

Induction of labour

Evidence-based Clinical Guideline Number 9



GUIDELINE

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Clinical Effectiveness Support Unit



Royal College of Obstetricians and Gynaecologists

Setting standards to Improve Women's Health

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Abbreviations and glossary of terms

Abbreviations

The following abbreviations are used within the Guideline.

AFI	Amniotic fluid index
BP	Blood pressure
CTG	Cardiotocograph(y)
EFM	Electronic fetal monitoring
FHR	Fetal heart rate
IUGR	Intrauterine growth restriction
LR	Likelihood ratio
NNT	Number needed to treat
IOL	Induction of labour
OR	Odds ratio
PG	Prostaglandin (E ₂ or E ₁)
PNMR	Perinatal mortality rate
RCT	Randomised controlled trial
RR	Risk ratio/Relative risk
VE	Vaginal examination

Glossary of terms

Case–control study	The study reviews exposures or risk factors, comparing the exposure in people who have the outcome of interest, for example the disease or condition (i.e. the cases) with patients from the same population who do not have the outcome (i.e. controls).
Cohort study	The study involves identification of two groups (cohorts) of patients, one of which has received the exposure of interest and one of which has not. These groups are followed forward to see if they develop the outcome (i.e. the disease or condition) of interest.
Likelihood ratio	The likelihood that a given test result would be expected in a patient with a disease compared with the likelihood that the same result would be expected in a patient without that disease.
Meta-analysis	An overview of a group of studies that uses quantitative methods to produce a summary of the results.
Nested case–control study	This term is used to identify those studies where cases and controls have been selected from among subjects in a cohort study. (i.e. a case–control study nested within a cohort).

Number needed to treat	The number of patients who need to be treated to prevent one outcome.
Odds ratio	Describes the odds that a case (a person with the condition) has been exposed to a risk factor relative to the odds that a control (a person without the condition) has been exposed to the risk.
Positive predictive value	The percentage of people who have a positive test who really have the condition. The predictive value is dependent upon the prevalence of the disease in the population being tested, i.e. if the disease is rare, the predictive value is low, due to the greater influence of false positive tests.
Randomised controlled trial	A group of patients is randomised into an experimental group and a control group. These groups are followed up for the variables and outcomes of interest. This study is similar to a cohort study but the exposure is randomly assigned. Randomisation should ensure that both groups are equivalent in all aspects except for the exposure of interest.
Risk Ratio	Risk is a proportion or percentage. The risk ratio is the ratio of risk of developing the outcome of interest in an exposed group compared with the risk of developing the same outcome in the control group. It is used in randomised controlled trials and cohort studies.
Risk difference	The difference in risk of developing the outcome of interest between the exposed and control groups.
Sensitivity	The ability of the test to detect those who have the disease, i.e. the proportion (%) of people with the condition who are detected as having it by the test.
Specificity	The ability of the test to identify those without the disease, i.e. the proportion of people without the condition who are correctly reassured by a negative test.

For further definitions readers are referred to the following link:
<http://cebm.jr2.ox.ac.uk/docs/glossary.html>

For the purposes of this Guideline, data are presented as risk ratios (RR) where relevant (i.e. in RCTs and cohort studies). Where these data are statistically significant they are converted into numbers needed to treat.

Guideline Development Group membership and acknowledgements

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The document was sent out to 61 peer reviewers (21 obstetricians, 16 midwives, 5 pharmaceutical industry representatives, 1 paediatrician, 1 public health consultant, 7 consumer representatives, 2 methodologists, 2 anaesthetists, 2 psychologists, 1 emergency services representative, 1 nurse, 1 general practitioner and 1 health economist). Responses were received from 33 peer reviewers (15 obstetricians, 8 midwives, 1 public health consultant, 1 consumer representative, 1 anaesthetist, 3 pharmaceutical industry representatives, 2 methodologists, 1 health economist and 1 general practitioner).

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1. Introduction

For the purposes of this Guideline, induction of labour is defined as an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. This includes both women with intact membranes and women with spontaneous rupture of the membranes but who are not in labour. As with any other intervention, induction of labour may have unwanted effects. Induction of labour is indicated only when it is agreed that the mother or fetus will benefit from a higher probability of a healthy outcome than if birth is delayed. The process of induction of labour should only be considered when vaginal delivery is felt to be the appropriate route of delivery.

Induction of labour is a common procedure: about 20% of pregnant women will have labour induced for a variety of reasons. Induction does not usually involve just a single intervention but is a complex set of interventions and, as such, presents challenges for both clinicians and mothers.

1.1 Aim of the Guideline

Clinical guidelines have been defined as: 'systematically developed statements that assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.¹

The parameters of practice included in this document were arrived at after careful consideration of the available evidence and should be considered as guidelines only. Clinicians involved in intrapartum care must use their professional knowledge and judgement when applying the recommendations to the management of individual women.

The Guideline Development Group has developed this Guideline with the following aims:

- to evaluate the role of induction of labour with a live fetus within a variety of clinical situations
- to evaluate and compare the various methods of induction of labour of women in relation to maternal and fetal outcome measures
- to consider the resource implications of the use of induction of labour.

1.2 Who has developed the Guideline?

The Guideline was developed by a multiprofessional and lay working group (Guideline Development Group) convened by the Royal College of Obstetricians and Gynaecologists and supported by funding awarded by the Department of Health and the National Institute for Clinical Excellence. Members included representatives from:

- Royal College of Obstetricians and Gynaecologists
- Royal College of Midwives
- Royal College of General Practitioners
- British Maternal Fetal Medicine Society
- British Association of Perinatal Medicine
- Faculty of Public Health

- Centre for Health Information Quality
- Health economists from the University of East Anglia
- Consumer groups, including the Association for Improvements in the Maternity Services and Maternity Alliance

Plus

- Staff from the RCOG Clinical Effectiveness Unit

Staff from the RCOG Clinical Effectiveness Unit provided support and guidance with the Guideline development process, undertook the systematic searches, retrieval appraisal of the evidence and composed successive drafts of the document.

The Guideline Development Group was convened by the RCOG prior to the adoption of this Guideline by NICE. Following adoption of the Guideline, the membership of the group was modified to include additional consumer input as well as input from a health economist.

All members of the Group made formal declarations of interest at the outset, which were recorded. This record is kept on file at the RCOG.

1.3 For whom is the Guideline intended?

The Guideline has been developed under the auspices of the RCOG Clinical Effectiveness Support Unit, funded by the Department of Health and the National Institute for Clinical Excellence for practitioners in the UK. The Guideline is of relevance to:

- pregnant women and their families
- professional groups who share in caring for women in labour, such as obstetricians, midwives and general practitioners
- those with responsibilities for planning intrapartum services, such as directors of public health and NHS trust managers.

1.4 Local protocol development

It is anticipated that this national Guideline will be used as the basis for the development of local protocols or guidelines, taking into account local service provision and the needs of the local population. Ideally, local development should take place in a multidisciplinary group setting that includes commissioners of health care, general practitioners, specialists and service users.

1.5 Methods used in the development of the Guideline

1.5.1 Topic areas

The Guideline Development Group constructed specific clinical questions relating to the risks and benefits of induction of labour in relation to specific maternal and neonatal outcomes. The systematic reviews that underpin many of the practice recommendations within the Guideline are based on trials that included women undergoing induction of labour with a live fetus after 36 weeks.

1.5.2 The remit of the Guideline

Indications for induction of labour for healthy women with an uncomplicated pregnancy are considered, e.g. prolonged pregnancy and

prelabour rupture of membranes at term. Variations in this policy for specific conditions are also included, e.g. diabetes and multifetal pregnancy.

Conditions that may affect the safety and efficacy of induction of labour are included, e.g. previous caesarean section.

The risks and benefits of induction of labour as an intervention for specific clinical conditions arising in pregnancy are not included, e.g. pre-eclampsia.

1.5.3 Literature search strategy

The aim of the literature review was to identify and synthesise relevant evidence within the published literature, in order to answer specific clinical questions. Thus, clinical practice recommendations are based on evidence where possible and gaps in the evidence for which future research is needed are identified. Searches were carried out for each topic of interest.

- The Cochrane Library, up to Issue 3 of 2000, was searched to identify systematic reviews (with or without meta-analyses) of randomised controlled clinical trials and randomised controlled trials.
- The Cochrane Pregnancy and Childbirth Group (CPCG) specialist register of completed and continuing controlled trials was searched by the CPCG Trials Search Co-ordinator.²
- The electronic database, MEDLINE (CD Ovid version), was searched for the period January 1966 to November 2000, including foreign-language publications.
- The electronic database EMBASE was searched between 1988 to November 2000 to identify publications, usually European, not indexed on MEDLINE.
- The Midwives Information and Resource Service (MIDIRS), CINAHL (Cumulative Index to Nursing and Allied Health Literature) and the British Nursing Index were searched to ensure that relevant nursing and midwifery literature were included.
- Guidelines by other development groups were searched for on the National Guidelines Clearinghouse database, as were the TRIP database and OMNI service on the Internet.
- The reference lists in these guidelines were checked against the Guideline Development Group's searches, in order to identify any missing evidence.
- The Database of Abstracts and Reviews of Effectiveness (DARE) was searched.
- Reference lists of non-systematic review articles and studies obtained from the initial search were reviewed and journals in the RCOG library were hand-searched to identify articles not yet indexed.
- There was no systematic attempt to search the 'grey literature' (conferences, abstracts, theses and unpublished trials).
- The economic evaluation included a search of the NHS Economic Evaluation Database (The Cochrane Library, Issue 1, 2001), MEDLINE January 1966 to November 2000 and EMBASE 1988 to November 2000. Relevant experts in the field were contacted for further information.
- Searches were performed using generic and specially developed filters, relevant MeSH (medical subject headings) terms and free text terms.

Details of literature searches are available on application to CESU, RCOG.

1.5.4 Sifting and reviewing the literature

A preliminary scrutiny of titles and abstracts was undertaken and full papers were obtained if the research addressed the Guideline Development Group's question on the topic. Following a critical review of the full version

of the study, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded.

For all the subject areas, evidence from the study designs least subject to sources of bias were included. Where possible, the highest levels of evidence were used, but all papers were reviewed using established guides (see below). Published systematic reviews or meta-analyses have been used if available.

For subject areas where neither was available, other appropriate experimental or observational studies were sought.

1.5.5 **Synthesising the evidence**

Identified articles were assessed methodologically and the best available evidence was used to form and support the recommendations. The highest level of evidence was selected for each clinical question. Using the evidence-level structure highlighted in Table 1.1, the retrieved evidence was graded accordingly.

The definitions of the types of evidence used in this Guideline originate from the US Agency for Health Care Policy and Research (Table 1.1).³ The clinical question dictates the highest level of evidence that should be sought. For issues of therapy or treatment, the highest level of evidence is meta-analyses of randomised controlled trials or randomised controlled trials. This would equate to a Grade A recommendation using the system outlined in Section 1.5.6.

For issues of prognosis, a cohort study is the best level of evidence available. The best possible level of evidence would equate to a grade B recommendation using the system outlined in Section 1.5.6. Thus, it should not be interpreted as an inferior grade of recommendation, as it represents the highest level of evidence attainable for that type of clinical question.

All retrieved articles have been appraised methodologically using established guides.⁴ Where appropriate, if a systematic review, meta-analysis or randomised controlled trial existed in relation to a topic, studies of a weaker design were ignored.

The evidence was synthesised using qualitative methods. These involved summarising the content of identified papers in the form of evidence tables and agreeing brief statements that accurately reflect the relevant evidence.

Following a preliminary review of the available evidence, it became apparent that there were in excess of 700 randomised controlled trials concerning induction of labour, which would need to be examined in the development of the Guideline. A collaboration between the Cochrane Pregnancy and Childbirth Group and the Clinical Effectiveness Support Unit of the Royal College of Obstetricians and Gynaecologists was formed in order to develop an integrated series of systematic reviews examining the various methods available for induction of labour. The methods used in the development of these systematic reviews are outlined in Appendix 1. These reviews included unpublished data in accordance with standard Cochrane methodology.

When making judgements about resource use implications, the Group tried as far as possible to rely on published economic evidence. On one occasion, however, the Guideline Development Group requested a simple costing exercise: the comparison of vaginal tablets versus vaginal gel for induction of labour. In this case, good evidence was available about clinical effectiveness and there were no major cost uncertainties that would preclude drawing conclusions from a simple costing exercise.

Table 1.1 Levels of evidence

Level	Evidence
Ia	Evidence obtained from systematic review of meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

1.5.6 Forming and grading the recommendations

The Guideline Development Group was presented with the available research evidence in order to answer its questions. From this, recommendations for clinical practice were derived using consensus methods. Where there were areas without available research evidence, consensus was again used.

Recommendations were based on, and explicitly linked to, the evidence that supports them. Consensus was reached using the nominal group technique.⁵ This consensus method involves the grading of draft recommendations by the members of the Guideline Development Group prior to the meeting. These recommendations and the gradings given to them were then considered during the meeting and a group opinion was reached. The recommendations were then graded according to the level of evidence upon which they were based. The grading scheme used was based on a scheme formulated by the Clinical Outcomes Group of the NHS Executive.¹ The strength of the evidence on which each recommendation is based is shown in Table 1.2.

Table 1.2 Grading of recommendations

Grade	Requirements
A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)
B	Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of the recommendation (evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV)

Good practice points

- ✓ Recommended good practice based on the clinical experience of the Guideline Development Group

It is accepted that, in this grading system, the evidence itself is not graded according to individual methodological quality of the studies, although it is discussed in the text supporting each recommendation. Limited results or data are presented in the text and these data are available in full in the relevant evidence tables.

Grade C recommendations and good practice points are not based on directly applicable research evidence. However, the views of the Guideline

Development Group, combined with comments from the extensive peer review as detailed below, suggest that the recommendations with these gradings are acceptable to a wide body of expert opinion.

1.5.7 Peer review: scope and methods of peer review process

Successive drafts of the Guideline were written and discussed by the Guideline Development Group. At the fourth draft stage, a formal peer review process was undertaken.

Reviewers included representatives from stakeholder organisations registered with NICE and individuals or organisations from the area of practice represented in the Guideline Development Group. The draft Guideline was submitted to these individuals or organisations with a request for appraisal and comment.

The comments made by the peer reviewers were collated and presented anonymously for consideration by the Guideline Development Group. All peer review comments were considered systematically by the Group and the resulting actions and responses were recorded. Seventy percent of the comments resulted in amendments to the Guideline. Further information is available on request.

The Guideline was also reviewed by the Guidelines Advisory Committee and Executive of NICE.

The Guideline was sent to a further group of reviewers who particularly concentrated on the methodology used in its development under the independent guideline appraisal system approved by the NHS Executive.

The Guideline was made available for public comment on the NICE Website for a period of four weeks.

1.6 How will the Guideline be disseminated and reviewed?

The Guideline has been produced in both full by the RCOG, in summary format by NICE, and in a consumer version by the RCOG. Summaries have been disseminated to all Fellows and Members of the RCOG and are available on the RCOG and NICE websites. Full copies of the printed Guideline are available to purchase from the RCOG bookshop.

Full copies of the Guideline are available on the RCOG website (www.rcog.org.uk) as a PDF. The Summary is available through the National Electronic Library for Health (www.nelh.nhs.uk/) and National Guideline Clearinghouse (www.guidelines.gov).

A consumer version of the Guideline, produced in association with the Guideline Development Group and the Centre for Health Information Quality, is available through NHS Direct Online (www.nhsdirect.nhs.uk/).

A national launch meeting took place on 12 June 2001 to disseminate the findings of the group to interested parties.

The Guideline will be reviewed and revised within three years by NICE.

2. Summary of recommendations and practice algorithm

2.1 Care during induction of labour

2.1.1 Woman-centred care (see Section 4.1)

C Women must be able to make informed choices regarding their care or treatment via access to evidence based information. These choices should be recognised as an integral part of the decision-making process.

2.1.2 Place of induction (see Section 4.2)

C For women who are healthy and have had an otherwise uncomplicated pregnancy, induction of labour with vaginal prostaglandin E₂ agents can be conducted on antenatal wards, prior to the active phase of labour.

C When undertaking induction of labour in women with recognised risk factors (including suspected fetal growth compromise, previous caesarean section and high parity), the induction process should not occur on an antenatal ward.

2.1.3 Fetal surveillance and induction of labour (see Section 4.3)

C Wherever induction of labour occurs, facilities should be available for continuous uterine and fetal heart rate (FHR) monitoring.

C Fetal wellbeing should be established immediately prior to induction of labour.

C Following induction of labour with vaginal prostaglandins (PGE₂), fetal wellbeing should be established once contractions are detected or reported.

C For women who are healthy and have had an otherwise uncomplicated pregnancy, the assessment of fetal wellbeing following the administration of vaginal prostaglandins should comprise an initial assessment with continuous electronic fetal monitoring and, once normality is confirmed, intermittent monitoring can be used.

- C** Where oxytocin is being used for induction or augmentation of labour, continuous electronic fetal monitoring should be used.

2.1.4 Uterine hypercontractility with induction agents (see Section 4.4)

- C** Prolonged use of maternal facial oxygen therapy may be harmful to the fetus and should be avoided. There is no research evidence evaluating the benefits or risks associated with the short-term use of maternal facial oxygen therapy in cases of suspected fetal compromise.
- B** In cases of uterine hypercontractility with a suspicious or pathological cardiotocograph (CTG) secondary to oxytocin infusions, the oxytocin infusion should be decreased or discontinued.
- A** In the presence of abnormal FHR patterns and uterine hypercontractility (not secondary to oxytocin infusion), tocolysis should be considered.
A suggested regimen is **subcutaneous terbutaline 0.25 milligrams**.
- B** In cases of suspected or confirmed acute fetal compromise, delivery should be accomplished as soon as possible, taking account of the severity of the FHR abnormality and relevant maternal factors. The accepted standard has been that, ideally, this should be accomplished within 30 minutes.

2.1.5 Care of higher-risk pregnancies (see Section 4.5)

- C** When undertaking induction of labour in women with recognised risk factors (including suspected fetal growth compromise, previous caesarean section and high parity), the clinical discussion regarding the timing and method of induction of labour should be undertaken at consultant level. The induction process should not occur on an antenatal ward.

2.2 Indications for induction of labour

2.2.1 Prolonged pregnancy (see Section 5.2)

- A** An ultrasound to confirm gestation should be offered before 20 weeks of gestation, as this reduces the need for induction for perceived post-term pregnancy.
- A** Women with uncomplicated pregnancies should be offered induction of labour beyond 41 weeks.
- A** From 42 weeks, women who decline induction of labour should be offered increased antenatal monitoring consisting of a twice weekly CTG and ultrasound estimation of maximum amniotic pool depth.

2.2.2 Diabetes in pregnancy (see Section 5.3)

- C** Women who have pregnancies complicated by diabetes should be offered induction of labour prior to their estimated date for delivery.

2.2.3 Induction of labour in the presence of prelabour rupture of the membranes (see Section 5.5)

A Women with prelabour rupture of the membranes at term (over 37 weeks) should be offered a choice of immediate induction of labour **or** expectant management.

A Expectant management of women with prelabour rupture of the membranes at term should not exceed 96 hours following membrane rupture.

2.2.4 Induction of labour for maternal request prior to 41 weeks (see Section 5.7)

✓ Where resources allow, maternal request for induction of labour should be considered when there are compelling psychological or social reasons and the woman has a favourable cervix.

Multifetal pregnancy, macrosomia and a history of precipitate labour were also considered by the Guideline Development Group for inclusion within this section, but there was insufficient evidence upon which to base any recommendations.

2.3 Method of induction of labour in specific clinical situations

2.3.1 Membrane sweeping (see Section 6.2)

A Prior to formal induction of labour, women should be offered sweeping of the membranes.

A When membrane sweeping is proposed, discussions should include information that informs women that membrane sweeping:

- is not associated with an increase in maternal or neonatal infection
- is associated with increased levels of discomfort during the examination and bleeding.

2.3.2 Oxytocin compared with prostaglandins for induction of labour (see Section 6.3)

A Prostaglandins should be used in preference to oxytocin when induction of labour is undertaken in either nulliparous or multiparous women with intact membranes, regardless of their cervical favourability.

A Either prostaglandins or oxytocin may be used when induction of labour is undertaken in nulliparous or multiparous women who have ruptured membranes, regardless of cervical status, as they are equally effective.

2.3.3 Comparison of intracervical and intravaginal prostaglandins (PGE₂) (see Section 6.4)

A When induction of labour is undertaken with prostaglandins, intravaginal PGE₂ should be used in preference to intracervical preparations, as they are equally effective and administration of vaginal PGE₂ is less invasive.

2.3.4 Comparison of different preparations of vaginal prostaglandin (PGE₂) (see Section 6.5)

A Given that they are clinically equivalent, when induction of labour is undertaken with vaginal PGE₂ preparations, vaginal tablets should be considered in preference to gel formulations.

C Recommended regimens for vaginal PGE₂ preparations include:

- PGE₂ tablets: 3 milligrams PGE₂ 6–8 hourly.
The maximum total dose is 6 milligrams for all women.
- PGE₂ gels: 2 milligrams PGE₂ in nulliparous women with an unfavourable cervix (Bishop's score less than 4), 1 milligram for all other women.
In either, a second dose of 1–2 milligrams can be administered six hours later.

The maximum dose is 4 milligrams PGE₂ for nulliparous women with an unfavourable cervix and 3 milligrams for all other women.

2.3.5 Comparison of different regimens of oxytocin administration (see Section 6.6)

C Oxytocin should not be started for six hours following administration of vaginal prostaglandins.

C In women with intact membranes, amniotomy should be performed where feasible prior to commencement of an infusion of oxytocin.

C When induction of labour is undertaken with oxytocin the recommended regimen is:

- a starting dose of 1–2 milliunits per minute
- increased at intervals of 30 minutes or more.

The minimum dose possible of oxytocin should be used and this should be titrated against uterine contractions aiming for a maximum of three to four contractions every ten minutes.

Adequate contractions may be established at 12 milliunits per minute.

In the summary of product characteristics the licensed maximum dose is 20 milliunits per minute.

If higher doses are used the maximum dose used should not exceed 32 milliunits per minute.

C Local protocols for delivery of oxytocin for induction of labour should:

- specify and use the dose of oxytocin being delivered (milliunits per minute) in preference to the volume of fluid being infused (millilitres per minute)
- be delivered through an infusion pump or via a syringe driver with a non-return valve.

C To reduce error, a standard dilution should always be used. Suggested standardised dilutions and dose regimens include:

- 30 iu in 500 ml of normal saline; hence 1 ml/hr = 1 milliunits per minute
- 10 iu in 500 ml of normal saline; hence 3 ml/hr = 1 milliunits per minute.

C

Table 2.1 Oxytocin infusion

Time after starting (minutes)	Oxytocin dose (milliunits per minute)	Volume infused (ml/hour)	
		Dilution 30 iu in 500 ml	Dilution 10 iu in 500 ml
0	1	1	3
30	2	2	6
60	4	4	12
90	8	8	24
120	12	12	36
150	16	16	48
180	20	20	60
210	24	24	72
240	28	28	84
270	32	32	96

Doses highlighted are quantities above those referred to in the summary of product characteristics of 20 milliunits per minute

2.4 Future research recommendations (See Section 6.8)

Adequately powered randomised controlled trials reporting relevant clinical outcomes in specific clinical groups are needed in order to:

- evaluate further the effectiveness of different vaginal PGE₂ formulations for induction of labour
- evaluate the risks and benefits of vaginal/oral misoprostol for induction of labour using commercially produced tablets of appropriate dose
- evaluate the risks and benefits of induction of labour for women whose pregnancies are complicated by:
 - diabetes (divided according to aetiology of diabetes)
 - multifetal pregnancy
 - suspected fetal growth compromise
 - macrosomia
- evaluate screening in the UK for abnormal vaginal colonisation in cases of prelabour rupture of the membranes at term.

Further studies are needed in order to develop and standardise measures of maternal satisfaction, attitude and response to induction of labour.

Clinical practice algorithm

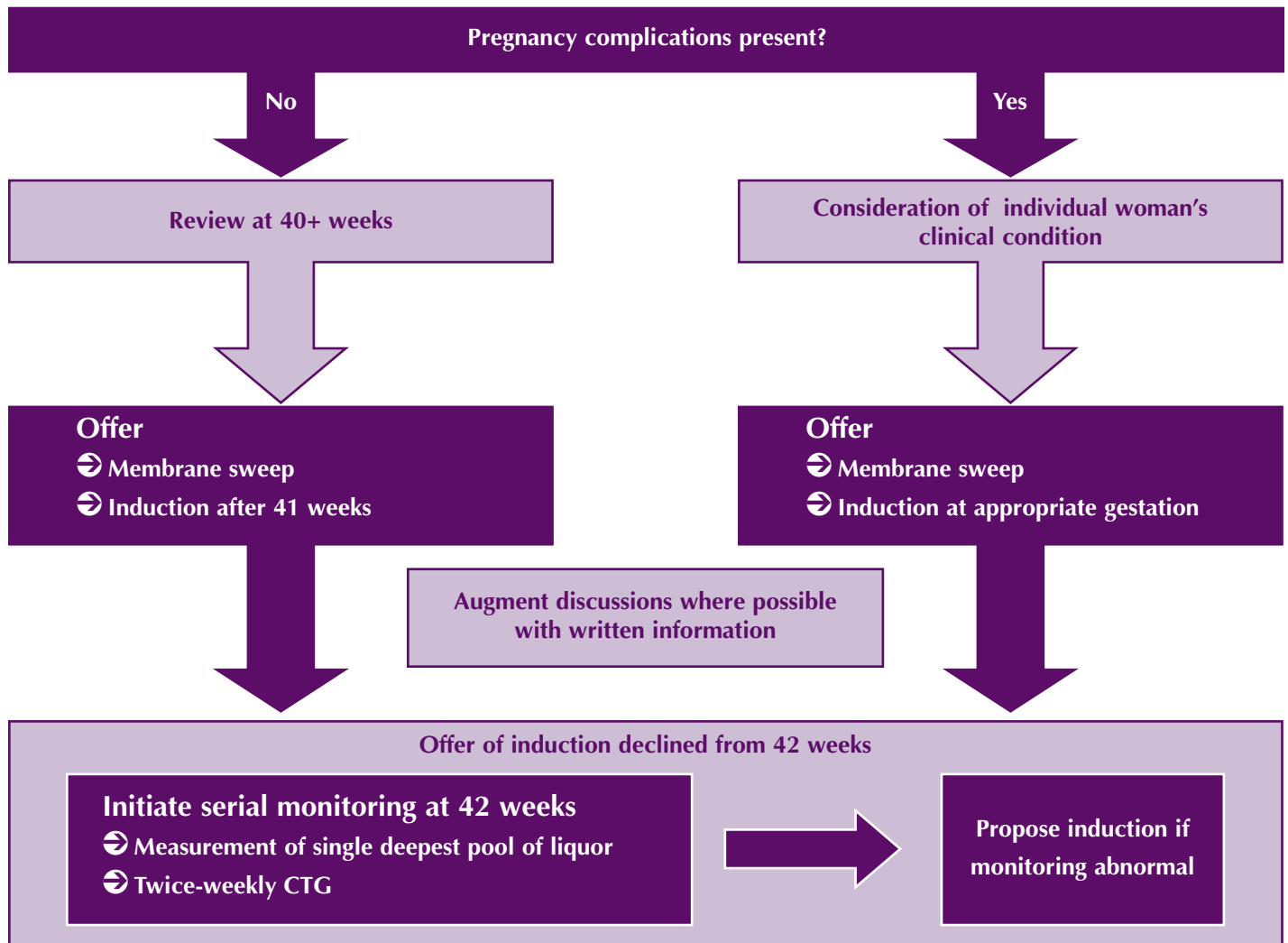
The recommendations have been combined into a clinical practice algorithm, in order to allow the findings from this Guideline to be integrated and implemented in clinical practice. The algorithm aims to guide users through the decision pathways for evaluation of the needs of any woman undergoing induction of labour. The algorithm draws directly on the evidence presented in the Guideline and, hence, is not recommended for use without prior consultation of this evidence.

Figure 1 Clinical practice algorithm for induction of labour

Induction of labour

- Offer booking scan at < 20 weeks by LMP ➤
- Confirm expected date of delivery prior to induction ➤

- Induction should only be considered when vaginal delivery is felt to be the most appropriate mode of delivery ➤
- Due consideration should be given to maternal preferences and priorities prior to commencement of induction ➤



Modified Bishop's score

Cervical feature	Pelvic score			
	0	1	2	3
Dilatation (cm)	< 1	1–2	2–4	> 4
Length of cervix (cm)	> 4	2–4	1–2	< 1
Station (relative to ischial spines)	–3	–2	–1/0	+1/+2
Consistency	Firm	Average	Soft	–
Position	Posterior	Mid/Anterior	–	–

CTG = Cardiotocograph
IV = Intravenous

LMP = last menstrual period
PGE₂ = Prostaglandin E₂

Method of induction of labour

Intact membranes

Irrespective of parity or cervical status



Consider

- Intravaginal PGE₂ tablet or gel

Ruptured membranes

Irrespective of parity or cervical status



Consider either

- Intravaginal PGE₂ (tablet or gel)
- IV oxytocin (in the presence of ruptured membranes, spontaneous or amniotomy)

Although parity does not appear to effect the choice of method of induction of labour it should influence the dosage of drugs used.

Induction with vaginal PGE₂ agents

- Consideration should be given to PGE₂ tablets in preference to gel where possible
- Oxytocin not to be started within six hours of last PGE₂

Intravaginal PGE₂ tablet

- 3 milligram PGE₂ tablet 6–8 hourly
- Maximum dose 6 milligrams

Intravaginal PGE₂ gel

- Nulliparous women with a modified Bishops score < 4 give 2 milligrams
- All other patients give 1 milligrams
- Repeat dose of 1–2 milligrams six hourly
- Maximum dose 4 milligrams

Induction with oxytocin

- Treatment regimes: milliunits per minute not millilitres per minute
- 30 iu in 500 ml normal saline
- 1 millilitres/hr = 1 milliunits/minute
- Deliver via either syringe driver or infusion pump with non-return valve
- Oxytocin performance optimised with ruptured membranes

Oxytocin (in the presence of ruptured membranes)

Time after starting (minutes)	Dose delivery (milliunits/minute)
0	1
30	2
60	4
90	8
120	12
150	16
180	20
210	24
240	28
270	32

- Most women should have adequate contractions at 12 milliunits per minute
- Trials have used doses up to 32 milliunits per minute
- Maximum licensed dose is 20 milliunits per minute
- If regular contraction not established after TOTAL of 5 iu (five hours on suggested regimen) then induction should be stopped

3. Definitions, abbreviations and outcome measures

Induction of labour is a common procedure within obstetric practice. Data on the rates of induction in England, Wales and Scotland are presented in Figure 2 below. These data are taken from a recently produced Department of Health report, but only reports on induction in England and Wales up to 1995 and for Scotland up to 1997.

It has been reported that some women who receive oxytocin augmentation may be misclassified as having had induction of labour. These data for England and Wales are probably overestimates as a result of this misclassification.

Overall, in England and Wales for the period 1980–1995, the induction rate varied between 16.8% and 20.6%. In Scotland there was a marked decrease in induction rate between 1980 and 1992, following which there was a return to the level seen in 1987.⁶

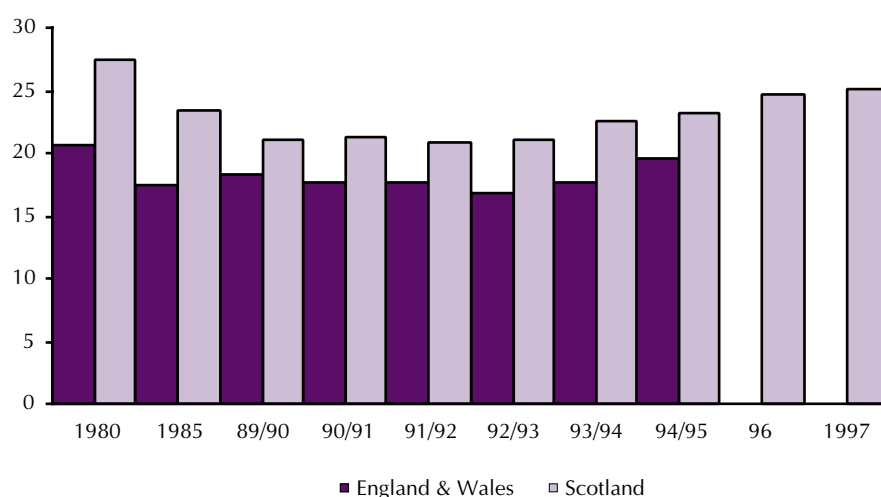


Figure 2 Trends in induction of labour in England, Wales and Scotland for the period 1980–97

3.1 Definitions

The definitions in Table 3.1 below relate to a number of terms discussed in the Guideline. These were agreed by the Guideline Development Group and are used as working definitions in the remainder of the document.

Table 3.1 Definitions and descriptions of terms relating to induction of labour

Term	Definition
Labour	The process of uterine contractions leading to progressive effacement and dilatation of the cervix and birth of the baby. The term is usually restricted to pregnancies at gestations greater than the legal definition of fetal viability (24 weeks in the UK)
Induction of labour	An intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. This includes both women with intact membranes and women with spontaneous rupture of the membranes but who are not in labour. The term is usually restricted to pregnancies at gestations greater than the legal definition of fetal viability (24 weeks in the UK)
Cervical ripening	A component part of induction of labour employed when the cervix is unfavourable in order to facilitate dilatation when labour is established
Augmentation	An intervention designed to increase the rate of progress of labour
Prolonged pregnancy	For the purpose of this Guideline, defined as those pregnancies continuing past 287 days (41 weeks) from the first day of the last menstrual period
Cervical favourability	<p>Within the systematic reviews focusing on induction of labour, the definition of favourable vs. unfavourable cervix varied depending on the scoring system used (see Appendix 2); however, the cut-off between unfavourable and favourable within the trials was set between four and eight.</p> <p>For the purposes of this Guideline, a favourable cervix is defined as one with a modified Bishop's score of greater than eight⁷</p>
Uterine hypercontractility (with or without FHR changes)	<p>The terminology of uterine hypercontractility is problematic. For the purpose of this Guideline, uterine hypercontractility without FHR changes included uterine tachysystole (more than five contractions per ten minutes for at least 20 minutes) and uterine hypersystole/hypertonus (a contraction lasting at least two minutes).</p> <p>Uterine hyperstimulation with FHR changes denoted uterine hyperstimulation syndrome (tachysystole or hypersystole with FHR changes such as persistent decelerations, tachycardia or decreased short term variability). However, due to varied reporting of this outcome there is the possibility of subjective bias in interpretation. In addition, it was not always clear from trials if these outcomes were reported in a mutually exclusive manner</p>

3.2 Outcome measures

A series of outcome measures was agreed during the production of the new series of Cochrane systematic reviews on induction of labour (See Appendix 1). The Guideline Development Group used these outcome measures as the basis for evaluating the efficacy of the different methods of induction of labour examined in Section 3.

All the outcomes listed below were examined for each clinical situation considered in the later sections.

3.3 Maternal outcomes

The main outcomes considered to be important in relation to induction of labour for the mother include:

- time to vaginal delivery or vaginal delivery rates within a specified time
- operative delivery rates (caesarean section and instrumental vaginal delivery)
- length of labour/incidence of prolonged labour
- measures of effectiveness (oxytocin augmentation rates, epidural usage, cervix unfavourable/unchanged at 12–24 hours)
- serious maternal morbidity or death
- other adverse outcomes (e.g. uterine hypercontractility, postpartum haemorrhage, maternal adverse effects)
- measures of maternal satisfaction.

Vaginal delivery rates *per se* can be assumed to be a reciprocal of operative delivery rates (instrumental and caesarean section). Therefore, it was felt to be more informative to include a time factor in the outcome, such as time to delivery or delivery achieved within a specific time interval. Data in trials are inconsistently reported, e.g. time from treatment to vaginal delivery or time from randomisation to delivery. As only summarised statistics of these variables are presented, for example mean number of hours, pooling of results from the trials is not possible.

Vaginal delivery not achieved in 24 hours is a useful benchmark to measure efficacy of a chosen induction method, as it was felt that this represented a realistic end-point for induction of labour. However, it is recognised a number of methods used for induction of labour (e.g. sweeping of the membranes) are not designed to initiate labour within 24 hours and, hence, will not report on this outcome. Delivery after this period therefore should not be interpreted as a failure of induction of labour.

Due to inconsistent reporting between trials, there is a paucity of available data in the Cochrane reviews relating to successful vaginal delivery within 24 hours. The data available are presented in the relevant sections.

Data relating to length of labour or incidence of prolonged labour were not collected for the new series of Cochrane reviews, due to the difficulties mentioned above.

Uterine hypercontractility with or without FHR changes is used as an adverse outcome measure related to the specific method of induction of labour. The division between episodes of hypercontractility with associated FHR changes and those without is often not clear in trial reports. The definitions used in this Guideline and in the systematic reviews have been standardised (see Appendix 2).

Maternal satisfaction was included as a pre-specified outcome in the series of systematic reviews. However, it was reported infrequently and was largely restricted to comparing different methods of induction of labour, rather than women's views of induction of labour generally. Evidence derived from qualitative or observational studies is not included, due to the availability of higher levels of evidence.

3.4 Fetal outcomes

The main outcomes examined in relation to induction of labour for the fetus include:

- serious neonatal morbidity or perinatal death

- other adverse perinatal outcomes (meconium-stained liquor, five-minute Apgar score of less than seven, neonatal intensive care unit admission).

Serious neonatal morbidity and perinatal death were reported as a composite outcome in the systematic reviews and included perinatal death, neonatal encephalopathy, disability in childhood, and seizures and birth asphyxia as defined by the trialists.

4. Care during induction of labour

Where research evidence was unavailable, the Guideline Development Group used other quality appraised Guidelines to support their recommendations.^{8,9} The recommendations regarding fetal surveillance during induction of labour are taken from *The Use of Electronic Fetal Monitoring: The use and interpretation of cardiotocography in intrapartum fetal surveillance*.¹⁰

Evidence level

4.1 Woman-centred care

One of the priorities of intrapartum care is to enable women to make informed choices regarding their care or treatment. To do so, they require access to evidence-based information to help them in making their choices. Verbal advice should be supported by accurate printed information, in a format that women can understand and which they may take away with them and read before the procedure.

Part of the dilemma of choice in relation to induction of labour can be summarised by the following quote: 'It is difficult to determine true "choice", especially for some clinical issues, but the extent to which women feel involved in such decisions may be one indicator of the quality of the interaction with the professional, from the women's perspective'.¹¹

III

Induction of labour should only follow informed consent by the woman. For consent to be fully informed it should include the reasons for induction, the choice of method to be used and the potential risks and consequences of accepting or declining an offer of induction of labour.

III

The process of induction of labour should only be considered when vaginal delivery is felt to be the appropriate route of delivery.⁹

III

C Women must be able to make informed choices regarding their care or treatment via access to evidence based information. These choices should be recognised as an integral part of the decision-making process.

4.2 Place of induction

In the absence of specific risk factors, induction of labour with vaginal PGE₂ may be initiated on the antenatal ward. However, there should be facilities for continuous electronic monitoring of both FHR and uterine activity.⁸

III

When oxytocin is used for induction of labour (or augmentation), the process should occur on a delivery suite.

III

Women receiving oxytocin for induction of labour (or augmentation) should receive one-to-one midwifery care.

III

The issue of outpatient induction of labour with prostaglandin agents has

been addressed in a number of studies.¹² However, none of these studies has been performed in the UK. In the absence of relevant evidence, the Guideline Development Group did not feel able to make any recommendations regarding the safety of outpatient treatment.

Readers are referred to Section 6.5.3 for further discussion regarding time of administration of vaginal PGE₂.

Continuous care of the mother in labour has been shown to reduce caesarean section rates and the use of analgesia. One systematic review of continuous support in labour considered a variety of outcomes. Continuous support in the included trials was provided by healthcare workers or lay people. Therefore, no extrapolation to the provision of one-to-one midwifery care can be made from these data.¹³

Ia

The importance of one-to-one midwifery care has been highlighted in a number of expert reports.^{14,15}

III

C For women who are healthy and have had an otherwise uncomplicated pregnancy, induction of labour with vaginal prostaglandin E₂ agents can be conducted on antenatal wards, prior to the active phase of labour.

C When undertaking induction of labour in women, with recognised risk factors (including suspected fetal growth compromise, previous caesarean section and high parity) the induction process should not occur on an antenatal ward.

4.3 Fetal surveillance and induction of labour

The assessment of fetal wellbeing is only one component of intrapartum care. It is an important area where due consideration must be given to maternal preference and priorities in light of potential risk factors to both mother and baby. The provision of accurate information in these circumstances is essential to allow each woman to make the right decision for her.

As with any other intervention induction of labour has unwanted effects. In the current series of systematic reviews of vaginal or intracervical prostaglandin PGE₂ the incidence of hypercontractility with or without FHR changes ranged from 1% to 5%. There was no difference between the different preparations.

Ia

When oxytocin is being used for induction of labour there is a similar risk of FHR changes and, hence, continuous electronic fetal monitoring should be used.¹⁰

III

Following instillation of prostaglandin agents, the woman should be advised to lie down for at least 30 minutes, followed by continuous electronic monitoring of the fetal heart until fetal wellbeing is established. This need not be initiated until contractions are detected or reported.⁸

III

When oxytocin is employed following prostaglandin agents, it should not be started within six hours of the administration of prostaglandins. This is as a result of the potential uterotonic effect of combining oxytocin with prostaglandin agents.

III

C Wherever induction of labour occurs, facilities should be available for continuous uterine and FHR monitoring.

- C** Fetal wellbeing should be established immediately prior to induction of labour.
- C** Following induction of labour with vaginal prostaglandins (PGE₂) fetal wellbeing should be established once contractions are detected or reported.
- C** For women who are healthy and have had an otherwise uncomplicated pregnancy, the assessment of fetal wellbeing following the administration of vaginal prostaglandins should comprise an initial assessment with continuous electronic fetal monitoring and, once normality is confirmed, intermittent monitoring can be used.
- C** Where oxytocin is being used for induction or augmentation of labour, continuous electronic fetal monitoring should be used.

4.4 Uterine hypercontractility with induction agents

The management of suspicious or pathological CTGs is directly addressed within the RCOG Evidence-based Clinical Guideline *The Use of Electronic Fetal Monitoring*.¹⁰ Readers are referred to Section 8.3. in that Guideline.

The recommendations arising from this section are shown below and the Guideline Development Group felt they were appropriate to include within this section.

If prostaglandin only has been used, removal of the remainder of the agent may help to alleviate the uterine hypercontractility. However, irrigation of the cervix or vagina is not beneficial.

///

Uterine hypercontractility with or without FHR changes during oxytocin infusions usually resolves with reduction or cessation of the infusion, but if this fails then tocolysis should be considered using the regimen published in *The Use of Electronic Fetal Monitoring*.¹⁶ Although discussed in further detail in Section 5.6 of that Guideline, the frequency of contractions with oxytocin use should not exceed three to four contractions in every ten-minute interval.

la

- C** Prolonged use of maternal facial oxygen therapy may be harmful to the fetus and should be avoided. There is no research evidence evaluating the benefits or risks associated with the short-term use of maternal facial oxygen therapy in cases of suspected fetal compromise.
- B** In cases of uterine hypercontractility with a suspicious or pathological CTG secondary to oxytocin infusions, the oxytocin infusion should be decreased or discontinued.
- A** In the presence of abnormal FHR patterns and uterine hypercontractility (not secondary to oxytocin infusion), tocolysis should be considered.
A suggested regimen is subcutaneous terbutaline 0.25 milligrams.
- B** In cases of suspected or confirmed acute fetal compromise, delivery should be accomplished as soon as possible, taking account of the severity of the FHR abnormality and relevant maternal factors. The accepted standard has been that, ideally, this should be accomplished within 30 minutes.

4.5 Care of higher-risk pregnancies

This section covers conditions of pregnancy where there may be a risk of increased adverse maternal or neonatal outcomes when induction of labour is undertaken.

4.5.1 Induction of labour of women with suspected fetal growth compromise

Risks associated with fetal growth compromise

Infants with fetal growth compromise are at a higher risk of perinatal death. One study found an association with perinatal mortality and growth restriction that was nearly five times that of normal weight infants.¹⁷ Infants with growth compromise enter labour in an increased state of vulnerability and are more likely to become acidotic because of:

- uteroplacental insufficiency
- lower metabolic reserves due to intrauterine malnutrition or pre-existing hypoxia
- an umbilical cord more prone to compression due to a reduction in amniotic fluid volume.

IIa

Reduction of risks associated with suspected fetal growth compromise

The Guideline Development Group was unable to locate any studies that considered induction of labour specifically in babies with suspected fetal growth compromise.

4.5.2 Induction of labour of women with a previous caesarean section

Risks associated with induction of labour in women with a previous caesarean section

There are small amounts of RCT data relating to induction of labour in women with a previous caesarean section. The Guideline Development Group is aware of only four RCTs that focused on or reported subgroup data relating to this group of women.¹⁸⁻²¹ These studies included only 137 patients and, hence, are underpowered to evaluate the risks associated with induction in this group or to comment on the relative efficacy of the agents considered.

Ib

One review of observational data focused on safety issues when undertaking induction of labour of women with a history of a previous caesarean section.²² The review focused on induction of labour in women with previous caesarean section with vaginal prostaglandins in comparison with other agents and reviewed evidence from seven studies. The authors concluded that the rate of vaginal delivery in this group of patients was similar to that quoted for spontaneous labour after a previous caesarean section, about 75%. The rate of uterine rupture from the largest of these observational studies was calculated as:

III

- 0.2% (0–0.6%) for symptomatic rupture
- 1.1% (0.1–2.1%) for asymptomatic dehiscence and symptomatic rupture.

The authors commented on the varied terminology used to define uterine rupture and the difficulty this posed for collecting reliable data on the risk of induction of women with a previous caesarean section.

Reduction of risk with induction of labour of women with a history of a previous caesarean section

In view of the sparsity of data specifically reporting in this subgroup, it is difficult to make specific recommendations for practice. Careful consideration of the risks of an induction of labour versus the risks of an elective caesarean

section should be made in light of the woman's wishes and views. From the review of observational data and extrapolation of the data relating to induction of labour of women in other subgroups, vaginal prostaglandins appear to be safe. If and when oxytocin is used, the dose schedules employed should be carefully considered. Overall, induction of women with previous caesarean section should follow the working algorithm presented in the next section with careful consideration of cervical status and membrane status.

4.5.3 Induction of labour of women with a breech presentation

About 3–4% of all pregnancies reach term with a fetus in the breech presentation.²³ A recent trial²⁴ provides information on the risks and benefits of planned caesarean section compared with planned vaginal breech delivery. The data within the trials relating to those women with a breech presentation who underwent induction of labour are not reported separately from the whole group who were randomised to a planned vaginal delivery.

The perinatal mortality was lower for planned caesarean section compared with planned vaginal breech delivery (1.6% vs. 5.0%; RR 0.33; 95% CI 0.19–0.56; NNT 29). Hence, no conclusions can be reached from these data regarding induction of labour with a breech presentation.

Ib

4.5.4 Induction of labour of women of high parity

Risks associated with induction of labour in women of high parity

Induction of labour in women of high parity may be associated with an increased incidence of precipitate labour, uterine rupture and postpartum haemorrhage. One case–control study examined the role of vaginal prostaglandins in the induction of labour in women of high parity and with unfavourable cervixes. This study examined 101 grand multiparae with unfavourable cervixes who underwent induction of labour. The control group consisted of 202 grand multiparae who went into labour spontaneously. There was a reduction in the rates of vaginal delivery (88.1% vs. 96.5%; OR 0.27; 95% CI 0.10–0.70) when induction was compared with spontaneous labour.

Caesarean section rates were increased in the induction group (8.9% vs. 3%; OR 3.20; 95% CI 1.10–9.25) when compared with the spontaneous group. One fetal death and one ruptured uterus occurred in the induction group. Although this study is small it does highlight the risks associated with induction of labour in women of high parity.

IIa

The 5th CESDI report included a focus group on cases involving a ruptured uterus.²⁵ Of the 42 cases of ruptured uterus, 30 (71%) women had a previous caesarean section (only one woman had more than one previous caesarean section). Of the 12 women with no uterine scar, 11 were parous (three were para 1, two were para 2, three were para 3 and three were para 4).

III

Reduction of risk with induction of labour in women of high parity

The Guideline Development Group found one randomised controlled trial that examined the role of a fast versus slow incremental regimen of intravenous oxytocin infusion for the induction of labour in women of high parity.²⁶ The trials included 90 women of parity five or more requiring induction of labour for medical or obstetric reasons. Both groups had the same starting dose of two milliunits per minute. In the control (fast) group this was doubled every 15 minutes. In the experimental (slow) group it was doubled every 45 minutes until the women were experiencing three contractions every ten minutes. This rate was maintained until delivery, with a maximum of 32 milliunits per minute. The results showed little difference in mode of delivery in both groups.

Ib

There were 13 precipitate labours in the fast group and no instances of precipitate labour in the slow group (OR 0.09; 95% CI 0.03–0.30).

There were 17 instances of uterine hypercontractility (FHR changes were unspecified) in the fast group and five instances in the slow group (OR 0.23; 95% CI 0.09–0.59).

There were no uterine ruptures in the slow group and three in the fast group (OR 0.12; 95% CI 0.01–1.22).

No fetal/neonatal outcomes were reported.

Ib

4.5.5 Summary

- There are insufficient data to comment on the risks of induction of labour of women with babies with known growth restriction.
- Induction of labour with a history of a previous caesarean section is not contraindicated but careful consideration of the mother's clinical condition should be taken before induction is started.
- Induction of labour with a history of previous caesarean section can be undertaken with vaginal prostaglandins with or without the use of oxytocin and/or amniotomy, although the safety data is limited.
- There is an increased risk associated with planned vaginal breech delivery. The risks associated with induction of labour with a breech presentation cannot be quantified from the available trial literature.
- Induction of labour in women of high parity with standard oxytocin regimens may be associated with an increase in uterine rupture.

4.5.6 Practice recommendations

C When undertaking induction of labour in women, with recognised risk factors (e.g. including suspected fetal growth compromise, previous caesarean section and high parity) the clinical discussion regarding the timing and method of induction of labour should be undertaken at consultant level. The induction process should not occur on an antenatal ward.

4.6 Future research recommendations

Adequately powered RCTs reporting relevant clinical outcomes in specific clinical groups are needed to evaluate the risks and benefits of induction of labour for women whose pregnancies are complicated by:

- diabetes (divided according to aetiology of diabetes)
- multifetal pregnancy
- suspected fetal growth compromise
- macrosomia.

Further research is also needed to investigate the role of outpatient cervical ripening within a UK setting.

Diabetic pregnancy

See Section 5 Indications for Induction of Labour.

Multifetal pregnancy

See Section 5 Indications for Induction of Labour.

5. Indications for induction of labour

5.1 Introduction

Induction of labour is indicated when it is agreed that the fetus or mother will benefit from a higher probability of a healthy outcome than if birth is delayed. An exception to this is induction of labour at maternal request for social reasons. In this section, specific indications for induction of labour are considered.

Evidence level

The process of induction of labour should only be considered when vaginal delivery is felt to be the appropriate route of delivery.⁹

Induction of labour should only follow informed consent by the woman. For consent to be fully informed, it should include the reasons for induction, the choice of method to be used and the potential risks and consequences for accepting or refusing an offer of induction of labour. The Guideline Development Group was unable to locate any current epidemiological data regarding the numbers of women being induced for specific indications.

The list provided is not exhaustive. It covers:

- prolonged pregnancy
- diabetic pregnancy
- breech presentation
- multifetal pregnancy
- high parity
- prelabour rupture of membranes
- macrosomia
- the presence of fetal growth restriction
- previous caesarean section
- maternal request
- history of precipitate labour

(See Section 4 for breech presentation, high parity, suspected fetal growth restriction and previous caesarean section).

Conditions where there are specific risks attached to induction of labour are discussed in Section 4: Care During Induction of Labour.

5.2 Prolonged pregnancy

5.2.1 Risk associated with prolonged pregnancy

Population studies indicate that, in women who are healthy and have otherwise uncomplicated pregnancies, perinatal mortality and morbidity is increased in pregnancies of more than 42 weeks. The risk of stillbirth increases from one per 3000 continuing pregnancies at 37 weeks to three per 3000 continuing pregnancies at 42 weeks to six per 3000 continuing pregnancies at 43 weeks.²⁷ A similar increase in neonatal mortality is also reported. Further analysis of the same data attempted to clarify the gestation

IIa

specific risk for unexplained stillbirth,²⁸ the results obtained are approximations from three sources of data but the methodology of this study has been criticised.^{29–32}

5.2.2 Reduction of risk in prolonged pregnancy

One systematic review evaluates interventions aimed at preventing or improving the outcome of delivery beyond term.³³ The conclusions are summarised below.

Early Ultrasound in Pregnancy

A policy of early pregnancy ultrasound reduced the induction of labour for prolonged pregnancy (1.9% vs. 2.8%; RR 0.69; 95% CI 0.58–0.82; NNT 111).³³ These data were extracted from four trials from a previous review,³⁴ which focused on the use of ultrasound for early fetal assessment in pregnancy.

Ia

Policy of offering induction of labour after 41 weeks

The benefit of a policy of active induction of labour compared with expectant management is derived from the trials of routine induction of labour after 41 weeks (0.02% vs. 0.23%; Peto OR 0.23; 95% CI 0.06–0.90; NNT 476)³³

Ia

The rate of caesarean section is reduced with a policy of routine induction of labour in those trials comparing a policy of routine induction with conservative management in pregnancies beyond 41 weeks (19.6% vs. 21.7%; RR 0.90; 95% CI 0.81–0.99; NNT 47). Similar findings were seen in those trials restricted to induction in nulliparous women. No effect was evident on caesarean section rates if the analysis was divided up by cervical favourability or background caesarean section rates (either less or greater than 10% in the populations in the included trials).³³

There is no effect on instrumental delivery rates, use of epidural analgesia or FHR abnormalities during labour with a routine policy of induction of labour.

There is a reduction in meconium staining of the amniotic fluid with routine induction (20.0% vs. 25.3%; RR 0.78; 95% CI 0.72–0.86; NNT 19). However, this finding is probably related to the increase in meconium-stained liquor seen with increasing gestation in the conservative management arm of these trials.³³

The Guideline Development Group was unable to find any reports or surveys of practice on the current induction policies in the UK with regard to the timing of routine induction for prolonged pregnancy.

Data from one cohort²⁷ revealed that at 40 weeks of gestation only 58% of women had delivered. This increased to 74% by 41 weeks and to 82% by 42 weeks. Hence, a policy of induction of labour prior to 41 weeks would generate increases in workload but with no reduction in perinatal mortality.

Ila

Alternative policy of screening high/low risk pregnancies from 42 weeks

The review included data on one trial comparing complex antenatal fetal monitoring (computerised cardiotocography, amniotic fluid index and assessment of fetal breathing, tone and gross body movements) with more simple monitoring (standard cardiotocography and ultrasound measurement of maximum pool depth) for identification of high-risk pregnancies from 42 weeks. There was no difference between the two policies with respect to

Ia

perinatal mortality or caesarean section. However, the number of included patients in this trial was small ($n = 145$) and, hence, the trial was underpowered to detect any significant differences in perinatal mortality.³³

The Guideline Development Group was unable to locate any data comparing simple or more complex monitoring packages with no monitoring in prolonged pregnancy.

5.2.3 Economic considerations

Two published economic studies have examined the costs of induction of labour versus expectant management of prolonged pregnancy, in different settings.^{35,36} The first study, based on a Canadian multicentre trial, found that expectant management was more costly than induction with prostaglandin gel, due mainly to costs of additional monitoring and a higher caesarean-section rate.³⁵ The second study, based on the TERMPROM international multicentre trial, found that there was no difference in cost between expectant management and induction with prostaglandin.³⁶ The difference is largely due to assumptions made about the operative delivery rate differential: the TERMPROM trial found only small and statistically insignificant operative delivery rate differences between the treatment arms.

An important issue not dealt with by these published studies is that, in the context of local staff shortages, increased numbers of women being induced for prolonged pregnancy may have local opportunity costs in terms of delivery suite workload. Other women and babies may be exposed to risk if the induction of labour workload is increased. This is a matter for local discussion and debate, since it depends crucially on local staffing circumstances.

5.2.4 Summary

- A policy of offering routine early-pregnancy ultrasound reduces the incidence of induction for perceived prolonged pregnancy.
- A policy of offering routine induction of labour after 41 weeks reduces perinatal mortality without an increase in caesarean section rates.
- The type of antenatal monitoring in the identification of high-risk pregnancies beyond 42 weeks is uncertain, but the simpler modalities used have been as effective as the more complex.

5.2.5 Practice recommendations

- A** An ultrasound to confirm gestation should be offered before 20 weeks of gestation, as this reduces the need for induction for perceived post-term pregnancy.
- A** Women with uncomplicated pregnancies should be offered induction of labour beyond 41 weeks.
- A** From 42 weeks, women who decline induction of labour should be offered increased antenatal monitoring consisting of a twice weekly CTG and ultrasound estimation of maximum amniotic pool depth.

5.3 Diabetes in pregnancy

5.3.1 Risk associated with diabetes in pregnancy

The complications associated with diabetes in pregnancy vary according to the type and severity of the diabetes. Diabetes complicates 2.6% of pregnancies.

Ila

In women with pre-existing diabetes, major concerns during the third trimester include:

- a higher perinatal mortality rate, which incorporates an increased rate of late fetal death. Three UK population studies show a four or fivefold increase in perinatal mortality rate in diabetic pregnancies in comparison with either the local or national population.^{37–39} One of the studies showed a stillbirth rate five times that of the general population.³⁸
- increased rate of other complications necessitating preterm delivery (e.g. pre-eclampsia)⁴⁰.
- increased potential for birth trauma associated with increased fetal size.^{38–40} Infants of diabetic mothers are particularly prone to brachial plexus injury caused by shoulder dystocia.⁴¹ One population cohort study showed that the mean birthweight in the sample was 1.3 standard deviations greater than infants of mothers without diabetes, after correction for gestational age.³⁸

IIa

IIa

IIa

While there is insufficient data clarifying the gestation-specific risk for unexplained stillbirth in diabetic pregnancy gestation, the Guideline Development Group considered that it is currently usual practice in the UK to induce women with insulin-dependent diabetes prior to 40 weeks. Previously published guidelines have recommended that women with good diabetic control and no complications of pregnancy could be delivered at 39–40 weeks.⁴²

IV

5.3.2 Reduction of risk in diabetic pregnancies

Induction or elective delivery before full term has been proposed as a means of improving maternal and neonatal outcome. However, the potential benefits of induction need to be balanced against the potential to increase the risk of pulmonary complications in the fetus.

One systematic review compared the policy of elective induction of labour at 38 weeks with expectant management.⁴³ Only one pragmatic RCT was included in this review.⁴⁴ This trial had 200 participants, none of whom had type I diabetes. Three of the reviewers' pre-specified outcomes were reported upon. There was no difference in the risk of caesarean section (either elective or in labour) between interventions (25% vs. 31%; RR 0.81; 95% CI 0.52–1.26). The risk of macrosomia (birthweight over 4000 g) was reduced in those women who were actively induced (15% vs. 27%; RR 0.56; 95% CI 0.32–0.98; NNT 8). The trial is too small to draw conclusions regarding the effect of this policy on perinatal mortality.

Ia

5.3.3 Summary

- Induction of labour of term pregnancies in women with diabetes is associated with a reduced risk of macrosomia.
- Routine induction does not appear to increase the risk of caesarean section or neonatal morbidity, cases of which were rare and mild.

5.3.4 Practice recommendations

C Women who have pregnancies complicated by diabetes should be offered induction of labour prior to their estimated date for delivery.

5.4 Multifetal pregnancy

The discussion below relates only to twin pregnancies and the Guideline

Development Group was unable to locate any specific studies relating to higher-order pregnancies.

5.4.1 Risk associated with twin pregnancy

Nearly 70% of multifetal pregnancies deliver between 35 and 37 weeks of gestation.⁴⁵ A proportion will deliver prior to this time because of complications relating to chorionicity and growth restriction or are delivered electively due to maternal request relating to discomfort. In the remaining multifetal pregnancies there has been concern over potential increased risk of adverse outcome according to duration of gestation.

IIa

A retrospective study of all singleton and multiple pregnancies in Japan between 1989 and 1993 demonstrated that the risk of perinatal death was increased for fetuses of multiple pregnancy compared with singleton pregnancies born at 40 weeks (1.8% vs. 0.16%).⁴⁵ The same study showed that, in multiple pregnancies, the percentage of perinatal deaths between 37 and 39 weeks of gestation was 1.1–1.2%; at 40 weeks of gestation it was 1.8%, at 41 weeks it was 2.2% and at 42 or more weeks it was 3.7%.

IIa

5.4.2 Reduction of risk in twin pregnancies

One RCT examined the role of induction of labour in multiple pregnancies in comparison with expectant management.⁴⁶ The study examined 36 twin pregnancies at 37 weeks of gestation and randomised them to immediate induction with oral prostaglandins or expectant management with continued surveillance (consisting of daily non-stress testing, twice weekly ultrasound evaluation and cervical assessment).

IIb

There were 17 women in the immediate-induction arm of the trial and 19 in the expectant-management arm. The study was underpowered to detect any difference in perinatal mortality rates. There was no difference in caesarean section rates (32% vs. 18%), birthweight, Apgar scores of less than seven at five minutes or postpartum haemorrhage rates. There was an increase in meconium-stained liquor in the expectant-management group (13% vs. 0%). This may be related to a higher gestational age at delivery.

5.4.3 Summary

- The perinatal mortality rate in twin pregnancies is increased in comparison with singleton pregnancies at term.
- No conclusions can be drawn from the available trial evidence relating to the merits of an active policy of induction of labour in uncomplicated multifetal pregnancies.

5.5 Induction of labour in the presence of prelabour rupture of the membranes

5.5.1 Risk associated with prelabour rupture of the membranes

Prelabour rupture of the membranes (PROM) occurs in 6–19% of term pregnancies.^{47,48} The risks of PROM at term relate to maternal and neonatal infection, prolapsed cord and fetal distress resulting in operative delivery or low five-minute Apgar score.^{49–59} Fetal distress may be caused by any of the complications listed.

Epidemiological data on time interval from term PROM to spontaneous labour demonstrates that most women go into spontaneous labour within 24 hours of rupturing their membranes.⁶⁰

IIa

- 86% of women will labour within 12–23 hours

- 91% will labour within 24–47 hours
- 94% will labour within 48–95 hours.
- 6% of women will not be in spontaneous labour within 96 hours of PROM.

As the time between the rupture of the membranes and the onset of labour increases, so may the risks of maternal and fetal infection. Induction of labour may reduce these risks^{47,48}.

IIa

5.5.2 Reduction of risk in prelabour rupture of the membranes

A series of systematic reviews examined the outcome of pregnancies with PROM at or near term.^{47,61–63} Two of the reviews focused on outcome in pregnancies where a policy of no intervention was compared with induction with either prostaglandin⁶² or oxytocin.⁶³ The operative delivery rates were not different in the induction group compared with the no treatment group in either review.

Ia

Maternal infection was reduced in both reviews with a policy of active management.

An active policy of induction of labour with oxytocin reduced the incidence of chorioamnionitis (4.5% vs. 7.2%; RR 0.63; 95% CI 0.51–0.99; NNT 37). An active policy of induction of labour with prostaglandins reduces the incidence of chorioamnionitis (6.5% vs. 8.2%; RR 0.78; 95% CI 0.63–0.98; NNT 56).^{62,63}

Neonatal infection risks were reduced if induction was undertaken with oxytocin (1.3% vs. 2.4%; RR 0.65; 95% CI 0.45–0.95; NNT 90)⁶³ However, there were insufficient patients in these reviews to draw any conclusions regarding perinatal or maternal mortality.

The trials included in these reviews used a variety of protocols for conservative management. One trial dominates the analysis. The trial included a number of policies of induction of labour up to a maximum of 96 hours after membrane rupture.

The trials included in the systematic reviews include a mixture of inpatient and outpatient management policies with expectant management. There is insufficient evidence to base a recommendation on the effect of place on outcome for mother or baby that is dependent on the place that expectant management occurs.

The systematic reviews do not specifically address any difference between those groups who received or who did not receive screening for microbiological organisms. In view of this, the Guideline Development Group did not feel able to make recommendations regarding the use of vaginal swabs with PROM, regardless of the subsequent management.

5.5.3 Summary

- There is no difference in operative delivery rates between induction versus a conservative approach in women with prelabour rupture of the membranes.
- A policy of induction of labour is associated with a reduction in infective sequelae for mother and baby.

5.5.4 Practice recommendations

- A** Women with prelabour rupture of the membranes at term (over 37 weeks) should be offered a choice of immediate induction of labour or expectant management.

- A** Expectant management of women with prelabour rupture of the membranes at term should not exceed 96 hours following membrane rupture.

5.6 Induction of labour for suspected fetal macrosomia

5.6.1 Risk associated with suspected fetal macrosomia

It has been postulated that induction of labour for suspected fetal macrosomia will avoid caesarean section or difficult instrumental vaginal delivery. However, for a policy to be effective, fetal size needs to be estimated accurately and all methods currently used to estimate fetal size especially for large fetuses are poorly predictive.⁶⁴

5.6.2 Reduction of risk associated with suspected fetal macrosomia

One systematic review addressed the question of whether a policy of active induction versus expectant management in cases of suspected fetal macrosomia had any impact on maternal or neonatal outcomes.⁶⁵ The review included two trials involving 313 women. Both trials included an active induction arm for babies estimated to weigh more than 4000 g in pregnant women who were not diabetic. In both trials, the mean gestational age at birth in both experimental and control groups was similar, despite one group being managed expectantly.

Overall perinatal mortality and morbidity were similar for both policies. However, in total there were two babies who had brachial plexus injuries and four who had fractures. These all occurred in the control groups. There was no difference in rates of caesarean section or instrumental vaginal delivery between the two groups.

lb

5.6.3 Summary

Currently, the evidence is inconclusive that a policy of induction of labour for suspected fetal macrosomia in women who are not diabetic can reduce maternal or neonatal morbidity.

5.7 Induction of labour for maternal request prior to 41 weeks

5.7.1 Reasons why women request induction of labour

One study examined women's motives for opting for elective induction of labour.⁶⁶ The study reported that, within a series of 237 women offered elective induction, 50% accepted. Women's reasons for accepting this option included increased feelings of safety and a desire to shorten the duration of pregnancy.

Women who requested induction were more likely to have had problems during their current pregnancy, complications in their previous pregnancies, problematic menstrual periods, and to be more anxious about their labours than those women who chose a spontaneous onset of labour.

///

5.7.2 Risk associated with induction of labour for maternal request

The Guideline Development Group has not formally addressed the risks associated with induction of labour for maternal request. Assuming that the woman is healthy, with an uncomplicated pregnancy, the risks of continuing the pregnancy should be equivalent to that of the general population. The

risks of induction of labour for the mother will also be equivalent to those of the general population. However, any potential benefits accrued are less easy to quantify. There is an increased risk of respiratory distress syndrome in the baby if labour is induced before term. Therefore, it is important that these risks are highlighted in any discussions regarding induction prior to term.

5.7.3 Economic considerations

A policy of routinely offering 'elective' induction for psychological or social reasons would have resource implications. However, no published study has examined these costs. The costs would include both the immediate costs of drugs, equipment and staff time, and the indirect costs due to an increased risk of operative delivery. These costs would then have to be set against the benefits from the woman's point of view of having the freedom to choose 'elective' induction. One key uncertainty is how many women would in fact opt for 'elective' induction if this were routinely offered on the NHS.

Further economic evaluation research is therefore needed to evaluate both the costs and the benefits of a policy of routinely offering 'elective' induction of labour for psychological or social reasons.

5.7.4 Summary

There is insufficient evidence to allow comment on the risks associated with elective induction of labour for maternal request.

5.7.5 Practice recommendations



Where resources allow, maternal request for induction of labour should be considered when there are compelling psychological or social reasons and the woman has a favourable cervix.

5.8 Induction of labour of women with a history of precipitate labour

Precipitate labour has been defined as labour having a duration of two hours or less.⁶⁷

5.8.1 Risk associated with induction of labour of women with a history of precipitate labour

One cohort study included 4976 women who gave birth over a period of two years. Among these women, there were 106 women who had non-augmented spontaneous labours of two hours or less.⁶⁷ The incidence of spontaneous precipitate labour was 2.1%. Two controls were selected for every woman in the precipitate labour group. There were no perinatal deaths in the study and operative delivery rates were not reported. The babies born in the precipitate group did not suffer any adverse neonatal outcomes.

The Guideline Development Group was unable to identify any studies highlighting potential problems relating to the place of birth in women with a history of precipitate labour. The hypothesis is that induction of labour in these women will avoid birth outside of hospital, in cases where this is the preferred place of birth for that woman.

Ila

5.8.2 Reduction of risk with induction of labour of women with a history of precipitate labour

The Guideline Development Group was unable to locate any specific studies that examined the reduction of risk associated with precipitate labour.

5.8.3 Summary

No conclusions can be drawn from the available evidence in relation to the timing of induction of labour of women with a history of precipitate labour.

5.9 Future research recommendations

Adequately powered RCTs reporting relevant clinical outcomes in specific clinical groups are needed to evaluate the risks and benefits of induction of labour for women whose pregnancies are complicated by:

- diabetes (divided according to aetiology of diabetes)
- multifetal pregnancy
- macrosomia.

Research is needed to evaluate screening in the UK for abnormal vaginal colonisation in cases of prelabour rupture of the membranes at term.

6. Method of induction

6.1 Introduction

Induction of labour is indicated when it is agreed that the fetus or mother will benefit from a higher probability of a healthy outcome than if birth is delayed. The process of induction of labour should only be considered when vaginal delivery is felt to be the appropriate route of delivery.⁹

Evidence level

Induction of labour should only follow informed consent by the woman. For consent to be fully informed it should include the reasons for induction, the choice of method to be used, and the potential risks and consequences for accepting or refusing an offer of induction of labour.

Recommendations are based on evidence from the series of Cochrane reviews on induction of labour. Pooled data from the reviews are presented and, where it is available, evidence relating to clinical subgroups (parity, membrane status and cervical favourability) is presented.

6.2 Membrane sweeping

6.2.1 Performance

Sweeping the membranes in women at term reduced the delay between randomisation and spontaneous onset of labour, or between randomisation and birth, by a mean of three days.⁶⁸

1a

Sweeping the membranes increased the likelihood of both:

- spontaneous labour within 48 hours (63.8% vs. 83.0%; RR 0.77; 95% CI 0.70–0.84; NNT 5)
- birth within one week (48.0% vs. 66.0%; RR 0.73; 95% CI 0.66–0.80; NNT 5).

Sweeping the membranes performed as a general policy from 38–40 weeks onwards decreased the frequency of prolonged pregnancy:

- over 42 weeks: 3.4% vs. 12.9%; RR 0.27; 95% CI 0.15–0.49; NNT 11
- over 41 weeks: 18.6% vs. 29.87%; RR 0.62; 95% CI 0.49–0.79; NNT 8.

Membrane sweeping reduced the frequency of using other methods to induce labour (formal induction of labour). The overall risk reduction in the available trials was 15%. This risk reduction of a formal induction of labour was 21.3% vs. 36.3% (RR 0.59; CI 0.50–0.70; NNT 7).

The risk of operative delivery is not changed by the intervention. There was no difference in other measures of effectiveness or adverse maternal outcomes.

Sweeping the membranes was not associated with an increase in maternal infection or fever rates (4.4% vs. 4.5%; RR 0.97; 95% CI 0.60–1.57). Similarly, there was no increase in neonatal infection (1.4% vs. 1.3%; RR 0.92; 95% CI 0.30–2.82).

No major maternal adverse effects were reported in the trials. A trial that systematically assessed minor adverse effects and women's discomfort during the procedure found that women in the sweeping group reported more discomfort during vaginal examination. Median pain scores were higher in women allocated to sweeping of membranes. Pain was assessed by the Short Form of the McGill Pain Questionnaire,⁶⁹ which included three scales:

- a visual analogue scale (0–10 cm)
- the present pain index (0–5)
- a set of 15 descriptors of pain scoring 0–3.

In addition, more women allocated to sweeping experienced vaginal bleeding and painful contractions not leading to the onset of labour during the 24 hours following the intervention. There was no difference in any fetal outcome between the membrane sweeping and the non-membrane sweeping groups. These results must be interpreted with caution due to the presence of heterogeneity. The trials included in this review did not report in relevant clinical subgroups.

la

6.2.2 Summary

- Membrane sweeping is associated with a reduction in the length of time between treatment and spontaneous labour.
- Sweeping of the membranes reduces the incidence of prolonged pregnancy.
- Sweeping of the membranes reduces the need for the use of formal methods of induction of labour.
- Sweeping of the membranes is associated with an increase in maternal discomfort.

6.2.3 Practice recommendations

A Prior to formal induction of labour, women should be offered sweeping of the membranes.

A When membrane sweeping is proposed, discussions should include information that informs women that membrane sweeping:

- is not associated with an increase in maternal or neonatal infection
- is associated with increased levels of discomfort during the examination and bleeding.

6.3 Comparison of oxytocin and prostaglandins for induction of labour

Oxytocin and prostaglandins are currently the main agents used for formal induction of labour in the UK. Oxytocin was considered in two of the current systematic reviews on induction of labour in the Cochrane Library. One of these⁷⁰ considered the use of oxytocin alone (i.e. included trials where induction of labour was undertaken in the presence of ruptured membranes or where oxytocin had not been used within two hours of amniotomy). The other⁷¹ examined the use of oxytocin with amniotomy (i.e. included trials where induction of labour was undertaken with oxytocin with immediate amniotomy or within two hours of amniotomy).

la

Within the systematic reviews, there were often few data reported in the clinical subgroups. This was especially true with regard to comparisons of oxytocin and prostaglandin agents in women with intact membranes. For the purpose of this Guideline, data from the oxytocin alone and the oxytocin with amniotomy reviews were conflated.^{70,71} The additional groups formed and details of the sources of the data are shown in Appendix 3.

1a

6.3.1 All women

When comparing induction of labour using either oxytocin (alone or in combination with amniotomy) or PGE₂ (vaginal or intracervical), overall, induction with PGE₂ was associated with:

1a

- an increase in successful vaginal delivery within 24 hours
- a reduction in caesarean-section rate
- a reduction in the risk of the cervix remaining unfavourable/unchanged at 24–48 hours
- a reduction in the use of epidural analgesia
- an increase in the number of women satisfied with the method of induction.

6.3.2 Evaluating the effect of parity

Induction of labour in women who are nulliparous

For induction of labour in nulliparous women comparing the use of either oxytocin (alone or in combination with amniotomy) or PGE₂ (vaginal or intracervical), overall, induction with PGE₂ was associated with:

1a

- an increase in successful vaginal delivery within 24 hours.
- an increase in the number of women satisfied with the method of induction.
- no difference in caesarean section rate
- no difference in the use of epidural analgesia.

The risk of the cervix remaining unfavourable or unchanged at 24–48 hours was not reported in this subgroup.

Induction of labour in women who are multiparous

For induction of labour in all multiparous women comparing the use of either oxytocin (alone or in combination with amniotomy) or PGE₂ (vaginal or intracervical), overall, induction with PGE₂ was associated with:

1a

- an increase in successful vaginal delivery within 24 hours
- no difference in caesarean section rate
- no difference in the use of epidural analgesia.

The risk of the cervix remaining unfavourable or unchanged at 24–48 hours and the number of women satisfied with the method of induction were not reported in this subgroup.

6.3.3 Evaluating the effect of membrane status

Induction of labour in women with intact membranes

For induction of labour in women with intact membranes, comparing the use of either oxytocin (alone or in combination with amniotomy) or PGE₂ (vaginal or intracervical) in these women, overall induction with PGE₂ was associated with:

1a

- an increase in successful vaginal delivery within 24 hours
- a reduction in caesarean section rate
- a reduction in the cervix remaining unfavourable/unchanged at 24–48 hours

- an increase in the number of women satisfied with the method of induction
- there was no reduction in the use of epidural analgesia.

To evaluate the effect of parity for induction of labour in women with intact membranes, the data were further subdivided into nulliparous and multiparous women. For nulliparous women with intact membranes there was no difference in the proportion of women achieving successful vaginal delivery in 24 hours or in the caesarean section rates. The risk of the cervix remaining unfavourable or unchanged at 24–48 hours, the use of epidural analgesia or the number of women satisfied with the method of induction were not reported in this subgroup.

There were no data in the reviews on multiparous women with intact membranes and so no conclusions have been drawn.

To evaluate the effect of cervical favourability on the choice of method of induction of labour in women with intact membranes, the data were subdivided into groups of women with favourable or unfavourable cervixes. For induction of labour of women with intact membranes and an unfavourable cervix comparing the use of either oxytocin (alone or in combination with amniotomy) or PGE₂ (vaginal or intracervical), overall, induction with PGE₂ was associated with:

- an increase in successful vaginal delivery within 24 hours
- a reduction in caesarean section rate
- a reduction in the cervix remaining unfavourable/unchanged at 24–48 hours
- no difference in the number of women satisfied with the method of induction.

The use of epidural analgesia was not reported in this subgroup.

For induction of labour of women with intact membranes and an unfavourable cervix comparing the use of either oxytocin (alone or in combination with amniotomy) or PGE₂ (vaginal or intracervical), overall, induction with PGE₂ was associated with:

- an increase in successful vaginal delivery within 24 hours
- no difference in caesarean section rate
- no difference in the risk of the cervix remaining unfavourable/unchanged at 24–48 hours.

The use of epidural analgesia and the number of women satisfied with the method of induction were not reported in this subgroup.

Induction of labour in women with ruptured membranes

In women with ruptured membranes, comparing the use of oxytocin to PGE₂ (vaginal or intracervical), the use of prostaglandins resulted in:

- an increase in successful vaginal delivery within 24 hours
- no difference in caesarean section rate
- no difference in the risk of the cervix remaining unfavourable/unchanged at 24–48 hours.
- a reduction in the use of epidural analgesia
- no difference in the number of women satisfied with the method of induction.

la

la

la

Further consideration should also be given to the results presented in Section 5.5 on the management of ruptured membranes at term, which showed that induction with oxytocin in preference to vaginal PGE₂ reduced the rate of some infective sequelae such as chorioamnionitis.⁴⁷

la

To evaluate if this effect varies by parity, for both nulliparous and multiparous women with ruptured membranes, the use of vaginal PGE₂ was associated with an increase successful vaginal delivery within 24 hours. There was no difference in caesarean-section rates or the use of epidural analgesia.

la

6.3.4 The effect of cervical favourability

Within the systematic reviews, the data were extracted and divided according to cervical status where possible. Cervical status was divided into three groups: cervix unfavourable, cervix favourable and cervix variable or undefined. The cervix was assessed using a variety of cervical scoring systems. The two main systems used were the original and modified Bishop's score (see Appendix 1). For the purposes of the reviews, a cervix was viewed as unfavourable if the derived score was less than six.

la

Women with an unfavourable cervix

When comparing oxytocin (alone or in combination with amniotomy) with PGE₂ (vaginal or intracervical), in women with an unfavourable cervix, the use of prostaglandins was associated with:

la

- an increase in successful vaginal delivery within 24 hours
- a reduction in caesarean section rate
- a reduction in the risk of the cervix remaining unfavourable/unchanged at 24–48 hours
- no difference in the use of epidural analgesia
- no difference in the number of women satisfied with the method of induction.

Women with a favourable cervix

When comparing oxytocin (alone or in combination with amniotomy) with PGE₂ (vaginal or intracervical), in women with a favourable cervix, the use of prostaglandins was associated with:

la

- an increase in successful vaginal delivery within 24 hours
- no difference in caesarean section rate
- no difference in the risk of the cervix remaining unfavourable/unchanged at 24–48 hours
- no difference in the use of epidural analgesia
- a reduction in the number of women satisfied with the method of induction.

When these data were further divided according to parity there were insufficient data to draw any further meaningful conclusions.

6.3.5 Economic considerations

One main study examined the costs of oxytocin compared with prostaglandin as first-line method of labour induction.⁷² Based on earlier Cochrane review data, this study found that prostaglandin was cost neutral or cost saving compared with oxytocin, once non-medicine costs were taken into account. Although the medicines cost was higher with use of prostaglandin, this cost was offset by savings associated with a reduced rate of caesarean section, a reduced rate of postpartum haemorrhage requiring blood transfusion and reduced monitoring costs.

A more recent study found that oxytocin may not be more costly than prostaglandin. However, this conclusion may not be generally applicable, as it was based on the findings of the TERMPROM multicentre trial, which found no significant differences in operative delivery rates between the two methods of induction.³⁶

6.3.6 Summary

Overall, induction of labour using prostaglandins seem to improve the rate of successful vaginal delivery, lower the rate of caesarean section, lower epidural usage and to be associated with improved maternal satisfaction. The benefits of prostaglandin are less marked in women with ruptured membranes in comparison with women with intact membranes. Unfortunately, there were insufficient data to evaluate fully the possible differential effects of parity or cervical favourability.

6.3.7 Practice recommendations

A Prostaglandins should be used in preference to oxytocin when induction of labour is undertaken in either nulliparous or multiparous women with intact membranes, regardless of their cervical favourability.

A Either prostaglandins or oxytocin may be used when induction of labour is undertaken in nulliparous or multiparous women who have ruptured membranes, regardless of cervical status, as they are equally effective.

6.4 A comparison of intracervical and intravaginal prostaglandins (PGE₂)

The two most commonly used preparations and routes of administration of prostaglandins are intravaginal or intracervical PGE₂. Methods of administration, doses and intervals between doses, are discussed in the subsequent sections. It should be noted, however, that intracervical PGE₂ is no longer available in the UK for induction of labour.

1a

There were no differences between operative delivery rates when intracervical and vaginal prostaglandins were compared, irrespective of patient group.⁷³

1a

There was no difference in any of the other defined outcomes between intracervical and intravaginal prostaglandins.⁷³

1a

6.4.1 Summary

There was no difference in relation to outcome between the use of intravaginal or intracervical prostaglandins.

6.4.2 Practice recommendations

A When induction of labour is undertaken with prostaglandins, intravaginal PGE₂ should be used in preference to intracervical preparations, as they are equally effective and administration of vaginal PGE₂ is less invasive.

6.5 A comparison of different preparations of vaginal prostaglandin (PGE₂)

6.5.1 Method of administration

In the current Cochrane systematic review,⁷⁴ the varying formulations of vaginal PGE₂ were evaluated. Comparisons were made between vaginal PGE₂ gel, tablet, pessary or suppository and sustained-release formulations.

1a

For the purpose of this Guideline and within the current structure of systematic reviews, the term 'suppository' or 'pessary' refers to older formulations where the PGE₂ formulation was often made 'in-house' into a pessary. These should not be confused with sustained-release formulations.

1a

In the four trials comparing PGE₂ gel with PGE₂ tablets:

1a

- there was no difference between operative delivery rates between the groups
- oxytocin augmentation was reduced with the use of gel formulations compared with tablet (50% vs. 59.7%; RR 0.84; 95% CI 0.72–0.99; NNT 10). However, there was significant heterogeneity between the trials and, hence, this result must be interpreted with caution
- There was no difference in uterine hypercontractility or in the risk of the cervix remaining unchanged/unfavourable at 24–48 hours.

Two trials compared PGE₂ gel with either pessary or suppository formulations. Operative delivery rates were not different between the three formulations. Uterine hypercontractility with FHR changes was reduced with the use of gel formulations in comparison with suppositories (1.3% vs. 11.2%; RR 0.16; 95% CI 0.03–0.87; NNT 9). However, there was no difference in hypercontractility without FHR changes.

1a

Three trials compared PGE₂ tablets with PGE₂ pessary or suppository. There was no difference between caesarean-section rates between tablets and pessaries. Instrumental vaginal delivery rates were increased with the use of PGE₂ tablets compared with pessaries (17.8% versus 10.2%; RR 1.72; 95% CI 1.09–2.70; NNT 13). There were insufficient data to comment on uterine hypercontractility, epidural usage or maternal adverse effects.

1a

Four trials compared PGE₂ slow-release formulations with any other route of administration of PGE₂. Operative delivery rates were not different between the formulations. Uterine hypercontractility was not different between the two groups. Oxytocin augmentation was reduced with the use of sustained-release formulations (23.3% vs. 41.3%; RR 0.55; 95% CI 0.35–0.88; NNT 6). However, there was significant heterogeneity between the results of the trials.

1a

6.5.2 Dose comparisons of vaginal PGE₂ preparations

There are limited data available regarding comparisons of different dosage regimens for vaginal prostaglandins. In the current Cochrane review, the authors have made an arbitrary comparison of 'low' and 'high' dose regimens. Of the seven included trials, all used varying dosages and methods of administration.

1a

One trial included nearly two-thirds of the total women in this section of the review ($n = 995$).⁷⁵ This trial compared a policy of one versus two doses of vaginal PGE₂ gel (2 milligrams). Overall there was no difference in operative delivery rates between single or repeated doses. A reduction in the need for amniotomy or oxytocin augmentation was seen in parous women who received two doses of PGE₂. This reduction was not seen in nulliparous women.

1b

Within the review, comparisons did not reveal any difference between PGE₂ formulations when compared with placebo. The data were divided into three subgroups: once-only administration, repeated administration and sustained release formulations. There was a marked increase in uterine hypercontractility (with and without FHR changes) with sustained-release formulations when compared with the once-only and repeated-dose regimens.

Ia

In the absence of compelling clinical evidence from the systematic review, the Guideline Development Group considered that the manufacturer's recommendations should be used for the administration of vaginal PGE₂ preparations.

C Recommended regimens for vaginal PGE₂ preparations include:

- PGE₂ tablets: 3 milligrams PGE₂ 6–8 hourly.
The maximum total dose is 6 milligrams for all women.
- PGE₂ gels: 2 milligrams PGE₂ in nulliparous women with an unfavourable cervix (Bishop's score less than 4), 1 milligram for all other women.
In either, a second dose of 1–2 milligrams can be administered six hours later.

The maximum dose is 4 milligrams PGE₂ for nulliparous women with an unfavourable cervix and 3 milligrams for all other women.

6.5.3 Timing of administration

One trial compared a policy of administration of endocervical PGE₂ in the evening (followed by amniotomy the following morning if the cervix was favourable) with endocervical PGE₂ in the morning (with amniotomy later that day). The outcomes assessed were time of birth (daytime, evening or night) and patient satisfaction. Regarding time of birth, the hypothesis was that administration of prostaglandins in the evening would reduce the number of evening and night-time deliveries.

Ib

Overall, no difference was seen between the two policies with regard to time of birth. Women preferred administration of PGE₂ in the morning. This trial is, however, small ($n = 126$) and no details are given regarding the format of the patient questionnaire used to assess maternal preference. As such, the results should be interpreted with caution.

Ib

6.5.4 Failed induction

The Guideline Development Group was unable to locate any evidence that specifically addressed the issues surrounding failed induction. In the absence of evidence, the Guideline Development Group considered that the induction process should follow the manufacturer's recommendations for the administration of prostaglandin agents.

IV

According to the recommendations made regarding the administration of induction agents in Section 6.3, if the cervix is favourable, induction can be undertaken with amniotomy and oxytocin. If vaginal prostaglandins are used instead and labour does not ensue after the maximum dose of vaginal prostaglandin has been used then amniotomy can be considered and oxytocin started.

IV

If the woman has an unfavourable cervix and intact membranes and induction has been undertaken with vaginal PGE₂, it may not be possible to perform amniotomy following a course of this treatment. In these cases, consideration must be given to the administration of further prostaglandin agents. However, the suggested time interval between courses of prostaglandin agents is not known.

IV

The decisions made regarding the management of a 'failed induction' must be made in accordance with maternal wishes but must be made clinically at consultant level.

IV

6.5.5 Economic considerations

One study examined the economic considerations of comparing a regimen of one versus two doses of prostaglandin gel for induction of labour.⁷⁶ It found that, once a full range of costs was taken into account, the two-dose regimen was slightly cheaper. This was largely due to savings associated with a slightly lower rate of assisted deliveries in the two-dose group. However, there is a degree of uncertainty surrounding this estimate, because, in this study, any necessary augmentation with amniotomy and oxytocin infusion was delayed in the one-dose group until 14–20 hours after initial application of prostaglandin. Further research is therefore needed, to examine outcomes when augmentation in the one-dose regimen is commenced at an earlier stage.

No published study has examined cost effectiveness of slow-release pessary versus gel or tablets. An unpublished economic study submitted by a slow-release pessary manufacturer comparing their product with gel was considered not to provide convincing evidence of cost effectiveness. The drug cost of the slow-release pessary is considerably higher: about £15 per induction more costly than gel and £40 per induction more costly than tablets. However, there was no statistically significant difference in any of the main clinical outcomes, apart from a slightly reduced need for oxytocin augmentation – by about 20% in absolute terms. This may be an overestimate of any differential in routine practice since, in the trial, only one dose of gel was used in many cases rather than the normal practice of using two or more doses and a 10-milligram pessary was used (only the 5-milligram pessary is available in the UK). Even if this estimate is accepted, however, the cost savings from reduced oxytocin augmentation only partially offset the higher drug cost. The cost per oxytocin augmentation is approximately £12 to £21 (see calculations below) and 20% of this yields an offset of £2.50 to £4.50 per induction.

No published study has examined costs of vaginal tablets versus vaginal gel. It was therefore considered appropriate to conduct a simple costing exercise to examine this, which is summarised below. The basic conclusion of this simple costing exercise is that vaginal tablets are more cost effective than vaginal gel. This costing exercise assumes, in line with the clinical evidence presented above, that both preparations are equally effective in terms of all neonatal outcomes, apart from a slightly greater need for oxytocin augmentation in the case of vaginal tablets. There are no major cost uncertainties that could alter this conclusion – in particular, the existing trial evidence shows that it is highly unlikely that there is a substantial difference in the caesarean-section rate between the two preparations.

Drug-only cost saving of using vaginal tablets rather than vaginal gel

Assuming an average of two doses are used, the drug-only cost per induction is:

- about £15.53 for vaginal tablets, compared with £27.74 to £30.56 for vaginal gel.
- In terms of drug cost alone, therefore, there is a saving of about £12 to £15 per induction from using tablets rather than gel.

These costs are based on the following prices quoted in the *British National Formulary*, March 2001 (page 371):

Vaginal tablets dinoprostone 3 mg (Prostin E2®; Pharmacia & Upjohn)	£15.53 for two doses (£62.11 for 8-tab pack, i.e. £7.76 per tab)
Vaginal gel dinoprostone 3 mg (Prostin E2®; Pharmacia & Upjohn)	£27.74 to £30.56 for two doses (£13.87 for one 1-mg dose; £15.28 for one 2-mg dose required for unfavourable nulliparous)

Oxytocin augmentation cost of using tablets rather than gel

In addition to the drug cost, the costs of oxytocin augmentation must also be taken into account, since vaginal gel is slightly more effective than vaginal tablets in preventing the need for oxytocin augmentation. Based on analysis of four trials with a pooled sample of 504 women, the use of vaginal gel leads to a 9.3% lower rate of oxytocin augmentation than use of vaginal tablets; 50.4% required oxytocin augmentation with vaginal tablets and 59.7% with vaginal gel – a 9.3% difference in absolute terms.

Based on the assumptions set out below, the cost per oxytocin augmentation is £12 to £21. Thus, the oxytocin-augmentation cost of using tablets rather than gel is 9.3% of £12 to £21 = £1.15 to £2.01 per induction.

Details of the oxytocin augmentation cost calculations

The estimated cost per oxytocin augmentation was based on the following costings:

Extra staff time	£6.16 to £14.18
Equipment	£0
Disposables	£5.00 to £6.00 (estimate)
Drug cost	£1.23 to £1.40
Total	£12.00 to £21.00 (estimate)

Notes

Staff time

If one-to-one care during induction is available, there is no extra staff time required for oxytocin infusion. If one-to-one care is otherwise not available, however, then the time it takes to set up the oxytocin drip should be accounted for (although not the time taken to perform checks, since these can be done beside standard checks of vital signs). This has been estimated as varying between 10 minutes and 23 minutes per oxytocin augmentation, with estimates varying depending on whether retrospective reports or concurrent time records are used. This assumes that a midwife is not otherwise available to perform this task and, as such, may be an overestimate of

the true opportunity cost. The cost per hour of contact time for a midwife is approximately £37 (see more detailed calculations below); thus, this time cost per oxytocin infusion is between £6.17 and £14.18.

Equipment

It is assumed that spare infusion equipment would be available. If it is not, then the cost per augmentation would increase by a matter of pence (roughly the cost of buying new equipment divided by the large number of uses over a working lifetime).

Oxytocin drug cost

Based on price quoted in the *British National Formulary* March 2001 (page 372), oxytocin (Syntocinon; Alliance®) for intravenous infusion is £1.23 for 5 units/ml, 1-ml ampoule; £1.40 for 10 units/ml, 1-ml ampoule.

Net cost saving from using tablets rather than gel

Taking into account both drug and oxytocin augmentation costs, the net cost saving from using tablets rather than gel is £11.07 to £13.03 per induction. This represents a saving per 1000 inductions of about £11,000 to £13,000 (1000 is roughly the number of inductions expected in a typical sized maternity unit dealing with 5000 women a year).

The opportunity cost in terms of midwifery services foregone

The cost of vaginal gel represents only about 1.3% of the average costs to the NHS of a single delivery. This is based on a total cost of NHS maternity services in 1997–78 of £1,343m (NHS Executive, Leeds) divided by 600 000 deliveries per year yields an estimated cost of £2,238 per delivery. Although this represents a small fraction of total maternity costs, there is a real opportunity cost of using gel rather than tablets. This can be expressed, for example, in terms of what midwifery services the NHS could otherwise purchase (see notes below).

The NHS could thus buy approximately 35–50% of one E-grade midwife (including all associated costs) for every 1000 inductions performed using vaginal tablets rather than vaginal gel. Alternatively, one extra hour of midwife contact time with a mother could be purchased for every three inductions performed using tablets rather than gel.

Notes on the estimated cost of midwifery services

The total annual cost of an E-grade midwife, including on-costs and training costs, can be estimated at £29,203. This cost was estimated using the Ready Reckoner software developed by the Personal Social Sciences Research Unit, 1998 version.⁷⁷ In the estimation, default parameter values were used (e.g. for training and work patterns) and salary costs updated to 2000–01 using the midpoint of the salary scale from the Royal College of Midwives' web site. On the basis of 50% contact time, the cost per hour with the mother for this midwife is estimated at £37.

Potential total NHS saving

The NHS volume of inductions is approximately 120 000 per year. This is on the basis that 20% of women are induced, out of 600 000 deliveries per year. Assuming a scenario in which all women were induced using PGE₂ gel, the potential total cost saving to the NHS through switching all women to PGE₂ vaginal tablets would therefore be 120 000 × £11.07 to £13.03, or £1,300,000 to £1,600,000 per

year. This is an overestimate of the likely actual saving of switching patterns of usage towards vaginal tablets, however, since not all inductions are currently performed using prostaglandin gel (although unfortunately the precise baseline pattern of usage is not known).

Summary of economic considerations

<i>Economic variable</i>	<i>Estimate</i>
NHS financial saving of using tablets rather than gel	£11.07 to £13.03 per induction £11,000 to £13,000 per 1000 inductions
Examples of the NHS opportunity cost of using tablets rather than gel	Approximately 35–50% of one E-grade midwife per year per 1000 inductions Approximately 1 hour of midwife contact time per 3 inductions
Potential total NHS financial saving of using	£1.3m to £1.6m per annum tablets rather than gel

6.5.6 Summary

- Vaginal PGE₂ tablets seem to be as effective as gel formulations.
- In the absence of clinical benefit, prostaglandins PGE₂ tablets offer financial savings when compared with PGE₂ gel.
- Vaginal PGE₂ gel and tablets appear to be more effective than pessary formulations.
- Sustained-release formulations of PGE₂ do not appear to be more effective than other PGE₂ preparations.
- There are limited data regarding the use of different dose regimens and the timing of administration of prostaglandins.
- In the absence of data regarding dose and timing of administration the Guideline Development Group recommend adherence to the manufacturer's instructions.

6.5.7 Clinical practice recommendations

A Given that they are clinically equivalent, when induction of labour is undertaken with vaginal PGE₂ preparations, vaginal tablets should be considered in preference to gel formulations.

6.6. A comparison of different regimens of oxytocin administration

6.6.1 Method of administration

Data from the systematic reviews does not address the question of whether oxytocin used in women with intact membranes should be used in combination with amniotomy.

1a

In the systematic review that focused on the use of oxytocin with amniotomy, two trials compared the use of oxytocin alone to that of oxytocin with amniotomy in women with intact membranes.⁷¹ They showed

1a

no difference in caesarean-section rates but an increase in successful vaginal birth rates if oxytocin was used in combination with amniotomy. The small number of included women in these trials make meaningful conclusions difficult.

Ia

In trials where oxytocin alone is compared with vaginal or intracervical PGE₂ an increase in caesarean-section rates and unsuccessful vaginal birth rates was seen.⁷⁰ These increases were not apparent in those trials comparing oxytocin with amniotomy to the same prostaglandin agents.⁷¹

Ia

This indirect evidence suggests that oxytocin when used in women with intact membranes should be used in combination with amniotomy. It should be noted that these data are only reported in the 'all women' groups in the relevant reviews and are not reported in specific subgroups.

Ia

6.6.2 Timing of administration and dose comparisons for oxytocin

Within the current structure of Cochrane reviews, oxytocin dose regimens have not been compared. The Guideline Development Group examined dose regimens used for induction of labour in 11 RCTs that studied the use of oxytocin with or without immediate amniotomy.^{26,86,87} No formal meta-analysis of these trials has been undertaken and the results of these trials are summarised in Appendix 4.

Ib

The trials use a variety of regimens with differing starting doses of oxytocin and different incremental rises and intervals of increase. The maximum dose used varied in a similar fashion. Furthermore, the maximum dose of oxytocin used was titrated against frequency of contractions or uterine pressures via an intrauterine pressure catheter.

Ib

Comparing 'lower-dose' regimens of oxytocin (lower starting doses, slower incremental rises and lower maximal doses of oxytocin) with 'higher-dose' regimens, the conclusions drawn were:

- 'lower-dose' regimens were not associated with an increase in operative delivery rates
- oxytocin regimens with incremental rises in oxytocin dose more frequently than every 30 minutes were associated with a increase in uterine hypercontractility
- 'lower-dose' regimens were not associated with an increase in specified delivery intervals
- 'higher-dose' oxytocin regimens were associated with an increase in the incidence of precipitate labours.

Two current sets of guidelines currently recommend 'low-dose' oxytocin regimens.^{8,9,88} Both of these guidelines refer to a number of the trials reviewed above.

Ib

From the above evidence, a suggested regimen for the administration of oxytocin is outlined below.

III

The licensed maximum dose is currently 20 milliunits per minute. Trials have used regimens up to 32 milliunits per minute. Most found that adequate contractions can be achieved at 12 milliunits per minute.

Ib

Once a regular pattern of contractions is established, the rate of the infusion can often be reduced. The manufacturers recommend that, if regular contractions are not established after a total of 5 iu then the induction should be stopped. They also recommend that the infusion can be recommenced the following day.

IV

For the administration of oxytocin, the infusion should be in accordance with manufacturers' recommendations and should be delivered through an infusion pump. The Guideline Development Group considered that delivery

IV

could also be via a syringe driver and the infusion set should include a non-return valve.

6.6.3 Summary

From the available evidence when oxytocin with or without amniotomy is used for induction of labour, a regimen with a slow incremental rise and low maximum dose is appropriate.

When induction of labour of women with intact membranes is undertaken with oxytocin, it should be used in combination with amniotomy.

6.6.4 Clinical practice recommendations

C Oxytocin should not be started for six hours following administration of vaginal prostaglandins.

C In women with intact membranes, amniotomy should be performed where feasible prior to commencement of an infusion of oxytocin.

C When induction of labour is undertaken with oxytocin the recommended regimen is:

- a starting dose of 1–2 milliunits per minute
- increased at intervals of 30 minutes or more.

The minimum dose possible of oxytocin should be used and this should be titrated against uterine contractions aiming for a maximum of three to four contractions every ten minutes.

Adequate contractions may be established at 12 milliunits per minute.

In the summary of product characteristics the licensed maximum dose is 20 milliunits per minute.

If higher doses are used the maximum dose used should not exceed 32 milliunits per minute.

C Local protocols for delivery of oxytocin for induction of labour should:

- specify and use the dose of oxytocin being delivered (milliunits per minute) in preference to the volume of fluid being infused (millilitres per minute)
- be delivered through an infusion pump or via a syringe driver with a non-return valve.

C To reduce error, a standard dilution should always be used. Suggested standardised dilutions and dose regimens include:

- 30 iu in 500 ml of normal saline; hence 1 ml/hr = 1 milliunits oxytocin per minute
- 10 iu oxytocin in 500 ml of normal saline; hence 3 ml/hr = 1 milliunits oxytocin per minute.

C Table 6.1 Oxytocin infusion

Time after starting (minutes)	Oxytocin dose (milliunits per minute)	Volume infused (ml/hour)	
		Dilution 30 iu in 500 ml	Dilution 10 iu in 500 ml
0	1	1	3
30	2	2	6
60	4	4	12
90	8	8	24
120	12	12	36
150	16	16	48
180	20	20	60
210	24	24	72
240	28	28	84
270	32	32	96

Doses highlighted are quantities above those referred to in the summary of product characteristics of 20 milliunits per minute

6.7. Other methods of induction of labour

Twenty-three methods of induction of labour were examined within the series of systematic reviews on induction of labour. Most of these methods are not commonly used in current clinical practice and, hence, the results are not presented here. Many of the reviews contain very small amounts of trial evidence.

The other interventions considered are:

- mechanical methods⁸⁹
- extra amniotic prostaglandins⁹⁰
- intravenous prostaglandins⁹¹
- oral prostaglandins⁹²
- mifepristone⁹³
- oestrogen with/without amniotomy⁹⁴
- corticosteroids⁹⁵
- relaxin⁹⁶
- hyaluronidase.⁹⁷

For further information regarding these interventions, readers are referred to the Cochrane Library.

A number of these methods represent methods used outside of current UK practice or were not in current clinical use. All but mechanical methods are currently not licensed for use in the UK.

A number of the methods discussed in these new Cochrane reviews included reviews of alternative methods of induction of labour that have traditionally been used by women and midwives to induce labour naturally.

la

6.7.1 Castor oil, bath or enema

There was one included trial in this review⁹⁸ and involved the administration of castor oil to one group of women and no treatment in the other arm. The trial was small and no conclusion on the effectiveness of castor oil in induction of labour could be drawn. All women who ingested castor oil felt nauseous.

la

6.7.2 Breast stimulation

The review included data from six trials of breast stimulation.⁹⁹ Four trials assessed the impact of breast stimulation compared with no intervention. In these trials there was no difference in the caesarean-section rate or the rates of meconium staining between the groups. The rates of postpartum haemorrhage were reduced in the breast stimulation group (0.7% vs. 6%; RR 0.16; 95% CI 0.03–0.87). Two trials compared breast stimulation with oxytocin alone. No difference in the caesarean-section rate was reported. One of the RCTs was stopped after there were three perinatal deaths in the breast stimulation group and one in the oxytocin group. The trial was the only study that included a high-risk population.

la

6.7.3 Sexual intercourse

This review included data from one randomised controlled trial.¹⁰⁰ The trial compared one group who had regular sexual intercourse with vaginal semen deposition to another group who refrained from sexual intercourse. Breast stimulation was prohibited in both groups. There was no benefit from having sexual intercourse as an induction agent. There were no adverse outcomes encountered.

la

6.7.4 Acupuncture and homeopathic methods

There were no trials of acupuncture¹⁰¹ or homeopathic methods¹⁰² included in these systematic reviews and hence the use of these interventions for induction of labour has not been assessed.

6.8 Future research recommendations

- Adequately powered RCTs reporting relevant clinical outcomes in specific clinical groups are needed to evaluate further the effectiveness of different vaginal PGE₂ formulations for induction of labour.
- Future trials in induction of labour should attempt to standardise the definitions of the outcomes collected.
- Future trials should attempt to use recommended doses of prostaglandins and oxytocin to allow meaningful comparisons between studies.
- Where possible, in future studies on induction of labour, where interventions are compared, consideration should be given to the collection of relevant economic outcomes.

7. Vaginal or oral misoprostol (PGE₁): research to date

7.1 Background

Misoprostol has been widely investigated as an agent for induction of labour. There are two current systematic reviews that focus on the use of both oral and vaginal misoprostol.^{103,104}

According to the evidence currently available, misoprostol appears to be more effective than vaginal prostaglandins and oxytocin in the presence of ruptured membranes (either spontaneous or artificial) for induction of labour.

There are safety aspects of misoprostol that have not been fully evaluated and it is not currently licensed for obstetric use. Its use must therefore be restricted to RCTs.

*Evidence level
1a*

7.2 Misoprostol compared with other induction agents

When comparing vaginal misoprostol with PGE₂ (either intracervical or vaginal) or oxytocin alone:

- caesarean-section rates were reduced when vaginal misoprostol was compared with oxytocin alone
- the rate of successful vaginal delivery in 24 hours was increased with misoprostol
- the cervix was less likely to remain unfavourable or unchanged after 24–48 hours when vaginal misoprostol was used
- uterine hypercontractility with FHR changes was increased when vaginal misoprostol was compared with intracervical PGE₂
- uterine hypercontractility without FHR changes was increased with vaginal misoprostol, compared with all three interventions.

1a

7.3 Method of administration of misoprostol

Oral and vaginal misoprostol were compared in one review.¹⁰⁴ The studies included in the review used varying oral misoprostol regimens, ranging from 50-microgram tablets every four hours to 200-microgram tablets every six hours. Oral misoprostol appeared to be less effective than vaginal misoprostol. More women in the oral misoprostol group failed to achieve vaginal birth within 24 hours of randomisation. The caesarean-section rate was not different between oral and vaginal preparations.

1a

Oral misoprostol resulted in fewer cases of hypercontractility without FHR changes. There was no difference in uterine hypercontractility with FHR

1a

changes. Meconium-stained liquor was more common following oral administration. There are only limited data available on the combination of vaginal and oral misoprostol.

7.4 Safety issues

As highlighted above, the use of misoprostol is associated with an increase in uterine hypercontractility. This is not translated into an increase in operative delivery rates. The safety issues surrounding the use of misoprostol have not been fully evaluated.

la

There has been one maternal death due to amniotic fluid embolus in one trial.¹⁰⁵ This trial also reported two cases of caesarean hysterectomy for atonic uterine haemorrhage.¹⁰⁵ A trial examining the use of vaginal misoprostol for induction of labour of women, limited to women with a previous caesarean section, reported two cases of uterine rupture.²¹

la

What is unclear at present is whether misoprostol is associated with an increase in adverse events or whether they represent chance sporadic adverse events. Such adverse outcomes may be potentially under-reported in trials examining other induction agents.

la

Misoprostol tablets are currently available only in 200-microgram formulations. Trials examining 50-microgram and 25-microgram doses of misoprostol have involved cutting tablets or making up suspensions of the drug. Uniform concentration of the active drug thus cannot be guaranteed in individual pieces. This may result in variable amounts of the active drug being delivered. To allow further research on the use of lower doses of vaginal misoprostol, commercially available 25-microgram and 50-microgram tablets would be needed.

la

Recent articles have highlighted the large amount of trial data available presenting persuasive evidence of efficacy regarding the use of misoprostol as an induction agent. It also highlighted a number of the issues raised above, including those relating to the non-availability of misoprostol tablets in low-dose formulations due to the reluctance of the manufacturers to promote the use of misoprostol as an induction agent.^{106–108}

la

7.5 Economic considerations

Misoprostol is considerably cheaper than both intravaginal and intracervical PGE₂. With reference to the recommended regimen of vaginal PGE₂ tablet in this Guideline, the relative costs compared with vaginal misoprostol would be £0.18 for one 200-microgram tablet of misoprostol compared with £8.13 for a 3-milligram PGE₂ tablet. In addition, there would be further indirect cost savings to the NHS, given the reduced rate of operative delivery.

Further data are needed about the theoretical risks of misoprostol. Therefore, until these are available there will remain considerable uncertainty about its overall cost effectiveness.

7.6 Summary

- Vaginal misoprostol appears to be a more effective induction agent than either intravaginal or intracervical PGE₂ or oxytocin.
- Misoprostol is significantly cheaper than currently recommended PGE₂ preparations.

- The safety issues concerning the use of vaginal misoprostol are unclear.
- Further clinical trials are warranted in order to evaluate further the issues of safety regarding the use of vaginal and oral misoprostol for induction of labour using commercially produced low-dose tablets.

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Appendix 1

Cervical scoring systems

Bishop's score¹⁰⁹

Cervical feature	Pelvic score			
	0	1	2	3
Dilatation (cm)	0	1–2	3–4	5–6
Effacement (%)	0–30	40–60	60–70	80+
Station (cm) ^a	–3	–2	–1/0	+1/+2
Consistency	Firm	Medium	Soft	–
Position	Posterior	Mid-position	Anterior	–

Modified Bishop's score (Calder score)¹

Cervical feature	Pelvic score			
	0	1	2	3
Dilatation (cm)	<1	1–2	2–4	>4
Length of cervix (cm)		>4	2–4	1–2 <1
Station (cm) ^a	–3	–2	–1/0	+1/+2
Consistency	Firm	Average	Soft	–
Position	Posterior	Mid; Anterior	–	–

^a In both systems, station is measured in cm relative to the ischial spines.

For the purpose of this Guideline, the modified Bishop's score is used to assess the cervical condition.

Appendix 2

Methodology of collaboration between CESU and Cochrane Pregnancy and Childbirth group

Background

There are large numbers of agents currently employed in clinical practice to promote cervical ripening and initiate labour. The research base focusing on induction of labour is extensive. Systematic reviews published in the literature tend to compare specific agents with all other available agents, often without common or prespecified outcome measures. The Cochrane Library currently hold a limited number of induction of labour reviews on its database. The main bulk of systematic reviews focusing on other methods of induction have not been available since 1995.

In a bid to produce an up-to-date and structured series of reviews on induction of labour a collaboration between the RCOG Clinical Effectiveness Support Unit (CESU) and Cochrane Collaboration's Pregnancy and Childbirth group was formed. The members of this group included members of the Guideline Development Group, members of the RCOG CESU and experienced Cochrane reviewers with an interest in the subject of induction of labour.

The methodology used for these series of systematic reviews is highlighted below. In the later sections, evidence is presented relating to different methods of induction of labour and finally the evidence relating to induction of labour in specific clinical situations is presented.

The Cochrane Pregnancy and Childbirth Group/CESU collaboration

A generic protocol was developed by the group and published on the Cochrane Library. The protocol discussed below outlines the methodology used for all the reviews and standard outcome measures to be presented.

Clinically relevant outcomes for trials of methods of cervical ripening and labour induction were developed from previously published systematic reviews on induction of labour. These outcomes attempt to reflect both measures of success and failure of induction. Due to the nature of the reporting of outcomes within studies focusing on induction of labour, measures of failure are more commonly reported.

Primary outcomes

Five primary outcomes were chosen as being most representative of the clinically important measures of effectiveness and complications.

1. Vaginal delivery not achieved within 24 hours.
2. Uterine hyperstimulation with 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, septicæmia).

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 were explored as secondary outcomes (see below).

Secondary outcomes

These outcomes related to measures of effectiveness, complications and satisfaction.

Measures of effectiveness

6. Cervix unfavourable/unchanged after 12–24 hours.
7. Oxytocin augmentation.

Complications

8. Uterine hyperstimulation without FHR changes
9. Uterine rupture
10. Epidural anaesthesia
11. Instrumental vaginal delivery
12. Meconium stained liquor
13. Apgar score of less than seven at five minutes
14. Neonatal intensive care unit admission
15. Neonatal encephalopathy
16. Perinatal death
17. Disability in childhood
18. Maternal adverse effects (all)
19. Nausea (maternal)
20. Vomiting (maternal)
21. Diarrhoea (maternal)
22. Other (e.g. pyrexia)
23. Postpartum haemorrhage (as defined by the trial authors)
24. Serious maternal complications (e.g. intensive care unit admission, septicæmia but excluding uterine rupture)
25. Maternal death

Measures of satisfaction

26. Woman not satisfied
27. Caregiver not satisfied

While all the above outcomes were sought, only those where these data have been reported in the trials appear in the analysis tables.

The terminology of uterine hyperstimulation is problematic. In the reviews, the term 'uterine hyperstimulation without FHR changes' included uterine tachysystole (more than five contractions per ten minutes for at least 20 minutes) and uterine hypersystole/hypertonus (a contraction lasting at least two minutes) and 'uterine hyperstimulation with FHR changes' denoted uterine hyperstimulation syndrome (tachysystole or hypersystole with FHR changes such as persistent decelerations, tachycardia or decreased short term variability). However, due to varied reporting of this outcome there is the possibility of subjective bias in interpretation. Also, it was not always clear from trials if these outcomes are reported in a mutually exclusive manner.

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 strategy for identification of studies

This review drew on the search strategy developed for the Pregnancy and Childbirth Group as a whole. The search was performed simultaneously for all reviews of methods of inducing labour.

Relevant trials were identified in the Group's Specialised Register of Controlled Trials. The Cochrane Controlled Trials Register was searched and the reference lists of trial reports and reviews were searched by hand. These searches were cross-referenced with systematic searches of Medline and Embase performed by the research staff at CESU.

Method of the reviews

A strategy was developed to deal with the large volume and complexity of trial data relating to labour induction. Many methods of induction have been studied, in many different clinical situations. Most trials are 'intervention-driven', comparing two or more methods in various clinical situations. Clinicians and women need the information arranged by specific clinical situations in order to aid decision making. To extract these type of data from several hundred trial reports in a single step would not be feasible. A two-stage method of data extraction was developed. The initial data extraction was performed in a series of primary reviews arranged by methods of induction of labour, following a standardised methodology. The data were then extracted from the primary reviews into a series of secondary reviews, arranged by specific clinical scenarios.

To avoid duplication of data in the primary reviews, the labour induction methods have been listed in a specific order, from 1 to 23. Each primary review includes comparisons between one of the methods (from 2 to 23) with 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
3. Intracervical prostaglandins
4. Intravenous oxytocin alone
5. Amniotomy alone
6. Intravenous oxytocin with amniotomy
7. Vaginal misoprostol
8. Oral misoprostol

9. Mechanical methods
10. Membrane sweeping
11. Extra-amniotic prostaglandins
12. Intravenous prostaglandins
13. Oral prostaglandins
14. Mifepristone
15. Oestrogen with or without amniotomy
16. Corticosteroids
17. Relaxin
18. Hyaluronidase
19. Castor oil, bath, with or without enema
20. Acupuncture
21. Breast stimulation
22. Sexual intercourse
23. Homoeopathic methods.

The primary reviews included the following subgroup analysis:

1. Previous caesarean section or not
2. Nulliparity or multiparity
3. Membranes intact or ruptured
4. Cervix favourable, unfavourable or undefined.

The secondary reviews included all methods of labour induction for each of the subgroups based on clinical scenarios performed in the primary reviews. Originally, six reviews were proposed, divided by the above subgroups but due to the small amount of data available additional secondary reviews have been developed. There are therefore eight secondary reviews of methods of labour induction in the following clinical scenarios:

1. All women (not divided by membrane status or cervical status)
2. All women intact membranes (unfavourable cervix, favourable cervix, cervix not defined)
3. All women ruptured membranes (unfavourable cervix, favourable cervix, cervix not defined)
4. Nulliparous women, intact membranes (unfavourable cervix, favourable cervix, cervix not defined)
5. Nulliparous women, ruptured membranes (unfavourable cervix, favourable cervix, cervix not defined)
6. Parous women, intact membranes (unfavourable cervix, favourable cervix, cervix not defined)
7. Parous women, ruptured membranes (unfavourable cervix, favourable cervix, cervix not defined)
8. Previous caesarean section (not divided by membrane status or cervical status).

Data extraction

The trials included in the primary reviews were extracted from an initial set of trials covering all interventions used in induction of labour (currently approximately 700 RCTs). The data extraction process was conducted centrally from the RCOG Clinical Effectiveness Support Unit, in co-operation with the Cochrane Collaboration's Pregnancy and Childbirth Group. This process allowed the data extraction process to be standardised across all the reviews.

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.

Individual outcome data were included in the analysis if they met the prestated criteria in 'Types of outcome measures'. Included trial data were processed as described in the Cochrane Collaboration Handbook. 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 was sought from the original authors. If the attrition was such that it might significantly affect the results, these data were excluded from the analysis. These decisions rested with the reviewers of the primary reviews and was clearly documented.

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 reviewers for entry on to the Review Manager computer software, checked for accuracy and analysed as above using the same software. For dichotomous data, relative risks and 95% confidence intervals were calculated and, in the absence of heterogeneity, results were pooled using a fixed effects model.

The predefined criteria for sensitivity analysis included all aspects of quality assessment, including aspects of selection, performance and attrition bias.

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

Appendix 3

Conflated Oxytocin vs. prostaglandin E2 data

The data presented below represent individual trials data from two Cochrane reviews focusing on the use of oxytocin in comparison with PGE₂ (vaginal or intracervical).^{70,71} The data relate to the discussions and conclusions in Section 6.2. The data were derived from the reviews below and their corresponding comparison groups:

Oxytocin alone	Versus vaginal PGE ₂ ^{110–136} Versus intracervical PGE ₂ ^{137–147}
Oxytocin with amniotomy ⁷¹	Versus vaginal PGE ₂ ^{148–157} Versus intracervical PGE ₂ ¹⁵⁸

1. Any oxytocin vs. any PGE₂ (all women)

Includes all women:

oxytocin alone vs. vaginal PGE₂
oxytocin alone vs. intracervical PGE₂
oxytocin with amniotomy vs. intravaginal PGE₂
oxytocin with amniotomy vs. intracervical PGE₂

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	7	660	168/328	106/332	1.61	1.33–1.94	–
Caesarean section	51	7093	459/3533	395/3560	1.17	1.03–1.32	–
Cervix unfavourable or unchanged after 24–48 hours	9	952	102/476	57/476	1.73	1.29–2.32	0.0001
Epidural analgesia	14	3796	916/1898	828/1898	1.11	1.03–1.18	–
Women not satisfied	5	2861	119/1430	79/1431	1.50	1.14–1.97	0.001

2. Any oxytocin vs. any PGE₂ all women, intact membranes

Includes all women intact membranes:

oxytocin alone vs. vaginal PGE₂ with cervix: variable/undefined, unfavourable, favourable

oxytocin alone vs. intracervical PGE₂ with cervix: variable/undefined, unfavourable, favourable

oxytocin with amniotomy vs. intravaginal PGE₂: variable/undefined, favourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	3	400	102/200	72/200	1.42	1.13–1.78	–
Caesarean section	23	2278	196/1131	158/1147	1.25	1.04–1.51	–
Cervix unfavourable or unchanged after 24–48 hours	5	574	67/289	45/285	1.45	1.03–2.03	0.0003
Epidural analgesia	5	522	92/265	87/257	1.03	0.82–1.30	–
Women not satisfied	2	198	30/99	11/99	2.65	1.37–5.13	0.0001

3. Any oxytocin vs. any PGE₂ all women, ruptured membranes

Includes all women intact membranes:

oxytocin alone vs. vaginal PGE₂ with cervix: variable/undefined, unfavourable

oxytocin alone vs. intracervical PGE₂ with cervix: variable/undefined, unfavourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	2	120	31/60	14/60	2.21	1.33–3.68	–
Caesarean section	20	4172	217/2082	197/2090	1.10	0.92–1.32	–
Cervix unfavourable or unchanged after 24–48 hours	1	90	6/46	7/44	0.82	0.30–2.25	–
Epidural analgesia	9	3274	824/1633	741/1641	1.11	1.04–1.19	–
Women not satisfied	1	2517	74/1258	64/1259	1.16	0.84–1.60	–

4. Any oxytocin vs. any PGE₂ all nulliparae

Includes all nulliparae:

oxytocin alone vs. vaginal PGE₂

oxytocin alone vs. intracervical PGE₂

oxytocin with amniotomy vs. intravaginal PGE₂

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	1	100	22/50	10/50	2.20	1.16–4.16	–
Caesarean section	7	1438	34/728	29/710	1.13	0.70–1.81	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	3	204	16/106	17/98	0.84	0.46–1.53	–
Women not satisfied	1	100	26/50	0/50	53.00	3.32–,846.51	–

5. Any oxytocin vs. any PGE₂ all multiparae

Includes all multiparae:

oxytocin alone vs. vaginal PGE₂

oxytocin alone vs. intracervical PGE₂

oxytocin with amniotomy vs. intravaginal PGE₂

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	2	120	31/60	18/60	1.72	1.10–2.70	–
Caesarean section	12	2212	167/1100	163/1112	1.04	0.85–1.27	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	3	182	61/90	52/92	1.18	0.94–1.49	–
Women not satisfied	–	–	–	–	–	–	–

6. Any oxytocin vs. any PGE₂ all primiparae intact membranes

Includes all nulliparae intact membranes:

oxytocin alone vs. intracervical PGE₂ unfavourable cervix and favourable cervix

Outcome	Trials (<i>n</i>)	Women (<i>n</i>)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	1	100	22/50	14/50	1.57	0.91–2.71	–
Caesarean section	1	98	14/49	8/49	1.75	0.81–3.79	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	–	–	–	–	–	–	–
Women not satisfied	–	–	–	–	–	–	–

7. Any oxytocin vs. any PGE₂ all multiparae intact membranes

Includes all multiparae intact membranes:

No available trial evidence.

8. Any oxytocin vs. any PGE₂ all primiparae ruptured membranes

Includes all nulliparae ruptured membranes:

oxytocin alone vs. vaginal PGE₂ with cervix: variable/undefined or unfavourable

Outcome	Trials (<i>n</i>)	Women (<i>n</i>)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	3	278	73/135	50/143	1.55	1.18–2.04	–
Caesarean section	8	1887	136/942	141/945	0.97	0.78–1.20	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	3	182	61/90	52/90	1.18	0.94–1.49	–
Women not satisfied	–	–	–	–	–	–	–

9. Any oxytocin vs. any PGE₂ all multiparae ruptured membranes

Includes all multiparae ruptured membranes:

oxytocin alone vs. vaginal PGE₂ with cervix: variable/undefined or unfavourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	1	100	22/50	10/50	2.20	1.16–4.16	–
Caesarean section	5	1272	28/647	19/625	1.39	0.79–2.42	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	3	204	16/106	17/98	0.84	0.46–1.53	–
Women not satisfied	–	–	–	–	–	–	–

10. Oxytocin alone vs. vaginal PGE₂ all primiparae intact membranes

No available trial evidence.

11. Oxytocin alone vs. intracervical PGE₂ all primiparae intact membranes

Includes all nulliparae intact membranes:

oxytocin alone vs. intracervical PGE₂ unfavourable cervix and favourable cervix

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	1	100	22/50	14/50	1.57	0.91–2.71	–
Caesarean section	1	98	14/49	8/49	1.75	0.81–3.79	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	–	–	–	–	–	–	–
Women not satisfied	–	–	–	–	–	–	–

12. Oxytocin with amniotomy vs. intravaginal PGE₂ all primiparae intact membranes

No available trial evidence.

13. Oxytocin with amniotomy vs. intracervical PGE₂ all primiparae intact membranes

No available trial evidence.

14. Oxytocin alone vs. vaginal PGE₂ all multiparae intact membranes

No available trial evidence.

15. Oxytocin alone vs. intracervical PGE₂ all multiparae intact membranes

No available trial evidence.

16. Oxytocin with amniotomy vs. intravaginal PGE₂ all multiparae intact membranes

No available trial evidence.

17. Oxytocin with amniotomy vs. intracervical PGE₂ all multiparae intact membranes

No available trial evidence.

18. Oxytocin vs. vaginal PGE₂ all primiparae ruptured membranes

Includes all nulliparae ruptured membranes:

oxytocin alone vs. vaginal PGE₂ with cervix: variable/undefined or unfavourable

Outcome	Trials (<i>n</i>)	Women (<i>n</i>)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	3	278	73/135	50/143	1.55	1.18–2.04	–
Caesarean section	8	1887	136/942	141/945	0.97	0.78–1.20	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	3	182	61/90	52/90	1.18	0.94–1.49	–
Women not satisfied	–	–	–	–	–	–	–

19. Oxytocin alone vs. intracervical PGE₂ all primiparae ruptured membranes

No available trial evidence.

20. Oxytocin with amniotomy vs. intravaginal PGE₂ all primiparae ruptured membranes

No available trial evidence.

21. Oxytocin with amniotomy vs. intracervical PGE₂ all primiparae ruptured membranes

No available trial evidence.

22. Oxytocin alone vs. vaginal PGE₂ all multiparae ruptured membranes

Includes all multiparae ruptured membranes:

oxytocin alone vs. vaginal PGE₂ with cervix: variable/undefined or unfavourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	1	100	22/50	10/50	2.20	1.16–4.16	–
Caesarean section	5	1272	28/647	19/625	1.39	0.79–2.42	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	3	204	16/106	17/98	0.84	0.46–1.53	–
Women not satisfied	–	–	–	–	–	–	–

23. Oxytocin alone vs. intracervical PGE₂ all multiparae ruptured membranes

No available trial evidence.

24. Oxytocin with amniotomy vs. intravaginal PGE₂ all multiparae ruptured membranes

No available trial evidence.

25. Oxytocin with amniotomy vs. intracervical PGE₂ all multiparae ruptured membranes

No available trial evidence.

26. Any oxytocin vs. any PGE₂ all women, unfavourable cervix:

Includes all women:

oxytocin alone vs. vaginal PGE₂ cervix unfavourable

oxytocin alone vs. intracervical PGE₂ cervix unfavourable

oxytocin with amniotomy vs. intravaginal PGE₂ cervix unfavourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	7	616	164/304	106/312	1.60	1.33–1.92	–
Caesarean section	27	2096	194/1023	149/1073	1.34	1.11–1.62	–
Cervix unfavourable or unchanged after 24–48 hours	6	447	53/223	23/224	2.22	1.43–3.45	0.023
Epidural analgesia	7	662	92/333	93/329	0.99	0.78–1.24	0.048
Women not satisfied	2	156	12/80	14/76	0.81	0.39–1.67	–

27. Any oxytocin vs. any PGE₂ all women, favourable cervix

Includes all women:

oxytocin alone vs. vaginal PGE₂ cervix favourable

oxytocin alone vs. intracervical PGE₂ cervix favourable

oxytocin with amniotomy vs. intravaginal PGE₂ cervix favourable

oxytocin with amniotomy vs. intracervical PGE₂ cervix favourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	3	306	58/157	38/149	1.45	1.05–2.01	–
Caesarean section	9	1051	61/526	63/525	0.96	0.69–1.33	–
Cervix unfavourable or unchanged after 24–48 hours	3	457	30/228	34/229	0.86	0.56–1.34	–
Epidural analgesia	1	52	9/25	7/27	1.39	0.61–3.17	–
Women not satisfied	3	248	34/122	2/126	14.19	3.97–50.69	–

28. Any oxytocin vs. any PGE₂ all nulliparae, unfavourable cervix

Includes all nulliparae:

oxytocin alone vs. vaginal PGE₂ cervix unfavourable

oxytocin alone vs. intracervical PGE₂ cervix unfavourable

oxytocin with amniotomy vs. intravaginal PGE₂ cervix unfavourable

Outcome	Trials (<i>n</i>)	Women (<i>n</i>)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	2	76	27/36	18/40	1.66	1.12–2.47	–
Caesarean section	7	406	51/194	43/212	1.29	0.90–1.84	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	1	50	10/23	16/27	0.73	0.42–1.29	–
Women not satisfied	–	–	–	–	–	–	–

29. Any oxytocin vs. any PGE₂ all nulliparae, favourable cervix

Includes all nulliparae:

oxytocin alone vs. intracervical PGE₂ cervix favourable

Outcome	Trials (<i>n</i>)	Women (<i>n</i>)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (<i>P</i> value)
Vaginal delivery not achieved within 24 hours	1	44	4/24	0/20	7.56	0.43–132.49	–
Caesarean section	–	–	–	–	–	–	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	–	–	–	–	–	–	0.048
Women not satisfied	–	–	–	–	–	–	–

30. Any oxytocin vs. any PGE₂ all multiparae, unfavourable cervix

Includes all multiparae:

oxytocin alone vs. vaginal PGE₂ cervix unfavourable

oxytocin alone vs. intracervical PGE₂ cervix unfavourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	1	100	22/50	10/50	2.20	1.16–4.16	–
Caesarean section	2	161	6/81	7/80	0.84	0.32–2.24	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	1	100	1/50	2/50	0.50	0.05–5.34	–
Women not satisfied	–	–	–	–	–	–	–

31. Any oxytocin vs. any PGE₂ all Multiparae, favourable cervix

Includes all multiparae:

oxytocin alone vs. intravaginal PGE₂ cervix favourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	–	–	–	–	–	–	–
Caesarean section	1	100	2/50	1/50	2.00	0.19–21.36	–
Cervix unfavourable or unchanged after 24–48 hours	–	–	–	–	–	–	–
Epidural analgesia	–	–	–	–	–	–	–
Women not satisfied	1	100	26/50	0/50	53.00	3.32–846.51	–

32. Any oxytocin vs. any PGE₂ all women, intact membranes, unfavourable cervix

Includes all women intact membranes:

oxytocin alone vs. vaginal PGE₂ cervix unfavourable

oxytocin alone vs. intracervical PGE₂ cervix unfavourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	2	258	71/129	48/129	1.49	1.14,1.96	–
Caesarean section	8	749	98/363	68/368	1.48	1.14,1.93	–
Cervix unfavourable or unchanged after 24–48 hours	2	225	33/112	11/113	3.02	1.63,5.57	–
Epidural analgesia	–	–	–	–	–	–	–
Women not satisfied	1	98	4/49	11/49	0.36	0.12,1.06	–

33. Any oxytocin vs. any PGE₂ all women, intact membranes, favourable cervix

Includes all women intact membranes:

oxytocin alone vs. vaginal PGE₂ cervix favourable

oxytocin alone vs. intracervical PGE₂ cervix favourable

oxytocin with amniotomy vs. intravaginal PGE₂ cervix favourable

Outcome	Trials (n)	Women (n)	Experimental group	Control group	Relative risk	95% Confidence intervals	Heterogeneity (P value)
Vaginal delivery not achieved within 24 hours	2	246	57/127	34/119	1.59	1.14,2.21	–
Caesarean section	4	624	50/316	48/308	1.02	0.71,1.47	—
Cervix unfavourable or unchanged after 24–48 hours	2	372	29/118	34/184	0.83	0.53,1.30	–
Epidural analgesia	–	–	–	–	–	–	–
Women not satisfied	–	–	–	–	–	–	–

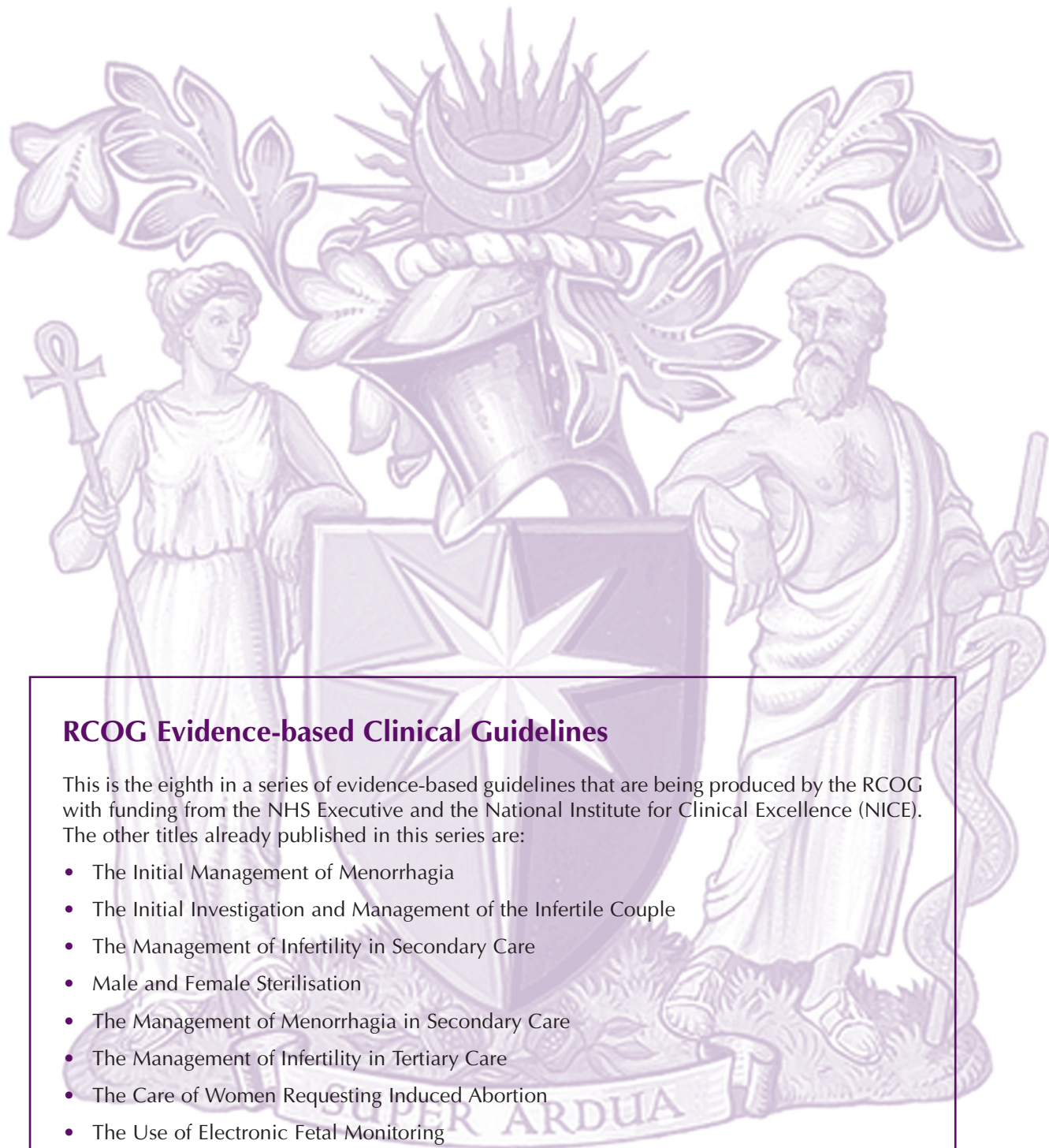
Appendix 4: Comparison of differing dosages for induction of labour with oxytocin with/without amniotomy

Study	Population	Intervention details	Outcomes	Results	Comments	Study type	Evidence level
Oxytocin alone							
Ross <i>et al.</i> ⁷⁸	384 high-risk labours Uterine risk factors present: – previous LSCS – twins – hydramnios – parity >4 – large fibroids	<i>Standard-dose protocol</i> Starting: 2 mu/min Increase by 2 mu/min every 20 minutes No maximum stated <i>High-dose protocol</i> Starting: 6 mu/min Increase by 6 mu/min every 20 minutes. No maximum stated	Caesarean section rate Hyperstimulation episodes Uterine rupture	RR 1.14 (95% CI 0.82–1.57) RR 1.72 (95% CI 1.18–2.48) RR 1.14 (95% CI 0.82–1.57)	Data from abstract; hence limited information	RCT	Ib
Hourvitz <i>et al.</i> ⁷⁹							
178 low-risk labours		<i>Low-dose protocol</i> Starting: 1.25 mu/min Increase by 1.25 mu/min every 30 minutes up to 7.5 mu/min then by 2.5 mu/min up to 15 mu/min then by 5 mu/min up to maximum 30 mu/min <i>High-dose protocol</i> Starting: 2.5 mu/min Increase by 2.5 mu/min every 30 minutes up to 15 mu/min then by 5 mu/min up to maximum of 30 mu/min Amniotomy once in active labour	Hyperstimulation with FHR changes Hyperstimulation without FHR changes Caesarean section Instrumental vaginal delivery rates Epidural analgesia Postpartum haemorrhage	RR 1.65 (95% CI 0.96–2.85) RR 1.32 (95% CI 0.74–2.35) RR 0.47 (95% CI 0.14–1.56) RR 1.58 (95% CI 0.81–3.08) RR 1.07 (95% CI 0.81–1.42) RR 1.57 (95% CI 0.30–8.29)	No difference in delivery intervals seen	RCT	Ib
Goni <i>et al.</i> ⁸⁰							
100 low-risk labours		<i>Low-dose protocol</i> Starting: 1 mu/min Doubled every 60 minutes Maximum dose 32 mu/min <i>Traditional protocol</i> Starting: 1mu/min Doubled every 20 minutes Max dose 32mu/min Amniotomy as and when indicated	Caesarean section Hyperstimulation (relation to FHR not stated) Instrumental vaginal delivery	RR 1.80 (95% CI 0.65–4.99) RR 8.00 (95% CI 1.04–61.02) RR 5.00 (95% CI 1.15–21.68)	No significant difference between delivery intervals, small numbers used in subgroup analysis.	RCT	Ib

Study	Population	Intervention details	Outcomes	Results	Comments	Study type	Evidence level
Crane <i>et al.</i> ⁸¹	130 low-risk labours	<i>Low-dose protocol</i> Starting: 1.4 mu/min Increase by 1.4 mu/min every 30 minutes Maximum dose 20 mu/min <i>High-dose protocol</i> Starting: 7 mu/min Increase by 7 mu/min every 15 minutes Maximum dose 40 mu/min Amniotomy as and when indicated	Hyperstimulation with FHR changes Caesarean section	RR 1.57 (95% CI 1.04–2.37) RR 1.47 (95% CI 0.70–3.11)	No significant differences in delivery intervals	RCT	Ib
Lazor <i>et al.</i> ⁸²	378 low-risk labours	<i>Low-dose protocol</i> Starting: 1.0 mu/min Increase by 1.5 mu/min every 40 minutes Maximum dose 30 mu/min <i>High-dose protocol</i> Starting: 1.0 mu/min Increase by 1.0 mu/min every 15 minutes Max dose 30 mu/min Amniotomy as and when indicated	Caesarean section Uterine hyperstimulation	RR 0.79 (95% CI 0.53–1.17) RR 1.72 (95% CI 1.20–2.46)	No difference in delivery intervals	RCT	Ib
Satin <i>et al.</i> ⁸³	80 women with unfavourable cervix	<i>Low-dose protocol</i> Starting: 2.0 mu/min Increase by 1.0 mu/min every 30 minutes No maximum stated <i>High-dose protocol</i> Starting: 2.0 mu/min Increase by 2.0 mu/min every 15 minutes No maximum stated Amniotomy as and when indicated	Uterine hyperstimulation with FHR changes Caesarean section Epidural analgesia Instrumental vaginal delivery	RR 1.58 (95% CI 0.91–2.72) RR 3.33 (95% CI 0.41–27.22) RR 1.08 (95% CI 0.51–2.31) RR 0.67 (95% CI 0.10–4.49)	Significant increase in overall delivery times with 30 minute increment protocol, for both nulliparous and parous women	RCT	Ib

Study	Population	Intervention details	Outcomes	Results	Comments	Study type	Evidence level
Orhue ⁸⁴	124 nulliparous labours	Amniotomy if possible prior to oxytocin. If not possible, all women had ARM within 2 hours of oxytocin starting <i>Low-dose protocol</i> Starting: 2.0 mu/min Doubled every 30 minutes Maximum dose 32 mu/min <i>High-dose protocol</i> Starting: 2.0 mu/min Doubled every 15 minutes Maximum dose 32 mu/min	Uterine hyperstimulation Caesarean section (all) Instrumental vaginal delivery Postpartum haemorrhage	RR 5.00 (95% CI 1.14–21.90) RR 2.14 (95% CI 0.94–4.89) RR 0.82 (95% CI 0.36–1.83) RR 1.58 (95% CI 0.81–3.08)	Significant reduction in induction to delivery interval in 15-minute increment regimen Significant increase in precipitate labour in 15-minute group, all associated with episodes of 'fetal distress' prior to birth Significant increase in LSCS for fetal distress in 15-minute group (all preceded by hyperstimulation) RR 3.50; 95% CI 0.76–16.19	RCT	Ib
Orhue ⁸⁵	245 labours	Amniotomy if possible prior to oxytocin. If not possible all women had ARM within two hours of oxytocin starting <i>Low-dose protocol</i> Starting: 2.0 mu/min Doubled every 30 minutes Maximum dose 32 mu/min <i>High-dose protocol</i> Starting: 2.0 mu/min Doubled every 15 minutes Maximum dose 32 mu/min	Uterine hyperstimulation Caesarean section Instrumental vaginal delivery Postpartum haemorrhage Uterine rupture	RR 3.02 (95% CI 1.24–7.36) RR 1.76 (95% CI 0.70–4.05) RR 1.41 (95% CI 0.46–4.33) RR 1.85 (95% CI 0.96–3.57) RR 3.02 (95% CI 0.12–73.53)	Significant reduction in induction to delivery interval in 15-minute increment regimen Significant increase in precipitate labour in 15-minute group, all associated with episodes of 'fetal distress' prior to delivery	RCT	Ib

Study	Population	Intervention details	Outcomes	Results	Comments	Study type	Evidence level
Orhue ²⁶	90 women of parity greater than five	Amniotomy if possible prior to oxytocin. If not possible all women had ARM within two hours of oxytocin starting <i>Low-dose protocol</i> Starting: 2.0 mu/min Doubled every 45 minutes Maximum dose 32 mu/min <i>High-dose protocol</i> Starting: 2.0 mu/min Doubled every 15 minutes Maximum dose 32 mu/min	Uterine hyperstimulation Caesarean section Instrumental vaginal delivery Postpartum haemorrhage Uterine rupture	RR 3.55 (95% CI 1.43–8.81) RR 2.09 (95% CI 0.40–10.85) RR 1.31 (95% CI 0.38–4.55) RR 2.61 (95% CI 0.88–7.72) RR 7.31 (95% CI 0.39–137.59)	Significant increase in precipitate labour in 15-minute group, (RR 30.29; 95% CI 1.86,492.86) all associated with episodes of 'fetal distress' prior to delivery	RCT	Ib
Mercer <i>et al.</i> ⁸⁶	123 labours	Amniotomy if possible prior to oxytocin <i>Low-dose protocol</i> Starting: 0.5 mu/min Increased every 60 minutes to 1, 2, 4, 8, 12 and 16 mu/min as needed <i>High-dose protocol</i> Starting: 0.5 mu/min Increased every 20 minutes to 1, 2, 4, 8, 12, 16, 20 and 24 mu/min as needed	Uterine hyperstimulation Caesarean section Epidural analgesia	RR 1.97 (95% CI 1.27,3.06) RR 2.34 (95% CI 1.11,4.93) RR 1.00 (95% CI 0.83,1.22)	Nearly half of patients in low-dose group received 'priming' with oxytocin prior to amniotomy	RCT	Ib
Chua <i>et al.</i> ⁸⁷	224 labours	Amniotomy if possible prior to oxytocin <i>Low-dose protocol</i> Starting: 2.5 mu/min Increased by 2.5 mu/min every 30 minutes <i>High-dose protocol</i> Starting: 2.5 mu/min Increased by 2.5 mu/min every 30 minutes	Uterine hyperstimulation with FHR changes Uterine hyperstimulation without FHR changes Caesarean section Instrumental vaginal delivery	RR 0.89 (95% CI 0.36–2.22) RR 1.59 (95% CI 0.70–3.19) RR 0.67 (95% CI 0.28–1.57) RR 1.25 (95% CI 0.68–2.28)	No difference in delivery intervals between two groups	RCT	Ib



RCOG Evidence-based Clinical Guidelines

This is the eighth in a series of evidence-based guidelines that are being produced by the RCOG with funding from the NHS Executive and the National Institute for Clinical Excellence (NICE). The other titles already published in this series are:

- The Initial Management of Menorrhagia
- The Initial Investigation and Management of the Infertile Couple
- The Management of Infertility in Secondary Care
- Male and Female Sterilisation
- The Management of Menorrhagia in Secondary Care
- The Management of Infertility in Tertiary Care
- The Care of Women Requesting Induced Abortion
- The Use of Electronic Fetal Monitoring

Guidelines still in production include:

- Antenatal Care for Healthy Women
- Caesarean Section

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