

WHO recommendations for **Induction of labour**



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The standardized criteria used in grading the evidence and the GRADE tables **are not included in this document** (although table numbers – prefixed with ‘EB – are included for ease of reference). The tables have been published in a separate document entitled *Evidence base for WHO recommendations for induction of labour* and can be accessed by clicking on the following link.

http://whqlibdoc.who.int/hq/2011/WHO_RHR_11.10_eng.pdf

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
AGREE	Appraisal of Guidelines Research and Evaluation
CI	confidence interval
CREP	Centro Rosarino de Estudios Perinatales
GREAT	Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (project)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MMR	maternal mortality ratio
PICO	population, interventions, comparisons, and outcomes
REVMAN	Review Manager Software
RR	relative risk
SOGC	Society of Obstetricians and Gynaecologists of Canada
USAID	United States Agency for International Development



EXECUTIVE SUMMARY

Over recent decades, more and more pregnant women around the world have undergone induction of labour (artificially initiated labour) to deliver their babies. In developed countries, up to 25% of all deliveries at term now involve induction of labour. In developing countries, the rates are generally lower, but in some settings they can be as high as those observed in developed countries.

Induction of labour is not risk-free and many women find it to be uncomfortable. With a view to promoting the best known clinical practices in labour and childbirth and to improving maternal outcomes worldwide, WHO has developed the present recommendations using the procedures outlined in the *WHO Handbook for guideline development*. The steps involved in the guideline development process included: (i) identification of priority questions and outcomes; (ii) evidence retrieval; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations; and (v) planning for dissemination, implementation, impact evaluation and updating. Using the Grading of Recommen-

dations Assessment, Development and Evaluation (GRADE) methodology, evidence profiles related to preselected topics were prepared based on 18 up-to-date Cochrane systematic reviews. An international group of experts participating in a WHO technical consultation – held in Geneva, Switzerland, on 13–14 April 2010 – formulated the recommendations based on the evidence profiles using a process that was participatory and consensus-driven. The participants also identified important knowledge gaps that needed to be addressed through primary research. Overall, the participants placed high emphasis on implementation research related to induction of labour and developed a list of 10 priority research questions, which are presented in this document (see Section 5, Research implications). Issues related to dissemination, adaptation and implementation (including the anticipated impact on the organization of care and monitoring and evaluation of the implementation) of the present guidelines are also addressed herein.

General principles related to the practice of induction of labour

- ▶ Induction of labour should be performed only when there is a clear medical indication for it and the expected benefits outweigh its potential harms.
- ▶ In applying the recommendations, consideration must be given to the actual condition, wishes and preferences of each woman, with emphasis being placed on cervical status, the specific method of induction of labour and associated conditions such as parity and rupture of membranes.
- ▶ Induction of labour should be performed with caution since the procedure carries the risk of uterine hyperstimulation and rupture and fetal distress.
- ▶ Wherever induction of labour is carried out, facilities should be available for assessing maternal and fetal well-being.
- ▶ Women receiving oxytocin, misoprostol or other prostaglandins should never be left unattended.
- ▶ Failed induction of labour does not necessarily indicate caesarean section.
- ▶ Wherever possible, induction of labour should be carried out in facilities where caesarean section can be performed.

Specific recommendations and their strength and quality of available evidence

Context	Recommendation	Quality of evidence	Strength
When induction of labour may be appropriate	1. Induction of labour is recommended for women who are known with certainty to have reached 41 weeks (>40 weeks + 7 days) of gestation.	Low	Weak
	2. Induction of labour is not recommended in women with an uncomplicated pregnancy at gestational age less than 41 weeks.	Low	Weak
	3. If gestational diabetes is the only abnormality, induction of labour before 41 weeks of gestation is not recommended.	Very low	Weak
	4. Induction of labour at term is not recommended for suspected fetal macrosomia.	Low	Weak
	5. Induction of labour is recommended for women with prelabour rupture of membranes at term.	High	Strong
	6. For induction of labour in women with an uncomplicated twin pregnancy at or near term, no recommendation was made as there was insufficient evidence to issue a recommendation.	—	—
Methods of induction of labour	7. If prostaglandins are not available, intravenous oxytocin alone should be used for induction of labour. Amniotomy alone is not recommended for induction of labour.	Moderate	Weak
	8. Oral misoprostol (25 µg, 2-hourly) is recommended for induction of labour.	Moderate	Strong
	9. Low-dose vaginal misoprostol (25 µg, 6-hourly) is recommended for induction of labour.	Moderate	Strong
	10. Misoprostol is not recommended for induction of labour in women with previous caesarean section.	Low	Strong
	11. Low doses of vaginal prostaglandins are recommended for induction of labour.	Moderate	Strong
	12. Balloon catheter is recommended for induction of labour.	Moderate	Strong
	13. The combination of balloon catheter plus oxytocin is recommended as an alternative method of induction of labour when prostaglandins (including misoprostol) are not available or are contraindicated.	Low	Weak
	14. In the third trimester, in women with a dead or an anomalous fetus, oral or vaginal misoprostol are recommended for induction of labour.	Low	Strong
	15. Sweeping membranes is recommended for reducing formal induction of labour.	Moderate	Strong
Management of adverse events related to induction labour	16. Betamimetics are recommended for women with uterine hyperstimulation during induction of labour.	Low	Weak
Setting for induction of labour	17. Outpatient induction of labour is not recommended for improving birth outcomes.	Low	Weak

1. BACKGROUND

Induction of labour is defined as the process of artificially stimulating the uterus to start labour (1). It is usually performed by administering oxytocin or prostaglandins to the pregnant woman or by manually rupturing the amniotic membranes.

Over the past several decades, the incidence of labour induction for shortening the duration of pregnancy has continued to rise. In developed countries, the proportion of infants delivered at term following induction of labour can be as high as one in four deliveries (2–4). Unpublished data from the WHO Global Survey on Maternal and Perinatal Health, which included 373 health-care facilities in 24 countries and nearly 300 000 deliveries, showed that 9.6% of the deliveries involved labour induction. Overall, the survey found that facilities in African countries tended to have lower rates of induction of labour (lowest: Niger, 1.4%) compared with Asian and Latin American countries (highest: Sri Lanka, 35.5%) (5).

Over the years, various professional societies have recommended the use of induction of labour in circumstances in which the risks of waiting for the onset of spontaneous labour are judged by clinicians to be greater than the risks associated with shortening the duration of pregnancy by induction. These circumstances generally include gestational age of 41 completed weeks or more, prelabour rupture of amniotic membranes, hypertensive disorders, maternal medical complications, fetal death, fetal growth restriction, chorioamnionitis, multiple pregnancy, vaginal bleeding and other complications. Although currently available guidelines do not recommend this, induction of labour is being used more and more at the request of pregnant women to shorten the

duration of pregnancy or to time the birth of the baby according to the convenience of the mother and/or health-care workers (6, 7).

During induction of labour, the woman has restricted mobility and the procedure itself can cause discomfort to her. To avoid potential risks associated with the procedure, the woman and her baby need to be monitored closely. This can strain the limited health-care resources in under-resourced settings. In addition, the intervention affects the natural process of pregnancy and labour and may be associated with increased risks of complications, especially bleeding, caesarean section, uterine hyperstimulation and rupture and other adverse outcomes (2, 8).

The primary goal of the present guidelines is to improve the quality of care and outcomes for pregnant women undergoing induction of labour in under-resourced settings. The target audience of these guidelines includes obstetricians, midwives, general medical practitioners, health-care managers and public health policy-makers. The guidance provided is evidence-based and covers selected topics related to induction of labour that were regarded as critical priority questions by an international, multidisciplinary group of health-care workers, consumers and other stakeholders. These guidelines do not cover the process of stimulating the uterus during labour to increase the frequency, duration and strength of contractions (labour augmentation), and are not intended as a comprehensive guide on the management of induction of labour.



2. METHODS

The present guidelines have been prepared in accordance with the process described in the *WHO Handbook for guideline development* (9). In summary, the process included: (i) identification of priority questions and critical outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations; and (v) planning for dissemination, implementation, impact evaluation and updating.

First, a guideline development group was constituted, which included staff of the WHO Departments of Reproductive Health and Research, and Making Pregnancy Safer and two outside experts (see Annex 1). This group drafted a list of questions and outcomes related to induction of labour (Annex 2). Next, via an online survey, WHO consulted a group of international stakeholders (midwives, obstetricians, neonatologists, researchers, experts in research synthesis, experts in health-care programmes, and a member of the Cochrane Consumers and Communication Review Group) to review and prioritize the draft questions and outcomes. The international stakeholders commented on the importance of the drafted questions and outcomes and rated them on a scale of 1 to 9. In this context, a “critical question or outcome” was defined as a question or outcome that received an average score of 7 or more. Questions and outcomes that scored between 4 and 6 were considered “important but not critical”, while those that scored less than 4 were not considered to be important for the purposes of these guidelines. The international stakeholders were encouraged to revise the questions or suggest new questions and outcomes. The responses to the online survey were reviewed by the guideline development group. The questions and outcomes rated as critical were included in the scope of this document for evidence grading and formulation of recommendations and were further refined in order to make them conform to the PICO format (population, interventions, comparisons, and outcomes).

Cochrane systematic reviews of randomized controlled trials were the primary source of evidence for the recommendations. Based on the list of selected questions and outcomes, the guideline development group identified the relevant Cochrane systematic reviews and determined whether they needed to be updated. Relevant and possibly relevant Cochrane systematic reviews that were considered to be outdated were updated using their specific standard search strategies.

A review was considered to be outdated if the last date of search for new trials was two years old, or if there were relevant studies awaiting assessment, as identified by the standard search procedures of the Cochrane Pregnancy and Childbirth Group. For the outdated reviews, the corresponding review authors were invited to update them. Not all authors were in a position to do that within the set deadline. Hence, the review authors who could comply with the deadline and members of the guideline development group jointly updated the systematic reviews. The search strategies employed to identify the trials and the specific criteria for inclusion and exclusion of the trials are described in the individual systematic reviews.

The following standard operating procedures were used to process in a consistent manner each systematic review used to extract the evidence for these guidelines. First, the up-to-date Review Manager Software (REVMAN) file was retrieved from the Cochrane Pregnancy and Childbirth Cochrane Group. Next the REVMAN file was customized in order to reflect the priority comparisons and outcomes (comparisons and outcomes not relevant to the guidelines were excluded). The next step was to export the REVMAN file to the GRADE profiler software and apply the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for critical appraisal to the retrieved scientific evidence. As a final step, evidence profiles (GRADE tables) were prepared for each comparison.

The standardized criteria used in grading the evidence and the GRADE tables **are not included in this document** (although table numbers – prefixed with ‘EB – are included for ease of reference): they are being published online separately in a document entitled *Evidence base for WHO recommendations for induction of labour* (www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241501156/en/). Each GRADE table relates to one specific question or comparison. The evidence presented in the GRADE tables was derived from a larger body of data extracted primarily from Cochrane reviews, which in many cases contained multiple comparisons. In some GRADE tables data are not presented for all priority outcomes. This is because data for those outcomes were not available in the Cochrane reviews. The background data which constitute the basis of the GRADE tables are also not included in this document, but can be made available upon request to researchers interested in finding out how the GRADE tables were constructed. The guideline development group used the information presented in the GRADE tables to draft the recommendations.

In order to review and finalize the draft recommendations and the supporting evidence, a technical consultation was organized at WHO headquarters, in Geneva, Switzerland, on 13–14 April 2010. A subset of the international group of experts that had participated in the initial online consultation and other experts were invited to participate in this consultation (see Annex 1 for the list of participants). The draft recommendations and supporting documents were provided to the consultation participants in advance of the technical consultation.

Declaration of interest by participants in the WHO technical consultation

Before participating in the meeting, all participants in the WHO technical consultation (except WHO staff) made a declaration of interest on a standard WHO form. The declarations were reviewed by WHO before the consultation. Dr Justus Hofmeyr, Dr Michel Boulvain, and Dr Andrew Weeks declared that they had conducted primary research and systematic reviews on topics related to induction of labour. None of the participants declared either any commercial conflict of interests or any other interest requiring their exclusion from the meeting.

Decision-making during the technical consultation

It was planned that the participants in the technical consultation would discuss each of the recommendations drafted by the guideline development group and aim to arrive at a consensus, which was defined as agreement by the large majority of the participants (three quarters of participants), provided that those who disagreed did not feel strongly about their position. Strong disagreements would be recorded as such in the guidelines. If the participants are unable to reach a consensus, the disputed recommendation, or any other decision, would be put to a vote. The recommendation or decision would stand if a simple majority (more than half) of the participants vote for it, unless the disagreement relates to a safety concern, in which case the WHO Secretariat may choose not to issue a recommendation at all. WHO staff present at the meeting and other external technical experts involved in the collection and grading of the evidence would not be allowed to vote. If the issue to be voted upon involves primary research or systematic reviews conducted by any of the participants who have declared an academic conflict of interest, the participants in question would be allowed to participate in the

discussion, but would not be allowed to vote on it. In addition to the scientific evidence and its quality, applicability issues, costs and other judgements would be taken into consideration in the formulation of the final recommendations.

The strength of each recommendation was determined by assessing each intervention on the basis of: (i) desirable and undesirable effects; (ii) quality of available evidence; (iii) values and preferences related to interventions in different settings; (iv) cost of options available to health-care workers in different settings; and (v) the perceived likelihood of the recommendation being modified as a result of further research. In general, a high-quality, strong recommendation indicates that further research on that question is not considered to be a priority.

Document preparation and peer review

Prior to the technical consultation, the guideline development group had prepared a preliminary document containing the draft recommendations. This document was made available to the participants in the technical consultation about one week before the meeting. The statements in the preliminary document were modified

during the meeting itself in line with as the participants' deliberations. After the meeting, the WHO staff involved with these guidelines worked on the draft document to ensure that it reflected accurately the deliberations and decisions of the participants. This revised version was sent electronically back to the participants in the technical consultation for their approval. The comments and feedback received from the participants were incorporated into the document and that version of the document was then sent for external critical appraisal and peer review by a consumer representative and an expert in induction of labour. The external peer reviewers were asked to review the document with regard to its editorial aspects, presentation, wording, inclusion of consumers' views, scoping and the relevance of the recommendations to developing countries. Inputs received from the peer reviewers were carefully evaluated by the guideline development group and the suggestions considered as relevant were included in the document. The concerned WHO staff refrained from making any substantive changes to the scoping (e.g. further expansion of the guideline scoping) of the guidelines or the recommendations agreed upon during the technical consultation.

3. RESULTS

The draft questions and outcomes were sent for scoring and comments to 72 experts from all six WHO regions. After two reminders, a total of 48 responses were received. Based on those responses, the questions and outcomes were modified slightly. Annex 2, Table 1 shows the average scores given to the scoping questions by the external experts. The priority questions to be addressed by the technical consultation were identified based on those average scores. A total of 13 questions are included in the present guidelines: five relate to indications for labour induction, six to methods of labour induction and two to setting and monitoring of the procedure.

Labour induction in women with hypertensive disorders of pregnancy and augmentation of established labour are not included in the present guidelines. The former will be covered separately in a future guideline. A total of 18 Cochrane systematic reviews were selected for providing the evidence related to the selected questions.



4. EVIDENCE AND RECOMMENDATIONS

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General principles related to the practice of induction of labour

The participants in the technical consultation agreed on the following general statements that apply to all recommendations contained in these guidelines:

- ▶ Induction of labour should be performed only when there is a clear medical indication for it and the expected benefits outweigh its potential harms.
- ▶ In applying the recommendations, consideration must be given to the actual condition, wishes and preferences of each woman, with emphasis being placed on cervical status, the specific method of induction of labour and associated conditions such as parity and rupture of membranes.
- ▶ Induction of labour should be performed with caution since the procedure carries the risk of uterine hyperstimulation and rupture and fetal distress.
- ▶ Wherever induction of labour is carried out, facilities should be available for assessing maternal and fetal well-being.
- ▶ Women receiving oxytocin, misoprostol or other prostaglandins should never be left unattended.
- ▶ Failed induction of labour does not necessarily indicate caesarean section.
- ▶ Wherever possible, induction of labour should be carried out in facilities where caesarean section can be performed.



Induction of labour in specific circumstances

► Induction of labour in women at or beyond term

Evidence summary

Evidence related to induction of labour at term and beyond term was extracted from one Cochrane systematic review of 22 randomized controlled trials (10). Most of the trials were judged by the Cochrane review authors to likely have a moderate risk of bias, largely due to unclear concealment of allocation and generation of the sequence of randomization. The trials had evaluated the effect of inducing labour at 37–40 weeks, 41 completed weeks, and 42 completed weeks of gestation, and the intervention was compared with expectant management with fetal monitoring at varying intervals.

There were no statistical and clinical differences in the priority comparisons and outcomes, except for a reduction in perinatal deaths when labour was induced at 41 completed weeks. A total of 12 studies had compared the incidence of perinatal deaths at 41 weeks. The total number of women included in this comparison (labour induction versus expectant management with fetal monitoring at 41 completed weeks) was 6274. Only eight perinatal deaths occurred in the 12 trials, all in the expectant management group. The resulting relative risk (RR) was 0.27, with the 95% confidence interval (CI) being 0.08–0.98 (EB Table 1.1.1).

Recommendations

1. Induction of labour is recommended for women who are **known with certainty** to have reached 41 weeks (> 40 weeks + 7 days) of gestation.
(Low-quality evidence. Weak recommendation.)
2. Induction of labour is not recommended for women with an uncomplicated pregnancy at gestational age less than 41 weeks.
(Low-quality evidence. Weak recommendation.)

Remarks

1. Recommendation No. 1 above does not apply to settings where the gestational age cannot be estimated reliably.
2. There is insufficient evidence to recommend induction of labour for uncomplicated pregnancies before 41 weeks of pregnancy.



► Induction of labour in women with gestational diabetes

Evidence summary

The evidence related to induction of labour in women with gestational diabetes comes from a systematic review (11) of a single trial. The 200 participants in that trial were women with either gestational diabetes or diabetes type I or type II who were receiving insulin and who had good metabolic control over their condition. There is paucity of data related to the priority comparisons and outcomes. The trial was considered to have a moderate risk of bias and the effect was estimable for only one priority outcome, namely caesarean section. The finding for caesarean section was imprecise and not statistically significant (RR 0.81, 95% CI 0.52–1.26) (EB Table 1.2.1).

Recommendation

1. If gestational diabetes is the only abnormality, induction of labour before 41 weeks of gestations is not recommended.
(Very-low-quality evidence. Weak recommendation.)

Remark

1. Participants in the WHO technical consultation acknowledged that labour induction may be necessary in some women with diabetes – for example, those with placental insufficiency and uncontrolled diabetes.



► Induction of labour for suspected fetal macrosomia

Evidence summary

To obtain evidence for this indication, the existing systematic review (12) with three trials was updated by the guideline development group with data from a recent unpublished trial that had evaluated induction of labour for suspected macrosomia. For the priority comparisons and outcomes, induction of labour at term was similar to expectant management. With regard to other outcomes that are relevant for this comparison, but not a priority for the present guidelines, induction of labour was associated with fewer clavicle and arm fractures due to shoulder dystocia (four trials, 1189 participants, RR 0.2, 95% CI 0.05–0.79) (EB Table 1.3.1).

Recommendation

1. Induction of labour at term is not recommended for suspected fetal macrosomia
(Low-quality evidence. Weak recommendation.)

Remark

1. Confirmation of suspected macrosomia is based on reliable determination of fetal age and weight, which requires ultrasound assessments early in pregnancy and then at near term. Considering that in under-resourced settings ultrasound facilities may not be available or accessible to all women, the participants in the technical consultation preferred not to recommend induction of labour for suspected macrosomia, even though they acknowledged that in cases of confirmed macrosomia induction of labour could reduce the incidence of clavicle fracture due to shoulder dystocia.

► Induction of labour in women with prelabour rupture of membranes at term

Evidence summary

The evidence related to induction of labour in women with prelabour rupture of membranes was obtained from a systematic review (13) of 16 randomized controlled trials. There were no major concerns related to the risk of bias in the trials, although for some of the priority outcomes the number of events was small.

Overall, induction of labour performed for the indication of prelabour rupture of membranes was not associated with increased caesarean section rates or other adverse outcomes. The risk related to the critical outcome of perinatal mortality was similar in both groups, but there were only 10 perinatal deaths in five trials included in the review (5870 participants, RR 0.46, 95% CI 0.13–1.66) (EB Table 1.4.1). There was a reduction in admissions to a neonatal intensive care unit with induction of labour (five trials, 5679 participants, RR 0.73, 95% CI 0.58–0.91) (EB Table 1.4.1). This effect was more evident when induction of labour was carried out with oxytocin (three trials, 2883 participants, RR 0.58; 95% CI 0.39–0.85) (EB Table 1.4.2) rather than with prostaglandins (three trials, 2796 participants, RR 0.87, 95% CI 0.73–1.03) (EB Table 1.4.3).

Recommendation

1. Induction of labour is recommended for women with prelabour rupture of membranes at term.
(High-quality evidence. Strong recommendation.)

Remark

1. Participants in the WHO technical consultation noted that in the trials included in the Cochrane review, induction of labour had been initiated within 24 hours of rupture of membranes. They also noted that oxytocin should be regarded as the first option for induction of labour in women with prelabour rupture of membranes.



► Induction of labour in women with uncomplicated twin pregnancy at or near term

Evidence summary

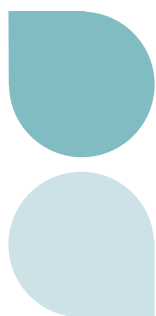
Available evidence for induction of labour in women with a twin pregnancy came from a systematic review (14) with only one small and statistically underpowered randomized controlled trial that had assessed labour induction at 37 weeks of gestation in women carrying twins. Only one priority outcome, namely caesarean delivery, could be evaluated from this trial (36 participants, RR 0.56, 95% CI 0.16–1.90) (EB Table 1.5.1), but the imprecise findings of this study make it difficult to draw any conclusions about this outcome. No large observational studies that could be helpful in decision-making were identified.

Recommendation

1. None.

Remark

1. The participants in the technical consultation noted that there was insufficient evidence to issue a recommendation on induction of labour in women with an uncomplicated twin pregnancy at or near term.



Methods of cervical ripening and induction of labour

► Oxytocin for induction of labour at term

Evidence summary

Evidence related to the use of intravenous oxytocin for induction of labour at term was available from a Cochrane systematic review (15). Compared with placebo or expectant management, the use of oxytocin alone was associated with fewer vaginal births not achieved within 24 hours of induction of labour (three trials, 399 participants, RR 0.16, 95% CI 0.1–0.25), fewer admissions to a neonatal intensive care unit (seven trials, 4387 participants, RR 0.79, 95% CI 0.68–0.92), and increased risk of caesarean section (24 trials, 6620 participants, RR 1.17, 95% CI 1.01–1.35) (EB Table 2.1.1).

Only one small trial (184 participants) had been included in the review (16) that had compared oxytocin plus amniotomy with placebo or oxytocin plus amniotomy with expectant management (EB Table 2.2.1). Two small trials with 309 participants had compared oxytocin plus amniotomy with oxytocin alone (EB Table 2.2.4). In both those trials, no advantages were observed with the addition of amniotomy to intravenous oxytocin for induction of labour. The combined use of intravenous oxytocin and amniotomy was also compared with amniotomy alone in two trials with 296 participants (EB Table 2.2.5). The risk of not achieving vaginal birth within 24 hours was reduced in the group that received oxytocin (RR 0.12, 95% CI 0.04–0.41), which favours a crucial role for oxytocin in this combination.

Intravenous oxytocin plus amniotomy was compared to vaginal prostaglandins in 10 trials (EB Table 2.2.2). These trials found that caesarean section rates were similar in both groups. Other critical outcomes of perinatal death, vaginal birth not achieved within 24 hours, maternal mortality and severe morbidity and admission to a neonatal intensive care unit were reported in a small number of trials, yielding very-low- to low-quality evidence.

The use of intravenous oxytocin alone has also been compared with prostaglandins (EB Tables 2.1.2, 2.1.3, 2.1.4). Overall, the use of prostaglandins was associated with a reduced risk of vaginal birth not achieved within 24 hours and fewer caesarean births. The relationship between oxytocin use and prostaglandins will be further evaluated in sections 4.3.2 (Misoprostol for induction of labour at term) and 4.3.3 (Prostaglandins other than misoprostol for induction of labour).

Recommendation

1. If prostaglandins are not available, intravenous oxytocin alone should be used for induction of labour. Amniotomy alone is not recommended for induction of labour. (Moderate-quality evidence. Weak recommendation.)

Remark

1. Immediately after the initiation of intravenous oxytocin, it is advisable to monitor closely the oxytocin infusion rate, response of the uterus to oxytocin, and fetal heart rate. Specific guidance on how to use oxytocin for induction of labour can be found in the WHO manual *Managing complications in pregnancy and childbirth: a guide for midwives and doctors* (1).



► Misoprostol for induction of labour at term

Evidence summary

Evidence on misoprostol for induction of labour at term was derived from three systematic reviews (17–19) which include a large number of randomized controlled trials. Historically, most trials have studied the vaginal route of administration for misoprostol use in induction of labour. However, owing to concerns about the risk of uterine hyperstimulation with vaginal misoprostol, more recent trials have focused on lower vaginal misoprostol doses and the oral route for misoprostol administration.

A. Vaginal misoprostol

Compared with either placebo or expectant management, vaginal misoprostol was associated with a reduced risk of not achieving vaginal birth within 24 hours of labour induction (five trials, 769 participants, RR 0.51, 95% CI 0.37–0.71) (EB Table 2.3.1).

Compared with intravenous oxytocin alone (EB Table 2.3.4), vaginal misoprostol was associated with a reduced risk of vaginal birth not achieved within 24 hours (nine trials, 1200 participants, RR 0.62, 95% CI 0.43–0.9), fewer caesarean sections (25 trials, 3074 participants, RR 0.76, 95% CI 0.60–0.96) and fewer infants with Apgar score below seven at 5 minutes of life (13 trials, 1906 participants, RR 0.56, 95% CI 0.34–0.92).

Compared with other prostaglandins (EB Tables 2.3.2 and 2.3.3), vaginal misoprostol was associated with a reduced risk of vaginal birth not achieved within 24 hours (vaginal and intracervical prostaglandins), fewer caesarean sections (vaginal prostaglandins), and increased risk of uterine hyperstimulation with fetal heart rate changes, but without increased risk of other priority outcomes (vaginal and intracervical prostaglandins). Compared with higher doses of vaginal misoprostol, lower doses (25 µg, 6-hourly) were associated with a reduced risk of uterine hyperstimulation with fetal heart rate changes (16 trials, 2540 participants, RR 0.51, 95% CI 0.37–0.69). The risk of vaginal birth not being achieved within 24 hours was similar with both higher and lower doses (EB Table 2.3.5).

B. Oral misoprostol

Compared with placebo or expectant management, oral misoprostol lowered the risk not only of vaginal birth not achieved within 24 hours (one study, 96 participants, RR 0.16, 95% CI 0.05–0.49), but also of caesarean births (six trials, 629 participants, RR 0.61, 95% CI 0.41–0.93) (EB Table 2.4.1). Comparisons between oral misoprostol and intravenous oxytocin (eight trials, 1026 participants) showed the two to be similar with regard to the risk of priority outcomes (EB Table 2.4.2).

Oral misoprostol was more effective than intracervical prostaglandins in achieving vaginal birth within 24 hours (three trials, 452 women, RR: 0.78, 95%, CI 0.63–0.97) (EB Table 2.4.4). The comparison between oral misoprostol and vaginal prostaglandins favoured oral misoprostol: a reduced risk of caesarean births was observed (12 trials, 4350 participants, RR 0.87, 95% CI 0.78–0.97) without any increase in the risks of adverse maternal and perinatal outcomes (EB Table 2.4.5). Lower doses of oral misoprostol (up to 50 µg) were associated with similar outcomes compared with higher doses (100 µg) (EB Table 2.4.6). Most trials that had compared vaginal prostaglandins with oral misoprostol had studied dosages of 20–25 µg, 2-hourly (EB Table 2.4.6); oral misoprostol was associated with a reduction in caesarean section rates.

C. Oral misoprostol versus vaginal misoprostol

Priority outcomes have been evaluated in direct comparisons between oral and vaginal misoprostol in 25 trials involving 5096 women (EB Table 2.4.3). Oral and vaginal misoprostol were similar with regard to all but one of the priority outcomes: compared with vaginal misoprostol, oral misoprostol was associated with a lower risk of Apgar score being less than seven at 5 minutes of life (14 trials, 3270 participants, 94 events, RR 0.65, 95% CI 0.44–0.97).

D. Oral or vaginal misoprostol versus sublingual/buccal misoprostol

Vaginal misoprostol has been compared with sublingual/buccal misoprostol in nine trials with 2385 participants. These trials indicate that vaginal and sublingual/buccal misoprostol are similar with regard to all the priority outcomes (EB Table 2.5.1). Data on oral versus sublingual/buccal misoprostol are limited and no firm conclusions can be drawn from them (EB Table 2.5.2).

Recommendations

1. Oral misoprostol (25 µg, 2-hourly) is recommended for induction of labour.
(Moderate-quality evidence. Strong recommendation.)
2. Vaginal low-dose misoprostol (25 µg, 6-hourly) is recommended for induction of labour.
(Moderate-quality evidence. Weak recommendation.)
3. Misoprostol is not recommended for women with previous caesarean section.
(Low-quality evidence. Strong recommendation.)

Remarks

1. Recommendations Nos. 1 and 2 refer to women with a non-scarred uterus.
2. The participants in the technical consultation noted the importance of closer monitoring of the mother and her fetus starting immediately after the administration of misoprostol. The participants noted also that labour induction with misoprostol in women with previous caesarean section had not been included as a priority topic in the process of scoping for the present guidelines. However, the participants felt that it was important to address this issue in these guidelines. The participants noted too that one randomized controlled trial (20) was interrupted at the early recruitment stage due to safety concerns (i.e. occurrence of uterine rupture) and that there were observational studies showing mixed results. The participants placed high value on safety and agreed not to recommend the use of misoprostol for induction of labour in women with a scarred uterus. The panel noted that a method with a low risk of uterine hyperstimulation (e.g. balloon catheter) may be preferred in women with a scarred uterus.



► Prostaglandins other than misoprostol for induction of labour

Evidence summary

Four systematic reviews (14, 21–23) summarize the evidence related to the use of prostaglandins other than misoprostol for induction of labour. In these reviews, various preparations of prostaglandin E2 and prostaglandin F2 alpha have been evaluated.

Overall, prostaglandin E2 (all regimens) preparations were more effective than placebo for induction of labour at term (EB Table 2.6.1). There was a reduced risk of vaginal births not achieved within 24 hours (two trials, 384 participants, RR 0.19, 95% CI 0.14–0.25) and fewer caesarean births (34 trials, 6399 participants, RR 0.89, 95% CI 0.79–1.00). A higher risk of uterine hyperstimulation with fetal heart rate changes was observed (14 trials, 1259 participants, RR 4.14, 95% CI 1.93–8.9), but without additional adverse maternal and perinatal priority outcomes (Apgar score, admission to a neonatal intensive care unit, perinatal death and serious maternal morbidity or death).

Direct comparisons between intracervical prostaglandin E2 and intra-vaginal prostaglandin E2 were made in 28 studies (3781 participants) and the results were in the favour of the latter (EB Table 2.8.2). Although similar in terms of other priority outcomes, intra-cervical prostaglandins have been associated with an increased risk of vaginal birth not achieved within 24 hours (eleven studies, 2200 participants, RR 1.26, 95% CI 1.12–1.41). There is limited evidence from randomized controlled trials (three trials, 113 participants) on oral versus intra-cervical prostaglandins (EB Table 2.7.3) and oral versus vaginal prostaglandins (EB Table 2.7.4); no differences were found between the two types of intervention.

The comparison between oxytocin alone and vaginal prostaglandins favoured the prostaglandins (EB Table 2.1.3): oxytocin alone was associated with an increased risk of vaginal birth not achieved within 24 hours (three trials, 260 participants, RR 1.77, 95% CI 1.31–2.38); comparisons involving other priority outcomes, which were made in 26 trials involving 4514 participants, showed similar results.

Vaginal prostaglandin E2 gel has been compared with vaginal prostaglandin E2 tablets and, overall, both formulations were found to have similar effects (five trials, 881 participants evaluated for five priority outcomes) (EB Table 2.6.4). Vaginal prostaglandin E2 gel has also been compared with vaginal prostaglandin E2 suppository/pessary (EB Table 2.6.5). In this comparison, the gel was associated with less uterine hyperstimulation (two trials, 159 participants, RR 0.16, 95% CI 0.03–0.87) and there was no statistically significant difference between the gel and suppository/pessary in terms of the risk of caesarean section (two trials, 159 participants, RR 0.65, 95% CI 0.38–1.11) and Apgar score less than seven at 5 minutes of life (one trial, 69 participants, RR 0.21, 95% CI 0.01–4.13). There was limited, low-quality evidence showing no statistically significant differences between controlled-release prostaglandin E2 and other prostaglandin E2 formulations (eight trials, 929 participants, five priority outcomes evaluated).

Low-dose prostaglandin E2 has been compared with its high-dose counterpart in seven trials (EB Table 2.6.8). The use of lower doses may present comparative advantages over the higher doses: (i) lower risk of uterine hyperstimulation with fetal heart rate changes (two trials, 140 participants, RR 0.18, 95% CI 0.03–0.99); (ii) similar risk of caesarean section (seven trials, 1466 participants, RR 1.07, 95% CI 0.8–1.42) and Apgar score less than seven at 5 minutes of life (three trials, 1064, RR 0.51, 95% CI 0.2–1.31); and (iii) a trend towards reduced risk of admission to a neonatal intensive care unit (one trial, 955 participants, RR 0.51, 95% CI 0.24–1.09).

Recommendation

1. Low doses of vaginal prostaglandins are recommended for induction of labour.
(Moderate-quality evidence. Strong recommendation.)

Remarks

1. Prostaglandin preparations other than misoprostol are expensive and may not be a priority for implementation, especially in low- and middle-income countries.
2. When prostaglandins are used, close monitoring of the woman and fetus should begin immediately after administration of the drug.



► Mechanical methods for induction of labour

Evidence summary

Evidence related to the use of mechanical methods of induction of labour has been summarized in one systematic review (24), which evaluated comparisons of the balloon catheter (Foley or Atad) with prostaglandins (including misoprostol), oxytocin and placebo. In one small trial with 44 participants, the balloon catheter was found to be similar to placebo with regards to caesarean section rates (EB Table 2.9.6). However, compared with prostaglandins, the balloon catheter was associated with a lower risk of uterine hyperstimulation with fetal heart rate changes (seven trials, 823 participants, RR 0.51, 95% CI 0.30–0.86) and the risk of caesarean section with the two methods was similar (19 trials, 2050 participants, RR 1.01, 95% CI 0.88–1.17). With regard to other priority outcomes, the results for the prostaglandins versus the balloon catheter comparison were statistically non-significant (EB Table 2.9.7).

Compared with oxytocin, the balloon catheter was associated with a lower risk of caesarean section (two trials, 125 participants, RR 0.43, 95% CI 0.22–0.83) (EB Table 2.9.9). In the comparison of balloon catheter plus oxytocin with misoprostol, the combination approach was associated with fewer vaginal births not achieved within 24 hours (one trial, 158 participants, odds ratio 0.30, 95% CI 0.16–0.58); for other priority outcomes this comparison yielded very similar results (EB Table 2.9.10).

The evidence related to the use of laminaria tent is of low quality. In general, comparisons of laminaria tent with placebo, oxytocin and prostaglandins found that, in terms of the priority outcomes, there were no statistically significant differences between the interventions. However, compared with prostaglandins, laminaria tent was associated with a lower risk of uterine hyperstimulation with fetal heart rate changes (five trials, 538 participants, RR 0.13, 95% CI 0.04–0.48) (EB Table 2.9.2).

Recommendations

1. Balloon catheter is recommended for induction of labour.
(Moderate-quality evidence. Strong recommendation.)
2. The combination of balloon catheter plus oxytocin is recommended as an alternative method when prostaglandins (including misoprostol) are not available or are contraindicated.
(Low-quality evidence. Weak recommendation.)

Remark

1. The participants in the technical consultation noted that when using the balloon catheter for induction of labour it is important to monitor the woman and her fetus closely once labour is established. They also noted that balloon catheter and vaginal prostaglandins may have similar effectiveness. However, balloon catheter may be preferred for women with scarred uterus, since it is less likely to be associated with hyperstimulation of the uterus.



► **Misoprostol for termination of pregnancy in women with a fetal anomaly or after intrauterine fetal death**

Evidence summary

Labour induction in women carrying an anomalous or dead fetus requiring pregnancy presents a different scenario for clinical management than labour induction in women with a normal live fetus. First, increased uterine contractility leading to fetal distress is no longer a major concern. Second, often induction of labour in women with an anomalous or dead fetus is performed before term, when the uterus may be less responsive to uterotonics than it is at term.

Evidence concerning the use of misoprostol for induction of labour associated with fetal anomaly or intrauterine fetal death is summarized in a systematic review (25) that evaluated several comparisons between various misoprostol preparations on the one hand, and misoprostol and various prostaglandins on the other. Overall, in this review contains few trials with small numbers of participants, which created substantial uncertainty regarding the size of the effect.

Compared with oral misoprostol, vaginal misoprostol was associated with a lower risk of vaginal birth not achieved within 24 hours (six trials, 507 participants, RR 0.37, 95% CI 0.15–0.87) (EB Table 2.10.1). A combination of oral plus vaginal misoprostol did not produce better results than vaginal misoprostol alone (two trials, less than 100 participants), although moderate differences cannot be ruled out due to the small number of studies (EB Table 2.10.7). When the same combination was compared with oral misoprostol alone, there was a reduced risk of women not achieving vaginal birth within 24 hours in those receiving the combined regimen (one trial, 56 participants, RR 0.47; 95% CI 0.23–0.96) (EB Table 2.10.8). The addition of laminaria tent to vaginal misoprostol resulted in no additional benefits (EB Table 2.10.6). One trial reported that a lower cumulative dose of vaginal misoprostol (< 800 µg) was associated with an increased risk of vaginal birth not being achieved within 24 hours (RR 1.85, 95% CI 1.13–3.03), although there was a lower risk of surgery to evacuate the uterus (RR 0.57, 95% CI 0.33–0.98) (EB Table 2.10.12). In terms of dosing intervals of vaginal misoprostol, no differences were observed between 6-hourly versus 12-hourly dosing (three trials, 416 participants) (EB Table 2.10.2).

Sublingual misoprostol was found to be more effective than vaginal misoprostol for reducing the risk of vaginal birth not achieved within 24 hours (two trials, 202 participants, RR 0.24, 95% CI 0.08–0.74) (EB Table 2.10.9). A similar trend was seen in the comparison with oral misoprostol (two trials, 204 participants, RR 0.22, 95% CI 0.01–4.99) (EB Table 2.10.10). In the same comparison, the induction-to-delivery interval was reduced in women receiving sublingual misoprostol (mean difference –7.17 hours, 95% CI –13.73 to –0.6). No differences were observed in terms of dosing (100 µg versus 200 µg, sublingual; one trial, 81 participants) (EB Table 2.10.11).

There are limited data on comparisons of vaginal misoprostol with other prostaglandins. In a comparison of vaginal misoprostol versus prostaglandin F2 alpha, women receiving vaginal misoprostol showed a reduced risk of surgical evacuation of the uterus (five trials, 439 participants, RR 0.63, 95% CI 0.41–0.98) (EB Table 2.10.5).

Recommendation

1. In the third trimester of pregnancy, in women with a dead or anomalous fetus, oral or vaginal misoprostol are recommended for induction of labour (Low-quality evidence. Strong recommendation.)

Remarks

1. The doses and regimens recommended for use of misoprostol for induction of labour at term also apply to the above recommendation.
2. The participants in the technical consultation considered the risk of tachysystole and hypertonus and uterine rupture to be high during labour induction in women with a fetal anomaly or after fetal death. Hence, the participants noted the importance of close monitoring of the woman once labour is established.
3. The participants noted also that the trials included in the systematic review that provided evidence for the above recommendation included women in the second and third trimesters of pregnancy. The participants re-discussed the body of evidence related to misoprostol for induction of labour at term and found it to be applicable to that section also. Hence, the evidence related to induction of labour at term using misoprostol was downgraded for indirectness when applied to termination of pregnancy in women with a fetal anomaly or after intrauterine fetal death.



► Sweeping membranes for reducing formal induction of labour

Evidence summary

In this document, formal induction of labour is restricted to the use of oxytocin, misoprostol and other prostaglandins, and balloon catheter for bringing the uterus into labour. In this context, sweeping membranes is regarded as an intervention that aims to reduce the need of formal induction of labour.

A systematic review (26) including 21 studies involving 3443 women summarizes the evidence on sweeping membranes and induction of labour. Comparison of sweeping membranes with expectant management found that the latter was not associated with an increased risk of caesarean section, Apgar score less than seven at 5 minutes of life, serious maternal morbidity or death, admission to a neonatal intensive care unit, or perinatal death. However, sweeping membranes was associated with a 33% reduction in the risk of formal induction of labour (14 trials, 2446 women, RR 0.67, 95% CI 0.59–0.76). Moreover, there was also a 23% lower risk of not being in labour or not delivering within 48 hours (5 trials, 726 women, RR 0.77, 95% CI 0.7–0.84). Compared with expectant management, an increased risk of vaginal bleeding and discomfort during vaginal examination has been observed with sweeping of membranes, although no major differences have been observed with regard to the priority outcomes (EB Table 2.11.1).

Recommendation

1. Sweeping membranes is recommended for reducing formal induction of labour. (Moderate quality evidence. Strong recommendation.)

Remarks

1. The panel acknowledged that maternal discomfort and bleeding associated with the procedure should be balanced with the anticipated benefits. Since the interval between intervention and result (i.e. sweeping membranes and initiation of labour) can be longer than with formal methods of induction of labour, this intervention would be suitable for non-urgent indications for pregnancy termination.
2. Regarding breast stimulation, sexual intercourse and other similar methods of pre-induction of labour, the participants in the technical consultation agreed that there was insufficient evidence for recommending those methods.



Management of complications of induction of labour: hyperstimulation

► Tocolytics for women with uterine hyperstimulation during induction of labour

Evidence summary

In these guidelines, uterine hyperstimulation is defined as either occurrence of uterine contractions lasting more than 60 seconds, or occurrence of more than four contractions within 10 minutes, regardless the state of the fetus. The available systematic review (27) focusing on tocolytics for hyperstimulation contains evidence related to interventions aimed at stopping uterine contractions in pregnancies diagnosed with fetal distress. Overall, the evidence is limited and is based on a few small trials. The use of betamimetics is the main intervention studied, being compared with magnesium sulfate, nitroglycerin and atosiban. The use of tocolytics was compared in terms of immediate delivery versus no treatment.

Compared with nitroglycerin, terbutaline was associated with a lower risk of failure to reduce uterine activity (one trial, 109 participants, RR 0.09, 95% CI 0.01–0.71), but there was no other statistically significant effect related to the priority outcomes (EB Table 3.1.3). Compared with magnesium sulfate, terbutaline was associated with a trend towards lower risk of failure to reduce uterine activity (two outcomes, one trial, 46 participants) (EB Table 3.1.2). The comparison of betamimetics with atosiban favoured the latter: the risk of tachycardia was lower in women who received atosiban (one trial, 26 participants, RR 0.1, 95% CI 0.01–0.67). In terms of other selected outcomes, the two drugs were similar (EB Table 3.1.4).

Compared with no treatment, tocolytics reduced the risk of having no improvement in fetal heart rate changes (two trials, 43 participants, RR 0.28, 95% CI 0.14–0.55) with no other statistically significant findings in terms of Apgar score less than seven at five minutes of life, perinatal mortality and admission to a neonatal intensive care unit (EB Table 3.1.1). Tocolytics were also compared with emergent delivery in one trial involving 390 participants. In that trial, the overall caesarean section rate was higher among the participants that had received tocolytics (90.7% versus 80.7%, RR 1.12, 95% CI 1.04–1.22), but there were fewer admission to a neonatal intensive care unit with tocolytics (8.3% versus 17.8%, RR 0.47, 95% CI 0.27–0.81) (EB Table 3.1.5). No other statistically significant effects related to adverse maternal events and Apgar score were observed.

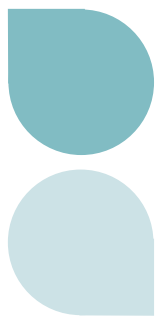
Recommendation

1. Betamimetics are recommended for women with uterine hyperstimulation during induction of labour.
(Low-quality evidence. Weak recommendation.)

Remark

1. There is insufficient evidence to recommend tocolytics other than betamimetics. The participants in the consultation acknowledged that caution should be exercised in using betamimetics because of their side-effects. Their contraindications (e.g. cardiac diseases) should be respected. The participants noted that various preparations of betamimetics are available in different countries.





Setting for induction of labour

► Outpatient induction of labour for improving birth outcomes

Evidence summary

Three small trials that had compared outpatient with inpatient induction of labour have been included in a systematic review (28) and comprise randomized-controlled-trial-based evidence related to the choice of setting for induction of labour. Each of these trials had used a different method for induction of labour: vaginal prostaglandin E2 (201 participants), controlled-release vaginal prostaglandin E2 (299) and Foley catheter (111 participants).

None of the trials found any statistically significant differences between inpatient and outpatient induction of labour with regard to the priority outcomes. However, with the use of vaginal prostaglandin E2 (without the controlled-release function), there was a non-statistically significant increased risk for all priority outcomes. The available evidence is still too sparse to issue a recommendation regarding outpatient induction of labour for improving birth outcomes (EB Tables 3.1.1 and 3.1.2).

Recommendation

1. Outpatient induction of labour is not recommended for improving birth outcomes. (Low-quality evidence. Weak recommendation.)

Remark

1. The participants in the consultation noted that research is ongoing on this issue. They placed a high value on safety issues and choose to recommend against the practice of outpatient induction of labour until new information becomes available.



5. RESEARCH IMPLICATIONS

The participants in the technical consultation identified important knowledge gaps that need to be addressed through primary research. In general, in these guidelines, the weak recommendations are based on evidence of “very low quality” or “low quality”, indicating that further research is needed. Conversely, strong recommendations are based on “moderate-quality” or “high-quality” evidence, suggesting that further research is not a priority. Overall, the participants in the technical consultation placed a high value on implementation research related to induction of labour and noted that, with the exception of research on the comparison between oral and vaginal misoprostol 25 µg, research on alternative doses and routes of misoprostol for induction of labour should not be regarded as a priority. In addition, the participants agreed that the questions below should be considered by the international community as high-priority topics for research:

1. What risks (for both the mother and the fetus) are associated with induction of labour and, in terms of those risks, how does induction of labour compare with elective caesarean section? What is the role of caesarean section in the management of women in whom induction of labour has failed?
2. In under-resourced settings with weak health systems and staff shortages, how can effective monitoring of women be ensured during induction of labour?
3. How can the Bishop score be used in selecting the method of induction of labour in clinical practice?
4. In settings where reliable gestational age determination is problematic, what should be the policy for labour induction at term and post term?
5. In uncomplicated gestational diabetes, at what gestational age should labour be induced, if at all?
6. Should induction of labour be offered to women with an uncomplicated twin pregnancy at or near term?
7. Regarding the combination of amniotomy and oxytocin for induction of labour, how long after, and based on what indicators, should amniotomy be performed?
8. What is the best regimen for oral misoprostol that would give superior results to those achieved with vaginal misoprostol 25 µg?
9. With regard to the technique of using the balloon catheter, what should be: (i) the ideal size of the balloon; (ii) the volume of the bulb; and (iii) the ideal pulling force during traction? In addition, how long should the traction be applied and what is relationship between balloon use and maternal infection? Additional research comparing the balloon catheter use with placebo is needed to consolidate (or not) the recommendation on induction of labour using balloon catheters.
10. What is role of calcium channel blockers and atosiban in the treatment of uterine hyperstimulation?



6. DISSEMINATION AND IMPLEMENTATION OF THE GUIDELINES

The WHO Department of Reproductive Health and Research has adopted a formal knowledge-to-action framework for the dissemination, adaptation and implementation of guidelines (29). According to this framework, the present guidelines may be adapted for use in different settings, but in general, any modifications to the recommendations should be limited to weak recommendations and justification for any changes should be made in an explicit and transparent manner.

Guideline dissemination

The recommendations in these guidelines will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies and nongovernmental organizations. They will also be published on the WHO web site and in *The WHO Reproductive Health Library* (30), where it will be accompanied by an independent critical appraisal based on the AGREE (Appraisal of Guidelines Research and Evaluation, <http://www.agreecollaboration.org/instrument/>) instrument. In addition, a policy brief aimed at a wide range of policy-makers, programme managers and clinicians will be developed and disseminated through WHO country offices.

Guideline implementation

The successful introduction into national programmes and health-care services of evidence-based policies related to induction of labour depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this document.

The recommendations contained in the present guidelines should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. However, beyond that, a set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations (including, for example, the availability of misoprostol/oxytocin/balloon catheter and monitoring capacity), and that the behaviour of the health-care practitioner changes towards the use evidence-based practices. In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged. The WHO Department of Reproductive Health and Research has published specific guidance on the introduction of WHO's reproductive health guidelines and tools into national programmes (31).

7. APPLICABILITY ISSUES

Anticipated impact on the organization of care and resources

Induction of labour can be achieved with the use of relatively inexpensive drugs. However, the participants in the consultation noted that the following issues should be considered before applying the recommendations made in the present guidelines:

- ▶ Women receiving pharmacological methods for induction of labour should never be left alone and resources to monitor the well-being of both the woman and her fetus should be made available.
- ▶ In settings where resources are limited, to monitor women closely during induction of labour, the procedure should be utilized only when it is absolutely necessary.
- ▶ Oral misoprostol is currently available in the form of 200 µg tablets. The recommended dose of oral misoprostol for induction of labour is 25 µg, 2-hourly. It is suggested that rather than breaking the 200 µg tablet into eight pieces, the tablet should be dissolved into 200 ml of water and 25 ml of that solution be administered as a single dose.
- ▶ When oxytocin is used for induction of labour, the infusion rate of oxytocin should be monitored.
- ▶ Health-care facilities performing induction of labour should have tocolytics available in case of need.
- ▶ Health-care facilities that perform induction of labour should be prepared to perform caesarean sections.

Monitoring and evaluating the guideline implementation

Ideally, implementation of the recommendations should be monitored at the health-service level. Interrupted time series clinical audits or criterion-based clinical audits could be used to obtain relevant data related to induction of labour practices. Clearly defined review criteria and indicators are needed and could be associated with locally agreed targets. In this context, three basic indicators are suggested:

1. Induction of labour as a proportion of all births, calculated as the number of women undergoing induction of labour divided by the total number of births over a defined period of time.
2. Proportion of women receiving the locally agreed first option method of induction of labour, calculated as the number of women receiving the method that has been locally agreed as the first option method (e.g. misoprostol, vaginal prostaglandins, balloon catheter) divided by the total number of women undergoing induction of labour.
3. Caesarean section rate among women undergoing induction of labour, calculated as the number of caesarean sections in women undergoing induction of labour divided by the total number of women undergoing induction of labour.

The first indicator provides an overall assessment of the use of induction of labour and the second directly assesses adherence to the local recommendation (as it is based on the existence of a locally predefined, standard first option method of induction of labour). Finally, the third indicator provides an evaluation of success of the intervention and could be compared to the overall caesarean section rates in the local context.

8. UPDATING OF THE GUIDELINES

These guidelines are part of WHO's GREAT (Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge) project (29), which incorporates a systematic and continuous process for identifying new scientific evidence for the existing guidelines issued under the aegis of the project. After five years, or following the identification of new evidence showing a need to change the recommendations, the process of updating the guidelines will be initiated. WHO welcomes suggestions regarding additional questions for inclusion in the guidelines when they come up for updating. Please e-mail your suggestions to rhl@who.int.

Future WHO guidelines on induction of labour may include:

- ▶ induction of labour in women with previous caesarean section
- ▶ induction of labour in women with pre-eclampsia
- ▶ monitoring of induction of labour
- ▶ labour augmentation.

REFERENCES

1. *Managing complication in pregnancy and childbirth: a guide for midwives and doctors*. Geneva, World Health Organization, 2000 (available at: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9241545879/en/index.html).
2. Caughey AB et al. Maternal and neonatal outcomes of elective induction of labor. Evidence Report/Technology Assessment No. 176. (Prepared by the Stanford University-UCSF Evidenced-based Practice Center.) Rockville, MD, Agency for Healthcare Research and Quality, 2009 (AHRQ Publication No. 09-E005).
3. Declercq ER et al. Listening to mothers II. Report of the Second National US Survey of Women's Childbearing Experiences. New York, NY, Childbirth Connection, 2006.
4. Martin JA et al. Births: final data for 2005. *National Vital Statistics Report*, 2007, 56:1–104.
5. WHO Global Survey on Maternal and Perinatal Health. Induction of labour data. Geneva, World health Organization, 2010 (available at: http://www.who.int/reproductivehealth/topics/best_practices/global_survey).
6. Mozurkewich E et al. Indications for induction of labour: a best-evidence review. *BJOG, An International Journal of Obstetrics & Gynaecology*, 2009, 116:626–636.
7. *Induction of labour*. London, National Institute for Health and Clinical Excellence (NICE), 2008 (available at: <http://www.nice.org.uk/guidance/CG70>).
8. Guerra GV et al. and World Health Organization 2005 Global Survey on Maternal and Perinatal Health Research Group. Factors and outcomes associated with the induction of labour in Latin America. *BJOG, An International Journal of Obstetrics & Gynaecology*, 2009, 116:1762–1772.
9. *WHO Handbook for Guideline Development*. Geneva, World Health Organization, 2008.
10. Gülmezoglu AM, Crowther CA, Middleton P. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database of Systematic Reviews*, 2006, Issue 4. Art. No.: CD004945; DOI: 10.1002/14651858.CD004945.pub2. (This review was updated for the present guidelines.)
11. Boulvain M, Stan CM, Irion O. Elective delivery in diabetic pregnant women. *Cochrane Database of Systematic Reviews*, 2001, Issue 2. Art. No.: CD001997; DOI: 10.1002/14651858.CD001997. (This review was updated for the present guidelines.)
12. Irion O, Boulvain M. Induction of labour for suspected fetal macrosomia. *Cochrane Database of Systematic Reviews*, 1998, Issue 2. Art. No.: CD000938; DOI: 10.1002/14651858.CD000938. (This review was updated for the present guidelines.)
13. Dare MR et al. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). *Cochrane Database of Systematic Reviews*, 2006, Issue 1. Art. No.: CD005302; DOI: 10.1002/14651858.CD005302.pub2. (This review was updated for the present guidelines.)
14. Dodd JM, Crowther CA. Elective delivery of women with a twin pregnancy from 37 weeks' gestation. *Cochrane Database of Systematic Reviews*, 2003, Issue 1. Art. No.: CD003582; DOI: 10.1002/14651858.CD003582.
15. Alfirevic Z, Kelly AJ, Dowswell T. Intravenous oxytocin alone for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews*, 2009, Issue 4. Art. No.: CD003246; DOI: 10.1002/14651858.CD003246.pub2.
16. Howarth G, Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour. *Cochrane Database of Systematic Reviews*, 2001, Issue 3. Art. No.: CD003250; DOI: 10.1002/14651858.CD003250. (This review was updated for the present guidelines.)
17. Hofmeyr GJ, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews*, 2003, Issue 1. Art. No.: CD000941; DOI: 10.1002/14651858.CD000941. (This review was updated for the present guidelines.)
18. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database of Systematic Reviews*, 2006, Issue 2. Art. No.: CD001338; DOI: 10.1002/14651858.CD001338.pub2.

19. Amorim MMR, Muzonzini G, Hofmeyr GJ. Buccal or sublingual misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews*, 2004, Issue 4. Art. No.: CD004221; DOI: 10.1002/14651858.CD004221.pub2. (This review was updated for the present guidelines.)
20. Wing DA, Lovett K, Paul RH. Disruption of prior uterine incision following misoprostol for labour induction in women with previous cesarean delivery. *American Journal of Obstetrics and Gynecology*, 1998, 91:828–830.
21. Kelly AJ et al. Vaginal prostaglandin (PGE2 and PGF2) for induction of labour at term. *Cochrane Database of Systematic Reviews*, 2009, Issue 4. Art. No.: CD003101; DOI: 10.1002/14651858.CD003101.pub2. (This review was updated for the present guidelines.)
22. French L. Oral prostaglandin E2 for induction of labour. *Cochrane Database of Systematic Reviews*, 2001, Issue 2. Art. No.: CD003098; DOI: 10.1002/14651858.CD003098. (This review was updated for the present guidelines.)
23. Boulvain M, Kelly AJ, Irion O. Intracervical prostaglandins for induction of labour. *Cochrane Database of Systematic Reviews*, 2008, Issue 1. Art. No.: CD006971. DOI: 10.1002/14651858.CD006971. (This review was updated for the present guidelines.)
24. Boulvain M et al. Mechanical methods for induction of labour. *Cochrane Database of Systematic Reviews*, 2001, Issue 4. Art. No.: CD001233; DOI: 10.1002/14651858.CD001233. (This review was updated for the present guidelines.)
25. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. *Cochrane Database of Systematic Reviews*, 2010, Issue 4. Art. No.: CD004901. DOI: 10.1002/14651858.CD004901.pub2.
26. Boulvain M, Stan CM, Irion O. Membrane sweeping for induction of labour. *Cochrane Database of Systematic Reviews*, 2005, Issue 1. Art. No.: CD000451. DOI: 10.1002/14651858.CD000451.pub2. (This review was updated for the present guidelines.)
27. Kulier R, Hofmeyr GJ. Tocolytics for suspected intrapartum fetal distress. *Cochrane Database of Systematic Reviews*, 1998, Issue 2. Art. No.: CD000035; DOI: 10.1002/14651858.CD000035. (This review was updated for the present guidelines.)
28. Kelly AJ, Alfirevic Z, Dowswell T. Outpatient versus inpatient induction of labour for improving birth outcomes. *Cochrane Database of Systematic Reviews*, 2009, Issue 2. Art. No.: CD007372. DOI: 10.1002/14651858.CD007372.pub2.
29. *Knowledge to action framework and the G.R.E.A.T project*. Geneva, World Health Organization (available at: http://www.who.int/reproductivehealth/topics/best_practices/greatproject_KTAframework/en/index.html).
30. *The WHO Reproductive Health Library*. Geneva, World Health Organization (www.who.int/rhl).
31. *Introducing WHO's sexual and reproductive health guidelines and tools into national programmes: principles and process of adaptation and implementation*. Geneva, World Health Organization, 2007 (available at: http://www.who.int/reproductivehealth/publications/general/RHR_07_09/en/index.html)

ANNEX 1. EXTERNAL EXPERTS AND WHO STAFF INVOLVED IN THE PREPARATION OF THE GUIDELINES

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ANNEX 2. SCOPING AND PRIORITIZATION OF THE TOPICS COVERED IN THE GUIDELINES

Table 1. Average scores given to scoping questions by external experts consulted by WHO (1 = not important; 9 = critical)

Questions	Average score
1. What are the clinical indications for induction of labour?	8.1
2. What is the appropriate place and timing of induction of labour?	6.7
3. What care should be offered to women during the induction process?	7.0
a. When should fetal monitoring be considered?	7.1
b. When should maternal monitoring be considered?	6.8
c. When should analgesia be offered?	6.6
d. When should emotional support be provided?	6.3
4. What is the information that should be provided to women and their families?	6.4
5. What methods should be used for cervical ripening?	7.4
a. Should intra-vaginal prostaglandins be used?	7.6
b. Should intra-cervical prostaglandins be used?	6.4
c. Should mechanical devices (Foley catheter/balloon) be used?	6.9
6. What methods should be used for induction of labour?	7.7
a. Should membrane sweeping be used?	6.7
b. Should pharmacological methods (prostaglandins and oxytocin) be used?	6.9
c. Should amniotomy be used?	6.6
7. How should induction of labour be managed in women with an unfavourable cervix?	7.8
8. How should complications of labour induction be managed?	7.6

Table 2. Average scores given to priority outcomes by external experts consulted by WHO (1= not important; 9 = critical)

Outcomes		Average score
1.	Vaginal delivery not achieved within 24 hours	7.5
2.	Uterine hyperstimulation with fetal heart rate changes	7.9
3.	Caesarean section	8.1
4.	Serious neonatal morbidity	8.2
5.	Perinatal death	8.4
6.	Severe maternal morbidity or death	8.6
7.	Cervix unfavourable/unchanged after 24 hours	6.7
8.	Oxytocin augmentation	5.9
9.	Epidural rate	5.4
10.	Uterine hyperstimulation without fetal heart rate changes	6.3
11.	Uterine rupture	8.0
12.	Instrumental delivery	6.4
13.	Meconium stained liquor	6.8
14.	Apgar score less than seven at 5 minutes	7.4
15.	Admission to a neonatal intensive care unit	7.3
16.	Neonatal encephalopathy	7.3
17.	Disability in childhood	7.0
18.	Maternal side-effects (all)	6.9
19.	Nausea	5.6
20.	Vomiting	5.4
21.	Diarrhoea	5.4
22.	Postpartum haemorrhage	7.6
23.	Women not satisfied the care related to induction of labour	6.7
24.	Caregiver not satisfied the care related to induction of labour	5.3

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