 0.1488 | 0.1684 | 0.1734 | 0.1761 | 0.1792 | 0.1795 |
| β-Human chorionic gonadotrophin/Calcium channel blockers +ve | 0.0808 | 0.1174 | 0.1448 | 0.1506 | 0.1515 | 0.1523 |
| Measurement of cervical length (15 mm)/Atosiban +ve | 0.0179 | 0.0348 | 0.0524 | 0.0603 | 0.0656 | 0.068 |
| Measurement of cervical length (15 mm)/Terbutaline +ve | 0.0246 | 0.0285 | 0.028 | 0.0288 | 0.0287 | 0.0285 |
| Measurement of cervical length (15 mm)/ Prophylactic antibiotics (intact membranes) +ve | 0.013 | 0.0152 | 0.0158 | 0.0162 | 0.0166 | 0.0166 |
| β-Human chorionic gonadotrophin/Atosiban +ve | 0.0056 | 0.0161 | 0.0306 | 0.0399 | 0.0462 | 0.0482 |
| β-Human chorionic gonadotrophin/Terbutaline +ve | 0.0113 | 0.018 | 0.0238 | 0.0242 | 0.0247 | 0.0248 |
| β-Human chorionic gonadotrophin/Prophylactic antibiotics (intact membranes) +ve | 0.0068 | 0.0103 | 0.0125 | 0.0127 | 0.0127 | 0.0127 |
| C-reactive protein/Atosiban +ve | 0.0253 | 0.0215 | 0.0127 | 0.0076 | 0.0052 | 0.0041 |
| C-reactive protein/Indomethacin +ve | 0.1753 | 0.0886 | 0.0363 | 0.0214 | 0.0133 | 0.0111 |
| C-reactive protein/Calcium channel blockers +ve | 0.1351 | 0.0707 | 0.0312 | 0.0177 | 0.0099 | 0.0079 |
| C-reactive protein/Terbutaline +ve | 0.0258 | 0.0124 | 0.0054 | 0.0028 | 0.0018 | 0.0015 |
| C-reactive protein/Prophylactic antibiotics (intact membranes) +ve | 0.0145 | 0.0076 | 0.0031 | 0.0018 | 0.001 | 0.0006 |
| Amniotic interleukin-6/Atosiban +ve | 0.0002 | 0.0002 | 0.0002 | 0.0003 | 0.0004 | 0.0003 |
| Amniotic interleukin-6/Indomethacin +ve | 0.0013 | 0.0014 | 0.0023 | 0.0021 | 0.0024 | 0.0025 |
| Amniotic interleukin-6/Calcium channel blockers +ve | 0.0013 | 0.0013 | 0.0008 | 0.0008 | 0.0012 | 0.001 |
| Amniotic interleukin-8/Atosiban +ve | 0.0018 | 0.0021 | 0.0016 | 0.0017 | 0.0013 | 0.001 |
| Amniotic interleukin-8/Indomethacin +ve | 0.0072 | 0.0058 | 0.0035 | 0.0023 | 0.0024 | 0.0021 |
| Amniotic interleukin-8/Calcium channel blockers +ve | 0.006 | 0.0048 | 0.003 | 0.0028 | 0.002 | 0.0018 |

a Per case of spontaneous preterm birth avoided.

were available for this case and so a PSA was not carried out.

### *Case 5 – Symptomatic women at 37 weeks*

The results presented in *Table 57* show that none of the tests met the necessary criteria for inclusion in the model which suggests that the best option will be that of 'no test/treat_all'. However, the fetal fibronectin test, which had the highest ranking sensitivity for this group, was included in the model although it did not meet the required criteria. The sensitivity and specificity of the fetal fibronectin test were adjusted to find the necessary characteristics of this or another test at the same cost as the fetal fibronectin test which was £11.50. The required characteristics for the sensitivity and specificity of this test are 0.92 and 0.99 respectively but these characteristics were not included in the model.

***TABLE 55*** *Case 4: Symptomatic women – 34 weeks. Threshold analysis based on test characteristics to determine which tests should be considered in the model*

| Tests | Sensitivity | Specificity | Cost of test | Cost limit[a] | Comment[b] |
|---|---|---|---|---|---|
| Amniotic fluid interleukin-6 | 0.88 | 0.88 | £216.7 | £766 | Included |
| Measurement of cervical length (30 mm) | 0.83 | 0.56 | £69.47 | £243 | Included |
| phIGFBP-1 | 0.75 | 0.82 | £11.50 | £285 | Included |
| Fetal fibronectin | 0.73 | 0.82 | £11.50 | £285 | Included |
| Serum interleukin-6 | 0.70 | 0.51 | £9.50 | £0 | Not included |
| CV-Prolactin | 0.57 | 0.88 | The combined criteria of these tests did not meet the required threshold | | |
| Presence of funnelling | 0.45 | 0.90 | | | |
| CRP | 0.38 | 0.94 | | | |
| Relaxin (serum) | 0.33 | 0.77 | | | |
| Cervicovaginal interleukin-6 | 0.31 | 0.94 | | | |

a For the given test accuracy characteristics the cost of the test is required to be below this limit for the test to be worth considering in the modelling analysis.
b 'Included' refers to the test being considered in the modelling analysis.

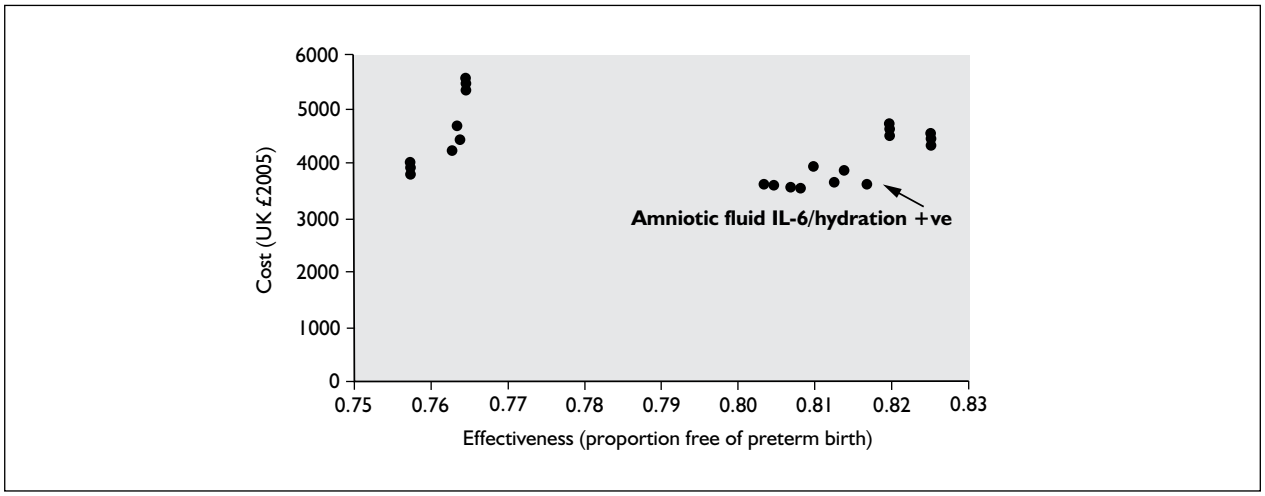


***FIGURE 288*** *Case 4: Symptomatic women – 34 weeks. Results: costs, effects and incremental cost-effectiveness ratios on cost-effectiveness plane for all combinations of test and treatment pairs.*

Table 58 presents the results of the deterministic model where only the fetal fibronectin test was included and this test was combined with the full range of relevant interventions for 37 weeks. The results show that the least costly test and treat option is 'Fetal fibronectin test/ Indomethacin_positive' but this is not the most cost-effective option. The strategy of providing 'No test/Indomethacin_all' is the most cost-effective strategy, which implies that the strategy should be to provide indomethacin to all without any preceding test (as predicted by the earlier threshold analysis). The 'No test/Indomethacin_all' strategy has an average cost of £2609 per woman treated and the strategy saves 34 cases of spontaneous preterm birth per 1000 women, an NNT of 29. There is an additional cost of £16,336 per case of additional spontaneous preterm birth averted. *Figure 289* shows the results of the deterministic analysis presented diagrammatically with all the cost-effectiveness estimates produced by case 5. The majority of the points represent dominated



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***TABLE 56*** *Case 4: Symptomatic women – 34 weeks. Costs, effects and incremental cost-effectiveness ratios for most cost-effective combinations of test and treatment*

| Test/treatment combination | Mean cost per woman (UK£ 2005) | Difference in costs (UK£ 2005) | Effectiveness[a] | Absolute risk reduction | ICER[b] | NNT |
|---|---|---|---|---|---|---|
| phIGFBP-1/Hydration +ve[c] | £3541.30 | | 0.8084 | | | |
| Amniotic fluid interleukin-6/ Hydration +ve | £3584.00 | £42.70 | 0.817 | 0.0086 | £4976 | 116.28 |
| No test/Hydration all | £4384.30 | £800.30 | 0.8254 | 0.0084 | £95,430 | 119.05 |

ICER, incremental cost-effectiveness ratio; NNT, number needed to treat.
a Effectiveness is defined as the proportion of women avoiding spontaneous preterm birth. Therefore the difference in effectiveness between two strategies is the absolute risk reduction.
b ICER – Incremental cost-effectiveness ratio expressed as the additional cost per additional case of spontaneous preterm birth avoided.
c This represents the least costly option and is the baseline with which subsequent options are compared, but it is not the most cost-effective option.

options, where greater effectiveness can be achieved at lower cost by an alternative. The most cost-effective option from this analysis is shown to be 'No test/Indomethacin_all', which is at the bottom right hand corner (low cost/high effect) of the diagram.

In *Table 59* the results of the PSA for case 5 are presented. The interventions that are included in the PSA are those for which the 95% CI for the relative risks was <1 as shown in *Table 43*: this includes only indomethacin, terbutaline (intravenously) and atosiban (the latter by indirect comparison). The results reaffirm that 'No test/ Indomethacin_all' has a 75% chance of being the preferred option at all values of willingness to pay after £30,000. The results are presented diagrammatically in *Figure 290*, as a cost-effectiveness acceptability curve.

#### *Case 6 – Symptomatic women – perinatal mortality*

From the accuracy reviews there were no data available for tests that detect risk factors for perinatal mortality in relation to spontaneous preterm birth. Data were available from the effectiveness reviews for interventions only.

Therefore the data were analysed by using a cost–consequence approach in the first instance. The interventions were ranked according to their effectiveness. If the most effective strategy was also the least costly strategy, then it would be the dominant strategy and no further economic analysis or model would be required. The results of the cost–consequence analysis for case 6 are presented in *Table 60*. Since all intervention strategies apply to women who are hospitalised they are all reasonably expensive and are estimated to cost approximately the same with corticosteroids being very slightly more expensive. However, it is likely that the most cost-effective intervention for treating women who are at risk of perinatal mortality in relation to spontaneous preterm birth, based on a cost–consequence analysis, is treatment with corticosteroids. Although it is very slightly more expensive than the alternatives in this group, vitamin K and indomethacin, it is much more effective and has a 95% CI upper limit <1. A note of caution is necessary in the interpretation of corticosteroid use because the measure of mortality available is neonatal rather than perinatal mortality.

## Asymptomatic analysis

#### *Case 7 – Asymptomatic women at 34 weeks*

A range of potential possible tests were identified in the literature for detecting risk factors for spontaneous preterm birth in asymptomatic women at 34 weeks and these are presented in Table 61. Although the mammary stimulation test had the highest ranking sensitivity for this group, the test which ascertains a woman's previous history of spontaneous preterm birth was the only test to

***TABLE 57*** *Case 5: Symptomatic women – 37 weeks. Threshold analysis based on test characteristics to determine which tests should be considered in the model*

| Tests | Sensitivity | Specificity | Cost of test | Cost limit[a] | Comment[b] |
|---|---|---|---|---|---|
| Fetal fibronectin | 0.89 | 0.89 | £11.50 | £0 | Included but did not meet the required threshold |
| Measurement of cervical length (30 mm) | 0.81 | 0.65 | The combined criteria of these tests did not meet the required threshold | | |
| Rheobase (3.4 mA) | 0.76 | 0.68 | | | |
| Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) | 0.74 | 0.81 | | | |
| Salivary estriol (threshold 2.1 ng/ml) | 0.73 | 0.69 | | | |
| 18 mm | 0.73 | 0.78 | | | |
| β-Human chorionic gonadotrophin | 0.70 | 0.67 | | | |
| C-reactive protein | 0.67 | 0.71 | | | |
| Matrix metalloproteases (MMP-9) | 0.66 | 0.91 | | | |
| Digital examination | 0.66 | 0.72 | | | |
| Interleukin-8 (3.739 ng/ml in cervical swab) | 0.63 | 0.55 | | | |
| Rheobase (2.8 mA) | 0.54 | 0.76 | | | |
| Cervicovaginal interleukin-6 | 0.50 | 0.73 | | | |
| Serum interleukin-6 | 0.45 | 0.60 | | | |
| Serum corticotrophin-releasing hormone | 0.38 | 0.91 | | | |
| Amniotic fluid interleukin-6 | 0.35 | 0.99 | | | |
| CV-Prolactin | 0.31 | 0.88 | | | |
| Presence of funnelling | 0.21 | 0.92 | | | |
| Relaxin (serum) | 0.21 | 0.74 | | | |
| ***Sensitivity analysis*** | | | | | |
| Hypothetical test | 0.92 | 0.99 | £11.50 | | |

a For the given test accuracy characteristics the cost of the test is required to be below this limit for the test to be worth considering in the modelling analysis.
b 'Included' refers to the test being considered in the modelling analysis.

meet the criteria for inclusion in the model. This was because it was assumed to have a zero cost, so that despite having a very low sensitivity of only 0.38 it met the combined required criteria because of its negligible cost.

The sensitivity of the 'previous history' test was also adjusted to see how low the sensitivity could be to be included in the model given that the cost was zero. The results showed that the sensitivity was already at its lowest limit to be acceptable. The sensitivity and specificity of the mammary stimulation test were also adjusted to find the necessary characteristics of this or another test (at the same cost) that would be worth including in the model. Holding the cost of the mammary stimulation test constant at £26.66 the required characteristics for the sensitivity and specificity of this test are 0.81 and 0.99 respectively, although this hypothetical test was not included in the model.

*Table 62* presents the results of the deterministic model where the previous history test is combined with the full range of relevant interventions for 34 weeks. The estimated full costs of becoming symptomatic, which was estimated by the symptomatic model at 48 h to be approximately



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***TABLE 58*** *Case 5: Symptomatic women – 37 weeks. Costs, effects and incremental cost-effectiveness ratios for most cost-effective combinations of test and treatment*

| Test/treatment combination | Mean cost per woman (UK £ 2005) | Difference in costs (UK £ 2005) | Effectiveness[a] | Absolute risk reduction | ICER[b] | NNT |
|---|---|---|---|---|---|---|
| Fetal fibronectin test/ Indomethacin_+ve [c] | £2052.70 | | 0.886 | | | |
| No test/Indomethacin_all | £2608.90 | £556.20 | 0.92 | 0.034 | £16,336 | 29 |

ICER, incremental cost-effectiveness ratio; NNT, number needed to treat.
a Effectiveness is defined as the proportion of women avoiding spontaneous preterm birth. Therefore the difference in effectiveness between two strategies is the absolute risk reduction.
b ICER – incremental cost-effectiveness ratio expressed as the additional cost per additional case of spontaneous preterm birth avoided.
c This represents the least costly option and is the baseline with which subsequent options are compared, but it is not the most cost-effective option.

£669, is the cost in the comparator arm of the model.

The results show that the strategy of providing 'Previous history test/Fish oil_positive' is the baseline least costly option but this is not the most cost-effective strategy. According to the deterministic model the most cost-effective option is the option 'Previous history test/Fish oil_all'. Although this result is somewhat counter intuitive it is thrown up by the deterministic model as a cost-effective option because the sensitivity of the test is so low. The results are presented incrementally compared to the previous least costly option so 'Previous history test/Fish oil_all' avoids nearly 14 more cases of spontaneous preterm birth in 1000 women than 'Previous history test/Fish oil_positive' and costs only £6 more, giving an ICER of £434 of additional test and treatment cost per additional case of spontaneous preterm birth avoided. These 14 cases would result in cases of spontaneous preterm birth if the strategy of giving fish oil to only the 'positives' was adopted. *Figure 291* shows the results of the deterministic analysis, presented diagrammatically alongside all the cost-effectiveness estimates produced by case 7. The majority of the points represent dominated options, where greater effectiveness can be achieved at lower cost by an alternative. The most cost-effective option from this analysis is shown to be 'Previous history of preterm birth/Fish oil_all', which is at the bottom right hand corner (low cost/ high effect) of the diagram.

In *Table 63* the results of the probabilistic sensitivity analysis for case 7 are presented. Again only one

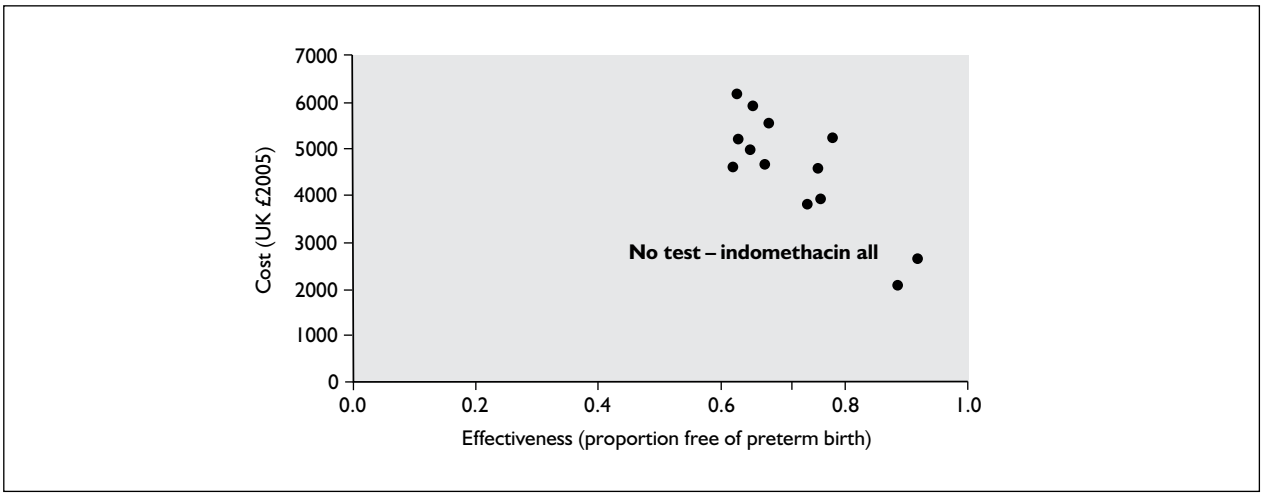


***FIGURE 289*** *Case 5: Symptomatic women – 37 weeks. Results: costs, effects and incremental cost-effectiveness ratios on cost-effectiveness plane for all combinations of test and treatment pairs.*

***TABLE 59*** *Case 5: Symptomatic Women – 37 weeks. Probabilistic sensitivity analysis results. Probability that stated options are the most cost-effective at different levels of willingness to pay for a case of spontaneous preterm birth avoided*

| | Willingness to pay (UK£ 2005/6)[a] | | | | | |
|---|---|---|---|---|---|---|
| **Test/treatment option** | **0** | **10,000** | **30,000** | **50,000** | **80,000** | **100,000** |
| No test/Indomethacin_all | 0.0215 | 0.271 | 0.7538 | 0.8993 | 0.9438 | 0.948 |
| No test/Atosiban_all | 0 | 0 | 0.0031 | 0.0108 | 0.0223 | 0.0266 |
| No test/Terbutaline_all | 0 | 0.0006 | 0.0073 | 0.0132 | 0.0159 | 0.0167 |
| Fetal fibronectin/Atosiban_+ve | 0.0148 | 0.0232 | 0.0244 | 0.0179 | 0.0082 | 0.0047 |
| Fetal fibronectin/Indomethacin_+ve | 0.9415 | 0.6857 | 0.2001 | 0.0537 | 0.008 | 0.0031 |
| Fetal Fibronectin/Terbutaline_+ve | 0.022 | 0.0195 | 0.0113 | 0.0051 | 0.0018 | 0.0009 |

a Per case of spontaneous preterm birth avoided

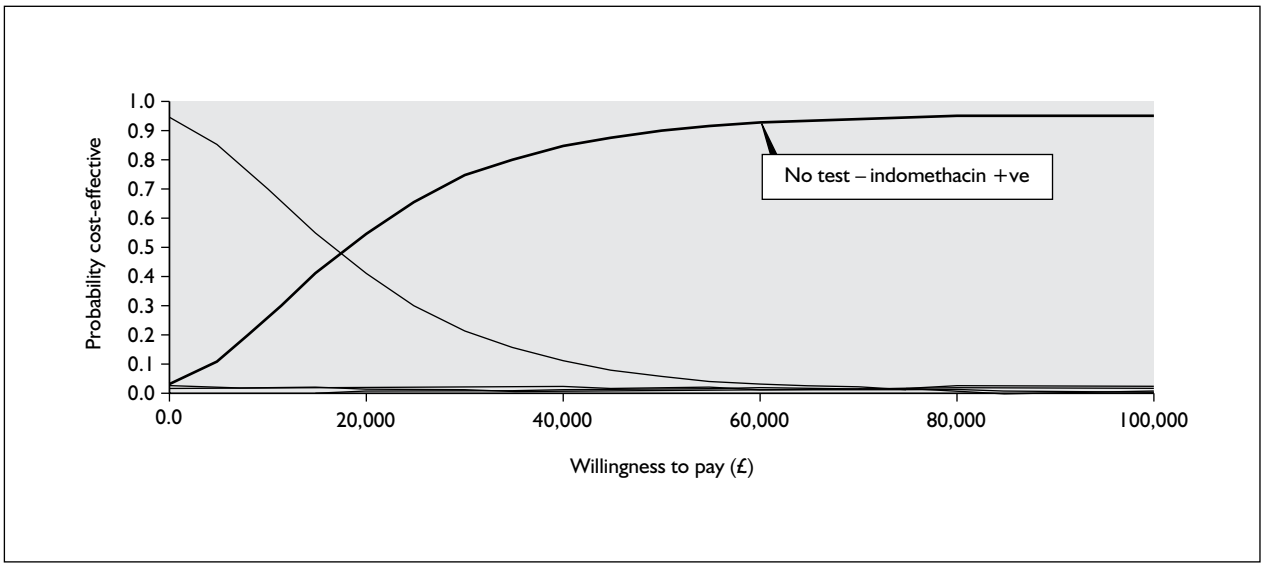


***FIGURE 290*** *Case 5: Symptomatic women – 37 weeks. Cost-effectiveness acceptability curve.*

***TABLE 60*** *Case 6: Symptomatic women. Cost-consequence analysis to estimate most cost-effective intervention for treating symptomatic women who have risk factors for perinatal mortality*

| **Intervention** | **RR (95% CI)** | **Cost (UK£ 2005) (average hospital cost + unit drug costs)** |
|---|---|---|
| Corticosteroids[a] (betamethasone) | 0.63[a] (0.51–0.79) | £1651 (£1644 + £7.32) |
| Vitamin K[b] | 0.79[b] (0.46–1.34) | £1646 (£1644 + £2.00) |
| Indomethacin[c] | 0.80[c] (0.25–2.58) | £1646 (£1644 + £2.01) |

CI, confidence interval; RR, relative risk
a Based on outcome of neonatal mortality.
b Based on outcome of early neonatal mortality.
c Based on outcome of perinatal mortality.



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***Table 61*** *Case 7: Asymptomatic women – 34 weeks. Threshold analysis based on test characteristics to determine which tests should be considered in the model*

| Test | Sensitivity | Specificity | Cost of test | Cost limit[a] | Comment[b] |
|---|---|---|---|---|---|
| Mammary stimulation test | 0.78 | 0.83 | £26.66 | £0 | Not included |
| Serum corticotrophin-releasing hormone | 0.73 | 0.78 | The combined criteria of these tests did not meet the required threshold | | |
| Digital examination | 0.57 | 0.94 | | | |
| Measurement of cervical length – 30 mm (20–24 weeks' gestation) | 0.54 | 0.76 | | | |
| CV-Prolactin | 0.50 | 0.97 | | | |
| Cervical mucus interleukin-8 (360 ng/ml) | 0.44 | 0.80 | | | |
| Previous history of spontaneous preterm birth | 0.38 | 0.92 | £0 | The combined criteria of this test did meet the required threshold. In fact, this test reached the cost limit of £0 and was used in the analysis | |
| Measurement of cervical length – 25 mm (20–24 weeks' gestation) | 0.37 | 0.92 | The combined criteria of these tests did not meet the required threshold | | |
| Relaxin (serum) | 0.34 | 0.79 | | | |
| Fetal fibronectin | 0.33 | 0.97 | | | |
| Measurement of cervical length – 22 mm (20–24 weeks' gestation) | 0.31 | 0.93 | | | |
| Presence of funnelling (16–20 weeks) | 0.30 | 0.94 | | | |
| Measurement of cervical length – 30 mm (14–20 weeks' gestation) | 0.28 | 0.89 | | | |
| Presence of funnelling (20–24 weeks) | 0.25 | 0.95 | | | |
| Measurement of cervical length – 20 mm (20–24 weeks' gestation) | 0.23 | 0.97 | | | |
| Measurement of cervical length – 25 mm (14–20 weeks' gestation) | 0.21 | 0.98 | | | |
| Amniotic fluid interleukin-6 | 0.14 | 0.95 | | | |
| Measurement of cervical length – 15 mm (14–20 weeks' gestation) | 0.11 | 1.00 | | | |
| Measurement of cervical length – 20 mm (14–20 weeks' gestation) | 0.10 | 1.00 | | | |
| Serum $\alpha$-fetoprotein (threshold 2.5 MoM) | 0.06 | 0.99 | | | |
| ***Sensitivity analysis*** | | | | | |
| Hypothetical Test 1[c] | 0.81 [c] | 0.99 | £26.66 | | |
| Hypothetical Test 2[c] | 0.38 [c] | 0.92 | £0 | | |

a For the given test accuracy characteristics the cost of the test is required to be below this limit for the test to be worth considering in the modelling analysis.
b 'Included' refers to the test being considered in the modelling analysis.
c Level of sensitivity needing to be achieved to make hypothetical test/treat positives a possible option in the cost-effectiveness analysis.

***TABLE 62*** *Case 7: Asymptomatic women – 34 weeks. Costs, effects and incremental cost-effectiveness ratios for most cost-effective combinations of test and treatment pairs. Complete analysis: includes the cost of spontaneous preterm birth in the comparator arm of model.*

| Test/treatment combination | Mean cost per woman UK£ 2005 | Difference in costs UK£ 2005 | Effectiveness[a] | Absolute risk reduction | ICER[b] | NNT |
|---|---|---|---|---|---|---|
| Previous history of PTB/Fish oil +ve [c] | £19.00 | | 0.9739 | | | |
| Previous history of PTB/Fish oil All | £25.10 | £6.10 | 0.9879 | 0.0140 | £434 | 71.42 |
| Previous history of PTB/Progestational agents All | £927.00 | £901.90 | 0.9948 | 0.0069 | £130,337 | 145 |
| No test/Progestational agents | £927.00 | £0.00 | 0.9948 | 0.0000 | (Undefined) | |

ICER, incremental cost-effectiveness ratio; NNT, number needed to treat; PTB, preterm birth.
a Effectiveness is defined as the proportion of women avoiding threatened preterm labour. Therefore the difference in effectiveness between two strategies is the absolute risk reduction.
b ICER – incremental cost-effectiveness ratio expressed as the additional cost per additional case of threatened preterm labour avoided.
c This represents the least costly option and is the baseline with which subsequent options are compared, but it is not the most cost-effective option.

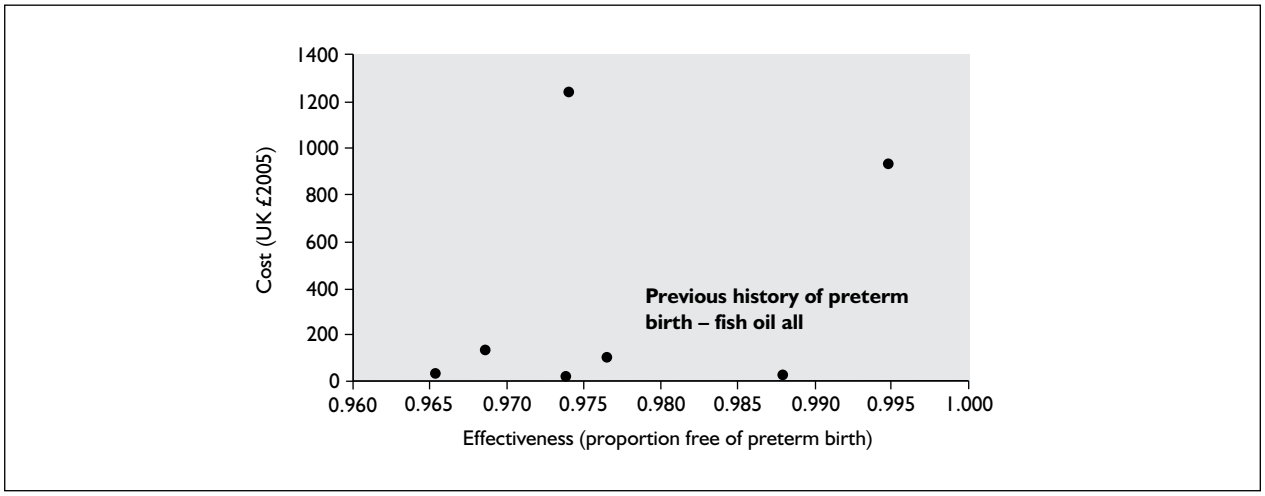


***FIGURE 291*** *Case 7: Asymptomatic Women – 34 weeks. Results: costs, effects and incremental cost-effectiveness ratios on cost-effectiveness plane for all combinations of test and treatment pairs.*

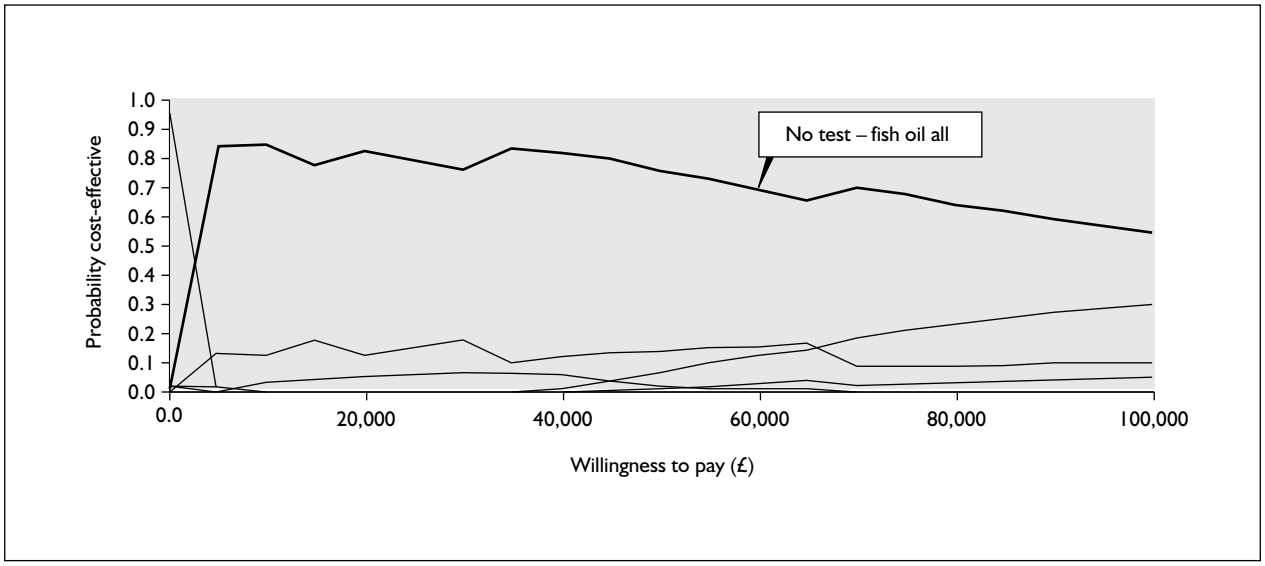


***FIGURE 292*** *Case 7: Asymptomatic women – 34 weeks. Cost-effectiveness acceptability curves.*



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***TABLE 63*** *Case 7: Asymptomatic women – 34 weeks. Probabilistic sensitivity analysis results. Probability that stated options are the most cost-effective at different levels of willingness to pay for a case of spontaneous preterm birth avoided*

| | Willingness to pay (UK £ 2005/6)[a] | | | | | |
|---|---|---|---|---|---|---|
| **Test/treatment option** | **0** | **10,000** | **30,000** | **50,000** | **80,000** | **100,000** |
| No test/no intervention | 0.022 | 0.0025 | 0 | 0 | 0 | 0 |
| No test/Fish oil_all | 0.0009 | 0.8418 | 0.7629 | 0.7639 | 0.648 | 0.5483 |
| No test/Progestational agents_all | 0 | 0 | 0.0001 | 0.0683 | 0.2274 | 0.305 |
| Previous history of PTB/No intervention | 0.0215 | 0.0004 | 0 | 0 | 0 | 0 |
| Previous history of PTB/Progestational agents_+ve | 0 | 0.0294 | 0.063 | 0.021 | 0.0017 | 0.0006 |
| Previous history of PTB/Fish oil_+ve | 0.9551 | 0.0017 | 0 | 0 | 0 | 0 |
| Previous history of PTB/Progestational agents_All | 0 | 0 | 0 | 0.0117 | 0.0302 | 0.0505 |
| Previous history of PTB/Fish oil_All | 0.0005 | 0.1242 | 0.174 | 0.1351 | 0.0927 | 0.0956 |

PTB, preterm birth.
a Per case of preterm labour symptoms avoided.

test was included in the PSA with all the relevant interventions for which the 95% CI for the relative risk was < 1. Contrary to the results of the deterministic model the results show that 'No test/ Fish oil_all' is the dominant option at all values of willingness to pay above £10,000.

The results are presented diagrammatically in Figure 292.

### *Case 8 – Asymptomatic women at 37 weeks*

The range of possible tests identified in the literature as possible for detecting risk factors for spontaneous preterm birth in asymptomatic women at 37 weeks are presented in *Table 64*.

However, the results presented in the table show that the test which ascertains a woman's previous history of spontaneous preterm birth, was again the only test that met the necessary criteria for inclusion in the model despite having a very low sensitivity of only 0.42. The sensitivity of the 'previous history' test was also adjusted to see how low the sensitivity could be to be included in the model given that the cost was zero. The results showed that the sensitivity in this model could fall as low as 0.20 and it would still be worth including it in the deterministic model.

*Table 65* presents the results of the deterministic model where only the previous history test is included. The estimated full cost of becoming symptomatic, which was estimated by the symptomatic model for 48 h to be approximately £669, is the cost in the comparator arm of the model. The results show that the strategy of providing 'Previous history of preterm birth/ Antibiotics for asymptomatic bacteriuria_all' and 'No test/Antibiotics for asymptomatic bacteriuria_ all' are jointly of equal cost and effectiveness. In *Table 66* the results of the probabilistic sensitivity analysis for case 8 are presented. Again, only the previous history test was combined with all the interventions for which the 95% CI for the relative risk was < 1. The results of the PSA show that 'No test/Antibiotics for asymptomatic bacteriuria_all' is the dominant option at all values of willingness to pay, having a probability of 52% of being the preferred option at the £30,000 threshold. The analysis shows that the next preferred option is 'No test/Periodontal therapy_all', which has a probability of 28% of being the preferred option at the willingness to pay threshold of £30,000.

The results are presented diagrammatically in *Figure 293*.

### *Case 9 – Asymptomatic women – perinatal mortality*

From the accuracy reviews there were no data available for tests that detect risk factors for perinatal mortality. Data were available only from the effectiveness reviews for interventions. As in Case 6, the data were again analysed using a cost–consequence approach in the first instance. The interventions were first ranked according to their effectiveness. If the most effective strategy

***TABLE 64*** *Case 8: Asymptomatic women – 37 weeks. Threshold analysis based on test characteristics to determine which tests should be considered in the model*

| Test | Sensitivity | Specificity | Cost of test | Cost limit[a] | Comment[b] |
|---|---|---|---|---|---|
| Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) | 0.83 | 0.80 | £11.50 | £0 | Not included |
| CV-Prolactin | 0.83 | 0.74 | | The combined criteria of these tests did not meet the required threshold | |
| Measurement of cervical length (32.5 mm) (20–24 weeks' gestation) | 0.73 | 0.82 | | | |
| Relaxin (serum) | 0.67 | 0.45 | | | |
| Mammary stimulation test | 0.60 | 0.82 | | | |
| Salivary estriol (threshold 2.1 ng/ml – single) | 0.56 | 0.78 | | | |
| Cervicovaginal interleukin-6 (serial testing) | 0.50 | 0.85 | | | |
| Digital examination | 0.49 | 0.58 | | | |
| Salivary estriol (threshold 2.1 ng/ml – repeat) | 0.44 | 0.92 | | | |
| Previous history of spontaneous preterm birth | 0.42 | 0.82 | £0 | The combined criteria of this test did meet the required threshold. In fact, this test reached the cost limit of £0 and was used in the analysis | |
| C-reactive protein | 0.37 | 0.82 | | The combined criteria of these tests did not meet the required threshold | |
| Periodontal evaluation | 0.32 | 0.86 | | | |
| Serum corticotrophin-releasing hormone | 0.29 | 0.80 | | | |
| Cervical mucus interleukin-8 (360 ng/ml) | 0.27 | 0.80 | | | |
| Detection of bacterial vaginosis Nugent's (single) | 0.24 | 0.87 | | | |
| Detection of bacterial vaginosis Nugent's (serial) | 0.19 | 0.86 | | | |
| Detection of bacterial vaginosis Amsel's (single) | 0.18 | 0.80 | | | |
| Serum estriol (threshold ≤ 0.75 MoM) | 0.11 | 0.90 | | | |
| Serum α-fetoprotein (threshold 2.0 MoM) | 0.10 | 0.94 | | | |
| Amniotic fluid interleukin-6 | 0.10 | 0.95 | | | |
| Cervicovaginal interleukin-6 (single testing) | 0.09 | 0.84 | | | |
| Fetal fibronectin | 0.06 | 1.00 | | | |
| Midstream urine culture | 0.06 | 0.98 | | | |
| Serum estriol (threshold ≤ 0.5 MoM) | 0.05 | 0.93 | | | |
| Maternal serum β-human chorionic gonadotrophin | 0.02 | 0.99 | | | |
| Serum α-fetoprotein (threshold 2.5 MoM) | 0.02 | 0.99 | | | |
| ***Sensitivity analysis*** | | | | | |
| Hypothetical test 1[c] | 0.99 [c] | 0.99 | £11.50 | | |
| Hypothetical test 2[c] | 0.20 [c] | 0.82 | £0 | | |

a For the given test accuracy characteristics the cost of the test is required to be below this limit for the test to be worth considering in the modelling analysis.
b 'Included' refers to the test being considered in the modelling analysis.
c Level of sensitivity needing to be achieved to make hypothetical test/treat positives a possible option in the cost-effectiveness analysis.



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***Table 65*** *Case 8: Asymptomatic women – 37 weeks. Costs, effects and incremental cost-effectiveness ratios for most cost-effective combinations of test and treatment pairs. Complete analysis: includes the cost of becoming 'symptomatic' in the comparator arm of model.*

| Test/treatment combination | Mean cost per woman (UK£ 2005) | Difference in costs (UK£ 2005) | Effectiveness[a] | Absolute risk reduction | ICER[b] | NNT |
|---|---|---|---|---|---|---|
| Previous history of preterm birth/ Asymptomatic bacteriuria_all | £22.00 | | 0.972 | | £23 | – |
| No test/Asymptomatic bacteriuria_all | £22.00 | £0.00 | 0.972 | 0.000 | £23 | – |

ICER, incremental cost-effectiveness ratio; NNT, number needed to treat' PTB, preterm birth.
a Effectiveness is defined as the proportion of women avoiding symptoms of preterm labour.

***TABLE 66*** *Case 8: Asymptomatic women-37 weeks) Probabilistic sensitivity analysis results. Probability that the stated options are the most cost-effective option at different levels of willingness to pay for a case of spontaneous preterm birth avoided*

| | Willingness to pay (UK£ 2005/6)[a] | | | | | |
|---|---|---|---|---|---|---|
| **Test/treatment option** | **0** | **10,000** | **30,000** | **50,000** | **80,000** | **100,000** |
| No test/Asymptomatic bacteriuria_all | 0.6287 | 0.6074 | 0.5191 | 0.528 | 0.5379 | 0.5207 |
| No test/Periodontal therapy_all | 0.0007 | 0.2494 | 0.2838 | 0.3037 | 0.3225 | 0.3104 |
| No test/Fish oil_all | 0.0012 | 0.0004 | 0.0003 | 0.0003 | 0.0002 | 0.0001 |
| No test/Nutritional advice_all | 0.0467 | 0.018 | 0.0143 | 0.0145 | 0.0144 | 0.0144 |
| Previous history of PTB/ Asymptomatic bacteriuria_all | 0.2979 | 0.0882 | 0.1166 | 0.0945 | 0.0773 | 0.0927 |
| Previous history of PTB/Periodontal therapy_all | 0 | 0.0341 | 0.063 | 0.0564 | 0.045 | 0.059 |
| Previous history of PTB/Nutritional advice_all | 0.0243 | 0.0022 | 0.0022 | 0.0016 | 0.0016 | 0.0015 |

PTB, preterm birth.
a Per case of symptoms avoided.

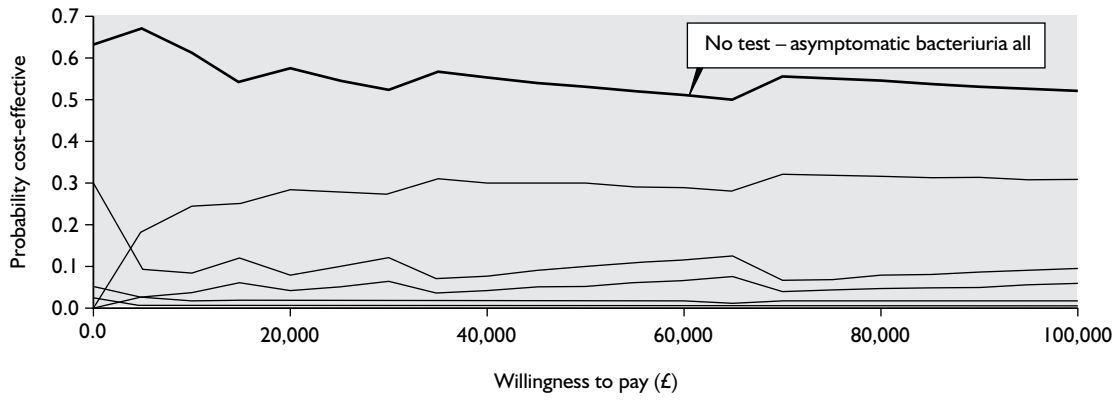


***FIGURE 293*** *Case 8: Asymptomatic women – 37 weeks. Cost-effectiveness acceptability curve.*

***TABLE 67*** *Cost–consequence analysis to estimate most cost-effective intervention for treating asymptomatic women who have risk factors for perinatal mortality*

| Intervention | RR (95% CI) | Cost (UK £ 2005) |
|---|---|---|
| Nutritional advice | 0.37 (0.07–1.90) | £0[a] |
| Vitamin C | 0.51 (0.05–5.54) | £1.08[a] |
| Antibiotics (intra-amniotic infections) | 0.53 (0.13–2.18) | £12.93 |
| Progestational agents | 0.55 (0.29–1.06) | £923.55 |
| Energy/protein supplementation | 0.55 (0.31–0.97) | £1.32[a,b] |
| Cervical cerclage | 0.66 (0.66–1.37) | £1,219 |

CI, confidence interval; RR, relative risk.
a Represents the cheapest and most effective options.
b Likely to be the most cost-effective strategy because it is both relatively cheap and effective and is the only intervention which has upper 95% CI that do not exceed 1.0.

was also the least costly strategy, then it would be the dominant strategy and no further economic analysis or model would be required.

The results of the cost–consequence analysis for Case 9, are presented in *Table 67*. The most cost-effective intervention for treating asymptomatic women who are at risk of perinatal mortality, based on this cost–consequence analysis, is nutritional advice, which is assumed to cost zero because it could be given in a routine antenatal session. If we assumed that the cost of nutritional advice is likely to be supported by a dietician then the cost would probably in practice be greater than the next most cost-effective intervention presented in *Table 67*, vitamin C. However, both interventions of vitamin C and nutritional advice have 95% CI which include 1 and therefore suggest that the possibility that harm may be associated with these interventions has not been completely excluded. However, energy/protein supplementation is cheap, effective and has 95% CI for RR that do not include 1 so, on balance, it probably represents the most cost-effective strategy.

# Discussion

## Summary of economic evaluation findings

The economic evaluation highlights a number of issues. Some of the results have pointed to areas where further research is required because they either contradict the perceived wisdom in current practice or present suggestions for interventions which have to date not been implemented at all in clinical practice. The results of the economic evaluation should not be considered in isolation and need to be considered alongside the clinical evidence and the potential weaknesses in the clinical evidence which result from either small numbers of trial participants or heterogeneity in the study populations of the dominating trials.

In the model, although the results of the deterministic analysis are noteworthy and highlight areas where further analysis may be of benefit, most confidence and weight should be given to the results of the PSA for which the full range of uncertainty in the estimates is incorporated. Furthermore, while the tests were initially subjected to analysis to ascertain tests that are of sufficient accuracy to be worth entering into the model, this was primarily performed to avoid laborious inclusion of additional redundant branches. However, for the interventions, only those for which the relative risk was < 1 were included in the PSA, also supporting greater confidence in the effectiveness of these interventions.

### *Cost of test/interventions/preterm birth*

The key results, not already highlighted in preceding parts of the project, emerging from the health economic and modelling evaluations, were as follows. The cost of the tests for both asymptomatic and symptomatic women varied. Many were modest, particularly venous blood tests like serum IL-6, serum β-human chorionic gonadotrophin, serum estriol and serum CRP. However, they could also be substantial, in excess of £200 for tests involving amniocentesis and uterine activity monitoring.



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There was also important variation in the cost of the interventions. For asymptomatic women they ranged from £1.08 for vitamin C to £14.50 for antibiotics for treating intra-amniotic infections to £140 for home visits to £1219 for cervical cerclage. The cost of all interventions for symptomatic women was significantly higher because of the inclusion of the costs of hospitalisation, estimated to be £1644. The variation in add-on costs of the interventions led to a range of total costs from £1645 for metronidazole to £2555 for atosiban (37 weeks' gestation models).

The best estimate of additional average cost associated with a case of spontaneous preterm birth is high at approximately £15,688 for up to 34 weeks' gestation and £12,104 for up to 37 weeks' gestation.

**Asymptomatic women**
The results of the economic model for prevention of threatened preterm labour in asymptomatic women (cases 7 and 8), particularly before 34 weeks, are of especial policy relevance because it is the women who give birth without any previous symptoms or warning that are of most concern and for whom the economic burden is likely to be greatest in terms of the knock-on effects associated with premature and low-birthweight infants.

The most cost-effective options with respect to prevention of threatened preterm birth for asymptomatic women up to 34 weeks' gestation were 'No test/Fish oil_all' or 'No test/Progestational agents_all' or 'Previous history of preterm birth/ Fish oil_all', and up to 37 weeks' gestation were 'No test/Antibiotics for asymptomatic bacteruria_all' and 'No test/Periodontal therapy_all'. In 'Previous history of preterm birth/Fish oil_all', 14 cases of threatened preterm labour are averted for every 1000 mothers treated, at a mean additional cost per mother of approximately £6 relative to the least cost option of 'Previous history of preterm birth/Fish oil_positive' – ICER £434 per additional case of threatened preterm labour avoided.

In the asymptomatic scenarios, when the focus was prevention of perinatal death, energy and protein supplementation was arguably the most cost-effective option, although the cost–consequence analysis suggested that nutritional advice and vitamin C might also be considered from an economic perspective.

Generally stated, in the asymptomatic scenarios it appears that all the tests considered in the economic model were insufficiently accurate relative to their cost to make prior testing preferable from an economic perspective. Only when the cost of the test was assumed to be virtually zero (positive history of preterm birth) did a test feature in a potentially cost-effective test/treatment pairing. The mammary stimulation test had the highest sensitivity and specificity and although it did not feature as a recommended test in the results of this model, it may be worthy of further investigation.

**Asymptomatic women – interventions**
In the absence of any observed influence of testing strategy, cost-effectiveness in the asymptomatic scenarios was determined by the effectiveness relative to the cost of the interventions in isolation. The RR and cost of:

- fish oil treatment at 34 weeks were 0.35 (95% CI 0.13–0.92; RR of preterm birth) and £16.99, respectively
- antibiotic therapy for asymptomatic bacteruria at 37 weeks were 0.14 (95% CI 0.04–0.52; RR of preterm birth) and £3.29, respectively
- energy protein supplementation were 0.55 (95% CI 0.31–0.97; RR of perinatal mortality) and £1.32, respectively
- periodontal therapy at 37 weeks were 0.19 (95% CI 0.04–0.85; RR of preterm birth) and £81.50, respectively
- progestational agents at 34 weeks were 0.15 (95% CI 0.04–0.64; RR of preterm birth) and £923.55, respectively (the RR at 37 weeks was 0.6; 95% CI 0.49–0.73).

**Symptomatic women**
In the symptomatic scenarios (cases 1 to 6) the most cost-effective options were:

- delaying delivery beyond 24 h (case 1): insufficient data to model so no most cost-effective option identified
- delaying delivery beyond 48 h (case 2): 'Cervical length measurement < 15 mm/ Indomethacin_positive'; eight additional cases of PTB are avoided for every 1000 mothers treated at an additional cost of £42 relative to the least cost option of 'Absence of fetal breathing movements/Indomethacin_positive'
- delaying delivery beyond 7 days (case 3): 'Cervical length measurement < 15 mm/ Indomethacin_positive'; 18 additional cases of PTB are avoided for every 1000 mothers treated at an additional cost of £42 relative to the least cost option of 'C-reactive protein/ Indomethacin_positive'

- avoiding preterm birth at 34 weeks' gestation (case 4): 'Amniotic fluid interleukin-6/Hydration_positive'; nine additional cases of preterm birth are avoided for every 1000 mothers treated at an additional cost of £43 relative to the least costly option of 'Phosphorylated insulin-like growth factor binding protein-1/Hydration_positive'
- avoiding preterm birth at 37 weeks (case 5): 'No test/Indomethacin_all'; three additional cases of preterm birth are avoided for every 1000 mothers treated at an additional cost of £560 relative to the least cost option of 'Fetal fibronection/Indomethacin_positive'
- perinatal death (case 6): cost–consequences analysis suggested corticosteroids were the most cost-effective option.

The recommended agents by RCOG for treatment consideration in women presenting with threatened preterm labour, atosiban and nifedipine, are cost-dominated by indomethacin (but see below in Provisos/limitations arising from economic evaluation methods section).

There is incomplete consistency between the findings of the different symptomatic scenarios. However, this is in part the result of data not being available for all tests and treatments for all the cases examined. For instance there was no effectiveness data on indomethacin for the reduction in preterm birth at 34 weeks, perhaps explaining why this treatment did not feature in the most cost-effective pairing in this case.

**Symptomatic women – tests**

Despite this, an important general feature in contrast to the asymptomatic scenarios, is that prior testing does appear to make a useful contribution with respect to maximising cost-effectiveness, particularly where better test accuracy was achieved. The LR+, LR– and cost of some of the tests featuring in cost-effective pairings were, respectively:

- cervical length < 15 mm (48 h): 6.43 (95% CI 5.17–8); 0.027 (95% CI 0.0017–0.42); £69.47
- cervical length < 15 mm (7 days): 8.61 (95% CI 6.65–11.14); 0.026 (95% CI 0.004–0.182); £69.47
- amniotic fluid interleukin-6 (34 weeks): 7.44 (95% CI 2.01–27.52); 0.14 (95% CI 0.056–0.36); £216.70.

Unfortunately test accuracy of all tests was too poor to make an impact where the focus was reducing spontaneous preterm birth at 37 weeks. No data on test accuracy were available where the focus was on reduction in perinatal deaths.

In addition to the most cost-effective options highlighted, the following results are worth noting because of clinical interest in the interventions in question.

*Calcium channel blocker*

It is noteworthy that the use of calcium channel blockers, a current recommendation of the RCOG, which were included in the deterministic analysis for the 48-hour, 7-day, 34-week and 37-week symptomatic models, was dominated in all models by other treatments and so was not shown to be a cost-effective intervention in any model. The data were of sufficient quality to be included in the PSA for the 7-day model only and in this case it was dominated by treatment with indomethacin. Furthermore, there were no trials identified in the review that compared calcium channel blockers directly with a placebo and so an indirect comparison was used.

*Cervical cerclage*

This is an acceptable treatment in UK practice which is offered to prevent preterm labour. The intervention was included in both asymptomatic deterministic models for 34 and 37 weeks' gestation and was included in the PSA for the 34-week asymptomatic model. In the 34-week asymptomatic model, treatment with fish oil dominated treatment with cerclage. This dominance is clear because cerclage was estimated to cost £1219 compared to a cost of fish oils of £16.99. The corresponding RRs for the cerclage and fish oils were 0.75 (95% CI 0.58–0.98) and 0.35 (95% CI 0.13–0.92), respectively. This result re-iterates the importance of pursuing further research on the potential benefits of fish oil, which based on current available evidence appears to be an effective and relatively cheap intervention.

*Testing for bacterial vaginosis*

This was not included on any of the asymptomatic models because it did not meet the required threshold criteria. This strategy was dominated by other test/treatment options because of the low accuracy of the test for BV.

The economic model showed that the costs applied to the tests and treatments were largely superfluous to the overall results. Key drivers in the analyses included the poor sensitivities and specificities of some of the tests, which meant that in some cases (Symptomatic women 37 weeks: No test/Indomethacin_all; Asymptomatic women



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34 weeks: Previous history of preterm birth/Fish oil_all; Asymptomatic women 37 weeks: No test/Asymptomatic bacteriuria_all) testing would not be recommended as 'worthwhile' options for 'Test/Treat_positive' strategies. For the treatments the key driver in the results was their relative risk, which led to the treatment with the lowest RR being recommended. The cost of spontaneous preterm birth used in the analysis was high, at approximately £15,689. The combination of poor test accuracy and relatively cheap effective interventions led to a 'No test/Treat_all' strategy dominating the results because spontaneous preterm birth is a serious and costly condition.

## Provisos/limitations arising from economic evaluation methods

The use of an economic model fed by data on accuracy of tests and effectiveness of the interventions from the most recently available systematic reviews and meta-analyses of the evidence is a major strength of the project reported. Similarly, the model was developed by an experienced health economic and modelling team with clinical and methodological input at all stages, from the original design of the model, through its execution, to the final interpretation of its results. It has important features such as probabilistic sensitivity analysis, which helps to deal with the ever-present challenges arising from uncertainty.

However, particularly given the accelerated time-scale of the work, the complexity of the problem and the fact that there were few previous health economic models on which to build (see Systematic review of economics and costs studies at the beginning of this chapter), it is inevitable that there are limitations as follows:

### *Single test results*

The model considers only single test results; combinations of tests or combinations of treatments may offer opportunities that are more cost-effective and these could not have been incorporated into the model as conceived unless data were available for combined tests or treatments (which they were not).

### *Spontaneous preterm birth outcome*

The existing model primarily focuses on the outcome spontaneous preterm birth. Although there is some consideration of perinatal mortality too, the impact of test/treatment combinations on other outcomes, particularly their effects on infants that do not result in death, will be overlooked. This is especially problematic if the effect on these other outcomes counteracts or offsets the benefit implied by the reduction in preterm birth. Indomethacin, a treatment that features in a number of potentially cost-effective pairings, is a possible example where reduction in spontaneous preterm birth may be offset by effects on infant circulation (persistent patent ductus arteriosus). However, it is also possible that the current model generally underestimates the effect of test/treatment combinations because benefits attributable to reduction in outcomes like infant morbidity and disability are not fully accounted for.

### *Side effects*

Similarly, the existing model assumes that side effects of tests and treatments are negligible. This seems a reasonable assumption for many of the tests and interventions, but may be definitely open to challenge for invasive tests involving amniocentesis (which carries the risk of rupturing the amniotic membrane and chorioamnionitis) and some pharmacological interventions like tocolytic agents. This may be particularly important in the asymptomatic scenarios where the universal use of interventions without prior testing is being speculated on, such as treatment of asymptomatic bacteriuria. If these are pursued, confirmation of absence of adverse events, particularly for the baby, will require detailed investigation. It should also be noted that not incorporating adverse events into the model would accentuate the apparent superiority of 'No test/Treat_all' strategies. If there were associated adverse events there would be added value from avoiding false positives, such as would be achieved by a predictive test for preterm birth with high specificity; something that is not captured in the current model.

### *Clinical relevance of test/treatment pairings*

Finally, care is required for the interpretation of some of the combinations of test/treatment pairs generated by the model. Antibiotics for asymptomatic bacteriuria provide an example in that a prior test, for bacteriuria, is implied as part of the 'intervention'. Thus test/treatment pairings are created in the modelling process without regard to clinical relevance, which must be carefully checked when results are interpreted.

### *Perspective of the economic analysis*

The restriction of the economic model to an NHS perspective could also be considered a potential limitation, given that there are likely to be obvious costs to patient, family and society beyond the

health-care sector. The main counterargument is that because most assessments of cost-effectiveness are performed from the perspective of the health-care payer, designing the economic model from the NHS perspective remains most relevant to facilitate comparison with other uses of health-care resources. Ideally cost-effectiveness taking into account societal and individual costs is worth exploring; however, experience suggests that data to do this accurately are rarely routinely available and would require primary data collection, which was outside the original agreed protocol. It must be acknowledged that limiting the analysis to the NHS perspective may particularly lead to underestimation of certain costs, such as advice to rest or diet change where the onus is placed on the individual, their family and society to achieve implementation. However, in the absence of versions of the model from an individual and societal perspective, such considerations can only be incorporated into the conclusions qualitatively.

## Provisos/limitations arising from problems with primary data

Despite features of the model like PSA, which help deal with limitations arising from the primary data, uncertainty about what the true accuracy, effectiveness or cost parameters are for particular tests and interventions remains a major challenge in this economic model. These limitations are discussed in more detail below and represent challenges and restrictions to conclusions that can be drawn concerning cost-effectiveness.

### *Stochastic variation in the model parameters*

There is marked stochastic variation in many of the parameters, manifest in wide 95% CI. The effect of this on conclusions of the economic modelling is largely taken into account through PSA. However, the implications of the 95% CI still need to be considered, particularly where the 95% CI include values of RR > 1.0, implying that the intervention causing increased numbers of cases of spontaneous preterm birth remains a possibility based on the available data. This was the rationale for separating Group 1 interventions, where 'harm' was unlikely to be a possibility, from Group 2 interventions, where it was.

### *Uncertainty from systematic variation*

In addition to chance, there is uncertainty arising from systematic variation, including operation of bias. Provisos sometimes need to be added concerning the fact that there may be threats to validity. Parameters based on single, small studies with very small numbers of outcomes raise not just concerns about the effect of chance (reflected in the 95% CI) but susceptibility to other related bias too.

### *Uncertainty from heterogenicity between studies*

There is sometimes further uncertainty arising where estimates of accuracy or effectiveness are based on several primary studies and there is heterogeneity between the results (more variation than can be accounted for by chance alone). If the cause of this heterogeneity cannot be isolated, there may be concern about use of a summary measure from a meta-analysis. This is a theoretically important issue for many estimates of test accuracy, but effectiveness estimates based on several of the included RCTs may also be affected.

### *Data from indirect comparisons*

Some of the estimates of effectiveness were derived from indirect comparison, e.g. atosiban. Although a useful method of deriving an estimate of effect when there is no direct comparison, in this case with placebo, caution does need to be observed as comparisons are potentially confounded despite the data being RCT based.

### *Uncertainty in cost estimates*

There is general uncertainty about the cost estimates used for many tests and some interventions too. The routinely available information is limited, particularly accurate and specific costs for any particular test, thus removing the differentiation between these tests in the analysis. Ideally, further primary data collection of costs would have been pursued if it had been predicted to be so important when the project was first designed and the protocol devised. The relative cost of available tests to treatments is critical to the current health economic conclusions, as is the effect of test cost on the level of test accuracy needing to be demonstrated by a test for it to have a chance of a 'Test/Treat_positive' option becoming the preferred approach with respect to its cost-effectiveness. A particular concern is the NHS costs associated with non-pharmacological interventions like dietary advice. Independent of concerns already discussed about incorporating costs to individuals and society, is the possibility that if implemented, hospital facilities might have to be used in ways not originally envisaged, such as support from dieticians.

Unfortunately, one or other of these sources of uncertainty alone or in combination affects many



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of the test/treatment pairings emerging as being most cost-effective in each of the scenarios. The following are specific limitations from particular reviews:

- Estimates of the effectiveness of fish oils are based on two studies involving around 250 women.
- For antibiotic treatment of asymptomatic bacteriuria the quality of trials was poor and the RR for the effect on preterm birth is based on just one trial of questionable quality including only 69 participants.
- Estimates of the effect of energy/protein supplementation on perinatal mortality are based on four trials of which only one is considered to be of adequate quality. In addition, one of the trials included looks at rural Gambian women with chronically marginal nutrition, and another looked at women in a Bogota slum, so their relevance to women in the UK might be questioned. Assumptions about the low cost of this intervention (£1.32) might also be open to challenge.
- For nutritional advice, the parameter in the model was based on two studies of questionable quality one of which was very small ($n = 20$) and the other, of 429 participants, was based in a rural population in Greece, many of whom had nutritional problems. Their generalisability to the UK is again questionable. Furthermore, the assumed near-zero costs to the NHS may be open to challenge because it is likely that advice/support would be required to achieve the desired dietary changes.
- For the test of cervical length < 15 mm in threatened preterm labour, *Figures 67* and *68* indicate that there is heterogeneity in the LR+ and LR– estimates among the included studies that is not completely captured by using the estimates and their 95% CI from the best quality included study.
- The effectiveness estimate for indomethacin is based on two small RCTs involving 70 subjects in all. Furthermore, as already indicated, indomethacin has effects on the infant that may counteract the beneficial effect of reduced spontaneous preterm birth.
- The estimates of test accuracy for amniotic fluid interleukin-6 predicting spontaneous preterm birth at 34 weeks are based on one study.
- The effectiveness parameters for the effect of hydration are based on only two small trials of 228 women in total.
- The evidence for periodontal therapy was provided by one quasi-RCT ($n = 351$).

## Provisos/limitations arising from omissions

There was absence or effective absence of information on certain key parameters. There may be new or established tests or interventions that have not yet been fully evaluated. Periodontal assessment is an intervention that falls into this category. In addition to this there may well be tests and treatments in development that do not appear in the literature at all, of which we would be unaware. Finally, some systematic reviews results or updates thereof, arrived after the modelling had been completed: β-human chorionic gonadotrophin testing and treatment of bacterial vaginosis. However, the RR for treatment for bacterial vaginosis was greater than 1 and so this would be extremely unlikely to lead to changes in the main findings.

## Findings in the light of limitations

The observed limitations do impinge on the initially stated main findings of the economic evaluation, particularly the confidence that can be placed on the specific tests and interventions emerging as potentially preferred from a cost-effectiveness perspective. However, the general findings probably remain unaffected.

In the asymptomatic scenarios, it seems likely that existing tests are not of sufficient accuracy relative to their cost, to improve the cost-effectiveness of strategies to reduce spontaneous preterm birth through use in all mothers of effective, low-cost interventions with low likelihood of side effects. The systematic reviews of effectiveness suggest what these might be, but confirmation of effectiveness is required for most of the front-runners, and in all cases greater scrutiny and evaluation of possible side effects would be essential. New tests may emerge that challenge the above conclusion, but the economic modelling indicates that the accuracy must be much higher than currently achieved, and any new tests must be of modest cost, less than the costs of the interventions being employed.

In the symptomatic scenarios the general possibility that prior testing may enhance the cost-effectiveness of strategies to delay delivery in threatened preterm labour again seems robust, although the specific test/treatment pairings that might achieve this definitely require further evaluation. Debatably, there

may be sufficient grounds to directly evaluate the overall effectiveness and cost-effectiveness of implementing systematic use of specific test/treatment pairs – say Cervical length < 15 mm/Indomethacin_positive versus cervical length < 15 mm/Calcium channel blockers_positive versus β-human chorionic gonadotrophin/Indomethacin_positive versus β-human chorionic gonadotrophin/Calcium channel blockers_positive. However, probably, better estimates of key effectiveness and test accuracy parameters are required before proceeding to this.

As indicated at the beginning of the section, there have been some previous economic evaluations with which we can compare our findings. However, we should highlight that we believe this project to be the only economic evaluation to have attempted to assess cost-effectiveness across the complete range of test and treatment combinations which might possibly be employed, rather than focusing on specific test/treatment pairings. Direct comparison of our findings with other economic evaluations is thus impeded. However, with this caution, and noting that we assessed all but one of the past economic evaluations to be open to bias:

- Our evaluation supports previous conclusions about lack of evidence that screening for and treatment of bacterial vaginosis is likely to be a cost-effective strategy. The systematically reviewed data on both test accuracy and effectiveness are not convincing.
- Suggestions that fetal fibronectin test or cervical length measurement may be useful are supported, more so for cervical length measurement. This is, however, only in the context of delaying delivery in symptomatic mothers and with the proviso that better test accuracy data are probably still required.
- Terbutaline was found to be a potentially cost-effective intervention in past evaluations, albeit in three studies with concerns about study quality. This evaluation, however, provided no direct support for the superiority of terbutaline relative to other tocolytic agents.

## Recommendations for practice

The findings of the current health economic evaluation are insufficient on their own to dictate changes in practice. Further research to clarify key aspects of test accuracy, effectiveness, cost and cost-effectiveness should be the priority.

## Recommendations for research

Improving estimates of effectiveness for the interventions appearing in the potentially cost-effective test/treatment pairings would appear to be the most important way of improving estimates of cost-effectiveness, particularly for:

- fish oils
- other dietary interventions, including nutritional advice
- treatment of asymptomatic bacteriuria
- indomethacin
- hydration
- periodontal therapy.

Improved test accuracy data should also be pursued on tests such as cervical length, amniotic interleukin-6 and the mammary stimulation test. As well as new evaluations, individual data meta-analysis of existing test accuracy studies may be an approach to better understand the heterogeneity between test accuracy study estimates. Detailed examination and improved cost estimates of all tests and treatments considered in this model are also essential.

There may also be value in further developing the existing economic model to consider simultaneously maternal and child outcomes associated with spontaneous preterm birth and to capture the impact of side effects where data on these were available. More ambitiously, the model could attempt to predict the effect of interventions on all the major inter-related threats to child and maternal health, spontaneous preterm birth, intrauterine growth retardation and pre-eclampsia. A number of tests and treatments are claimed to have predictive power and effectiveness in all these entities. The complexity of such a model would be great, particularly if it attempted to explore whether combinations of tests or combinations of treatments might be more cost-effective. However, given the importance of potential research recommendations stated, any priority assignment would be relative. Rigorous evaluation of tests with modest cost and minimal invasiveness, whose initial assessments suggest that they may have high levels of accuracy (e.g. phIGFBP-1, but there may be others), and undertaking RCTs evaluating effective interventions with modest cost would represent priorities that are familiar to clinicians.



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# Chapter 7
# Report conclusions

## Introduction

This project was undertaken to identify combinations of tests and treatments that would lead to reduction in spontaneous preterm birth, a major contributor to perinatal and neonatal morbidity and mortality. This health technology assessment completed three distinct pieces of work to contribute to this goal:

- a series of systematic reviews of test accuracy of the prediction of spontaneous preterm birth
- a series of systematic reviews of effectiveness of interventions with potential to reduce cases of spontaneous preterm birth and its complications
- a health economic evaluation, including an economic model, of the combined effect of tests and treatments on spontaneous preterm birth.

Each of these has been described in detail, their main findings reported and the conclusions discussed in the light of any limitations identified at the end of each of the three preceding chapters. This chapter attempts to focus on the key findings and limitations emerging from all the work undertaken. It is not a comprehensive summary of all the issues raised, for which the reader is encouraged to consult the previous three chapters.

## Main findings

The methodological quality of the literature reviewed for both accuracy and effectiveness was generally poor, with few exceptions (e.g. fetal fibronectin testing, cervical length measurement, fetal breathing movements, interleukin-6 (IL-6), non-steroidal anti-inflammatory agents and oxytocin antagonists).

- The accuracy of most of the tests purported to be of value in prediction of spontaneous preterm birth was disappointing. Likelihood ratios as a measure of the tests' ability to predict all mothers who will develop preterm birth spontaneously were particularly poor.
- The effectiveness of several interventions that might reduce the number of cases of spontaneous preterm birth or its complications was, in contrast, more promising. As well as well-known interventions like tocolysis for delaying birth and antenatal corticosteroids for lung maturity, the review has also focused attention on other interventions like bed rest, progesterone, fish oil, periodontal therapy, vitamin supplementation and antibiotic treatments.
- By the standard of many health-care interventions, those indicated to be potentially useful in avoiding spontaneous preterm birth were noted to be affordable (costs generally less than £1650 for the whole of pregnancy even in the most expensive case of having to use an oxytocin antagonist, often substantially so).
- From the perspective of cost-effectiveness among asymptomatic women in early pregnancy and based on the current proviso of the limited evidence, providing effective treatment, e.g. periodontal care, fish oil, progesterone etc. without prior testing is likely to be preferred to using a test followed by treating those who are positive. The provisos are that the true costs remain modest, that any effect on spontaneous preterm birth is not offset by contrary effects on important infant outcomes and that there are no serious adverse events associated with widespread use of the interventions in low-risk mothers. For women symptomatic of threatened preterm labour, prior testing before institution of therapy is likely to be more cost-effective, e.g. with ultrasound measurement of cervical length (15 mm) followed by indomethacin for those with shortened cervix.

## Strengths of the project

There have been no previous attempts to systematically assess the potential cost-effectiveness of different combinations of tests and treatments for preventing spontaneous preterm birth as a whole. The particular strength of this report is that it combines the results from a wide range of test accuracy systematic reviews with a wide range of



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different types of interventions in one economic model. The aim is to give clinicians and researchers a much more comprehensive overview of the current state of knowledge in this area than would be gained from single studies.

## Limitations of the project

- It is acknowledged that not all possibly relevant tests and interventions have been included in this report.
- It is possible that there are new tests and treatments which have either not been fully evaluated or have not reached evaluation stage.
- The systematic reviews of test accuracy encountered several challenges (see Chapter 3). However, none of these seriously threatened the validity of the main finding that the accuracy of most of the tests was disappointing. Better reviews and more primary research on those tests examined are unlikely to change the main conclusions (except for emerging tests, e.g. phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1), cervicovaginal β-human chorionic gonadotrophin).
- The main limitation with the systematic reviews of effectiveness (see Chapter 4) is the poor quality of many of the studies and the paucity of direct comparative data for some of the most commonly used interventions for threatened preterm labour, e.g. tocolytics.
- Although the direction and size of effect for the following interventions for asymptomatic women in early pregnancy: periodontal care, fish oil, progesterone and antibiotics for asymptomatic bacteriuria, suggested their effectiveness, there is continuing uncertainty as to whether beneficial effects to the baby in reducing risk of spontaneous preterm birth are offset by contrary trends in infant outcomes such as perinatal death.
- There are many limitations to the economic model used, partly arising from the quality of the accuracy and effectiveness data (see above), partly from lack of quality information concerning costs, and partly from the modelling approach. However, the main findings again do not seem to be highly susceptible to these limitations. It is virtually self-evident that an effective, affordable and safe intervention is unlikely to be improved upon by applying a test with poor accuracy. Furthermore, with a condition as serious and costly as spontaneous preterm birth, correct identification of those who will develop this outcome will be more important than correct categorisation of those who will not develop it (see Discussion in Chapter 4).
- The small amount of information on adverse events associated with interventions, particularly the longer-term effects to both mother and child, is an important limitation, as is the lack of information on side effects of the tests.

## Overall conclusion

The main initially stated findings appear largely unaffected by the limitations identified although it is difficult to know how much impact each of the limitations, together and in combination, would exert. Of these findings, the main driver of recommendations for practice and research is the likelihood that an effective intervention applied to all asymptomatic mothers in early pregnancy without preceding testing will be the most cost-effective approach to reducing spontaneous preterm birth. There are several candidates for an appropriate intervention: periodontal care, fish oil, progesterone and antibiotics for asymptomatic bacteriuria, but these require further investigation because current data are limited. For women symptomatic of threatened preterm labour with a viable fetus in later pregnancy, there is a need to delineate which of the most promising tests (cervical length, fibronectin, phIGFBP-1 and absence of fetal breathing movements) is most accurate and cost-effective on its own or in combination. Some interventions, like calcium channel blockers and oxytocin antagonists, require further direct evidence on effectiveness; others, like indomethacin, need confirmation of absence of adverse events and 'reasonableness' of their cost.

## Recommendations for practice

It is premature to suggest implementation at present. However, feasibility and acceptability to mothers and carers of application of the above strategies needs to be explored. Some consideration needs to be given to whether we should continue to do certain tests whose main perceived value up to now has been to help identify the risk of spontaneous preterm birth. Likewise, some consideration needs to be given to whether certain public health interventions e.g. smoking cessation programmes, may potentially reduce spontaneous preterm birth.

## Recommendations for research

- There is a need for systematic reviews to map the aetiopathogenesis of spontaneous preterm birth.
- Researchers may wish to consult more widely to ensure that all relevant screening, testing and interventions are considered for reviews in future projects. They may wish to explore ways of involving consumers in priority setting. Consensus conferences may be needed to define important questions and study designs for the future.
- There is a need for good-quality randomised controlled trials that directly investigate whether potentially effective interventions, e.g. periodontal care, smoking cessation, fish-oil supplementations, cervical cerclage, calcium channel blockers and oxytocin antagonists, are indeed effective not only in reducing spontaneous preterm birth but also in lowering perinatal mortality/morbidity.
- Evaluation of pilot schemes for universal treatment of mothers with effective pharmacological interventions like progesterone should be considered. Such evaluation should include investigation of adverse events and actual costs.
- There is a need for individual patient data meta-analyses of effectiveness literature to better delineate subgroup effects more powerfully.
- Test accuracy individual patient data meta-analyses are required for delineating the added value of tests and for studying the value of test combinations in light of the interdependence that exists between tests.
- Rigorous evaluation of tests with modest cost whose initial assessments suggest that they may have high levels of accuracy, e.g. phIGFBP-1, may fall into this category, but there may be other contenders in development which would need further investigation.
- Multiple (direct and indirect) comparisons considering all the tests and interventions may help delineate their rank. Methodological research is needed to assess if this could produce outputs suitable for decision analysis.
- There is a need for the development of an economic model that considers not just preterm birth, but other related outcomes, particularly those relevant to the infant, such as perinatal death and small-for-gestational-age. This would help to enable the development of comprehensive care pathways. Such a modelling project should make provision for primary data collection on costs.
- There is a need to study cost-effectiveness of test/treatment combinations for prevention of preterm birth in the subgroup of multiple pregnancies; to measure iatrogenic preterm birth rate as an outcome among all preterm birth; and last but not least, to simultaneously study cost-effectiveness of test/treatment combinations for prevention of all preterm birth, pre-eclampsia and fetal growth restriction.
- Value of information analysis is needed to determine prioritisation of future research.



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## Contribution of authors

All authors contributed to the idea, design and protocol for the project. K.S. Khan and H. Honest were responsible for the accuracy reviews. C.A. Forbes, K.H. Durée, G. Norman and S.B. Duffy were responsible for the effectiveness reviews. A. Tsourapas, T.E. Roberts, P.M. Barton and S.M. Jowett were responsible for the economic reviews and modelling. H. Honest was responsible for the day-to-day management of the project. All authors were involved in the final integration and interpretation of the results from the three components (accuracy, effectiveness and economics modelling) and the drafting of the report and have approved the final version.

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## Health economic analysis

Ariadna Juarez Garcia, Post-doctoral Research Fellow, Birmingham University, advised on the construction of the model, use of cost data and provided detailed advice on the probabilistic sensitivity analysis.

## Investigators who provided additional data and comments on previously published reviews

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# Appendix 10

# UK National Screening Committee's criteria

## Criteria for appraising the viability, effectiveness and appropriateness of a screening programme

### 1. The condition

Preterm birth is a heterogeneous condition in which up to 30–40% of all cases are the results of elective delivery for a maternal or fetal complication. The remaining 60–70% occur spontaneously. It complicates about 3% of pregnancies before 34 weeks' gestation and between 7 and 12% before 37 weeks' gestation. The former in particular has serious effects on mother, child and society; this makes preterm birth an important issue to public health worldwide. Additionally, the spontaneous preterm birth rate is increasing in many countries in spite of progressive health-care provisions. Because of the magnitude of the burden of spontaneous preterm birth on the society, it represents an important public-health issue such that if screening and/or testing were possible then such a screening programme would be desirable provided certain conditions are met.

The epidemiology and natural history of spontaneous preterm birth are gradually being elucidated with progressive insight into its aetiology and pathogenesis in recent years, but this understanding is far from complete. This existing knowledge has resulted in attempts at prediction and prevention of spontaneous preterm birth targeting detectable risk factor(s) (e.g. previous history of spontaneous preterm births), biochemical or inflammatory markers (either in cervical secretions or amniotic fluid), and measurable physical characteristics (e.g. ultrasound of cervical length) both in the early antenatal period with women who are asymptomatic and in later gestation when women present with symptoms of threatened preterm labour.

### 2. The test

There are many tests that purportedly predict spontaneous preterm birth, 22 of which were reviewed in this report. Screening typically involves use of a confirmatory test after initial testing, before institution of therapy. In this field, this is not the case because testing is used to identify a risk group in which preventative interventions (both intensive monitoring and treatments) are employed directly after the test results are known. In this situation, for a test to serve as a good tool for screening, it should perform very well.

The majority of tests appear to be safe, with the exception of tests that require amniocentesis. In asymptomatic antenatal women, tests that appear to have potential were ultrasonographic cervical length measurement, cervicovaginal fetal fibronectin screening, detection of uterine contraction (by home uterine monitoring device) and amniotic fluid C-reactive protein measurement. In symptomatic women with threatened preterm labour, tests with potential were absence of fetal breathing movements, cervical length and funnelling, amniotic fluid interleukin-6, serum C-reactive protein and matrix metalloprotease-9, cervicovaginal fetal fibronectin, measurement of cervicovaginal interleukin-8 and human chorionic gonadotrophin. Our project explored their validity, precision and costs in a model-based analysis. Where screening or testing were found to be relatively accurate in predicting spontaneous preterm birth, the distribution of test values in the target population was taken into account in cost-effectiveness analysis. For the majority of the tests, our analysis revealed that none were currently suitable for a screening programme for primary prevention among asymptomatic antenatal women in early pregnancy and some were potentially suitable for secondary prevention among women symptomatic with threatened preterm labour.

Acceptability of the tests was not explored. For tests where there is a lack of consensus as to the agreed cut-off level (threshold) for defining abnormality, our analysis provides guidance on which thresholds to consider for consensus development.

### 3. The treatment

Beyond the screening issue, consensus is also lacking in the management of individuals who are screened as positive. There are many interventions



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that purportedly prevent spontaneous preterm birth (primary prevention) or that improve neonatal outcome where preterm birth is inevitable (secondary prevention) of which 38 were reviewed in this project. However, only a few have been shown to be effective (with a few provisos, e.g. conclusions are from small studies or studies of poor quality). For other interventions, evidence is still lacking for their effectiveness and safety, effect on short-term and long-term neonatal outcomes as well as on perinatal mortality and morbidity.

Among asymptomatic women in early pregnancy antibiotic treatment for bacterial vaginosis in women with intermediate flora, smoking cessation programmes, progesterone, periodontal therapy and fish oil appeared promising (primary prevention). Antenatal corticosteroids were found to have a beneficial effect on the incidence of respiratory distress syndrome and the risk of intraventricular haemorrhage (28–34 weeks' gestation), but the effects of repeat courses were unclear because of insufficient data (secondary prevention). The role of tocolysis as an adjunct to the administration of corticosteroids in delaying spontaneous preterm birth, in particular with regards to which tocolytic agent is most effective, is unclear at present with many competing agents. However, cyclo-oxygenase inhibitors (including non-steroidal anti-inflammatory agents) were found to be the most cost-effective tocolytic agent in terms of reducing spontaneous preterm birth and prolongation of pregnancy in symptomatic women, although evidence to support a reduction in perinatal mortality and morbidity was less convincing.

## 4. The screening programme

An effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective approach to reducing spontaneous preterm births among asymptomatic antenatal women in early pregnancy for primary prevention. For secondary prevention among women symptomatic of threatened preterm labour in later pregnancy, a management strategy based on results of prior testing may be more cost-effective. It is premature to suggest implementation of a treat-all strategy of simple interventions such as fish oil for asymptomatic women. On the other hand, the case for universal provision of a high-quality ultrasound machine in labour wards is stronger for predicting spontaneous preterm birth among women with a viable pregnancy who present with threatened preterm labour to direct management (involving tocolysis and corticosteroids). The feasibility and acceptability to mothers and health providers of such strategies needs to be explored.

At present, there is insufficient evidence to recommend any screening programme. There is a need for high-quality, adequately powered, randomised 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, such as perinatal death and shorter-term and longer-term outcomes among survivors. Such a modelling project should make provision for primary data collection on the safety of interventions and their associated costs. Before such trials and economic analyses can be proposed, there should be evidence that the complete screening programme (both screening/testing and intervention) is clinically, socially and ethically acceptable to health-care professionals, the expectant mother and the public. In particular, there should be evidence that benefit from the screening programme would outweigh the physical and psychological harm that may arise from any of the screening, testing, and intervention and their related processes. Only then can the cost of the screening programme for spontaneous preterm birth be economically considered vis-à-vis expenditure on medical care as a whole.

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The printed version also excludes the appendices.

View/download the appendices

## Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***

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