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Risk-scoring systems for predicting preterm birth with the aim of reducing associated adverse outcomes (Review)

Davey MA, Watson L, Rayner JA, Rowlands S

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[Intervention Review]

Risk-scoring systems for predicting preterm birth with the aim of reducing associated adverse outcomes

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ABSTRACT

Background

Identification of pregnancies that are higher risk than average is important to allow the possibility of interventions aimed at preventing adverse outcomes like preterm birth. Many scoring systems designed to classify the risk of a number of poor pregnancy outcomes (e.g. perinatal mortality, low birthweight, and preterm birth) have been developed, but they have usually been introduced without evaluation of their utility and validity.

Objectives

To determine whether the use of a risk-screening tool designed to predict preterm birth (in combination with appropriate consequent interventions) reduces the incidence of preterm birth and very preterm birth, and associated adverse outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2015).

Selection criteria

All randomised or quasi-randomised (including cluster-randomised) or controlled clinical trials that compared the incidence of preterm birth between groups that used a risk-scoring instrument to predict preterm birth with those who used an alternative instrument, or no instrument; or that compared the use of the same instrument at different gestations.

The reports may have been published in peer reviewed or non-peer reviewed publications, or not published, and written in any language.

Data collection and analysis

All review authors planned to independently assess for inclusion all the potential studies we identified as a result of the search strategy. However, we did not identify any eligible studies.

Main results

Searching revealed no trials of the use of risk-scoring systems for preventing preterm birth.

Authors' conclusions

The role of risk-scoring systems in the prevention of preterm birth is unknown.

There is a need for prospective studies that evaluate the use of a risk-screening tool designed to predict preterm birth (in combination with appropriate consequent interventions) to prevent preterm birth, including qualitative and/or quantitative evaluation of their impact on women's well-being. If these prove promising, they should be followed by an adequately powered, well-designed randomised controlled trial.

PLAIN LANGUAGE SUMMARY

Risk-scoring systems for the prevention of preterm birth

Identification of women whose pregnancies are at higher than average risk of preterm birth would allow the possibility of providing the women with higher level antenatal care with the aim of preventing the preterm birth. Preterm birth (before 37 completed weeks' gestation) is a major public health problem worldwide, and occurs in 6% to 10% of births in high-income countries. The proportion of pregnancies which end prematurely, between 20 and 36 weeks, has not fallen in recent years. Perinatal interventions, both before birth (transfer of women to tertiary care, antenatal steroids), and after birth (intensive care, surfactant) have markedly improved perinatal outcomes. A number of scoring systems of risk factors associated with preterm birth have been used. Systematic, objective measures can include age, marital status, socio-economic factors, smoking, threatened miscarriage, previous low birthweight baby, previous stillbirth, maternal weight and height. Their ability to identify women at increased risk of preterm birth, and subsequently to prevent preterm birth, has not been evaluated by randomised controlled trials. The literature search for this review revealed no trials of the use of risk-scoring systems to prevent preterm birth. There are a number of ethical issues involved in the decision to implement risk scoring that have not been evaluated; for example, an intervention with potential morbidity and may be used, or used more frequently with no evidence of more favourable outcomes, or the woman may prefer not to disclose some sensitive information included in the measures. There is a need for prospective studies that evaluate the use of risk-scoring systems to prevent preterm birth, including an assessment of their impact on women's well-being. If these prove promising, they should be followed by an adequately powered, well-designed randomised controlled trial.

BACKGROUND

Identification of pregnancies that are at a greater than average risk of adverse outcome is the fundamental concept that underpins antenatal care. A number of investigators have been interested in whether a systematic, objective measure of the level of risk would enable correct classification of the pregnancy as being high or low risk more accurately than subjective clinical impression. Many scoring systems designed to classify the risk of a number of poor pregnancy outcomes (e.g. perinatal mortality, low birthweight, and preterm birth) have been developed over the last 40 years. However, they have usually been introduced without evaluation of their utility and validity. Some of those instruments developed to assess the risk of preterm birth in particular have included items such as age, marital status, smoking, plurality, threatened miscarriage, previous low birthweight baby, previous stillbirth, maternal weight and height (Creasy 1980; Fedrick 1976; Lambotte 1977).

Description of the condition

Preterm birth is a major public health problem worldwide. Preterm birth (before 37 completed weeks' gestation) occurs in 6% to 10% of births in high-income countries and the proportion of pregnancies which end preterm, at 20 to 36 weeks, has not fallen in the 15 to 20 years for which Australian state and national data are available (Tracy 2007). This is true in virtually all high-income countries (Ananth 2005; Buitendijk 2003; Joseph 2007; Tracy 2007). Although precise identification of preterm birth in lower-income countries is poor because information on gestational age is rarely available, it is estimated to be at least as prevalent as in more prosperous countries (Kramer 1987).

Preterm birth is the major factor associated with perinatal mortality, admission to neonatal intensive care, severe morbidity in the first weeks of life, a prolonged hospital stay after birth, and re-admission to hospital in the first year of life (Petrou 2003; Riley 2008). Surviving infants, especially those born before 32 weeks, have a substantially increased risk of chronic lung disease, and major and minor impairments (Anderson 2004; Costeloe 2006; Davis 2007; Doyle 2001a; Doyle 2001b; Doyle 2003; Doyle 2005; Doyle 2006; Ford 2000; Hack 2004; Larroque 2008; Wood 2005). There are considerable financial (Gilbert 2006; Petrou 2003; Petrou 2006) and emotional costs for the parents of preterm infants (Singer 1999).

A number of strategies are used in an attempt to delay preterm birth. These include insertion of a ligature around the cervix to prevent it opening (cervical suture), drugs to dampen the contractions (tocolytics), antibiotics, and admission to hospital for bed rest. There is little evidence for the effectiveness of these interventions. Cochrane reviews have found no evidence in favour of bed rest in preventing preterm birth in singleton (Sosa 2015) and multiple (Crowther 2010) pregnancies; or any reduction in preterm or very preterm birth after treatment with magnesium sulphate (Crowther 2015), and there was an increase in perinatal mortality in the group treated with magnesium sulphate. Another Cochrane review found no reduction in preterm birth when prophylactic antibiotics were given to women in preterm labour with intact membranes (Flenady 2013). Social support for women with 'at-risk' pregnancies did not reduce the proportion born preterm or low birthweight (Hodnett 2010). Reviews of progress on the primary and secondary prevention of preterm birth concluded that interventions tested in the past 15 years have not been found to be effective in well-designed trials (Johnston 2001; Stevens-Simon 1999).

In contrast to prevention, improved care of preterm infants before birth (transfer to tertiary care, antenatal steroids) (Crowther 2015), and afterwards (intensive care, surfactant) (Stevens 2007), has improved perinatal outcomes markedly over the last 15 years. These improvements mean that adverse outcomes of preterm birth are now concentrated in very preterm births (births at less than 32 weeks' gestation) (Buitendijk 2003; Slattery 2002).

A recent systematic review (Honest 2009) of the accuracy of screening tests to predict and reduce spontaneous preterm birth in symptomatic and asymptomatic women found the most cost-effective method of reducing spontaneous preterm birth in asymptomatic women would be a universal intervention used in early pregnancy. Interventions suggested as appropriate but which require further investigation were periodontal care, fish oil, progesterone and antibiotics for asymptomatic bacteriuria. For symptomatic women in later pregnancy (those in threatened preterm labour), there is a need to define which among the currently available tests (e.g. cervical length, fibronectin, phIGBP-1 and absence of fetal breathing movements) will provide the most efficacious outcomes when used alone or in combination. Other interventions such as calcium channel blockers and oxytocin antagonists require more evidence of efficacy and cost effectiveness (Honest 2009; Tsourapas 2009). Further, these authors recommend more methodological research into topics that could be considered in risk-scoring systems.

Description of the intervention

Reviews of the epidemiology of preterm birth (Berkowitz 1993; Kramer 2001; Lumley 1993; Tucker 2004) have identified consistent associations with material and social adversity, multiple gestation, assisted conception, structural abnormalities of the uterus and cervix, serious medical, surgical, or gynaecological conditions in the mother, stressful life events, 'perceived' stress, poor psychological health, lack of family/social support, and tobacco and cocaine use. Many of the known risk factors are rare, and others are difficult to modify.

The elements that make up the various risk-scoring systems will be likely to affect their accuracy. Indeed, a review of the area found widely divergent levels of accuracy (Honest 2004). For example, events that took place in a previous pregnancy may be most informative, making the prediction better for multigravid women. In evaluating risk-scoring systems related to preterm birth, it is important to take account of several of their characteristics: their ease of use; their accuracy amongst different groups, e.g. multiparous and primiparous women; using them at earlier versus later gestation; whether they differentiate between spontaneous labours and births that are induced or by elective caesarean section; the factors they measure; the cut-off points used to define preterm and very preterm birth; how well and appropriately the predictor variables are defined; the accuracy with which variables are measured; weightings given to elements of the score; whether 'dose' is considered, e.g. amount of smoking, duration of abnormal presentation; and their utility in varying healthcare environments (e.g. when no neonatal intensive care unit (NICU) is available).

There are a number of ethical issues involved in the decision to implement risk scoring: e.g. interventions may be used more frequently, with no evidence of better outcomes, and the possibility of harm to women and/or their babies (e.g. adverse effects of medications; deep venous thrombosis with rest in bed; time away from usual activities); resources may be inappropriately re-allocated from areas of greater need; the woman may prefer not to disclose some matters included in the instrument, e.g. socio-economic details and domestic violence; sensitive information needs to be recorded in the medical record; labelling may in fact be an additional risk factor; and women who refuse the interventions that flow from a high-risk label can be regarded by their caregivers as misguided (Alexander 1989), with the risk that this may affect the (real or perceived) quality of their care. Recent research indicates that labelling women to be 'at risk' in pregnancy may have an adverse effect on their psychosocial well-being, and may not accurately predict the outcome of interest (Stahl 2003).

Many of the factors included in the various risk-scoring systems are probably markers for unknown causes of preterm birth, rather than being causal themselves. As a result, 'treating' the marker is unlikely to alter the outcome. Many of the markers are not amenable to change even if they were aetiological, e.g. maternal weight at the beginning of the pregnancy, age, past reproductive performance. The labelling that results from scoring may thus cause extra anxiety, with no possible counterbalancing potential for effective intervention.

How the intervention might work

The main purpose of screening for an increased risk of preterm birth is to enable high-level antenatal care, aimed at prevention or delay of preterm birth in those identified as being at increased risk, or transfer in utero to a hospital with neonatal intensive care available. The focus of this review is on the capacity of screening to influence care and outcomes, rather than on the predictive power of the instruments per se. Accurate prediction of preterm birth is not in itself useful unless it enables interventions to be implemented that in some way reduce the mortality and morbidity associated with preterm birth (e.g. by delaying the birth; ensuring that birth occurs in a facility with a NICU). The primary outcomes of interest in this review are preterm birth and very preterm birth. The other neonatal outcomes (like mortality and morbidity) are included because delaying preterm birth may not be advantageous in some circumstances; i.e. preterm birth may remove some babies from a hostile environment (e.g. infection, poor placental function) and so reduce their risk of mortality or morbidity.

It is useful to know what proportion of women who go on to experience preterm labour are identified by risk scoring as being at high risk (sensitivity of the test), and what proportion of those who do not go on to experience preterm labour are identified by the test as being at low risk (specificity). Unless these measures of the screening system are quite high, the system will mis-classify women, with the resulting lack of intervention for those wrongly classified as low risk and unnecessary interventions for those wrongly classified as high risk. Another measure of the value of a system like this is the proportion of those identified as being at high risk who will go on to experience the outcome in question (preterm birth in this case). This is known as the positive predictive power, and is useful information for the clinical management of individual women.

Why it is important to do this review

The results of this review have the potential to guide caregivers and women alike in making decisions about the management of pregnancies at higher than average risk of preterm birth.

OBJECTIVES

To determine whether the use of a risk-screening tool designed to predict preterm birth (in combination with appropriate consequent interventions) reduces the incidence of preterm birth and very preterm birth, and associated adverse outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised or quasi-randomised (including cluster-randomised) or controlled clinical trials that compared the incidence of preterm birth between groups that used a risk-scoring instrument to predict preterm birth with those who used an alternative instrument, or no instrument; or that compared the use of the same instrument at different gestations.

The reports may have been published in peer reviewed or non-peer reviewed publications, or not published, and written in any language.

Types of participants

Pregnant women of gestation less than 37 weeks, not in labour, regardless of their previous obstetric or medical history or specific risk factors. We will include women with multiple pregnancies.

Types of interventions

This review focuses on risk scoring as a screening system; i.e. an instrument administered routinely for identifying women at risk of preterm birth. This is the intervention of interest. In addition, the results of the screening may mean that a variety of different management strategies are implemented (e.g. use of tocolytics or antibiotics, transfer to a hospital with NICU facilities). These strategies are also 'interventions' that are intermediate between screening and the primary outcomes of interest in this review. These interventions are not the focus of this review, except as outcome measures in that they may be used more widely as a result of screening.

Use of any risk-scoring system for preterm birth versus none.

Use of one risk-scoring system for preterm birth versus another.

Use of the same risk-scoring instrument administered at different gestations.

A risk-scoring system may include socio-demographic factors, previous medical and reproductive history, and risk factors in the current pregnancy, but not diagnostic tests carried out because of identified problems in the current pregnancy. In some countries, routine cervical ultrasound is performed at around 23 weeks' gestation. Where this is done routinely for screening, rather than being a diagnostic procedure for women at increased risk, we planned to include studies that include such scanning.

We planned to record the specific risk-scoring system used and the gestation at which it was administered.

Types of outcome measures

We planned to collect outcome measures relating to the baby, the mother and the pregnancy.

Primary outcomes

1. Delivery at less than 32 completed weeks (high-risk group) - definition of this very preterm group may differ between studies with respect to gestational cut-off and we will abide by the author's definition of very preterm birth; we selected 32 weeks as the cut-off because we refer locally to very preterm birth as birth before 32 completed weeks' gestation.
2. Delivery at less than 37 completed weeks (and not included in high-risk group) (low-risk group).
3. Death (we plan to report stillbirth, neonatal mortality, and infant mortality separately).

Secondary outcomes

Neonatal

(a) Short term

1. Neonatal morbidity (as defined by authors): sepsis, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, seizures.
2. Duration of ventilation (72 or more hours versus less than 72 hours).
3. Duration of admission to NICU/hospital.
4. Gestation at delivery, noting the method of assessing gestation.
5. Birthweight less than 2500 g.
6. Birthweight less than 1500 g.
7. Very preterm birth in a location not designed for the care of VPT neonates.
8. Developmental delay (up to five years if available).

(b) Long term: (up to five years if available)

1. Developmental delay.

Maternal

1. Morbidity: infection of any type, antepartum haemorrhage, postpartum haemorrhage as defined by authors; maternal medical complications, e.g. pre-eclampsia, renal disease, cardiac disease, diabetes.
2. Use of each type of intervention (e.g. cervical sutures, tocolytic agents, steroids, antibiotics).
3. Use of diagnostic tests (fetal fibronectin, ultrasound).
4. Antenatal admissions to hospital (including duration).
5. Operative delivery (caesarean or instrumental birth).
6. Psychological outcomes, in particular maternal anxiety (related to labelling as high risk) during pregnancy and after the birth.
7. Women's satisfaction with care (we will analyse whether or not this was assessed blinded to intervention status).
8. Side effects of interventions resulting from screening (e.g. discomfort from monitors/cervical scans; complications of invasive procedures; disruption to family unit related to prolonged periods of bed rest).
9. Onset of labour: spontaneous or induced.
10. Number of antenatal visits.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 June 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We planned to search reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Davey 2011.

We did not identify any studies for inclusion in this review. If studies are identified in future updates, we will use the methods described in Appendix 1.

Assessment of the quality of evidence using GRADE

For future updates, the quality of the evidence will be assessed using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following key outcomes.

1. Delivery at less than 32 completed weeks (high-risk group) - (as defined by the trial authors).

2. Delivery at less than 37 completed weeks (and not included in high-risk group) (low-risk group).
3. Death (stillbirth, neonatal mortality, and infant mortality).
4. Neonatal morbidity (as defined by authors): sepsis, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, seizures.
5. Developmental delay (up to five years if available).
6. Morbidity: infection of any type, antepartum haemorrhage, postpartum haemorrhage as defined by authors; maternal medical complications, e.g. pre-eclampsia, renal disease, cardiac disease, diabetes.
7. Psychological outcomes, in particular maternal anxiety (related to labelling as high risk) during pregnancy and after the birth.

We will use GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence would be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

RESULTS

Description of studies

We were unable to locate any studies that met the search criteria.

Results of the search

There were no relevant trial reports in the Pregnancy and Childbirth Group's Trials Register.

Risk of bias in included studies

Not applicable as we identified no studies.

Effects of interventions

We identified no trials that used a risk-scoring system to prevent preterm birth.

DISCUSSION

The search revealed no trials examining the use of risk-scoring systems to prevent preterm birth.

A recent health technology assessment (Honest 2009), included a series of systematic reviews of effectiveness of interventions (published before September 2005) with potential to reduce cases of spontaneous preterm birth in asymptomatic women in early pregnancy. The review found 40 studies using a variety of interventions, which they report were often of poor quality. Promising interventions for asymptomatic women included antibiotics for vaginal vaginosis, smoking cessation programs, progesterone, periodontal therapy and fish oil supplements. However, none of these studies were eligible for the current review because risk-scoring systems were not the intervention on which the studies focused. Rather, women were identified as being at increased risk of preterm birth, and an intervention was undertaken in an attempt to prevent preterm birth or improve neonatal outcomes.

The accuracy with which risk factor screening can predict preterm birth is poor. Creasy's prospective study (Creasy 1980) predicted that 10% of the screened women would have preterm labour and birth, of whom one-third in fact had preterm birth. These predicted preterm births represented two-thirds of all preterm births in the study. Two-thirds of those labelled 'high risk' did not have a preterm birth, and one-third of all preterm births in the study were to women not identified as 'high risk'. Fedrick conducted a survey and identified a number of factors associated with preterm birth (Fedrick 1976). From these he developed a risk-scoring system and scored 283 women who had preterm births, as well as 510 randomly selected respondents to the survey. He classified the 25% with the highest scores as being at increased risk, which identified 9% of the primiparous women who had preterm births, and 25% of the multiparous women who had preterm births (Fedrick 1976a). Honest examined testing to predict preterm birth in symptomatic and asymptomatic women and found generally poor accuracy (Honest 2009). The only 'testing' that potentially relates to this review is universal testing for asymptomatic women. Honest found that the only acceptably accurate tests were ultrasound measurement of cervical length, and fetal fibronectin screening. These differ from risk-factor screening because they are based on technical assessment, while risk-factor screening is based on information that can be obtained by careful history taking or administering a questionnaire.

It has long been accepted that screening should only be performed if (among other conditions) there is a suitable test available, and an acceptable, available treatment for the condition of interest (Wilson 1968). The benefits should also be expected to outweigh the harms associated with screening (Andermann 2008). Given that labelling women 'at risk' can result in unnecessary interventions (Jordan 2009), and negatively affect their psychological state (Jordan 2009; Stahl 2003), and the absence of trial evidence for the benefit of risk-factor screening, the case for its inclusion in routine antenatal care has not been established.

AUTHORS' CONCLUSIONS

Implications for practice

The role of risk-scoring systems in the prevention of preterm birth is unknown.

Implications for research

There is a need for prospective studies that evaluate the use of risk-scoring systems to prevent preterm birth, including qualitative and/or quantitative evaluation of their impact on women's well-being. If these prove promising, they should be followed by an adequately powered, well-designed randomised controlled trial.

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APPENDICES

Appendix 1. Methods of data collection and analysis to be used in future updates of this review

Data collection and analysis

Selection of studies

All review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third party.

Data extraction and management

We will design a form to extract data. For eligible studies, review authors L Watson, J Rayner and S Rowlands will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult review author MA Davey. We will enter data into Review Manager software (RevMan 2014) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. < 20% missing data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;

- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2011). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Other unit of analysis issues

We will use generalised estimating equations to adjust for the clustering effect of multiple births when sufficient information is available.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. We will exclude studies with greater than 25% missing data.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing. We will exclude studies with excessive numbers (more than 10%) of participants analysed in the wrong group.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if the Tau^2 is greater than zero and either an I^2 is greater than 30% or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. We

will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Spontaneous versus induced preterm birth and very preterm birth.
2. Multiple versus singleton births.

We will use the following outcomes in subgroup analysis.

1. Delivery at less than 32 weeks' gestation.
2. Delivery at less than 37 weeks' gestation.
3. Perinatal and infant mortality.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will perform sensitivity analyses to explore the effect of potential biases: e.g. greater than 20% losses to follow-up, unclear allocation concealment or blinding; and to explore the effects of fixed-effect or random-effects analyses or outcomes with statistical heterogeneity.

WHAT'S NEW

Date	Event	Description
30 June 2015	New search has been performed	Updated search identified no new relevant reports. There are still no randomised controlled trials of the use of risk-scoring systems for preventing preterm birth. A list of important outcomes has been added to be used for grading the evidence in future updates.
30 June 2015	New citation required but conclusions have not changed	Review updated.

HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 11, 2011

Date	Event	Description
7 July 2010	New citation required and major changes	Protocol substantially updated and reinstated.
11 November 2009	Amended	Protocol withdrawn from publication as it was out of date. Author contact details edited.
29 January 2009	Amended	Author contact details edited.

Date	Event	Description
24 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Mary-Ann Davey (MAD) was primarily responsible for the development of the protocol. Lyn Watson developed the framework for the initial draft of the protocol; Jo Rayner (JR) and Shelley Rowlands contributed to the development of the protocol, and reviewed the final draft. For the review, MAD and JR wrote the review. All authors reviewed the final draft.

For the 2015 update, MAD prepared the update with contributions from the other authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Mary-Ann Davey, Australia.

  Australian Postgraduate Award

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review has been updated to incorporate an updated synthesis of the background literature; the updated standard methods text of the Cochrane Pregnancy and Childbirth Group; and the latest recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy, High-Risk; Premature Birth [*diagnosis] [prevention & control]; Risk Assessment [methods]

MeSH check words

Female; Humans; Pregnancy