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Extra-amniotic prostaglandin for induction of labour (Review)

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Extra-amniotic prostaglandin for induction of labour (Review)

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
DISCUSSION	8
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	11
DATA AND ANALYSES	18
Analysis 1.1. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 1 Apgar score < 7 at 5 minutes.	19
Analysis 1.2. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 2 Uterine hyperstimulation with FHR changes.	19
Analysis 1.3. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 3 Caesarean section.	19
Analysis 1.4. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 4 Abnormal FHR.	20
Analysis 1.5. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 5 Dystocia.	20
Analysis 1.6. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 6 Intrapartum fever.	20
Analysis 1.7. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 7 Oxytocin augmentation. ...	20
Analysis 1.8. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 8 Uterine hyperstimulation without FHR changes.	21
Analysis 1.9. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 9 Postpartum haemorrhage.	21
Analysis 1.10. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 10 Instrumental vaginal delivery.	21
Analysis 1.11. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 11 Maternal side-effects. ...	22
Analysis 2.1. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 1 Uterine hyperstimulation with FHR changes.	23
Analysis 2.2. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 2 Caesarean section.	23
Analysis 2.3. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 3 Oxytocin augmentation.	24
Analysis 2.4. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 4 Uterine hyperstimulation without FHR changes.	24
Analysis 2.5. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 5 Instrumental vaginal delivery.	24
Analysis 2.6. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 6 Maternal side-effects.	25
Analysis 3.1. Comparison 3 Extra-amniotic PGE2 vs extra-amniotic placebo: all primiparae, Outcome 1 Caesarean section.	25
Analysis 3.2. Comparison 3 Extra-amniotic PGE2 vs extra-amniotic placebo: all primiparae, Outcome 2 Oxytocin augmentation.	26
Analysis 4.1. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 1 Caesarean section.	26
Analysis 4.2. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 2 Serious maternal morbidity or death.	27
Analysis 4.3. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 3 Uterine hyperstimulation without FHR changes.	27
Analysis 4.4. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 4 Instrumental vaginal delivery.	27
Analysis 4.5. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 5 Perinatal death. ..	28
Analysis 5.1. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 1 Caesarean section.	28

Analysis 5.2. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 2 Serious maternal morbidity or death.	29
Analysis 5.3. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 3 Uterine hyperstimulation without FHR changes.	29
Analysis 5.4. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 4 Instrumental vaginal delivery.	29
Analysis 5.5. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 5 Perinatal death.	30
Analysis 6.1. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 1 Caesarean section.	30
Analysis 6.2. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 2 Serious maternal morbidity or death.	31
Analysis 6.3. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 3 Uterine hyperstimulation without FHR changes.	31
Analysis 6.4. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 4 Instrumental vaginal delivery.	31
Analysis 6.5. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 5 Perinatal death.	32
Analysis 7.1. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 1 Caesarean section.	32
Analysis 7.2. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 2 Serious maternal morbidity or death.	33
Analysis 7.3. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 3 Uterine hyperstimulation without FHR changes.	33
Analysis 7.4. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 4 Instrumental vaginal delivery.	33
Analysis 7.5. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 5 Perinatal death.	34
Analysis 8.1. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 1 Vaginal delivery not achieved within 24 hours.	35
Analysis 8.2. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 2 Uterine hyperstimulation with FHR changes.	35
Analysis 8.3. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 3 Caesarean section.	35
Analysis 8.4. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 4 Maternal satisfaction.	36
Analysis 8.5. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 5 Oxytocin augmentation.	36
Analysis 8.6. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 6 Uterine hyperstimulation without FHR changes.	36
Analysis 8.7. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 7 Instrumental vaginal delivery.	37
Analysis 8.8. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 8 Meconium-stained liquor.	37
Analysis 8.9. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 9 Apgar score < 7 at 5 minutes.	37
Analysis 8.10. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 10 Maternal side-effects.	38
Analysis 8.11. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 11 Maternal satisfaction - embarrassment.	38
Analysis 9.1. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 1 Vaginal delivery not achieved in 24 hours.	39
Analysis 9.2. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 2 Uterine hyperstimulation with FHR changes.	40
Analysis 9.3. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 3 Caesarean section.	40
Analysis 9.4. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 4 Maternal satisfaction.	40
Analysis 9.5. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 5 Oxytocin augmentation.	41
Analysis 9.6. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 6 Uterine hyperstimulation without FHR changes.	41

Analysis 9.7. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 7 Instrumental vaginal delivery.	41
Analysis 9.8. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 8 Meconium-stained liquor.	42
Analysis 9.9. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 9 Apgar score < 7 at 5 minutes.	42
Analysis 9.10. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 10 Maternal side-effects.	42
Analysis 9.11. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 11 Maternal satisfaction - embarrassment.	43
Analysis 10.1. Comparison 10 Extra-amniotic PGE2 vs vaginal PGE2: all women, favourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.	43
Analysis 11.1. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 1 Vaginal delivery not achieved within 24 hours.	44
Analysis 11.2. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 2 Caesarean section.	44
Analysis 11.3. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 3 Instrumental vaginal delivery. ..	45
Analysis 11.4. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 4 Meconium-stained liquor.	45
Analysis 12.1. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.	46
Analysis 12.2. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 2 Caesarean section.	46
Analysis 12.3. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 3 Instrumental vaginal delivery.	46
Analysis 12.4. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 4 Meconium-stained liquor.	47
Analysis 13.1. Comparison 13 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, favourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.	47
Analysis 14.1. Comparison 14 Extra-amniotic PGE2 vs vaginal PGE2: all multiparae (without prior CS), Outcome 1 Vaginal delivery not achieved within 24 hours.	48
Analysis 15.1. Comparison 15 Extra-amniotic PGE2 vs vaginal PGE2: all multiparae, unfavourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.	48
Analysis 16.1. Comparison 16 Extra-amniotic PGE2 vs vaginal PGE2: all multiparae, favourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.	49
Analysis 17.1. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 1 Hyperstimulation with FHR changes.	50
Analysis 17.2. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 2 Meconium-stained liquor.	50
Analysis 17.3. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 3 Caesarean section.	50
Analysis 17.4. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 4 Vomiting.	50
Analysis 17.5. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 5 "Other" maternal infection.	51
Analysis 17.6. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 6 All maternal side-effects.	51
Analysis 17.7. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 7 "Other" maternal fever other than infection.	51
Analysis 17.8. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 8 instrumental vaginal delivery.	52
Analysis 17.9. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 9 Cervix unfavourable > 12-24 hours.	52
Analysis 17.10. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 10 Serious maternal complications.	52
Analysis 18.1. Comparison 18 Extra-amniotic PGE2 vs cervical PGE2: all primiparae, Outcome 1 Caesarean section.	53
Analysis 19.1. Comparison 19 Extra-amniotic PGE2 vs cervical PGE2: all women, unfavourable cervix, Outcome 1 Caesarean section.	53
Analysis 20.1. Comparison 20 Extra-amniotic PGE2 vs cervical PGE2: all primiparae, unfavourable cervix, Outcome 1 Caesarean section.	54
Analysis 21.1. Comparison 21 Extra-amniotic PGE2 vs cervical PGE2: all multiparae, Outcome 1 Caesarean section.	54
Analysis 22.1. Comparison 22 Extra-amniotic PGE2 vs cervical PGE2: all multiparae, unfavourable cervix, Outcome 1 Caesarean section.	55
Analysis 23.1. Comparison 23 Extra-amniotic PGE2 vs oxytocin: all women, Outcome 1 Caesarean section.	55

Analysis 23.2. Comparison 23 Extra-amniotic PGE2 vs oxytocin: all women, Outcome 2 Instrumental vaginal delivery.	56
Analysis 24.1. Comparison 24 Extra-amniotic PGE2 vs oxytocin: all women, unfavourable cervix, Outcome 1 Caesarean section.	56
Analysis 24.2. Comparison 24 Extra-amniotic PGE2 vs oxytocin: all women, unfavourable cervix, Outcome 2 Instrumental vaginal delivery.	56
Analysis 25.1. Comparison 25 Extra-amniotic PGE2 vs oxytocin: all primiparae, Outcome 1 Caesarean section.	57
Analysis 25.2. Comparison 25 Extra-amniotic PGE2 vs oxytocin: all primiparae, Outcome 2 Instrumental vaginal delivery.	57
Analysis 26.1. Comparison 26 Extra-amniotic PGE2 vs oxytocin: all primiparae, unfavourable cervix, Outcome 1 Caesarean section.	58
Analysis 26.2. Comparison 26 Extra-amniotic PGE2 vs oxytocin: all primiparae, unfavourable cervix, Outcome 2 Instrumental vaginal delivery.	58
Analysis 27.1. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 1 Uterine hyperstimulation with FHR changes.	59
Analysis 27.2. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 2 Caesarean section.	59
Analysis 27.3. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 3 Serious neonatal morbidity or perinatal death.	59
Analysis 27.4. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 4 Oxytocin augmentation. ...	60
Analysis 27.5. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 5 Instrumental vaginal delivery.	60
Analysis 27.6. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 6 Neonatal intensive care unit admission.	60
Analysis 27.7. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 7 Perinatal death.	61
Analysis 28.1. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 1 Uterine hyperstimulation with FHR changes.	62
Analysis 28.2. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 2 Caesarean section.	62
Analysis 28.3. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 3 Serious neonatal morbidity or perinatal death.	62
Analysis 28.4. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 4 Oxytocin augmentation.	63
Analysis 28.5. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 5 Instrumental vaginal delivery.	63
Analysis 28.6. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 6 Neonatal intensive care unit admission.	63
Analysis 28.7. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 7 Perinatal death.	64
Analysis 29.1. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 1 Caesarean section.	65
Analysis 29.2. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 2 Hyperstimulation with FHR changes.	65
Analysis 29.3. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 3 Meconium-stained liquor.	65
Analysis 29.4. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 4 All maternal side-effects.	65
Analysis 29.5. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 5 Vomiting.	66
Analysis 29.6. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 6 "Other" maternal infection.	66
Analysis 29.7. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 7 "Other" maternal fever other than infection.	66
Analysis 29.8. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 8 Cervix unfavourable > 12-24 hours.	67
Analysis 29.9. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 9 Serious maternal complications.	67
Analysis 29.10. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 10 Instrumental vaginal delivery.	67
Analysis 30.1. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 1 Vaginal delivery not achieved in 24 hours.	68
Analysis 30.2. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 2 Caesarean section.	69
Analysis 30.3. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 3 Serious maternal morbidity or death.	69
Analysis 30.4. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 4 Oxytocin augmentation.	69

Analysis 30.5. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 5 Uterine rupture.	70
Analysis 30.6. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 6 Meconium-stained liquor.	70
Analysis 30.7. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 7 Neonatal intensive care unit admission.	70
Analysis 30.8. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 8 Perinatal death.	70
Analysis 30.9. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 9 Postpartum haemorrhage.	71
Analysis 30.10. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 10 Fetal distress necessitating caesarean.	71
Analysis 30.11. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 11 Apgar < 5 (time unknown).	71
APPENDICES	72
WHAT'S NEW	72
HISTORY	72
CONTRIBUTIONS OF AUTHORS	72
DECLARATIONS OF INTEREST	73
SOURCES OF SUPPORT	73
INDEX TERMS	73

[Intervention Review]

Extra-amniotic prostaglandin for induction of labour

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ABSTRACT

Background

This is one of a series of reviews of methods of cervical ripening and labour induction using standardised methodology.

Objectives

To determine the effects of extra-amniotic prostaglandin for third trimester cervical ripening or induction of labour.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (June 2009) and bibliographies of relevant papers.

Selection criteria

Randomised and quasi-randomised trials comparing extra-amniotic prostaglandin used for third trimester cervical ripening or labour induction with placebo/no treatment or other methods listed above it on a predefined list of labour induction methods.

Data collection and analysis

Two review authors independently assessed eligibility and carried out data extraction for all reports identified by the search strategy.

Main results

Twelve studies are included. Of the primary outcomes, there were significantly fewer women delivered vaginally within 24 hours among those induced with extra-amniotic prostaglandin (PG) F2 alpha compared to vaginal misoprostol (risk ratio (RR) 2.43; 95% confidence interval (CI) 1.42 to 4.15). No other differences between groups for primary outcomes were found to be statistically significant. Oxytocin was used to initiate or augment labour significantly less frequently with extra-amniotic prostaglandins when compared to placebo (RR 0.51; 95% CI 0.39 to 0.67) but significantly more frequently when compared to vaginal misoprostol (RR 1.73; 95% CI 1.20 to 2.49). When extra-amniotic PGE2 was compared to Foley catheter only, the only difference between groups was that there were fewer cases of unfavourable cervix at 12 to 24 hours following treatment (RR 0.59; 95% CI 0.41 to 0.86). Women receiving extra-amniotic prostaglandin were more likely to be satisfied (mean difference 4.40; 95% CI 3.50 to 5.30) and less likely to be embarrassed by the treatment compared to vaginal PGE2 (RR 8.91; 95% CI 2.26 to 35.02). There were no other significant differences when extra-amniotic prostaglandins were compared with other methods of cervical ripening or induction of labour. Although this could suggest that extra-amniotic prostaglandins are as effective as other agents, the findings are difficult to interpret because they are based on very small numbers and may lack the power to show a real difference.

Authors' conclusions

The studies in this review are limited by sample size which are often divided into multiple comparison groups. Most comparisons showed no significant differences, with wide confidence intervals. Although extra-amniotic prostaglandins may be as effective as other modalities in initiating labour, there is little conclusive information from this review to guide clinical practice. An adequately powered randomised controlled trial would be useful to determine if the use of extra-amniotic prostaglandins would lower the rate of caesarean section.

PLAIN LANGUAGE SUMMARY**Extra-amniotic prostaglandin for induction of labour**

Not enough evidence to show any benefit of extra-amniotic prostaglandin for the induction of labour over other methods.

Sometimes it is necessary to start labour artificially because of safety concerns for the mother or baby. Drugs can be given as a gel placed inside the vagina or cervix or inside the uterine cavity in the space between the uterine wall and the amniotic sac. This gel is put in place using a catheter. Prostaglandins are drugs that are used to ripen the cervix or help start labour. The review of twelve trials compared different methods of giving prostaglandin to start labour. Extra-amniotic prostaglandin was found to be effective, but it is more invasive than other methods. There was not enough evidence to show benefits of extra-amniotic prostaglandin over other methods.

BACKGROUND

Sometimes it is necessary to bring on labour artificially because of safety concerns for the mother or baby. This review is one of a series of reviews of methods of labour induction using a standardised protocol. For more detailed information on the rationale for this methodological approach, please refer to the currently published 'generic' protocol ([Hofmeyr 2000](#)). The generic protocol describes how a number of standardised reviews will be combined to compare various methods of preparing the cervix of the uterus and inducing labour. The studies included in this review are primarily concerned with the action of extra-amniotic prostaglandins as cervical ripening agents in preparation for induction of labour.

Prostaglandins have been used since the early 1970s as cervical ripening agents in the 'pre-induction management' of women requiring induction of labour, but presenting with an unripe or unfavourable cervix. When induction is undertaken with an unripe cervix, there is a higher rate of failed induction and an ensuing increased rate of caesarean delivery. Amniotomy is often used with oxytocin to facilitate induction and is believed to be associated with the release of endogenous prostaglandins which promote cervical ripening. However, this procedure can be uncomfortable, difficult, or impossible with a closed cervix and has the disadvantage of imposing a time limit on the induction process.

Of the prostaglandins that have been used for ripening and induction, it is believed that PGE₂ acts primarily on cervical tissues, while PGF₂α acts on both the cervical and myometrial tissues. The characteristics of an ideal cervical ripening agent include the ability to act on the cervix without myometrial action (including contractions). Extra-amniotic placement of prostaglandins was first undertaken in the early 1970s and has been largely replaced with cervical or vaginal placement. Although there are reports of prostaglandin tablets being introduced into the extra-vaginal space, all the studies included in the review use prostaglandin gel, with one exception which uses prostaglandin in a saline solution (0.5 micrograms/ml), applied via a Foley catheter at a rate of 1 ml/min ([Sherman 2001](#)). When prostaglandin gel is used it is placed via a Foley catheter inserted through the cervix into the extra-amniotic space, and in most studies the catheter is left in place with the balloon inflated, with or without application of traction on the balloon by way of taping the Foley to the maternal leg.

OBJECTIVES

To determine, from the best available evidence, the effectiveness and safety of extra-amniotic prostaglandin for third trimester cervical ripening and induction of labour.

METHODS

Criteria for considering studies for this review

Types of studies

Clinical trials comparing extra-amniotic prostaglandin for cervical ripening or labour induction, with placebo/no treatment or other methods listed above it on a predefined list of methods of labour induction have been reviewed. All included trials incorporated some form of random allocation to either group and they reported one or more of the prestated outcomes (see '[Data collection and analysis](#)').

Types of participants

Pregnant women due for third trimester induction of labour, carrying a viable fetus were included.

Predefined subgroup analyses including nulliparity or multiparity; and cervix unfavourable, favourable or undefined, have been done. Only those outcomes with data appear in the analysis tables.

Types of interventions

Extra-amniotic prostaglandin compared with placebo/no treatment or several other methods for labour induction or preparation for labour induction, which are placed above extra-amniotic prostaglandin on a predefined list of methods of labour induction. The comparisons included in the studies in this review included:

- (i) placebo;
- (ii) vaginal prostaglandins;
- (iii) intracervical prostaglandins;
- (iv) intravenous oxytocin;
- (v) vaginal misoprostol;
- (vi) mechanical methods (Foley catheter with traction).

For the details of this selection strategy please refer to the section: '[Methods](#)'.

Types of outcome measures

Clinically relevant outcomes for trials of methods of cervical ripening/labour induction have been prespecified by two authors of labour induction reviews (Justus Hofmeyr and Zarko Alfirevic). Differences were settled by discussion.

Five primary outcomes were chosen as being most representative of the clinically important measures of effectiveness and complications. Sub-group analyses will be limited to the primary outcomes:

- (1) vaginal delivery not achieved within 24 hours (or period specified by trial authors);
- (2) uterine hyperstimulation with fetal heart rate (FHR) changes;
- (3) caesarean section;
- (4) serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood);
- (5) serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicemia).

Perinatal and maternal morbidity and mortality are composite outcomes. This is not an ideal solution because some components are clearly less severe than others. It is possible for one intervention to cause more deaths but less severe morbidity. However, in the context of labour induction at term this is unlikely. All these events will be rare, and a modest change in their incidence will be easier to detect if composite outcomes are presented. The incidence of individual components will be explored as secondary outcomes (see below).

Secondary outcomes relate to measures of effectiveness, complications and satisfaction:

Measures of effectiveness:

- (6) cervix unfavourable/unchanged after 12 to 24 hours;
- (7) oxytocin augmentation.

Complications:

- (8) uterine hyperstimulation without FHR changes;
- (9) uterine rupture;
- (10) epidural analgesia;
- (11) instrumental vaginal delivery;
- (12) meconium-stained liquor;
- (13) Apgar score less than seven at five minutes;
- (14) neonatal intensive care unit admission;
- (15) neonatal encephalopathy;
- (16) perinatal death;
- (17) disability in childhood;
- (18) maternal side-effects (all);
- (19) maternal nausea;
- (20) maternal vomiting;
- (21) maternal diarrhoea;
- (22) other maternal side-effects;
- (23) postpartum haemorrhage (as defined by the trial authors);
- (24) serious maternal complications (e.g. intensive care unit admission, septicaemia but excluding uterine rupture);
- (25) maternal death.

Measures of satisfaction:

- (26) woman not satisfied;
- (27) caregiver not satisfied.

'Uterine rupture' includes all clinically significant ruptures of unscarred or scarred uteri. Trivial scar dehiscence noted incidentally at the time of surgery are excluded.

Additional outcomes may appear in individual primary reviews, but will not contribute to the secondary reviews.

While all the above outcomes were sought, only those with data appear in the analysis tables.

The terminology of uterine hyperstimulation is problematic (Curtis 1987). In the reviews we use the term 'uterine hyperstimulation without FHR changes' to include uterine tachysystole (more than five contractions per 10 minutes for at least 20 minutes) and uterine hypersystole/hypertonus (a contraction lasting at least two minutes) and 'uterine hyperstimulation with FHR changes' to denote uterine hyperstimulation syndrome (tachysystole or hypersystole with FHR changes such as persistent decelerations, tachycardia or decreased short-term variability).

Outcomes were included in the analysis if reasonable measures were taken to minimise observer bias and data were available for analysis according to original allocation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (June 2009).

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

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;

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

Details of the search strategies for CENTRAL and MEDLINE, 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.

The search for the first version of this review was performed simultaneously for all reviews of methods of inducing labour, as outlined in the generic protocol for these reviews (Hofmeyr 2000).

Searching other resources

We searched the reference lists of trial reports and reviews by hand.

We did not apply any language restrictions.

Data collection and analysis

To avoid duplication of data the labour induction methods have been listed in a specific order, from one to 27. Each review includes comparisons between one of the methods (from two to 27) with only those methods above it on the list. Thus, the review of intravenous oxytocin (4) will include only comparisons with intracervical prostaglandins (3), vaginal prostaglandins (2) or placebo (1). Methods identified in the future will be added to the end of the list. The current list is as follows:

1. placebo/no treatment;
2. vaginal prostaglandins (Kelly 2003);
3. intracervical prostaglandins (Boulvain 2008);
4. intravenous oxytocin (Kelly 2001);
5. amniotomy (Bricker 2000);
6. intravenous oxytocin with amniotomy (Howarth 2001);
7. vaginal misoprostol (Hofmeyr 2003);
8. oral misoprostol (Alfirevic 2006)
9. mechanical methods including extra-amniotic Foley catheter (Boulvain 2001);
10. membrane sweeping (Boulvain 2005);
11. extra-amniotic prostaglandins (Hutton 2001);
12. intravenous prostaglandins (Luckas 2000);
13. oral prostaglandins (French 2001);
14. mifepristone (Neilson 2000);
15. estrogens (Thomas 2001);
16. corticosteroids (Kavanagh 2006);
17. relaxin (Kelly 2001a);
18. hyaluronidase (Kavanagh 2006a);
19. castor oil, bath, and/or enema (Kelly 2001b);
20. acupuncture (Smith 2004);
21. breast stimulation (Kavanagh 2005);
22. sexual intercourse (Kavanagh 2001);

23. homeopathic methods ([Smith 2003](#));
24. nitric oxide donors ([Kelly 2008](#));
25. buccal or sublingual misoprostol ([Muzonzini 2004](#))
26. hypnosis;
27. other methods for induction of labour.

The reviews will be analysed by the following subgroups:

1. previous caesarean section or not;
2. nulliparity or multiparity;
3. membranes intact or ruptured;
4. cervix favourable, unfavourable or undefined.

For most reviews, the initial data extraction process was conducted centrally. This was co-ordinated from the Clinical Effectiveness Support Unit (CESU) at the Royal College of Obstetricians and Gynaecologists, UK, in co-operation with the Pregnancy and Childbirth Group of the Cochrane Collaboration. This process allowed the data extraction process to be standardised across all the reviews. From 2001, the data extraction was no longer conducted centrally.

The trials were initially reviewed on eligibility criteria, using a standardised form and the basic selection criteria specified above. Following this, data were extracted to a standardised data extraction form which was piloted for consistency and completeness. The pilot process involved the researchers at the CESU and previous review authors in the area of induction of labour.

Information was extracted regarding the methodological quality of trials on a number of levels. This process completed without consideration of trial results. Assessment of selection bias examined the process involved in the generation of the random sequence and the method of allocation concealment separately. These were then judged as adequate or inadequate using the criteria described in [Appendix 1](#) for the purpose of the reviews.

Performance bias was examined with regards to whom was blinded in the trials, i.e. patient, caregiver, outcome assessor or analyst. In many trials the caregiver, assessor and analyst were the same party. Details of the feasibility and appropriateness of blinding at all levels is sought.

Individual outcome data were included in the analysis if they met the pre-stated criteria in [Types of outcome measures](#). Included trial data were processed as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)). Data extracted from the trials were analysed on an intention-to-treat basis (when this was not done in the original report, re-analysis was performed if possible). Where data were missing, clarification is sought from the original authors. If the attrition was such that it might significantly affect the results, these data have been excluded from the analysis. Once missing data become available, they will be included in the analyses.

Data were extracted from all eligible trials to examine how issues of quality influence effect size in a sensitivity analysis. In trials where reporting is poor, methodological issues are reported as unclear or clarification sought.

Due to the large number of trials, double data extraction was not feasible and agreement between the three data extractors was therefore assessed on a random sample of trials.

Once the data had been extracted, they were distributed to individual review authors for entry onto the Review Manager computer software ([RevMan 2008](#)), checked for accuracy, and analysed as above using the RevMan software. For dichotomous data, risk ratios and 95% confidence intervals are calculated, and in the absence of heterogeneity, results are pooled using a fixed-effect model.

The predefined criteria for sensitivity analysis include all aspects of quality assessment as mentioned above, including aspects of selection, performance and attrition bias.

Primary analysis was limited to the prespecified outcomes and subgroup analyses. In the event of differences in unspecified outcomes or sub-groups being found, these were analysed post hoc, but clearly identified as such to avoid drawing unjustified conclusions.

In 2008, the methods and software for carrying out reviews were updated, as a result of which new reviews and updates, where appropriate, will use these new methods ([Higgins 2008](#); [RevMan 2008](#)), which will be described in the Methods section of all the individual new and updated reviews.

For this update, we used the following methods when assessing the trials identified by the updated search.

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)). We described methods used for generation of the randomisation sequence for each trial.

(1) Selection bias (randomisation and allocation concealment)

We assigned a quality score for each trial, using the following criteria:

- adequate concealment of allocation: such as telephone randomisation, consecutively-numbered, sealed opaque envelopes;
- unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
- inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:

- less than 5% loss of participants;
- 5% to 9.9% loss of participants;
- 10% to 19.9% loss of participants;
- more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:

- (1) blinding of participants (yes/no/unclear);
- (2) blinding of caregiver (yes/no/unclear);
- (3) blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. If heterogeneity was found, we explored this by sensitivity analysis, followed by random-effects if required.

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but use different methods. Where there was evidence of skewness, this has been reported.

Dealing with missing data

We analysed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If, in the original reports, participants were not analysed in the group to which they were randomised and there is sufficient information in the trial report, we attempted to restore them to the correct group.

Assessment of heterogeneity

We applied tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we identified high levels of heterogeneity among the trials (exceeding 50%), we explored it by prespecified subgroup analysis and performed sensitivity analysis. We used a random-effects meta-analysis as an overall summary if this is considered appropriate.

Subgroup analyses

We conducted planned subgroup analyses as performed for the other reviews in this series (see [Data collection and analysis](#)). When assessing differences between sub groups e.g. within the comparison of vaginal PGE2 versus placebo, we explored this using an inverse variance method of meta analysis and presenting the statistics for subgroup differences using chi square and I^2 statistics.

Sensitivity analyses

We did not carry out sensitivity analysis because the number of studies was too small in any one analysis to justify this step.

RESULTS

Description of studies

Excluded studies

Nine studies have been excluded. [Salamalekis 1990](#), [Toppozada 1994](#) and [Tsalacopoulos 1982](#) were excluded because the entry criterion for the study was intrauterine death. Several studies were excluded because they reported none of the primary outcomes of interest ([Calder 1974](#); [Fletcher 1993](#); [Keirse 1982](#); [Reichel 1985](#); [Thiery 1981](#); [Thoumsin 1982](#)). For one additional study, we are awaiting confirmation that the data are original ([Majoko 2002b](#)).

Included studies

Twelve studies are included in this review.

PGF2alpha was studied in three of the trials ([Mahomed 1988](#); [Majoko 2002a](#); [Quinn 1981](#)) and the remaining studies used PGE2. In all of the included studies the prostaglandin introduced into the extra-amniotic space was in a gel preparation, with one exception which used prostaglandin in a saline solution (0.5 micrograms/ml), applied via Foley catheter at a rate of 1 ml/min ([Sherman 2001](#)). Neither [Parewicz 1986](#), [Shepherd 1976](#), nor [Wilson 1978](#) report on how the prostaglandin gel was introduced into the extra-amniotic space. Of the remaining studies, [Clarke 1980](#) and [Fenton 1985](#) removed the catheter after insertion of the gel, while all others left the catheter in situ. Of the studies with the catheter remaining in situ, [Quinn 1981](#) inflated the catheter balloon to 10 ml, [Greer 1989](#) and [Stewart 1985](#) to 20 ml, while [Mahomed 1988](#) and [Sherman 2001](#) inflated the catheter balloon to 30 ml; [Majoko 2002a](#) to 40 ml and [Allouche 1993](#) to 50 ml. When a Foley catheter is used as a mechanical method of induction, it is usually inflated to 30 to 40 ml and left in place. One study ([Allouche 1993](#)) administered 0.01% (0.5 mg) salbutamol prior to both the administration of PGE2 extra-amniotically and cervically.

There was a considerable variation in the interventions being compared to extra-amniotic prostaglandin including: vaginal PGE2 ([Clarke 1980](#); [Greer 1989](#); [Stewart 1985](#); [Wilson 1978](#)), vaginal PGE1 (misoprostol) ([Majoko 2002a](#)) intra-cervical PGE2 ([Allouche 1993](#); [Parewicz 1986](#)), oral PGE2 ([Wilson 1978](#)), intravenous oxytocin ([Wilson 1978](#)) extra-amniotic oestriol ([Quinn 1981](#)), Foley catheter with traction ([Allouche 1993](#); [Mahomed 1988](#)) and placebo ([Fenton 1985](#); [Quinn 1981](#); [Shepherd 1976](#); [Sherman 2001](#)).

Both the comparison with extra-amniotic oestriol ([Quinn 1981](#)) and oral PGE2 ([Wilson 1978](#)) have been excluded from this review, because they are below extra-amniotic prostaglandins on the pre-defined list of comparisons.

Risk of bias in included studies

Randomisation

Of the twelve studies included, six did not describe methods of randomisation ([Greer 1989](#); [Parewicz 1986](#); [Quinn 1981](#); [Sherman 2001](#); [Stewart 1985](#); [Wilson 1978](#)), one used allocation by date of birth ([Clarke 1980](#)), one used alternation ([Shepherd 1976](#)). The remaining five described adequate methods of random allocation and concealment of sequence ([Allouche 1993](#); [Fenton 1985](#); [Mahomed 1988](#); [Majoko 2002a](#); [Sherman 2001](#)).

Blinding

Several authors discussed the fact that given the nature of the interventions being compared blinding would be challenging (Mahomed 1988; Majoko 2002a; Wilson 1978). Blinding is known to have been used in three of the trials (Fenton 1985; Quinn 1981; Sherman 2001). Blinding was not discussed in any of the other studies. In the absence of blinding, there is a real possibility of bias particularly in clinical management decisions, which could impact on outcomes such as the number of vaginal deliveries not achieved within 24 hours, or caesarean section rates.

Effects of interventions

Extra-amniotic prostaglandin versus placebo

Extra-amniotic PGE2

Three studies compared extra-amniotic PGE2 with placebo. Fenton 1985 (n = 30) enrolled nulliparous women with a Bishop's score of less than four at more than 36 weeks while Shepherd 1976 (n = 30) and Sherman 2001 (n = 116) used the same cervical and gestational age criteria, but included multiparous women as well. Fenton 1985 and Shepherd 1976 inserted the placebo via a Foley catheter and removed the catheter, while Sherman 2001 left the inflated Foley catheter in place following administration of the treatment and placebo.

(i) Primary outcomes

All three studies of the above studies reported on caesarean section rates which averaged 10% with extra-amniotic PGE2 compared with 18% in the placebo group (risk ratio (RR) 0.56; 95% confidence interval (CI) 0.26 to 1.20). Only Shepherd 1976 reported on hyperstimulation with fetal heart rate changes, and of the 15 women in each arm of the study, there were no cases reported.

(ii) Other outcomes

Half as many women who received extra-amniotic PGE2 compared to placebo required oxytocin augmentation (40% versus 80%) (RR 0.51; 95% CI 0.39 to 0.67). There were no significant differences found between groups in instrumental vaginal delivery (RR 1.14; 95% CI 0.56 to 2.35) or in maternal side-effects (RR 1.52; 95% CI 0.55 to 4.23).

Extra-amniotic PGF2alpha

One study (Quinn 1981) compared PGF2alpha with placebo. In this study 40 nulliparous women with a Bishop's score of less than four were randomly assigned to extra-amniotic application of either PGF2alpha (n = 15), or placebo gel (n = 10). All gel was inserted via a Foley catheter which was inflated to 10 cm and left in place.

(i) Primary outcomes

The only primary outcome reported on was caesarean section, and there was no significant difference between the groups in this small study (RR 0.33; 95% CI 0.03 to 3.20).

(ii) Other outcomes

Quinn 1981 reported on maternal morbidity, uterine hyperstimulation without fetal heart rate change and instrumental vaginal delivery; there were no significant differences between groups. There was one reported perinatal death in the extra-amniotic PGF2alpha group.

Extra-amniotic prostaglandin E2 versus vaginal prostaglandin E2

Four studies reported on extra-amniotic prostaglandin E2 versus vaginal prostaglandin E2 (Clarke 1980; Greer 1989; Stewart 1985; Wilson 1978).

(i) Primary outcomes

Only Clarke 1980 reported on vaginal delivery not achieved within 24 hours, and reported a risk ratio of 1.26 (95% CI 1.00 to 1.59). The remaining three studies reported no significant difference in caesarean section rates (RR 0.89; 95% CI 0.42 to 1.89).

(ii) Other outcomes

Three studies (Greer 1989; Stewart 1985; Wilson 1978) reported no difference in instrumental vaginal delivery (RR 0.97; 95% CI 0.60 to 1.55). Greer and Stewart 1985 reported no difference in the need for oxytocin augmentation (RR 1.02; 95% CI 0.75 to 1.40).

Extra-amniotic prostaglandin E2 versus intracervical prostaglandin

(i) Primary outcomes

Only Parewicz 1986 and Allouche 1993 compared extra-amniotic prostaglandin E2 versus intracervical prostaglandin and reported no significant difference in caesarean section rates (RR 0.75; 95% CI 0.43 to 1.30). Allouche 1993 reported one case of hyperstimulation with non-reassuring fetal heart rate in the intracervical prostaglandin group and none in the extra-amniotic group (RR 0.37; 95% CI 0.01 to 9.11).

Extra-amniotic prostaglandin E2 versus intravenous oxytocin

(i) Primary outcomes

Wilson 1978 reported no difference in the caesarean section rate when comparing extra-amniotic prostaglandin E2 versus intravenous oxytocin (RR 0.20; 95% CI 0.03 to 1.51).

(ii) Other outcomes

No significant difference was found in the rate of instrumental delivery for women receiving extra-amniotic prostaglandin E2 compared with intravenous oxytocin (RR 2.00; 95% CI 0.43 to 9.32).

Extra-amniotic prostaglandin versus mechanical methods (Foley catheter)

Extra-amniotic PGF2

(i) Primary outcomes

Mahomed 1988 reported no difference in caesarean section rates when extra-amniotic prostaglandin F2 was compared with Foley catheter (RR 1.03; 95% CI 0.53 to 1.99).

(ii) Other outcomes

Mahomed 1988 also reported no differences between groups in the rate of oxytocin augmentation (RR 0.83; 95% CI .68 to 1.01), or instrumental vaginal delivery (RR 1.03; 95% CI 0.15 to 6.92) or in admissions to neonatal intensive care (RR 0.90; 95% CI 0.36 to 2.23).

Extra-amniotic PGF2 alpha versus vaginal misoprostol

(i) Primary outcomes

Comparing extra-amniotic PGF2 with vaginal misoprostol [Majoko 2002a](#) found an increased rate of vaginal delivery not occurring within 24 hours (RR 2.43; 95% CI 1.42 to 4.15) but no difference in caesarean section rates (RR 2.33; 95% CI 0.95 to 5.75). This study also reported no cases of serious maternal morbidity or death and found one case in each group of perinatal death.

(ii) Other outcomes

[Majoko 2002a](#) reported increased use of oxytocin augmentation in the extra-amniotic PGF2 group (RR 1.73; 95% CI 1.20 to 2.49) and no differences in meconium-stained liquor, neonatal intensive care unit admission, or postpartum haemorrhage.

DISCUSSION

All studies under review, have small sample sizes and only a small number of studies compare the same outcomes. When extra-amniotic PGE2 was compared to placebo, half as many women in the extra-amniotic PGE2 group required oxytocin augmentation (risk ratio 0.51; 95% confidence interval 0.40 to 0.68). This is the only finding where a significant difference was found in primary or secondary outcomes. Although the finding of no difference in comparisons with other induction modalities would suggest that extra-amniotic prostaglandins are as effective as the other modalities for the outcomes on which they were compared, the sample sizes were too small in all instances to draw conclusions,

as evidenced by the wide confidence intervals associated with the findings.

AUTHORS' CONCLUSIONS

Implications for practice

Although extra-amniotic prostaglandins may be effective in pre-induction cervical preparation and induction, there was no evidence of an advantage over other methods of induction, in particular cervical and vaginal gels, or Foley catheter. There is minimal information about fetal safety or maternal side effects including infection. The need to introduce the gel through the cervix by way of a catheter may be considered more invasive than other methods from a woman's perspective, although more women appeared satisfied with the Foley approach compared to vaginal insertion.

Implications for research

It would have been useful for researchers to have undertaken appropriately sized randomised controlled trials to understand the role of extra-amniotic prostaglandins when they were first introduced. Extra-amniotic prostaglandins have been largely replaced in practice by other methods of prostaglandin administration and interest in undertaking an adequately sized randomised controlled trial at this time is less likely.

ACKNOWLEDGEMENTS

None.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Allouche 1993

Methods	Randomised.
Participants	Women presenting for non urgent induction of labour and a Bishop's score of < 6. Excluded malpresentations multiple pregnancies, previous uterine scar, ruptured membranes acute fetal distress and women in labour.
Interventions	1. 18 G. Foley with 50 cc balloon plus traction with normal saline; 2. 18 G. Foley with 50 cc balloon plus traction with extraamniotic prostaglandin E2 preceded by 0.01% (0.5 mg) salbutamol; 3. prostaglandin E2 intracervically preceded by 0.01% (0.5 mg) salbutamol.
Outcomes	2, 3, 12, 20, 22.

Extra-amniotic prostaglandin for induction of labour (Review)

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Allouche 1993 (Continued)

Notes 3 study groups; all included under separate comparisons as per Cochrane Handbook 16.5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Sealed envelopes.

Clarke 1980

Methods	Quasi randomised - allocation by date of birth.
Participants	Multiparous or nulliparous, requiring induction. No information about multiple pregnancy inclusion.
Interventions	Vaginal PGE2 2.0 mgm (PGE2 - Upjohn) in 10 ml Tylose gel. Extra-amniotic PGE2 gel 0.3 mgm in 10 ml 6% tylose gel.
Outcomes	1, 8, 12, 17 (see footnotes).
Notes	Catheter removed after insertion. Oxytocin was initiated after 20 hours following ARM when indicated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	Inadequate.

Fenton 1985

Methods	Randomised double blind trial. Allocation unclear.
Participants	Nulliparous, Bishop's score < 4, > 36 weeks. No information available regarding inclusion of multiples.
Interventions	Extra-amniotic: - placebo gel; - PGE2 gel 400 mgm.
Outcomes	3.
Notes	Placebo and PGE2 inserted via catheter, which was then withdrawn. Oxytocin started 'the following morning'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Adequate.

Greer 1989

Methods	Randomised - allocation unclear.
Participants	50 nulliparous, Bishop's score < 4, singleton pregnancy.
Interventions	Extra-amniotic PGE2 (500 microgram). Vaginal PGE2 3 mg tablets x 2 in posterior fornix.
Outcomes	3, 10, 11, 12.
Notes	Catheter inflated to 20 ml, left in situ. Timing of oxytocin augmentation not known.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Unclear.

Mahomed 1988

Methods	RCT - allocation by computer generated sequence.
Participants	77 singleton, live vertex, Bishop's score < 6, admitted for induction.
Interventions	2.5 mg PGF2alpha in 20 ml Tylose gel via Foley catheter. Foley catheter with traction.
Outcomes	2, 3, 4, 7, 10, 13, 15
Notes	Catheter inflated to 30 ml, left in situ. Oxytocin and amniotomy 16 hours following treatment with PGF2alpha.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Adequate.

Majoko 2002a

Methods	RCT.
Participants	Women with singleton cephalic fetus at > 36 weeks' gestation. Women with prior uterine surgery, an abnormal FHR, any contraindication to vaginal delivery or a known sensitivity to PGF2alpha or misoprostol were excluded.
Interventions	Intervention group: PGF2alpha prepared by hospital pharmacy in 5 mg mixed in 20 ml Tylose gel inserted via 22 G Goley inflated to 40 ml and left in situ. Repeat dose q8 x 1 dose for women with catheter still in place.

Extra-amniotic prostaglandin for induction of labour (Review)

Majoko 2002a (Continued)

Control group: misoprostol 50microgram (divided from 200 microgram tablet) inserted into the posterior vaginal fornix and repeated q8h if Bishop's score < 10.

Outcomes	1, 3, 5, 7, 9, 12, 14, 16, 23. Other: fetal distress necessitating caesarean; Apgar < 5 (time not known).
Notes	It is unclear if the data reported in this paper are duplicate data from the publication in the Central African Journal of Medicine. Attempts have been made to contact the author in order to clarify. If there is no duplication, the data from the second paper will be added.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Sealed opaque sequentially numbered envelopes.

Parewicz 1986

Methods	Randomised trial - allocation unclear.
Participants	194 nulliparous or multiparous, 'clinically normal', Bishop's score < 6, clinically normal.
Interventions	Extra-amniotic 500 micrograms PGE2 in 8 ml Tylose gel. Intracervical 0.5 mg. PGE2 I in 2.5 ml triacetine gel.
Outcomes	3.
Notes	No information on catheter.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Unclear.

Quinn 1981

Methods	Double blind trial - allocation unclear.
Participants	40 nulliparous, modified Bishop's score < 4. Unknown if multiple pregnancy included.
Interventions	Extra-amniotic: - placebo gel; - 10 mg PGF2alpha in Tylose gel; - 15 mg oestriol in tylose gel.
Outcomes	3, 8, 10, 15.
Notes	Oxytocin augmentation initiated 12 hours following treatment. All gel via Foley catheter inflated to 10 ml, left in place.

Risk of bias

Quinn 1981 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Unclear.

Shepherd 1976

Methods	Quasi-randomised - allocation by alternation.
Participants	30 nulliparous or multiparous Bishop's score < 4, > 36 weeks. No information regarding singleton vs multiple or VBAC pregnancy included.
Interventions	Extra-amniotic: - placebo gel; - PGE2 250 microgram in Tylose gel.
Outcomes	2, 3, 7, 8, 10, 17.
Notes	All gel via catheter, no information re: catheter left in place or removed. Oxytocin induction initiated 14.5 hours following treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Unclear.

Sherman 2001

Methods	Double blinded RCT comparing balloon cervical ripening of the cervix with extra-amniotic infusion of saline vs PGE2alpha.
Participants	Women with singleton cephalic live fetuses and intact membranes with a Bishop's score < 4 were included; women with prior uterine surgery, vaginal bleeding an estimated fetal weight of > 4300 g, vaginal infection, low lying placenta or who were in labour or had urgent need of delivery were excluded.
Interventions	All women had a 22 G Foley balloon catheter placed with 30 ml of sterile water inflating the balloon. In the intervention group, an infusion pump was used to deliver PGE2 solution (10 mg/ml saline) at a rate of 1 ml/min. In the control group, normal saline was infused at the same rate.
Outcomes	3, 7, 13, 18. Other: intrapartum fever, abnormal FHR, dystocia.
Notes	This is a study of cervical ripening as opposed to induction, but as many women go on to labour spontaneously with this management it is included. The oxytocin induction outcome was added to the oxytocin augmentation outcome.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Computer-generated sequence; sealed opaque sequentially numbered envelopes.

Stewart 1985

Methods	RCT - allocation unclear.
Participants	62 nulliparous, Bishop's score < 4, singleton pregnancy, cephalic presentation.
Interventions	450 microgram extra-amniotic PGE2 in Tylose gel. Vaginal PGE2 3 mg tablet.
Outcomes	3, 5, 6, 7, 10, 12.
Notes	Catheter inflated to 20 ml and left in situ. Amniotomy performed when labour established. Oxytocin 18 hours following extra-amniotic PGE2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Unclear.

Wilson 1978

Methods	RCT - allocation unclear.
Participants	60 nulliparous Bishop's score < 5, with OB indication for induction. No information about multiple pregnancy inclusion.
Interventions	Extra-amniotic 400 micrograms PGE2 gel. IV oxytocin. Vaginal PGE2 tablets 2 mg in posterior fornex. Oral PGE2 of 1mg hourly for 10 hours.
Outcomes	3, 10.
Notes	No information on Foley.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Unclear.

Outcomes:

- 1: vaginal delivery not achieved in 24 hours
- 2: uterine hyperstimulation with fetal heart rate changes
- 3: caesarean section
- 4: serious neonatal morbidity/perinatal death
- 5: maternal satisfaction
- 6: maternal satisfaction, embarrassment
- 7: oxytocin augmentation
- 8: uterine hyperstimulation without fetal heart rate changes
- 10: instrumental vaginal delivery
- 11: meconium stained liquor
- 12: Apgar score < 7 at 5 minutes

Extra-amniotic prostaglandin for induction of labour (Review)

13: neonatal intensive care unit admission
15: perinatal death
17: maternal side-effects (nausea, fever, vomiting, diarrhoea)
21: women not satisfied
23: woman embarrassed
ARM: artificial rupture of membranes
IV: intravenous
OB: obstetric
RCT: randomised controlled trial
VBAC: vaginal birth after caesarean section
vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Calder 1974	Neonatal studies with incompatible outcomes.
Fletcher 1993	No relevant outcomes available in abstract.
Keirse 1982	Incomparable outcome - plasma levels of prostaglandin.
Reichel 1985	Incomparable outcome - plasma levels of prostaglandin.
Salamalekis 1990	Entry criterion intrauterine fetal death.
Thiery 1981	No primary outcomes reported.
Thoumsin 1982	No primary outcomes reported.
Toppozada 1994	Entry criterion intrauterine fetal death.
Tsalacopoulos 1982	Entry criterion intrauterine fetal death.

Characteristics of studies awaiting assessment [ordered by study ID]

[Majoko 2002b](#)

Methods	Randomised controlled trial with 4 intervention arms.
Participants	Women with singleton cephalic fetus at > 36 weeks' gestation. Women with prior uterine surgery, an abnormal FHR, any contraindication to vaginal delivery or a known sensitivity to PGF2alpha or misoprostol were excluded.
Interventions	4 group study: intervention group: PGF2alpha prepared by hospital pharmacy in 5 mg mixed in 20 ml Tylose gel inserted via 22 G Foley inflated to 40 ml and left in situ. Repeat dose q8 x 1 dose for women with catheter still in place. Control groups: 1. misoprostol 50 microgram (divided from 200 microgram tablet) inserted into the posterior vaginal fornix and repeated q8h if Bishop's score < 10 (n = 128); 2. oral misoprostol (n = 127); 3. PGE2 pessary (n = 75).
Outcomes	1, 3, 5, 7, 9, 12, 14, 16, 23. Other: fetal distress necessitating caesarean; Apgar < 5 (time not known).

Majoko 2002b (Continued)

Notes

Although it appears likely, it is unclear if the data reported in this paper are duplicate data from the publication in the International Journal of Obstetrics and Gynecology. Attempts have been made to contact the author in order to clarify. If there is no duplication, the data from this second paper will be added.

FHR: fetal heart rate

DATA AND ANALYSES

Comparison 1. Extra-amniotic PGE2 vs extra-amniotic placebo: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Apgar score < 7 at 5 minutes	1	116	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Uterine hyperstimulation with FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Caesarean section	3	176	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.26, 1.20]
4 Abnormal FHR	1	107	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.18, 1.60]
5 Dystocia	1	107	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.36, 1.87]
6 Intrapartum fever	1	107	Odds Ratio (M-H, Fixed, 95% CI)	1.2 [0.34, 4.20]
7 Oxytocin augmentation	3	167	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.39, 0.67]
8 Uterine hyperstimulation without FHR changes	2	146	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.37, 132.56]
9 Postpartum haemorrhage	1	116	Odds Ratio (M-H, Fixed, 95% CI)	4.22 [0.46, 38.98]
10 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.56, 2.35]
11 Maternal side-effects	2	167	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.55, 4.23]
11.1 GI side-effects (nausea and vomiting or diarrhea)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Non-GI side-effects (non-shivering)	2	137	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.55, 4.23]

Analysis 1.1. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 1 Apgar score < 7 at 5 minutes.

Analysis 1.2. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 2 Uterine hyperstimulation with FHR changes.

Analysis 1.3. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 3 Caesarean section.

Analysis 1.4. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 4 Abnormal FHR.

Analysis 1.5. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 5 Dystocia.

Analysis 1.6. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 6 Intrapartum fever.

Analysis 1.7. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 7 Oxytocin augmentation.

Analysis 1.8. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 8 Uterine hyperstimulation without FHR changes.

Analysis 1.9. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 9 Postpartum haemorrhage.

Analysis 1.10. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 10 Instrumental vaginal delivery.

Analysis 1.11. Comparison 1 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, Outcome 11 Maternal side-effects.

Comparison 2. Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine hyperstimulation with FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Caesarean section	2	60	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.14, 1.78]
3 Oxytocin augmentation	2	60	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.34, 0.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Uterine hyperstimulation without FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.56, 2.35]
6 Maternal side-effects	1	60	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 96.13]
6.1 GI side-effects (nausea and vomiting or diarrhea)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Non-GI side-effects (non-shivering)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 96.13]

Analysis 2.1. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 1 Uterine hyperstimulation with FHR changes.

Study or subgroup	Extra-amniotic PGE2 n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shepherd 1976	0/15	0/15			Not estimable
Total (95% CI)	15	15			Not estimable
Total events: 0 (Extra-amniotic PGE2), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable

Analysis 2.2. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 2 Caesarean section.

Study or subgroup	Extra-amniotic PGE2 n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Fenton 1985	2/15	5/15		83.33%	0.4[0.09,1.75]
Shepherd 1976	1/15	1/15		16.67%	1[0.07,14.55]
Total (95% CI)	30	30		100%	0.5[0.14,1.78]
Total events: 3 (Extra-amniotic PGE2), 6 (Control)					
Heterogeneity: Tau ² =0; Chi ² =0.35, df=1(P=0.56); I ² =0%					
Test for overall effect: Z=1.07(P=0.28)

**Analysis 2.3. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo:
all women, unfavourable cervix, Outcome 3 Oxytocin augmentation.**

**Analysis 2.4. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women,
unfavourable cervix, Outcome 4 Uterine hyperstimulation without FHR changes.**

**Analysis 2.5. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo:
all women, unfavourable cervix, Outcome 5 Instrumental vaginal delivery.**

Analysis 2.6. Comparison 2 Extra-amniotic PGE2 vs extra-amniotic placebo: all women, unfavourable cervix, Outcome 6 Maternal side-effects.

Comparison 3. Extra-amniotic PGE2 vs extra-amniotic placebo: all primiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.09, 1.75]
2 Oxytocin augmentation	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.29, 0.87]

Analysis 3.1. Comparison 3 Extra-amniotic PGE2 vs extra-amniotic placebo: all primiparae, Outcome 1 Caesarean section.

Analysis 3.2. Comparison 3 Extra-amniotic PGE2 vs extra-amniotic placebo: all primiparae, Outcome 2 Oxytocin augmentation.

Comparison 4. Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]
2 Serious maternal morbidity or death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
3 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
4 Instrumental vaginal delivery	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.20]
5 Perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]

Analysis 4.1. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 1 Caesarean section.

Analysis 4.2. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 2 Serious maternal morbidity or death.

Analysis 4.3. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 3 Uterine hyperstimulation without FHR changes.

Analysis 4.4. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 4 Instrumental vaginal delivery.

Analysis 4.5. Comparison 4 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, Outcome 5 Perinatal death.

Comparison 5. Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]
2 Serious maternal morbidity or death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
3 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
4 Instrumental vaginal delivery	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.20]
5 Perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]

Analysis 5.1. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 1 Caesarean section.

Analysis 5.2. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 2 Serious maternal morbidity or death.

Analysis 5.3. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 3 Uterine hyperstimulation without FHR changes.

Analysis 5.4. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 4 Instrumental vaginal delivery.

Analysis 5.5. Comparison 5 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all women, unfavourable cervix, Outcome 5 Perinatal death.

Comparison 6. Extra-amniotoc PGF2 alpha vs extra-amniotic placebo gel: all primiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]
2 Serious maternal morbidity or death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
3 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
4 Instrumental vaginal delivery	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.20]
5 Perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]

Analysis 6.1. Comparison 6 Extra-amniotoc PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 1 Caesarean section.

Analysis 6.2. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 2 Serious maternal morbidity or death.

Analysis 6.3. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 3 Uterine hyperstimulation without FHR changes.

Analysis 6.4. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 4 Instrumental vaginal delivery.

Analysis 6.5. Comparison 6 Extra-amniotic PGF2 alpha vs extra-amniotic placebo gel: all primiparae, Outcome 5 Perinatal death.

Comparison 7. Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]
2 Serious maternal morbidity or death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
3 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]
4 Instrumental vaginal delivery	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.20]
5 Perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.09, 46.11]

Analysis 7.1. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 1 Caesarean section.

Analysis 7.2. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 2 Serious maternal morbidity or death.

Analysis 7.3. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 3 Uterine hyperstimulation without FHR changes.

Analysis 7.4. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 4 Instrumental vaginal delivery.

Analysis 7.5. Comparison 7 Extra-amniotic PGF2 alpha vs placebo gel: all primiparae, unfavourable cervix, Outcome 5 Perinatal death.

Comparison 8. Extra-amniotic PGE2 vs vaginal PGE2: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	261	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.00, 1.59]
2 Uterine hyperstimulation with FHR changes	1	261	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Caesarean section	3	142	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.42, 1.89]
4 Maternal satisfaction	1	62	Mean Difference (IV, Fixed, 95% CI)	4.40 [3.50, 5.30]
4.1 Assessment of discomfort	1	62	Mean Difference (IV, Fixed, 95% CI)	4.40 [3.50, 5.30]
5 Oxytocin augmentation	2	112	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.75, 1.40]
6 Uterine hyperstimulation without FHR changes	1	261	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Instrumental vaginal delivery	3	142	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.60, 1.55]
8 Meconium-stained liquor	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.27, 8.22]
9 Apgar score < 7 at 5 minutes	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.12, 66.62]
10 Maternal side-effects	2	323	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.1 GI side-effects (nausea, vomiting or diarrhea)	1	261	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Non-GI side-effects (fevers)	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Maternal satisfaction - embarrassment	1	62	Risk Ratio (M-H, Fixed, 95% CI)	8.91 [2.26, 35.02]

Analysis 8.1. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 1 Vaginal delivery not achieved within 24 hours.

Analysis 8.2. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 2 Uterine hyperstimulation with FHR changes.

Analysis 8.3. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 3 Caesarean section.

Analysis 8.4. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 4 Maternal satisfaction.

Analysis 8.5. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 5 Oxytocin augmentation.

Analysis 8.6. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 6 Uterine hyperstimulation without FHR changes.

Analysis 8.7. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 7 Instrumental vaginal delivery.

Analysis 8.8. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 8 Meconium-stained liquor.

Analysis 8.9. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 9 Apgar score < 7 at 5 minutes.

Analysis 8.10. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 10 Maternal side-effects.

Analysis 8.11. Comparison 8 Extra-amniotic PGE2 vs vaginal PGE2: all women, Outcome 11 Maternal satisfaction - embarrassment.

Comparison 9. Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved in 24 hours	1	126	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.81, 1.36]
2 Uterine hyperstimulation with FHR changes	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	3	142	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.42, 1.89]
4 Maternal satisfaction	1	62	Mean Difference (IV, Fixed, 95% CI)	4.40 [3.50, 5.30]
4.1 assessment of discomfort	1	62	Mean Difference (IV, Fixed, 95% CI)	4.40 [3.50, 5.30]
5 Oxytocin augmentation	1	62	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.82, 1.79]
6 Uterine hyperstimulation without FHR changes	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Instrumental vaginal delivery	3	142	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.60, 1.55]
8 Meconium-stained liquor	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.27, 8.22]
9 Apgar score < 7 at 5 minutes	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.82 [0.12, 66.62]
10 Maternal side-effects	2	188	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.1 GI side-effects (nausea, vomiting or diarrhea)	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Non-GI side-effects (fevers)	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Maternal satisfaction - embarrassment	1	62	Risk Ratio (M-H, Fixed, 95% CI)	8.91 [2.26, 35.02]

Analysis 9.1. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 1 Vaginal delivery not achieved in 24 hours.

Analysis 9.2. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 2 Uterine hyperstimulation with FHR changes.

Analysis 9.3. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 3 Caesarean section.

Analysis 9.4. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 4 Maternal satisfaction.

**Analysis 9.5. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2:
all women, unfavourable cervix, Outcome 5 Oxytocin augmentation.**

**Analysis 9.6. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women,
unfavourable cervix, Outcome 6 Uterine hyperstimulation without FHR changes.**

**Analysis 9.7. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all
women, unfavourable cervix, Outcome 7 Instrumental vaginal delivery.**

Analysis 9.8. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 8 Meconium-stained liquor.

Analysis 9.9. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 9 Apgar score < 7 at 5 minutes.

Analysis 9.10. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 10 Maternal side-effects.

Analysis 9.11. Comparison 9 Extra-amniotic PGE2 vs vaginal PGE2: all women, unfavourable cervix, Outcome 11 Maternal satisfaction - embarrassment.

Comparison 10. Extra-amniotic PGE2 vs vaginal PGE2: all women, favourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.06, 2.32]

Analysis 10.1. Comparison 10 Extra-amniotic PGE2 vs vaginal PGE2: all women, favourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.

Comparison 11. Extra-amniotic PGE2 vs vaginal PGE2: all primiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	130	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
2 Caesarean section	2	80	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.31, 2.34]
3 Instrumental vaginal delivery	2	80	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.55, 2.17]
4 Meconium-stained liquor	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.27, 8.22]

Analysis 11.1. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 1 Vaginal delivery not achieved within 24 hours.

Analysis 11.2. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 2 Caesarean section.

Analysis 11.3. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 3 Instrumental vaginal delivery.

Analysis 11.4. Comparison 11 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, Outcome 4 Meconium-stained liquor.

Comparison 12. Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.73, 1.45]
2 Caesarean section	2	80	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.31, 2.34]
3 Instrumental vaginal delivery	2	80	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.55, 2.17]
4 Meconium-stained liquor	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.27, 8.22]

Analysis 12.1. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.

Analysis 12.2. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 2 Caesarean section.

Analysis 12.3. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 3 Instrumental vaginal delivery.

Analysis 12.4. Comparison 12 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, unfavourable cervix, Outcome 4 Meconium-stained liquor.

Comparison 13. Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, favourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	64	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.69, 1.48]

Analysis 13.1. Comparison 13 Extra-amniotic PGE2 vs vaginal PGE2: all primiparae, favourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.

Comparison 14. Extra-amniotic PGE2 vs vaginal PGE2: all multiparae (without prior CS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.11, 2.51]

Analysis 14.1. Comparison 14 Extra-amniotic PGE2 vs vaginal PGE2: all multiparae (without prior CS), Outcome 1 Vaginal delivery not achieved within 24 hours.

Comparison 15. Extra-amniotic PGE2 vs vaginal PGE2: all multiparae, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.61]

Analysis 15.1. Comparison 15 Extra-amniotic PGE2 vs vaginal PGE2: all multiparae, unfavourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.

Comparison 16. Extra-amniotic PGE2 vs vaginal PGE2: all multiparae, favourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved within 24 hours	1	71	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [1.31, 6.93]

Analysis 16.1. Comparison 16 Extra-amniotic PGE2 vs vaginal PGE2: all multiparae, favourable cervix, Outcome 1 Vaginal delivery not achieved within 24 hours.

Comparison 17. Extra-amniotic PGE2 vs cervical PGE2: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hyperstimulation with FHR changes	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.01, 9.11]
2 Meconium-stained liquor	1	184	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.60, 3.73]
3 Caesarean section	2	384	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.43, 1.30]
4 Vomiting	1	187	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.01, 9.22]
5 "Other" maternal infection	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.19, 2.11]
6 All maternal side-effects	1	187	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.42, 2.20]
7 "Other" maternal fever other than infection	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.18, 4.72]
8 instrumental vaginal delivery	1	154	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.27, 5.76]
9 Cervix unfavourable > 12-24 hours	1	190	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.24, 0.78]
10 Serious maternal complications	1	308	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.06, 2.68]
10.1 Chorioamnionitis	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 7.59]
10.2 Endometritis	1	154	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 5.13]

Analysis 17.1. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 1 Hyperstimulation with FHR changes.

Analysis 17.2. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 2 Meconium-stained liquor.

Analysis 17.3. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 3 Caesarean section.

Analysis 17.4. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 4 Vomiting.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=0$ ($P<0.0001$); $I^2=100\%$ Test for overall effect: $Z=0.6$ ($P=0.55$)					
Favours treatment 0.01 0.1 1 10 100 Favours control					

Analysis 17.5. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 5 "Other" maternal infection.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Allouche 1993	5/80	7/74		100%	0.64[0.19,2.11]
Total (95% CI)	80	74		100%	0.64[0.19,2.11]
Total events: 5 (Treatment), 7 (Control) Heterogeneity: Not applicable Test for overall effect: $Z=0.74$ ($P=0.46$)					
Favours treatment 0.01 0.1 1 10 100 Favours control					

Analysis 17.6. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 6 All maternal side-effects.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Allouche 1993	12/88	14/99		100%	0.96[0.42,2.2]
Total (95% CI)	88	99		100%	0.96[0.42,2.2]
Total events: 12 (Treatment), 14 (Control) Heterogeneity: Not applicable Test for overall effect: $Z=0.1$ ($P=0.92$)					
Favours treatment 0.01 0.1 1 10 100 Favours control					

Analysis 17.7. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 7 "Other" maternal fever other than infection.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Allouche 1993	3/80	3/74		100%	0.92[0.18,4.72]
Total (95% CI)	80	74		100%	0.92[0.18,4.72]
Total events: 3 (Treatment), 3 (Control) Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=0$ ($P<0.0001$); $I^2=100\%$ Test for overall effect: $Z=0.1$ ($P=0.92$)					
Favours treatment 0.01 0.1 1 10 100 Favours control					

Analysis 17.8. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 8 instrumental vaginal delivery.

Analysis 17.9. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 9 Cervix unfavourable > 12-24 hours.

Analysis 17.10. Comparison 17 Extra-amniotic PGE2 vs cervical PGE2: all women, Outcome 10 Serious maternal complications.

Comparison 18. Extra-amniotic PGE2 vs cervical PGE2: all primiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.02, 9.55]

Analysis 18.1. Comparison 18 Extra-amniotic PGE2 vs cervical PGE2: all primiparae, Outcome 1 Caesarean section.

Comparison 19. Extra-amniotic PGE2 vs cervical PGE2: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	194	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 4.99]

Analysis 19.1. Comparison 19 Extra-amniotic PGE2 vs cervical PGE2: all women, unfavourable cervix, Outcome 1 Caesarean section.

Comparison 20. Extra-amniotic PGE2 vs cervical PGE2: all primiparae, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.02, 9.55]

Analysis 20.1. Comparison 20 Extra-amniotic PGE2 vs cervical PGE2: all primiparae, unfavourable cervix, Outcome 1 Caesarean section.

Comparison 21. Extra-amniotic PGE2 vs cervical PGE2: all multiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.05, 11.55]

Analysis 21.1. Comparison 21 Extra-amniotic PGE2 vs cervical PGE2: all multiparae, Outcome 1 Caesarean section.

Comparison 22. Extra-amniotic PGE2 vs cervical PGE2: all multiparae, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.05, 11.55]

Analysis 22.1. Comparison 22 Extra-amniotic PGE2 vs cervical PGE2: all multiparae, unfavourable cervix, Outcome 1 Caesarean section.

Comparison 23. Extra-amniotic PGE2 vs oxytocin: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.51]
2 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.43, 9.32]

Analysis 23.1. Comparison 23 Extra-amniotic PGE2 vs oxytocin: all women, Outcome 1 Caesarean section.

Analysis 23.2. Comparison 23 Extra-amniotic PGE2 vs oxytocin: all women, Outcome 2 Instrumental vaginal delivery.

Comparison 24. Extra-amniotic PGE2 vs oxytocin: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.51]
2 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.43, 9.32]

Analysis 24.1. Comparison 24 Extra-amniotic PGE2 vs oxytocin: all women, unfavourable cervix, Outcome 1 Caesarean section.

Analysis 24.2. Comparison 24 Extra-amniotic PGE2 vs oxytocin: all women, unfavourable cervix, Outcome 2 Instrumental vaginal delivery.

Comparison 25. Extra-amniotic PGE2 vs oxytocin: all primiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.51]
2 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.43, 9.32]

Analysis 25.1. Comparison 25 Extra-amniotic PGE2 vs oxytocin: all primiparae, Outcome 1 Caesarean section.

Analysis 25.2. Comparison 25 Extra-amniotic PGE2 vs oxytocin: all primiparae, Outcome 2 Instrumental vaginal delivery.

Comparison 26. Extra-amniotic PGE2 vs oxytocin: all primiparae, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.51]
2 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.43, 9.32]

Analysis 26.1. Comparison 26 Extra-amniotic PGE2 vs oxytocin: all primiparae, unfavourable cervix, Outcome 1 Caesarean section.

Analysis 26.2. Comparison 26 Extra-amniotic PGE2 vs oxytocin: all primiparae, unfavourable cervix, Outcome 2 Instrumental vaginal delivery.

Comparison 27. Extra-amniotic PGF2 alpha vs Foley catheter: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine hyperstimulation with FHR changes	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Caesarean section	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.53, 1.99]
3 Serious neonatal morbidity or perinatal death	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Oxytocin augmentation	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
5 Instrumental vaginal delivery	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 6.92]
6 Neonatal intensive care unit admission	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.36, 2.23]
7 Perinatal death	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 27.1. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 1 Uterine hyperstimulation with FHR changes.

Analysis 27.2. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 2 Caesarean section.

Analysis 27.3. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 3 Serious neonatal morbidity or perinatal death.

Analysis 27.4. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 4 Oxytocin augmentation.

Analysis 27.5. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 5 Instrumental vaginal delivery.

Analysis 27.6. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 6 Neonatal intensive care unit admission.

Analysis 27.7. Comparison 27 Extra-amniotic PGF2 alpha vs Foley catheter: all women, Outcome 7 Perinatal death.

Comparison 28. Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Uterine hyperstimulation with FHR changes	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Caesarean section	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.53, 1.99]
3 Serious neonatal morbidity or perinatal death	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Oxytocin augmentation	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.68, 1.01]
5 Instrumental vaginal delivery	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 6.92]
6 Neonatal intensive care unit admission	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.36, 2.23]
7 Perinatal death	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 28.1. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 1 Uterine hyperstimulation with FHR changes.

Analysis 28.2. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 2 Caesarean section.

Analysis 28.3. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 3 Serious neonatal morbidity or perinatal death.

**Analysis 28.4. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter:
all women, unfavourable cervix, Outcome 4 Oxytocin augmentation.**

**Analysis 28.5. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter:
all women, unfavourable cervix, Outcome 5 Instrumental vaginal delivery.**

**Analysis 28.6. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all
women, unfavourable cervix, Outcome 6 Neonatal intensive care unit admission.**

Analysis 28.7. Comparison 28 Extra-amniotic PGF2 alpha vs Foley catheter: all women, unfavourable cervix, Outcome 7 Perinatal death.

Study or subgroup	Extra-amniotic PGE2 n/N	Vaginal PGE2 n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mahomed 1988	0/38	0/39			Not estimable
Total (95% CI)	38	39			Not estimable
Total events: 0 (Extra-amniotic PGE2), 0 (Vaginal PGE2)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
<div> <div></div> <div>Favours treatment0.10.20.512510Favours control</div> </div>					

Comparison 29. Extra-amniotic PGE2 alpha vs Foley only: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Caesarean section	1	187	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.46, 1.47]
2 Hyperstimulation with FHR changes	1	187	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Meconium-stained liquor	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.67, 3.65]
4 All maternal side-effects	1	182	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.51, 2.25]
5 Vomiting	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 "Other" maternal infection	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.19, 1.54]
7 "Other" maternal fever other than infection	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.17, 3.16]
8 Cervix unfavourable > 12-24 hours	1	187	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.41, 0.86]
9 Serious maternal complications	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.32]
9.1 Chorioamnionitis	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Endometritis	1	158	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.32]
10 Instrumental vaginal delivery	1	158	Risk Ratio (M-H, Fixed, 95% CI)	3.9 [0.45, 34.12]

Analysis 29.1. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 1 Caesarean section.

Analysis 29.2. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 2 Hyperstimulation with FHR changes.

Analysis 29.3. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 3 Meconium-stained liquor.

Analysis 29.4. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 4 All maternal side-effects.

Analysis 29.5. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 5 Vomiting.

Analysis 29.6. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 6 "Other" maternal infection.

Analysis 29.7. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 7 "Other" maternal fever other than infection.

Analysis 29.8. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 8 Cervix unfavourable > 12-24 hours.

Analysis 29.9. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 9 Serious maternal complications.

Analysis 29.10. Comparison 29 Extra-amniotic PGE2 alpha vs Foley only: all women, Outcome 10 Instrumental vaginal delivery.

Comparison 30. Extra-amniotic PGF2 alpha vs vaginal misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vaginal delivery not achieved in 24 hours	1	152	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [1.42, 4.15]
2 Caesarean section	1	152	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.95, 5.75]
3 Serious maternal morbidity or death	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Oxytocin augmentation	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.20, 2.49]
5 Uterine rupture	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Meconium-stained liquor	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.02, 1.67]
7 Neonatal intensive care unit admission	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.17, 1.06]
8 Perinatal death	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.70]
9 Postpartum haemorrhage	1	152	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.32, 28.20]
10 Fetal distress necessitating caesarean	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.21, 4.80]
11 Apgar < 5 (time unknown)	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.14, 6.91]

Analysis 30.1. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 1 Vaginal delivery not achieved in 24 hours.

Analysis 30.2. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 2 Caesarean section.

Analysis 30.3. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 3 Serious maternal morbidity or death.

Analysis 30.4. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 4 Oxytocin augmentation.

Analysis 30.5. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 5 Uterine rupture.

Analysis 30.6. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 6 Meconium-stained liquor.

Analysis 30.7. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 7 Neonatal intensive care unit admission.

Analysis 30.8. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 8 Perinatal death.

Analysis 30.9. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 9 Postpartum haemorrhage.

Analysis 30.10. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 10 Fetal distress necessitating caesarean.

Analysis 30.11. Comparison 30 Extra-amniotic PGF2 alpha vs vaginal misoprostol, Outcome 11 Apgar < 5 (time unknown).

APPENDICES

Appendix 1. Methodological quality of trials

Methodological item	Adequate	Inadequate
Generation of random sequence	Computer generated sequence, random number tables, lot drawing, coin tossing, shuffling cards, throwing dice.	Case number, date of birth, date of admission, alternation.
Concealment of allocation	Central randomisation, coded drug boxes, sequentially sealed opaque envelopes.	Open allocation sequence, any procedure based on inadequate generation.

WHAT'S NEW

Date	Event	Description
22 September 2009	Amended	Corrections made re: reporting error in 'Results' of 'Abstract' and addition of text inadvertently missed from last update in 'Effects of interventions' section.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 2, 2001

Date	Event	Description
30 June 2009	New search has been performed	Search updated. Two new studies (Allouche 1993 ; Majoko 2002a) added and one excluded (Fletcher 1993).
14 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Both authors have reviewed the articles and extracted the data for this review. Hutton was the primary author, and Mozurkewich reviewed and edited the material.

DECLARATIONS OF INTEREST

None known.

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- No sources of support supplied

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INDEX TERMS

Medical Subject Headings (MeSH)

*Cervical Ripening; *Dinoprost; *Dinoprostone; *Oxytocics; Labor, Induced [*methods]; Pregnancy Trimester, Third; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy