Cochrane Library

**Cochrane** Database of Systematic Reviews

# Prostaglandins before caesarean section for preventing neonatal respiratory distress (Review)

Motaze NV, Mbuagbaw L, Young T

Motaze NV, Mbuagbaw L, Young T.
Prostaglandins before caesarean section for preventing neonatal respiratory distress.
*Cochrane Database of Systematic Reviews* 2013, Issue 11. Art. No.: CD010087.
DOI: 10.1002/14651858.CD010087.pub2.

**www.cochranelibrary.com**




WILEY

## TABLE OF CONTENTS

[Intervention Review]

# Prostaglandins before caesarean section for preventing neonatal respiratory distress

Nkengafac V Motaze[1,2], Lawrence Mbuagbaw[1], Taryn Young[3,4]

[1]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon. [2]Community Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. [3]Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. [4]South African Cochrane Centre, South African Medical Research Council, Cape Town, South Africa

Contact address: Nkengafac V Motaze, Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Henri Dunant Avenue, PO Box 87, Yaoundé, Centre Province, Cameroon. villyen@yahoo.com.

**Editorial group:** Cochrane Pregnancy and Childbirth Group.
**Publication status and date:** New, published in Issue 11, 2013.

**Citation:** Motaze NV, Mbuagbaw L, Young T. Prostaglandins before caesarean section for preventing neonatal respiratory distress. *Cochrane Database of Systematic Reviews* 2013, Issue 11. Art. No.: CD010087. DOI: 10.1002/14651858.CD010087.pub2.



## ABSTRACT

### Background

Respiratory distress (RD) can occur in both preterm and term neonates born through normal vaginal delivery or caesarean section (CS). It accounts for about 30% of neonatal deaths and can occur at any time following birth. Respiratory distress syndrome (RDS), transient tachypnoea (rapid breathing) of the newborn and persistent pulmonary hypertension (increased blood pressure of pulmonary vessels) of the newborn are the most frequent clinical presentations of neonatal RD. Prostaglandins are used in routine obstetric practice to ripen the uterine cervix and to trigger labour, with those of the E series being preferred over others due to the fact that they are more uteroselective. Administration of prostaglandins to an expectant mother before delivery causes reabsorption of lung fluid from the fetal lung and promotes surfactant secretion by inducing a catecholamine surge. As a result, significant reduction in neonatal respiratory morbidity following a CS could be obtained, leading to reduced long-term complications such as bronchopulmonary dysplasia (chronic lung disease with lung tissue modification) and asthma.

### Objectives

The objective of this review was to determine if administration of prostaglandins before CS can improve respiratory outcomes of newborns.

### Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2013). We also searched three clinical trial registries; ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry and the WHO Clinical Trials Registry Platform (ICTRP), for ongoing studies (24 June 2013).

### Selection criteria

We included all published and unpublished randomised controlled trials comparing the use of prostaglandins with other treatments (including placebo) to reduce neonatal respiratory morbidity. Participants were pregnant women with an indication for a CS, and we compared administration of prostaglandins prior to CS with no treatment, placebo or another treatment.

**Data collection and analysis**

Two review authors independently assessed studies for inclusion and assessed trial quality, with the third review author referred to for settling any disagreements. Two review authors extracted data. Data were checked for accuracy. We used the Cochrane tool for assessing risk of bias in the included study and contacted the study authors to request additional information where appropriate.

**Main results**

We found one randomised controlled trial with a low risk of bias which was carried out in a tertiary neonatal care centre in Australia. The study involved 36 women (18 received intravaginal prostaglandin $E_2$ gel and 18 received placebo).

There was one case of neonatal respiratory distress in the control group, which the trialist reported as transient tachypnoea of the newborn (risk ratio (RR) 0.33, 95% confidence interval (CI) 0.01 to 7.68, one study, n = 36).

None of the neonates required mechanical ventilation and the trial authors reported median Apgar scores at one and five minutes as being similar in both groups.

There were no treatment-related side effects in either group. Noradrenaline concentrations (median values (range)) were reported as being significantly higher in the cord blood samples of the intervention group compared to the control group.

**Authors' conclusions**

Although the trial authors reported a significant increase in catecholamine levels in the intervention group, there was no significant difference in the respiratory outcomes between intervention and control groups. The quality of evidence was graded as low because the sample size was small and there were few events. No definite conclusions can thus be drawn on the effects of prostaglandins on neonatal respiratory outcomes from this review.

## PLAIN LANGUAGE SUMMARY

### Administration of prostaglandins to pregnant women before caesarean section to prevent breathing difficulties in newborn babies

Respiratory difficulties in newborn babies are a common complication following birth. They are more frequent with caesarean section and when the pregnant woman is operated on before labour starts than when she is in labour. Prostaglandins are a group of substances that have been used successfully to induce labour in pregnant women. They also have the potential to help the lungs of the newborn to adapt to breathing air after delivery, by removing fluid from the lungs and increasing surfactant secretion. Caesarean sections are performed more frequently worldwide and it is important to find interventions that improve the newborn's breathing following this surgery.

We found one small randomised trial (involving 36 women) that compared prostaglandin $E_2$ intravaginal gel administered before caesarean section compared with a placebo gel. The information obtained from this study did not permit us to be certain that prostaglandins improve neonatal breathing following planned caesarean section at term. Only one baby in the placebo group had respiratory distress assessed as rapid breathing. Further studies have to be carried out in order to find out the impact of prostaglandins on the newborn lungs after caesarean section.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

**Prostaglandin E2 versus placebo before caesarean section for prevention of neonatal respiratory distress**

**Patient or population:** pregnant women at term.
**Settings:** Regional tertiary neonatal care centre.
**Intervention:** prostaglandin E2 administered per vagina before caesarean section
**Control:** K-Y jelly as placebo.

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Prostaglandin E2 administered before caesarean section | | | | |
| **Respiratory distress**<br>Respiratory rate at rest > 60/min and/or signs of respiratory distress.<br>Follow-up: 1 day. | **Study population** | | RR 0.33, 95% CI 0.01 to 7.68, | 36<br>(1 study) | ⊕⊕◯◯<br>**low**[1] | |
| | **83 per 1000** | **27 per 1000**<br>(0.01 to 637) | | | | |
| **Need for mechanical ventilation**<br>Follow-up: 1 day. | **Study population** | | Not estimable | 36<br>(1 study) | ⊕⊕◯◯<br>**low**[1] | There was no neonate requiring mechanical ventilation in either groups |
| | See comment | See comment | | | | |
| | **Moderate** | | | | | |
| **All cause fetal mortality**<br>Follow-up: 1 day. | **Study population** | | Not estimable | 36<br>(1 study) | ⊕⊕◯◯<br>**low**[1] | There was no reported neonatal death in the study. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | See comment | See comment | | | | |
| **Maternal adverse events** | **Study population** | | Not estimable | 36 (1 study) | ⊕⊕◯◯ **low**[1] | There was no maternal adverse event reported in the study. |
| | See comment | See comment | | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** we are very uncertain about the estimate.

[1] The optimal information size was not met, confidence intervals were wide and event rates were low.

## BACKGROUND

Respiratory distress (RD) can occur in all newborns irrespective of gestational age or mode of delivery. It accounts for about 30% of neonatal deaths (Harrison 2008) and can occur at birth or several hours after delivery (Whitsett 2005). Infants born by elective caesarean section (CS) delivery at term are at increased risk for developing respiratory disorders, compared with babies delivered per vagina (Zanardo 2004) or by emergency CS (Hansen 2007), the relative risk increasing with decreasing gestational age. The prevalence of deliveries by CS has been steadily increasing worldwide over the last few years (Tampakoudis 2004). In 2007, 30.9% of Australian women gave birth by CS, increasing from 21% in 1998 (Laws 2009). Other countries have high rates of CS with prevalence rates of up to 50% reported in certain regions of Latin America (Villar 2006). Previous research has highlighted potential reasons for the increasing CS rate, including maternal request and associated ethical and litigious issues (Minkoff 2003; Robson 2008), obesity (Poobalan 2009) and increasing maternal age (Bell 2001; Callaway 2005).

### Description of the condition

RD in the neonate following CS can present as several clinical entities including respiratory distress syndrome (RDS), transient tachypnoea (rapid breathing) of the newborn and persistent pulmonary hypertension of the newborn. RDS, sometimes called hyaline membrane disease complicates about 1% of pregnancies (Whitsett 2005), often occurs after premature delivery (Bland 2008) and is due to quantitative and qualitative abnormalities in pulmonary surfactant (Whitsett 2005). Transient tachypnoea of the newborn (TTN), which is characterised by RD with an increase in respiratory rate following delivery, is caused by delayed reabsorption of lung fluid (Bland 2008; Whitsett 2005) and has an incidence of approximately 11% (Whitsett 2005). Persistent pulmonary hypertension of the newborn occurs when there is a failure to make the transition from high pulmonary vascular resistance (PVR) and low pulmonary blood flow (PBF) characteristic of the fetus to the relatively low PVR and high PBF of the postnatal infant (Whitsett 2005).

### Description of the intervention

Prostaglandins are used in obstetrics for cervical ripening and induction of labour with good results (Hofmeyr 2003; Witter 1992). Prostaglandins of the E series are preferred over the F series because they are more uteroselective (O'Brien 1995).The most widely used prostaglandins are misoprostol (prostaglandin $E_1$) and dinoprostone (prostaglandin $E_2$), which are available as oral tablets, vaginal tablets, pessaries or vaginal gels. For the purposes of cervical ripening and labour induction, prostaglandin $E_2$ starts acting in 10 minutes and results can be observed within 12 hours (Rayburn 1989). Prostaglandins can stimulate surfactant secretion and reduce lung fluid by provoking a catecholamine surge but it is unclear how early they have to be administered before CS in order to produce this effect. A randomised controlled trial found an increase in catecholamine levels in fetal blood in the intervention group compared with the placebo group, when prostaglandin $E_2$ was administered as intravaginal gel 60 minutes before CS (Singh 2004). Prostaglandins are not used in routine medical practice for the sole purpose of improving fetal respiratory outcomes. However, studies in animals have shown that when administered before CS, they accelerate fetal lung maturation and improve respiratory function after delivery (Zaremba 1997).

### How the intervention might work

Decades ago, it was suggested that poor respiratory outcomes in infants delivered by elective CS may be explained by delayed absorption of liquid in the lung due to lack of a catecholamine surge (Faxelius 1983). Studies in animals during spontaneous or oxytocin-induced labour show an association between an increase in plasma epinephrine and reduced production and increased absorption of lung liquid. It is known that prostaglandin $E_2$ stimulates production of surfactant in fetal lungs as term approaches (Torday 1998). Furthermore, the concentration of beta-adrenergic receptors in lung tissue is known to increase late in gestation, which might render the lungs more responsive to the effects of epinephrine (Bland 2008). Catecholamines thus promote surfactant secretion (Whitsett 2005) and stimulate reabsorption of lung fluid from the fetal lung (Bland 2008). This catecholamine surge can be stimulated by administering prostaglandins to the pregnant woman before delivery (Singh 2004).

### Why it is important to do this review

A study evaluating metabolic adaptation in the newborn revealed that infants delivered per vagina showed high catecholamine levels at birth compared with infants born by CS under epidural or general anaesthesia (Hägnevik 1984). Prostaglandins can stimulate surfactant secretion and reduce lung fluid by provoking a catecholamine surge (Singh 2004) and therefore significantly reducing neonatal respiratory morbidity following a CS. This could eventually reduce long-term complications such as bronchopulmonary dysplasia (Bland 2008), which results from prolonged ventilation in severe RDS and asthma, which develops more frequently in children aged zero to four years with a history of TTN (Whitsett 2005). It is important to collect and summarise evidence of the use of prostaglandins for improving fetal respiratory outcomes.

## OBJECTIVES

To determine if the administration of prostaglandins before caesarean section improves the respiratory outcomes of newborns.

# METHODS

## Criteria for considering studies for this review

### Types of studies

All published and unpublished randomised trials and if unavailable, quasi-randomised controlled trials comparing the use of prostaglandins with other treatments (including placebo) to reduce neonatal respiratory morbidity.

### Types of participants

All pregnant women with an indication for a caesarean section.

### Types of interventions

Administration of prostaglandins prior to caesarean section compared with no treatment, placebo or another treatment.

### Types of outcome measures

#### Primary outcomes

1. Incidence of respiratory distress in neonates: respiratory distress will be considered as defined by the authors.
2. Need for mechanical ventilation of the neonate: this could be the Ambu resuscitator or endotracheal intubation.
3. Apgar score of newborn: the Apgar score is usually used to represent the neonate's ability to initiate and maintain breathing after birth on a scale from zero to 10. It is measured at the first and fifth minute of life. Apgar scores less than three indicate severe respiratory depression and scores from four to six indicate mild to moderate respiratory depression. There is no respiratory depression when the scores are from seven to 10 (Apgar 1953; Harrison 2008).

#### Secondary outcomes

**Maternal outcomes**

We included all adverse events reported by the study authors.

**Fetal outcomes**

1. Catecholamine levels in the neonate.
2. Neonatal arterial oxygen, carbon dioxide partial pressures and fetal scalp pH measurements.
3. All cause fetal mortality: any death that occurs from the time the neonate is included in the study.
4. Proportion of neonates requiring admission into an intensive care unit.
5. Length of stay in neonatal intensive care unit.
6. Long-term complications related to respiratory distress.
7. Any other adverse event reported by the authors.

## Search methods for identification of studies

### Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2013).

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;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, 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.

In addition, to the search carried out by the Trials Search Co-ordinator, we searched ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry and the WHO Clinical Trials Registry Platform (ICTRP), for ongoing studies. Last searched 24 June 2013 (see Appendix 1).

We did not apply any language restrictions.

## Data collection and analysis

### Selection of studies

Two review authors (NM and LM) independently assessed identified studies for inclusion. We resolved disagreements through discussion.

### Data extraction and management

We used a pre-designed and tested data extraction form to collect data from the eligible studies. Data were extracted in duplicate using the agreed form. We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2011) and checked for accuracy. Some information regarding the only included study was unclear and we attempted to contact authors of the original reports to provide further details but did not obtain any response from them.

### Assessment of risk of bias in included studies

Two review authors (NM, LM) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved all disagreement by discussion.

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

We described for the single 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 assessed 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 described for the single included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed 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 described for the single included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed 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 described for the single included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed 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 described for the single included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated 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 was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.
We assessed the methods as:

- low risk of bias (e.g. no missing outcome 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. We intended to consider studies with more than 20% missing data as high risk of bias);
- unclear risk of bias.

#### (5) Selective reporting (checking for reporting bias)

We described for the single included study how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed 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 described for the single included study any important concerns we had about other possible sources of bias.
We assessed whether the 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 made explicit judgements about whether the study was at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias by undertaking sensitivity analyses - *see* Sensitivity analysis.

### Assessment of quality of evidence across studies

We assessed the quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Guyatt 2008), defining the quality of evidence for each outcome as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest (Higgins 2011). The quality rating across studies has four levels: high, moderate, low or very low. Randomised controlled trials are categorised as high quality but can be downgraded; similarly, other types of controlled trials and observational studies are categorised as low quality but can be upgraded. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. Factors that can increase the quality level of a body of evidence include having a large magnitude of effect, whether plausible confounding would reduce a demonstrated effect, and if there is a dose-response gradient.

## Measures of treatment effect

### Dichotomous data

We presented our results as summary risk ratio with 95% confidence intervals for dichotomous data. However, there were no events for some outcomes therefore, we applied a correction of 0.5 in order to calculate the risk ratio.

### Continuous data

For continuous data, we intended to use the mean difference where outcomes were measured in the same way between trials and the standardised mean difference to combine trials that measured the same outcome, but used different methods. Data obtained from the single included study did not permit us to do so and we thus reported medians and interquartile ranges in the text.

## Unit of analysis issues

We did not identify any cluster-randomised trials for inclusion in this review. However, if we identify cluster-randomised trials in future updates of this review we will include them in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane 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. 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 sensitivity analysis to investigate the effects of the randomisation unit.

## Dealing with missing data

For the single included study, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.
For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed 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 was the number randomised minus any participants whose outcomes were known to be missing.

### Assessment of heterogeneity

We planned to assess statistical heterogeneity in each meta-analysis using the Tau-squared ($T^2$), $I^2$ and Chi-squared ($X^2$) statistics, regarding heterogeneity as substantial if an $I^2$ was greater than 30% and either a $T^2$ was greater than zero, or there was a low P value (less than 0.10) in the $X^2$ test for heterogeneity. There was one included study which did not allow for any meta-analysis or analysis of heterogeneity.

### Assessment of reporting biases

In future, updates of this review, 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 carried out statistical analysis using Review Manager software (RevMan 2011). This review contains one included study and thus, we could not combine data in meta-analysis.

In future updates of this review, 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. The random-effects summary will be treated 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, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of $T^2$ and $I^2$.

### Subgroup analysis and investigation of heterogeneity

We did not carry out our prespecified subgroup analyses due to insufficient data. We plan to carry out the following subgroup analysis in future updates of this review.

1. Preterm neonates versus term neonates.
2. Emergency CS versus elective CS.
3. Various types of prostaglandins used.

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 use random-effects analysis to produce it.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2011). 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

Planned sensitivity analysis was not carried out due to insufficient data. In future updates, sensitivity analysis will be carried out to explore the effect of trial quality, including studies assessed as having adequate controls in place for the prevention of potential bias.

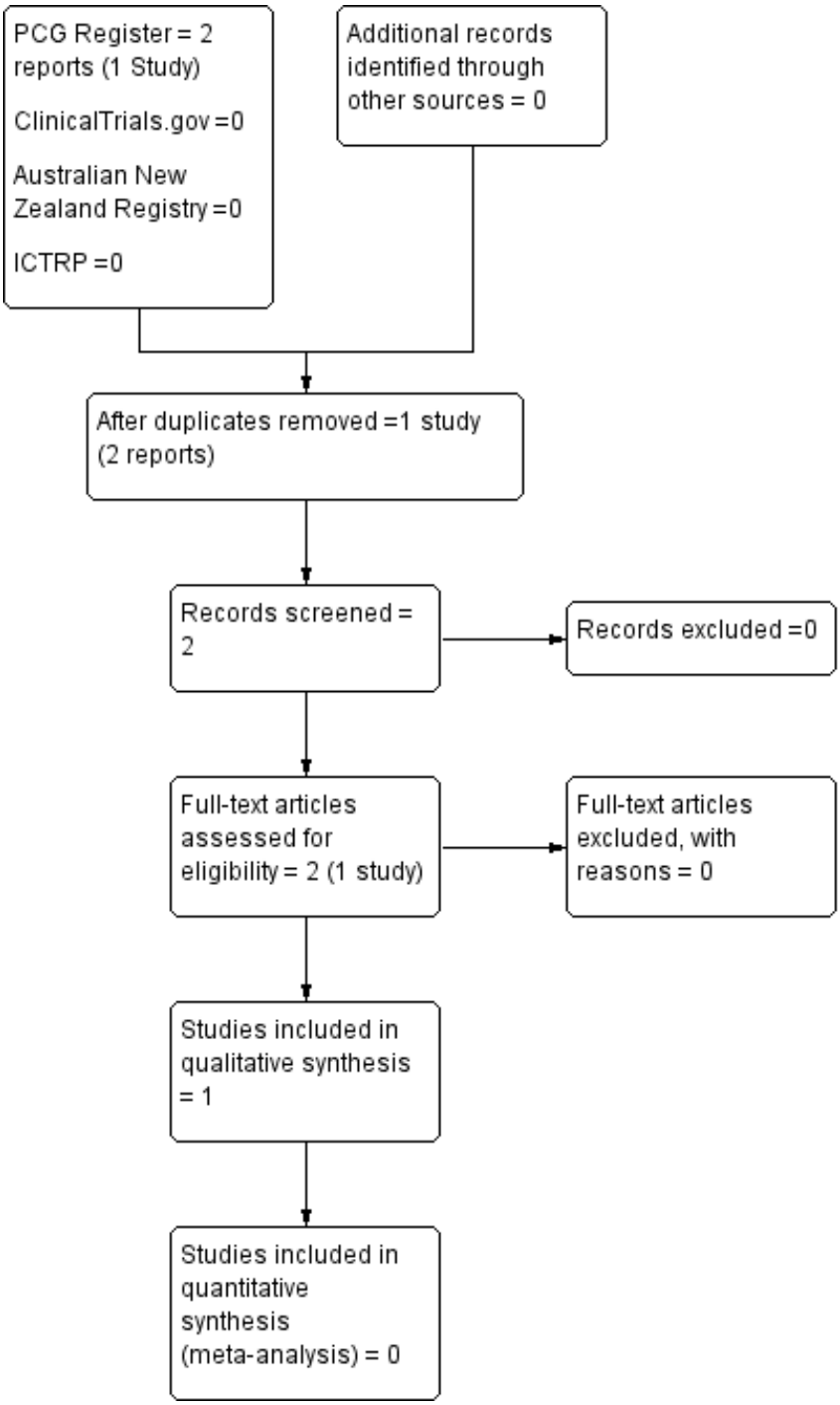
## RESULTS

## Description of studies

### Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved two reports. After verification, we realised that these were two reports of the same trial. We did not find any ongoing studies in the following trial registries: ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry and the WHO Clinical Trials Registry Platform (ICTRP) (see: Figure 1).

**Figure 1. Study flow diagram**



### Included studies

We included one randomised controlled trial in this review that compared prostaglandin $E_2$ with placebo (Singh 2004). It was a randomised placebo-controlled study that was carried out in a tertiary regional neonatal care centre in Australia. There were 36 participants, 18 in the intervention and 18 in the control group. Participants were pregnant women at term with an indication for elective caesarean section (ECS). Excluded from the study were: pregnancies with known fetal malformation/s or chromosomal aberration, presence of absolute contraindications for use of prostaglandin E2 vaginal gel, for example, history of adverse reactions to prostaglandin preparations, ECS deliveries before 38 weeks' gestation and failure to obtain informed consent. The study compared 2 mg of prostaglandin $E_2$ gel with placebo (K-Y jelly) when administered as intravaginal gel 60 minutes prior to ECS. The aim of the study was to compare catecholamine levels in neonatal cord blood between the prostaglandin $E_2$ group and the placebo group. Other outcomes assessed included Apgar score at one and five minutes, neonatal respiratory distress, admission into a neonatal special care, arterial and venous pH measurements.The study authors used non-parametric tests (Mann-Whitney-Wilcoxon test and Fisher's exact test) to compare both groups. P values were reported.

**Baseline characteristics:** the baseline characteristics of participants in the intervention and control groups were similar. These included the age of the mother, gestational age, Bishop score, parity, previous caesarean section (CS), cervical dilatation, time to delivery following prostaglandin administration and type of anaesthesia used during the CS.

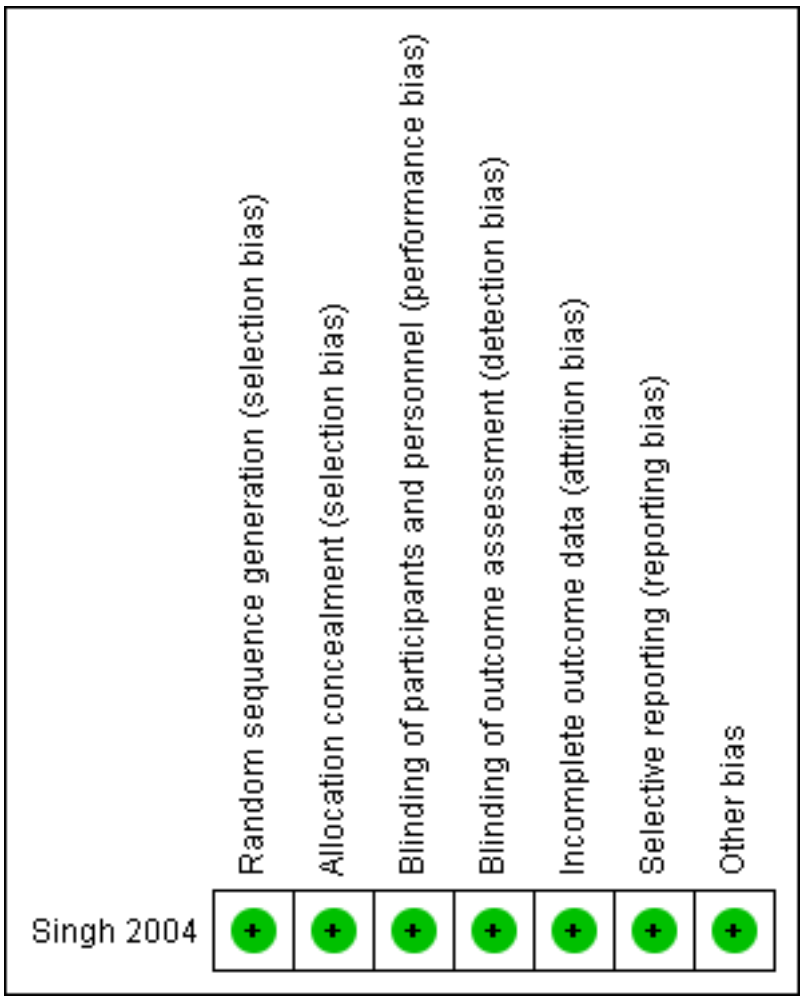
### Excluded studies

There were no excluded studies.

## Risk of bias in included studies

We assessed the risk of bias in the included study using the Cochrane 'Risk of bias' tool for randomised controlled trials (Figure 2).

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**




### Allocation

Allocation of participants to receive either the intervention or control was done using computer-generated random numbers. It was not specified if block randomisation was used but there were equal numbers in each arm. The allocation sequence was concealed using sequentially numbered opaque envelopes.

### Blinding

Enrolled participants received an equal volume of prostaglandin $E_2$ or K-Y jelly as intravaginal gel ensuring adequate blinding of participants.

Adequate blinding of the primary investigators, as well as the medical teams in charge of the mother and neonate was done. An independent research assistant was in charge of opening the sealed envelopes and administering the drug or placebo to the participants.

### Incomplete outcome data

There was one participant in the control group for whom no data were reported after randomisation. However, this did not represent any significant differential loss to follow-up.

### Selective reporting

The investigators reported all the outcomes specified in the manuscript. We were unable to find a published manuscript of the protocol for this study.

### Other potential sources of bias

We did not identify any other potential source of bias.

## Effects of interventions

See: **Summary of findings for the main comparison** Prostaglandin E2 Administered Before Caesarean Section for Prevention of Neonatal Respiratory Distress

The included study reported the following outcomes: respiratory distress, need for mechanical ventilation, Apgar score of newborns, neonatal catecholamine levels, neonatal blood pH, mortality, admission into an intensive care unit and adverse events. The continuous outcomes were reported as medians and interquartile ranges. Hence, the data could not be added to the data and analysis tables and are re-reported from the original trial report. This review had a number of other prespecified outcomes that were not reported in the included study: neonatal arterial oxygen, carbon dioxide partial pressures, length of stay in neonatal intensive care unit, and long-term complications related to respiratory distress.

### Primary outcomes

#### Incidence of respiratory distress in the neonate

There was one case of neonatal respiratory distress in the control group which the authors (Singh 2004) reported as transient tachypnoea of the newborn (risk ratio (RR) 0.33, 95% confidence interval (CI) 0.01 to 7.68, one study, n = 36 (Analysis 1.1)).

#### Need for mechanical ventilation of the neonate

None of the neonates required mechanical ventilation.

#### Apgar score of the newborn

Apgar score was reported at one and five minutes with the median (interquartile range) score being nine (eight to nine) and 9.5 (nine to 10) respectively for the intervention group. For the control group, the scores were nine (nine to nine) at one minute and nine (nine to nine) at five minutes.

### Secondary outcomes

#### Catecholamine levels in the neonate

Catecholamine levels in the neonate were reported as median values (interquartile range). Neonatal noradrenaline concentrations were reported as being significantly higher in the intervention group with respect to the control group, with measurements of 15.0 ng/L (9.8 to 28.92) and 4.6 ng/L (1.65 to 14.4) respectively (P = 0.03). The concentrations of adrenaline did not vary significantly between groups; 1.6 ng/L (below 0.5 to 3.1) for intervention group and 1.4 ng/L (below 0.5 to 2.75) for placebo group (P = 0.6).

#### Neonatal pH measurements

Arterial and venous pH measurements were similar in both intervention and control groups and were reported as median values (interquartile range). Arterial pH was 7.31 (7.28 to 7.37) for the intervention group and 7.31 (7.29 to 7.33) for the control group (P = 0.70). Venous pH measurements for intervention and control groups were 7.36 (7.34 to 7.39) and 7.37 (7.32 to 7.44) respectively (P = 0.89).

#### All cause fetal mortality

There were no deaths in the study population.

#### Proportion of neonates requiring admission into intensive care unit

No neonate was admitted into an intensive care unit.

#### Any other adverse event reported by the authors

The trialist reported that there were no treatment-related side effects reported in either group.

# DISCUSSION

## Summary of main results

There were 36 women in the one included study, 18 received intravaginal prostaglandin $E_2$ gel and 18 received placebo. One neonate in the control group developed respiratory distress, reported as transient tachypnoea of the newborn by the authors. None of the neonates required mechanical ventilation and the Apgar scores at one and five minutes where similar in both groups. Although no admissions to neonatal intensive care occurred, two neonates in the control group were admitted into special care. No further information was provided on the reasons for these admissions. Outcomes indicating respiratory status did not differ significantly between intervention and control groups and there was no treatment-related side effects. Noradrenaline concentrations were

significantly higher in the cord blood samples of the intervention group.

### Overall completeness and applicability of evidence

The only significant difference in outcomes reported was in noradrenaline measurements in neonatal cord blood. Although being a catecholamine, adrenaline measurements did not differ significantly between groups. The authors related this to the type of assay used to measure catecholamine concentrations in the study. Other indicators of neonatal respiratory well-being such as respiratory distress, mechanical ventilation, admission to special care and blood gas measurements did not differ between groups. The evidence from this review is drawn from a single small study and hence, may not be generalisable to other populations of pregnant women.

### Quality of the evidence

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) (Guyatt 2008) approach for grading the quality of evidence in this review (Higgins 2011) . We carried out one comparison: prostaglandin $E_2$ versus placebo before ECS for improving respiratory outcomes of the newborn at term. Given that the included study was a randomised controlled trial, we started at very high-quality evidence and we downgraded by two points for imprecision. We did not downgrade for risk of bias, inconsistency, indirectness and publication bias. We determined that there was low-quality evidence to determine if prostaglandins administered before caesarean could prevent neonatal respiratory distress.

### Potential biases in the review process

We were able to identify one randomised controlled trial (Singh 2004) using the comprehensive search strategy of the Cochrane Pregnancy and Childbirth Group which did not use any language limitations. We went further and searched three clinical trial registries and did not find any ongoing trials. It is possible, although unlikely that other trials have been conducted but not published, evaluating the effects of prostaglandins on neonatal respiratory outcomes. Other biases were limited by conducting the data extraction and quality assessment in duplicate.

### Agreements and disagreements with other studies or reviews

Studies in animals have demonstrated the effects of catecholamines on fetal lung adaptation to extra-uterine life (Torday 1998; Zaremba 1997). We found no reviews, trials or observational studies in humans involving the use of prostaglandins for the purpose of improving neonatal respiratory outcomes. As a result, we cannot compare the results we derived from this review to other studies.

## AUTHORS' CONCLUSIONS

### Implications for practice

Although the trial authors reported a significant increase in catecholamine levels in the intervention group, there was no significant difference in the respiratory outcomes between intervention and control groups. No definite conclusions can thus be drawn on the effects of prostaglandins on neonatal respiratory outcomes from this review due to the nature of the evidence available.

### Implications for research

Caesarean sections are increasingly performed worldwide, leading to an increase in the number of neonates at risk of respiratory distress (RD). It is important to develop interventions that prevent neonatal RD and its consequences. The study included in this review involved only prostaglandin $E_2$ vaginal gel and had a small sample size, therefore larger studies are required for better assessment of the impact of this intervention. Furthermore, the role of prostaglandins in situations such as emergency caesarean section and preterm neonates has to be defined,as well as the use of different dose regimens and routes of administration.

## ACKNOWLEDGEMENTS

We acknowledge the assistance of the Centre for the Development of Best Practices in Health (CDBPH) and the South African Cochrane Centre (SACC). This review is written within the scope of activities of the Effective Health Care Research Consortium (EHCRC).

The lead author also acknowledges the MSc in Clinical Epidemiology programme, Faculty of Medicine and Health Sciences, Stellenbosch University.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pregnancy and Childbirth Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

## REFERENCES

### References to studies included in this review


**Singh 2004** *{published data only}*

Rane A, Patole S, Singh M, Naidoo D, Buttener P. Intravaginal Prostin gel prior to elective cesarean section at term to induce catecholamine surge in cord blood - a randomised, placebo controlled pilot study. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2003;**43**: 176.

* Singh M, Patole S, Rane A, Naidoo D, Buettner P. Maternal intravaginal prostaglandin e2 gel before elective caesarean section at term to induce catecholamine surge in cord blood: randomised, placebo controlled study. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2004;**89** (2):F131–F135.


### Additional references


**Apgar 1953**

Apgar V. A proposal for a new method of evaluation of the newborn infant. *Current Research Anesthesia* 1953;**32**(4): 260–7.

**Bell 2001**

Bell JS, Campbell DM, Graham WJ, Penney GC, Ryan M, Hall MH. Do obstetric complications explain high caesarean section rates among women over 30?. *BMJ* 2001; **322**:894–5.

**Bland 2008**

Bland RD, Carlton DP, Jain L. Lung fluid balance during development and in neonatal lung disease. In: Bancalari E, Polin RA editor(s). *The Newborn Lung: Neonatalogy Questions and Controversies*. 1st Edition. Philadelphia: Saunders, 2008:141–65.

**Callaway 2005**

Callaway LK, Lust K, McIntyre HD. Pregnancy outcomes in women of very advanced maternal age. *Australian and New Zealand Journal of Obstetrics and Gynecology* 2005;**45**: 12–6.

**Faxelius 1983**

Faxelius G, Hägnevik K, Lagercrantz H, Lundell B, Irestedt L. Catecholamine surge and lung function after delivery. *Archives of Disease in Childhood* 1983;**58**:262–6.

**Guyatt 2008**

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6.

**Hansen 2007**

Hansen A, Wisborg K, Uldbjerg N, Henriksen T. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *BMJ* 2007;**336**:85.

**Harrison 2008**

Harrison VC. *The Newborn Baby*. 5th Edition. Cape Town: Juta & Company Ltd, 2008.

**Higgins 2011**

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

**Hofmeyr 2003**

Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD000941

**Hägnevik 1984**

Hägnevik K, Faxelius G, Irestedt L, Lagercrantz H, Lundell B, Persson B. Catecholamine surge and metabolic adaptation in the newborn after vaginal delivery and caesarean section. *Acta Paediatrica Scandinavica* 1984;**73** (5):602–9.

**Laws 2009**

Laws P, Sullivan EA. *Australia's Mothers and Babies 2007*. 23. Vol. **17**, Sydney: AIHW National Perinatal Statistics Unit, 2009.

**Minkoff 2003**

Minkoff H, Chervenak FA. Elective primary caesarean delivery. *New England Journal of Medicine* 2003;**348**: 946–50.

**O'Brien 1995**

O'Brien WF. The role of prostaglandins in labor and delivery. *Clinics in Perinatology* 1995;**22**(4):973–84. [PUBMED: 8665768]

**Poobalan 2009**

Poobalan AS, Aucott LS, Gurung T, Smith WC, Bhattacharya S. Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women-systematic review and meta-analysis of cohort studies. *Obesity Reviews* 2009;**10**:28–35.

**Rayburn 1989**

Rayburn WF. Prostaglandin E2 gel for cervical ripening and induction of labor: a critical analysis. *American Journal of Obstetrics and Gynecology* 1989;**160**(3):529–34. [PUBMED: 2648830]

**RevMan 2011 [Computer program]**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

**Robson 2008**

Robson S, Carey A, Mishra R, Dear K. Elective caesarean delivery at maternal request: a preliminary study of

motivations influencing women's decision-making. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2008;**48**:415–20.

**Tampakoudis 2004**
Tampakoudis P, Assimakopoulos E, Grimbizis G, Zafrakas M, Tampakoudis G, Mantalenakis S, et al. Cesarean section rates and indications in Greece: data from a 24 year period in a teaching hospital. *Clinical and Experimental Obstetrics and Gynecology* 2004;**31**:289–92.

**Torday 1998**
Torday J, Sun H, Qin J. Prostaglandin $E_2$ integrates the effects of fluid distension and glucocorticoid on lung maturation. *American Journal of Physiology* 1998;**274**: 106–11.

**Villar 2006**
Villar J, Valladares E, Wojdyla D, Zavaleta N, Carroli G, Velazco A, et al. Caesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. *Lancet* 2006;**367**: 1819–29.

**Whitsett 2005**
Whitsett JA, Rice WR, Warner BB, Wert SE, Pryhuber GS. Acute respiratory disorders. In: Macdonald MG, Mullett MD, Seshia MMK editor(s). *Avery's Neonatalogy: Pathophysiology and Management of the Newborn*. 6th Edition. Philadelphia: Lippincott Williams & Wilkins, 2005:553–77.

**Witter 1992**
Witter FR, Rocco LE, Johnson TR. A randomized trial of prostaglandin E2 in a controlled-release vaginal pessary for cervical ripening at term. *American Journal of Obstetrics and Gynecology* 1992;**166**(3):830–4.

**Zanardo 2004**
Zanardo V, Simbi AK, Franzoi M, Solda G, Salvadori A, Trevisanuto D. Neonatal respiratory morbidity risk and mode of delivery at term:influence of timing of elective caesarean delivery. *Acta Paediatrica* 2004;**93**:643–7.

**Zaremba 1997**
Zaremba W, Grunert E, Aurich JE. Prophylaxis of respiratory distress syndrome in premature calves by administration of dexamethasone or a prostaglandin F2 alpha analogue to their dams before parturition. *American Journal of Veterinary Research* 1997;**58**:404–7.

## References to other published versions of this review

**Motaze 2012**
Motaze NV, Mbuagbaw L, Young T. Prostaglandins before caesarean section for preventing neonatal respiratory distress. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD010087

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Singh 2004**

| | |
|---|---|
| Methods | Randomised placebo controlled trial. The trial was carried out in a regional tertiary neonatal centre in Australia |
| Participants | Expectant mothers eligible for ECS at 38 weeks' gestation or more who gave written consent<br>The study included 36 women (18 in the intervention group and 18 in the control group) |
| Interventions | **Active:** intravaginal administration of 2 mg of prostaglandin $E_2$ gel 60 minutes before ECS.<br>**Placebo:** intravaginal administration of 2 mg of K-Y jelly 60 minutes before ECS |
| Outcomes | The main outcome for the study was adrenaline and noradrenaline levels in neonatal umbilical cord blood. Measurements of umbilical venous and arterial pH were obtained. Incidence of neonatal respiratory distress, Apgar score of the newborn, need for mechanical ventilation and proportion of neonates requiring admission into intensive care unit were also assessed |
| Notes | The ethics committee of the tertiary neonatal care institution where the study was carried out provided ethics approval |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated random numbers. |
| Allocation concealment (selection bias) | Low risk | Sealed, coded, opaque, sequentially numbered envelopes. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Intervention group given prostaglandin E2 gel and control group given an equal volume of K-Y jelly<br>Independent research assistant administered trial drug or placebo to participants |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Outcome assessors blinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Intention-to-treat analysis done, no significant loss to follow-up |

**Singh 2004** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | All expected outcomes of interest to the review reported. |
| Other bias | Low risk | No other potential source of bias. |

ECS: elective caesarean section

## DATA AND ANALYSES

### Comparison 1. Prostaglandin E2 gel vs placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Respiratory distress | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

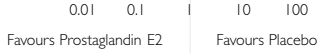
**Analysis 1.1. Comparison 1 Prostaglandin E2 gel vs placebo, Outcome 1 Respiratory distress.**

Review: Prostaglandins before caesarean section for preventing neonatal respiratory distress

Comparison: 1 Prostaglandin E2 gel vs placebo

Outcome: 1 Respiratory distress

| Study or subgroup | Prostaglandin E2 n/N | Placebo n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Singh 2004 | 0/18 | 1/18 | | 0.33 [ 0.01, 7.68 ] |




## APPENDICES

### Appendix 1. Search terms for clinical trial registries

Caesarean, prostaglandin, neonatal respiratory distress. The search combination used was (Caesarean AND prostaglandin AND neonatal respiratory distress)
(Authors wrote and ran this search)

## CONTRIBUTIONS OF AUTHORS

NV Motaze conceived of the idea of the review and developed the first draft of the protocol. All authors reviewed the draft and completed the protocol. NV Motaze and L Mbuagbaw carried out independent study selection, assessment of methodological quality and data extraction. The first review author entered data into RevMan and wrote the first draft of the completed review. All authors worked on the review and approved the final manuscript. T Young commented on the protocol, provided methodological guidance and support for the review conduct, contributed to the review write up and finalisation.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT


### Internal sources

- The Centre for the Development of Best Practices in Health, Cameroon.
- South African Cochrane Centre, Medical Research Council, South Africa.

### External sources

- No sources of support supplied


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used the GRADE approach to assess the quality of evidence in this review. Three additional clinical trial registries not reported in the protocol were searched. We did not find any ongoing studies in the following trial registries: ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry and the WHO Clinical Trials Registry Platform (ICTRP).

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Cesarean Section; Preoperative Care [*methods]; Prostaglandins E [*administration & dosage]; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn [*prevention & control]

### MeSH check words

Female; Humans; Infant, Newborn; Pregnancy