

# WHO recommendations: **Induction of labour at or beyond term**



World Health  
Organization

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# TABLE OF CONTENTS

|   |    |
|---|----|
| Acknowledgements  | 2  |
| Abbreviations   | 3  |
| Executive summary   | 4  |
| 1. Background   | 6  |
| Induction of labour   | 6  |
| Rationale and objectives  | 7  |
| Target audience   | 7  |
| Scope of the recommendations  | 7  |
| Persons affected by the recommendations   | 7  |
| 2. Methods  | 8  |
| Contributors to the guideline   | 8  |
| Identification of critical outcomes   | 9  |
| Evidence identification and retrieval   | 9  |
| Certainty assessment and grading of the evidence                                      | 10 |
| Formulation of recommendations  | 10 |
| Declaration of interests by external contributors                                     | 11 |
| Decision-making during the Guideline Development Group meeting                        | 11 |
| Document preparation  | 11 |
| Peer review   | 12 |
| 3. Recommendations and supporting evidence  | 12 |
| 4. Dissemination and implementation of the recommendations                            | 13 |
| Recommendation dissemination and evaluation   | 13 |
| Implementation considerations   | 13 |
| 5. Research implications  | 14 |
| 6. Applicability issues   | 14 |
| Monitoring and evaluating guideline implementation                                    | 14 |
| 7. Updating the recommendations   | 15 |
| References  | 16 |
| Annex 1. External experts and WHO staff involved in the preparation of the guidelines | 18 |
| Annex 2. Priority outcomes for decision-making  | 22 |
| Annex 3. Summary and management of declared interests from GDG members                | 23 |
| Annex 4. Evidence to decision framework   | 24 |
| Annex 5. GRADE Tables   | 35 |

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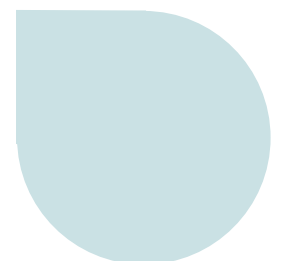
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## ABBREVIATIONS

|              |  |
|--------------|--|
| <b>BMGF</b>  | Bill & Melinda Gates Foundation  |
| <b>CI</b>    | Confidence interval  |
| <b>CS</b>    | Caesarean section  |
| <b>DOI</b>   | Declaration of Interest  |
| <b>FIGO</b>  | International Federation of Gynaecology and Obstetrics   |
| <b>FWC</b>   | Family, Women's and Children's Health (a WHO cluster)  |
| <b>GDG</b>   | Guideline Development Group  |
| <b>GRC</b>   | Guideline Review Committee   |
| <b>GRADE</b> | Grading of Recommendations, Assessment, Development, and Evaluation  |
| <b>GREAT</b> | Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (a WHO project) |
| <b>GSG</b>   | Executive Guideline Steering Group   |
| <b>HIC</b>   | High-income country  |
| <b>ICM</b>   | International Confederation of Midwives  |
| <b>IOL</b>   | Induction of labour  |
| <b>LMIC</b>  | Low and middle-income country  |
| <b>MCA</b>   | [WHO Department of] Maternal, Newborn, Child and Adolescent Health   |
| <b>MCSP</b>  | Maternal and Child Survival Programme  |
| <b>MPA</b>   | Maternal and Perinatal Health and Preventing Unsafe Abortion<br>(a team in WHO's Department of Reproductive Health and Research) |
| <b>MPH</b>   | Maternal and perinatal health  |
| <b>NNT</b>   | Number needed to treat   |
| <b>PICO</b>  | Population (P), intervention (I), comparison (C), outcome (O)  |
| <b>RHR</b>   | [WHO Department of] Reproductive Health and Research   |
| <b>RR</b>    | Relative risk  |
| <b>SDG</b>   | Sustainable Development Goals  |
| <b>UN</b>    | United Nations   |
| <b>UNFPA</b> | United Nations Population Fund   |
| <b>USAID</b> | United States Agency for International Development   |
| <b>WHO</b>   | World Health Organization  |



## EXECUTIVE SUMMARY

### Introduction

Induction of labour is defined as the process of artificially stimulating the uterus to start labour. It is usually performed by administering oxytocin or prostaglandins to the pregnant woman or by manually rupturing the amniotic membranes. Induction of labour is not risk-free, and many women find it uncomfortable. Over the past several decades, the incidence of inducing labour for shortening the duration of pregnancy has continued to rise. In high-income countries, the proportion of infants delivered at term following induction of labour can be as high as one in four births. In low- and middle-income countries the rates are generally lower, but in some settings, they can be as high as those observed in high-income countries.

Improving care for women around the time of childbirth is a necessary step towards the achievement of the health targets of the Sustainable Development Goals (SDGs). Efforts to prevent and reduce morbidity and mortality during pregnancy and childbirth could help address the profound inequities in maternal and perinatal health globally. To achieve these aims, healthcare providers, health managers, policy makers and other stakeholders need up-to-date and evidence-based recommendations to inform clinical policies and practices.

In 2017, the Executive Guideline Steering Group (GSG) on the World Health Organization's (WHO) maternal and perinatal health recommendations prioritized the updating of the existing WHO recommendations on the induction of labour at or beyond term in response to important new evidence on this intervention. These recommendations are a revalidation of the previous recommendations issued in 2011 in the *WHO recommendations on induction of labour*.

### Target audience

The primary audience of these recommendations includes health professionals who are responsible for developing national and local health protocols (particularly those related to induction of labour) and those directly providing care to pregnant women and their newborns, including: midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes, and relevant staff in ministries of health, in all settings.

### Guideline development methods

The updating of these recommendations was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendations were initially developed using this process, namely:

- (i) identification of the priority question and critical outcomes;
- (ii) retrieval of evidence;
- (iii) assessment and synthesis of evidence;
- (iv) formulation of the recommendation; and
- (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations.

The scientific evidence supporting the recommendations was synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This systematic review was used to prepare evidence profiles for the prioritized question. WHO convened an online meeting on 2 May 2018 where an international group of experts – the Guideline Development Group (GDG) – reviewed and approved the recommendations.

## The recommendations

The GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity. The GDG revalidated the WHO recommendations published in 2011 with

minor revisions to the remarks and implementation considerations.

To ensure that the recommendations are correctly understood and applied in practice, guideline users should refer to the remarks, as well as to the evidence summary if there is any doubt as to the basis for the recommendations and how best to implement them.

Table 1: WHO recommendations on the induction of labour at or beyond term

|  |
|--|
| <p><b>1. Induction of labour is recommended for women who are known with certainty to have reached 41 weeks (&gt;40 weeks + 7 days) of gestation. (conditional recommendation, low-certainty evidence)</b></p>   |
| <p><b>Remarks</b></p> <ul style="list-style-type: none"> <li>• This recommendation does not apply to settings where the gestational age cannot be reliably estimated.</li> <li>• The potential need for induction of labour for women with a post-term pregnancy should be discussed with women in advance, so that they have an opportunity to ask questions and understand the benefits and possible risks.</li> </ul> |
| <p><b>2. Induction of labour is not recommended for women with an uncomplicated pregnancy at gestational age less than 41 weeks. (conditional recommendation, low-certainty evidence)</b></p>  |
| <p><b>Remarks</b></p> <ul style="list-style-type: none"> <li>• There is insufficient evidence to recommend induction of labour for women with uncomplicated pregnancies before 41 weeks of pregnancy.</li> </ul>   |





# 1. BACKGROUND

An estimated 303 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2015, around 99% of which occurred in low-resource settings (1). Haemorrhage, hypertensive disorders and sepsis are responsible for more than half of all maternal deaths worldwide. Thus, improving the quality of maternal healthcare for women is a necessary step towards achievement of the health targets of the Sustainable Development Goals (SDGs). International human rights law includes fundamental commitments by states to enable women and adolescent girls to survive pregnancy and childbirth as part of their enjoyment of sexual and reproductive health and rights and living a life of dignity (2). The World Health Organization (WHO) envisions a world where “every pregnant woman and newborn receives quality care throughout the pregnancy, childbirth and the postnatal period” (3).

There is evidence that effective interventions exist at reasonable cost for the prevention or treatment of virtually all life-threatening maternal complications (4). Almost two-thirds of the global maternal and neonatal disease burden could be alleviated through optimal adaptation and uptake of existing research findings (5). To provide good quality care, healthcare providers at all levels of maternal healthcare services (particularly in low- and middle-income countries) need to have access to appropriate medications and training in relevant procedures. Healthcare providers, health managers, policymakers and other stakeholders also need up-to-date, evidence-based recommendations to inform clinical policies and practices, in order to optimize quality of care, and enable improved healthcare outcomes. Efforts to prevent and reduce morbidity and mortality in pregnancy and childbirth could reduce the profound inequities in maternal and perinatal health globally.

## Induction of labour

Induction of labour is the process of artificially stimulating the uterus to start labour (6). It is usually performed by administering oxytocin or prostaglandins to the pregnant woman, or by artificially rupturing the amniotic membranes. Induction of labour is not risk-free, and many women find it uncomfortable.

Over the past several decades, the incidence of labour induction for shortening the duration of pregnancy has continued to rise. In high-income countries (HICs), the proportion of infants delivered at term following induction of labour can be as high as one in four births (7-9). In low- and middle- income countries (LMICs), the rates are generally lower, but in some settings, they can be as high as those observed in HICs (10, 11).

In 2011, the World Health Organization (WHO) published 17 recommendations on induction of labour, including two recommendations on the induction of labour at or beyond term (12). These recommendations were developed according to the WHO guideline development standards, including synthesis of available research evidence, use of the GRADE methodology and formulation of recommendations by a guideline panel of international experts. The 2011 recommendations also included several general principles related to the practice of induction of labour, which are reiterated here:

- 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 on induction of labour, 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; and
- Wherever possible, induction of labour should be carried out in facilities where caesarean sections can be performed.

### Rationale and objectives

In 2017, WHO established a new process for prioritizing and updating maternal and perinatal health recommendations whereby an Executive Guideline Steering Group (GSG) oversaw a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating (13). Recommendations were prioritized on the basis of changes or important, new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized the updating of the existing WHO recommendations on induction of labour at or beyond term in response to new, potentially important evidence on this question.

The primary goal of these recommendations is to improve the quality of care and outcomes for pregnant women, particularly related to the use

of induction of labour. These recommendations provide a foundation for the sustainable implementation of the intervention globally.

### Target audience

The primary audience includes health professionals who are responsible for developing national and local health guidelines and protocols (particularly those related to induction of labour) and those directly providing care to women during labour and childbirth, including midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes and relevant staff in ministries of health, in all settings.

These recommendations will also be of interest to professional societies involved in the care of pregnant women, nongovernmental organizations concerned with promoting people-centred maternal care, and implementers of maternal and child health programmes.

### Scope of the recommendations

Framed using the population (P), intervention (I), comparison (C), outcome (O) (PICO) format, the question for these recommendations was:

- In pregnant women at or beyond term (P), does induction of labour (I), compared to expectant management (C), improve maternal and perinatal outcomes (O)?

### Persons affected by the recommendations

The population affected by these recommendations includes pregnant women in low, middle or high-income settings, particularly those who experience a post-term pregnancy.



## 2. METHODS

The recommendations were first developed using standardized operating procedures in accordance with the process described in the WHO handbook for guideline development (14). In summary, the process included:

- (i) identification of the priority question and critical outcomes;
- (ii) retrieval of the evidence;
- (iii) assessment and synthesis of evidence;
- (iv) formulation of the recommendations; and
- (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations.

WHO recommendations on induction of labour at or beyond term were identified by the Executive GSG as a high priority for updating in response to new, potentially important evidence on this question. Six main groups were involved in this process, with their specific roles described in the following sections.

### Contributors to the guideline

#### *Executive Guideline Steering Group (Executive GSG)*

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing questions in maternal and perinatal health for recommendation development or updating (15).

#### *WHO Steering Group*

The WHO Steering Group, comprising WHO staff members from the Departments of Reproductive Health and Research (RHR), Maternal, Newborn, Child and Adolescent Health (MCA) and Nutrition for Health and Development (NHD) managed the updating process. The

Group drafted the key recommendation questions in PICO format, identified the systematic review team and guideline methodologist, as well as the guideline development and external review groups. In addition, the WHO Steering Group supervised the syntheses and retrieval of evidence, organized the Guideline Development Group meeting, drafted and finalized the guideline document, and managed the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

#### *Guideline Development Group*

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool is a diverse group of experts who are skilled in the critical appraisal of research evidence, implementation of evidence-based recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health. Members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance, and there were no significant conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 16 external experts and relevant stakeholders were invited to constitute the Guideline Development Group (GDG) for updating these recommendations. Those selected were a diverse group with expertise in research, guideline development methods, and clinical policy and programmes relating to maternal and perinatal health.

The 16 GDG members invited for the update of these two recommendations were also selected in a way that ensured geographic representation and gender balance and there were no important conflicts of interest. The Group appraised the evidence that was used to inform the recommendations, advised on

the interpretation of this evidence, formulated the final recommendations based on the draft prepared by the Steering Group, and reviewed and approved the final document. The members of this Group are listed in Annex 1.

### *External Review Group*

This Group included eight technical experts with interest and expertise in the provision of evidence-based obstetric care. None of its members declared a conflict of interest. The Group reviewed the final document to identify any errors of fact and commented on clarity of the language, contextual issues and implications for implementation. The Group ensured that the decision-making processes had considered and incorporated contextual values and preferences of potential users of the recommendations, healthcare professionals and policy makers. They did not change the recommendations that were formulated by the GDG. The members of the External Review Group are listed in Annex 1.

### *Systematic review team and guideline methodologists*

A Cochrane systematic review on this question was updated, supported by the Cochrane Pregnancy and Childbirth Group (15). The WHO Steering Group reviewed and provided input into the protocol and worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Representatives of the Cochrane Pregnancy and Childbirth Group attended the GDG meeting to provide an overview of the available evidence and GRADE tables, and to respond to technical queries from the GDG.

### *External partners and observers*

Representatives of the United States Agency for International Development (USAID), the Maternal and Child Survival Programme (MCSP)/

Jhpiego, the Bill & Melinda Gates Foundation (BMGF), the International Confederation of Midwives (ICM), the International Federation of Gynaecology and Obstetrics (FIGO) and Population Council participated in the GDG meeting as observers. These organizations, with a long history of collaboration with the RHR Department in guideline dissemination and implementation, are implementers of the recommendations. The list of observers who participated in the GDG meeting is included in Annex 1.

### **Identification of critical outcomes**

The critical and important outcomes were aligned with the prioritized outcomes of the 2011 *WHO recommendations on induction of labour* (12). These outcomes were initially identified through a search of key sources of relevant, published, systematic reviews and a prioritization of outcomes by the 2011 GDG panel. All the outcomes were included in the scope of this document for evidence searching, retrieval, grading and formulation of the recommendations. The list of outcomes is provided in Annex 2.

### **Evidence identification and retrieval**

A Cochrane systematic review was updated and was the primary source of evidence for these recommendations (15).

Randomized controlled trials (RCTs) relevant to the key question were screened by the review authors and data on relevant outcomes and comparisons were entered into Review Manager (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendations were excluded). Then the RevMan file was exported to GRADE profiler software (GRADEpro) and GRADE criteria were used to critically appraise the retrieved scientific evidence.

Finally, evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

### Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach (16). The certainty of evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

**Study design limitations:** The risk of bias was first examined at the level of individual study and then across studies contributing to the outcome. For randomized trials, certainty was first rated as 'high' and then downgraded by one ('moderate') or two ('low') levels, depending on the minimum criteria met by the majority of the studies contributing to the outcome.

**Inconsistency of the results:** The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

**Indirectness:** The certainty of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence, that is, whether there were important differences between the research reported and the context for which the recommendations were being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

**Imprecision:** This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and num-

ber of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

**Publication bias:** The certainty rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. Downgrading evidence by one level was considered where there was strong suspicion of publication bias.

**Certainty of evidence** assessments are defined according to the GRADE approach:

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

### Formulation of recommendations

The WHO Steering Group used the evidence profiles to summarise evidence on effects on the pre-specified outcomes. The evidence summary and corresponding GRADE tables, other related documents for assessment of values and preferences, resource requirements and cost-effectiveness, acceptability, feasibility and equity were provided in advance to meeting participants, who were invited to submit their comments electronically in advance of the meeting.

The GDG members and other participants were then invited to attend an online GDG meeting (see Annex 1 for the list of participants) organized by the Steering Group on



2 May 2018. During the meeting, the GDG members reviewed and discussed the balance between the desirable and undesirable effects of the intervention and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity, before finalizing the recommendations and remarks.

### Declaration of interests by external contributors

According to WHO regulations, all experts must declare their relevant interests prior to participation in WHO guideline development processes and meetings. All GDG members were therefore required to complete a standard WHO Declaration of Interest (DOI) form before engaging in the guideline development process and before participating in the guideline-related meeting. The WHO Steering Group reviewed each declaration before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the Steering Group determined whether such conflicts were serious enough to affect the expert's objective judgement on the guideline and recommendation development process. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflict of interests in the *WHO Handbook for Guideline Development* to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting and no further actions were taken.

Annex 3 shows a summary of the DOI statements, and how the conflicts of interest declared were managed by the Steering Group.

### Decision-making during the Guideline Development Group meeting

During the meeting, the GDG reviewed and discussed the evidence summary and sought clarification. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the GDG applied additional criteria based on the GRADE evidence-to-decision framework to determine the direction and strength of the recommendations. These criteria included stakeholders' values, resource implications, acceptability, feasibility and equity. Considerations were based on the experience and opinions of members of the GDG and supported by evidence from a literature search where available. Evidence-to-decision tables were used to describe and synthesize these considerations.

Decisions were made based on consensus defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendations.

### Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, evidence summary and other documents relevant to the deliberation of the GDG. The draft documents were made available to the participants of the meeting two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted a recommendation document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members and the External Review Group for final review and approval.

### Peer review

Following review and approval by GDG members and the External Review Group, the final document was sent to eight external independent experts who were not involved in the guideline panel for peer review. The WHO Steering Group evaluated the inputs of the

peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Steering Group to the document consisted only of correcting factual errors and improving language to address any lack of clarity.



## 3. RECOMMENDATIONS AND SUPPORTING EVIDENCE

The following section outlines the recommendations and the corresponding narrative summary of evidence for the prioritized question. The evidence-to- decision table, summarizing the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the

strength and direction of the recommendations, is included in the evidence-to- decision framework (Annex 4).

The following recommendations were adopted by the GDG. Evidence on the effectiveness of the intervention was derived from one systematic review and was summarized in GRADE tables (Annex 5). The certainty of the supporting evidence was rated as 'low' for most critical outcomes. To ensure that the recommendations are correctly understood and appropriately implemented in practice, additional 'remarks' reflecting the summary of the discussion by GDG are included under each recommendation.

### WHO recommendations on the induction of labour at or beyond term

**1. Induction of labour is recommended for women who are known with certainty to have reached 41 weeks (>40 weeks + 7 days) of gestation. (conditional recommendation, low-certainty evidence)**

#### Remarks

- This recommendation does not apply to settings where the gestational age cannot be reliably estimated.
- The potential need for induction of labour for women with a post-term pregnancy should be discussed with women in advance, so that they have an opportunity to ask questions and understand the benefits and possible risks.

**2. Induction of labour is not recommended for women with an uncomplicated pregnancy at gestational age less than 41 weeks. (conditional recommendation, low-certainty evidence)**

#### Remarks

- There is insufficient evidence to recommend induction of labour for women with uncomplicated pregnancies before 41 weeks of pregnancy.

## 4. DISSEMINATION AND IMPLEMENTATION OF THE RECOMMENDATIONS

The dissemination and implementation of these recommendations is to be considered by all stakeholders and organizations involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase access and strengthen the capacity of health centres to provide high quality services to all women giving birth. It is therefore crucial that these recommendations are translated into antenatal and intrapartum care packages and programmes at country and health facility levels (where appropriate).

### Recommendation dissemination and evaluation

A shorter document containing the recommendations, remarks, implementation considerations and research priorities will be formulated for public dissemination. This document will have annexes (also made publicly available) containing all the information in this document, including methods, evidence-to-decision frameworks and GRADE tables.

The recommendations will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. These recommendations will be also available on the WHO website and in the WHO Reproductive Health Library. Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by WHO MPH staff.

The recommendation document will be translated into the six UN languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full recommendations into any of these languages.

### Implementation considerations

- The successful introduction of recommendations into national programmes and health-care services 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 these recommendations;
- The recommendations should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner;
- 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 induction agents and monitoring capacity), and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice;
- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged;
- Providers and implementers should consider discussing with women the potential need for induction of labour at  $\geq 41$  weeks during antenatal care contacts. This would provide women with the opportunity to ask questions, understand the benefits and possible risks of available options and allow them to make informed decisions should post-term pregnancy occur;
- In 2016, WHO recommended the routine use of one ultrasound scan before 24 weeks of gestation (30). Implementation of these recommendations can assist in improving the accuracy of gestational age estimation, to ensure that the recommendations on induction of labour at  $\geq 41$  weeks are used appropriately;
- Other WHO resources (such as the clinical handbook *Managing Complications of Pregnancy and Childbirth*) provide further guidance on applying these recommendations in clinical settings (17).





## 5. RESEARCH IMPLICATIONS

The GDG identified important knowledge gaps that need to be addressed through primary research, which may have an impact on these recommendations. The following questions were identified as those that demand urgent priority:

- 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?
- In settings where reliable gestational age determination is problematic, what should be the policy for labour induction at term and post-term?
- Is further research required on the experience of women undergoing labour induction, and how much women value the main outcomes associated with labour induction?



## 6. APPLICABILITY ISSUES

### Anticipated impact on the organization of care and resources

Implementing these evidence-based recommendations will require resources to ensure it is done safely, including staff time for monitoring of women undergoing induction of labour. The GDG noted that updating training curricula and providing training would increase impact and facilitate implementation. Standardization of care by including recommendations into existing maternity care packages and protocols can encourage healthcare provider behaviour change.

### Monitoring and evaluating guideline implementation

Implementation should be monitored at the health-service level as part of broader efforts to monitor and improve the quality of maternal and newborn care. For example, interrupted time series, clinical audits or criterion-based clinical audits can be used to obtain data related to the induction of labour. Clearly defined review criteria and indicators are needed and these could be associated with locally agreed targets and aligned with the standards and indicators described in the WHO document *Standards for improving quality of maternal and newborn care in health facilities (31)*.

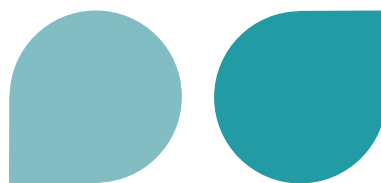


## 7. UPDATING THE RECOMMENDATIONS

The Executive GSG convenes annually to review WHO's current portfolio of maternal and perinatal health recommendations and to advise WHO on prioritization of new and existing questions for recommendation development and updating. Accordingly, these recommendations will be reviewed and prioritized by the Executive GSG. In the event that new evidence that could potentially impact the current evidence base is identified, the recommendations may be updated. If no new reports or information is identified, the recommendations may be revalidated.

Following publication and dissemination of the updated recommendations, any concern about the validity of the recommendations will be promptly communicated to the guideline implementers, in addition to any plans to update the recommendations.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendations. Please email your suggestions to [mpa-info@who.int](mailto:mpa-info@who.int).



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## ANNEX 2. PRIORITY OUTCOMES FOR DECISION-MAKING

### ► **Woman:**

- Vaginal delivery not achieved within 24 hours
- Uterine hyperstimulation with fetal heart rate changes
- Caesarean section
- Severe maternal morbidity or death
- Cervix unfavourable/unchanged after 24 hours
- Oxytocin augmentation
- Epidural rate
- Uterine hyperstimulation without fetal heart rate changes
- Uterine rupture
- Instrumental delivery
- Meconium stained amniotic fluid
- Maternal side-effects (all)
- Nausea
- Vomiting
- Diarrhoea
- Postpartum haemorrhage
- Women not satisfied the care related to induction of labour
- Caregiver not satisfied the care related to induction of labour

### ► **Infant/Child:**

- Serious neonatal morbidity
- Perinatal death
- Apgar score less than seven at 5 minutes
- Admission to a neonatal intensive care unit
- Neonatal encephalopathy
- Disability in childhood



## ANNEX 3. SUMMARY AND MANAGEMENT OF DECLARED INTERESTS FROM GDG MEMBERS

| Name              | Expertise contributed to guideline development | Declared interest              | Management of conflict of interest   |  |
|-------------------|--|--------------------------------|--|--|
| <b>Edgardo</b>    | <b>ABALOS</b>                                  | Content expert and end-user    | None declared  | Not applicable   |
| <b>Ebun</b>       | <b>ADEJUYIGBE</b>                              | Content expert and end-user    | None declared  | Not applicable   |
| <b>Shabina</b>    | <b>ARIFF</b>                                   | Content expert and end-user    | None declared  | Not applicable   |
| <b>Jemima</b>     | <b>DENNIS-ANTWI</b>                            | Content expert and end-user    | None declared  | Not applicable   |
| <b>Luz Maria</b>  | <b>DE-REGIL</b>                                | Content expert and end-user    | Global Affairs Canada awarded a grant to Dr De-Regil's institution to implement nutrition interventions in low and middle-income countries. Some of the funded work included support for implementation research on calcium supplementation in pregnancy in Kenya and Ethiopia. The work was sub-granted to Cornell University, and Dr De-Regil was not part of the research team.<br>As a former WHO staff member, she supported the development of a guideline on calcium supplementation in pregnancy (led by NHD). | The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation |
| <b>Christine</b>  | <b>EAST</b>                                    | Content expert and end-user    | None declared  | Not applicable   |
| <b>Lynn</b>       | <b>FREEDMAN</b>                                | Content expert and end-user    | None declared  | Not applicable   |
| <b>Pisake</b>     | <b>LUMBIGANON</b>                              | Content expert and end-user    | None declared  | Not applicable   |
| <b>Anita</b>      | <b>MAEPIOH</b>                                 | Content expert and end-user    | None declared  | Not applicable   |
| <b>James</b>      | <b>NEILSON</b>                                 | Content expert and end-user    | None declared  | Not applicable   |
| <b>Hiroshi</b>    | <b>OBARA</b>                                   | Content expert and implementer | None declared  | Not applicable   |
| <b>Rachel</b>     | <b>PLACHCINSKI</b>                             | Consumer representative        | None declared  | Not applicable   |
| <b>Zahida</b>     | <b>QURESHI</b>                                 | Content expert and end-user    | None declared  | Not applicable   |
| <b>Kathleen</b>   | <b>RASMUSSEN</b>                               | Content expert and end-user    | None declared  | Not applicable   |
| <b>Niveen Abu</b> | <b>RMEILEH</b>                                 | Content expert and implementer | None declared  | Not applicable   |
| <b>Eleni</b>      | <b>TSIGAS</b>                                  | Consumer representative        | Ms Tsigas represents patient experiences around preeclampsia and other hypertensive disorders of pregnancy to organizations, committees, and other multidisciplinary bodies. She is also a voting member on the Council for Patient Safety in Women's Healthcare (USA).  | The conflict was not considered serious enough to affect GDG membership or participation in the Technical Consultation |

## ANNEX 4. EVIDENCE TO DECISION FRAMEWORK

### A) QUESTION

*In pregnant women at or beyond term (P), does induction of labour (I), compared to expectant management (C), improve maternal and perinatal outcomes (O)?*

**Problem:** Perinatal risks associated with post-term pregnancy

**Perspective:** Clinical practice recommendation – population perspective

**Population:** Pregnant women at or beyond term

**Intervention:** labour induction

**Comparison:** expectant management

**Critical Outcomes:** <sup>1</sup>

#### ► Maternal

- Vaginal delivery not achieved within 24 hours
- Caesarean section
- Uterine hyperstimulation with fetal heart rate changes
- Postpartum haemorrhage
- Uterine rupture
- Severe maternal morbidity or death

#### ► Fetal/Neonatal

- Apgar score less than seven at 5 minutes
- Admission to a neonatal intensive care unit
- Neonatal encephalopathy
- Serious neonatal morbidity
- Disability in childhood
- Perinatal death

**Important outcomes:** <sup>1</sup>

#### ► Maternal

- Cervix unfavourable or unchanged after 24 hours
- Oxytocin augmentation
- Epidural rate
- Uterine hyperstimulation without fetal heart rate changes
- Instrumental vaginal birth
- Meconium stained amniotic fluid
- Maternal side-effects (all)
- Nausea
- Vomiting
- Diarrhoea
- Women not satisfied with the care related to induction of labour
- Caregiver not satisfied with the care related to induction of labour

<sup>1</sup> These outcomes reflect the outcomes used in the WHO recommendations for induction of labour (2011). An outcome ranked as 7 or more was considered "critical", and an outcome ranked as 4 to 6 was considered "important"

## B) ASSESSMENT

### 1. EFFECTS OF INTERVENTIONS

#### *Research evidence*

#### Summary of the evidence

Evidence relating to induction of labour at term and beyond term was extracted from one updated Cochrane systematic review of 30 randomized controlled trials involving 12 479 women (15). One trial involving 248 women did not contribute data to the meta-analysis. Most of the trials were judged by the Cochrane review authors to have a moderate risk of bias, largely due to unclear methods of random sequence generation and allocation concealment.

The review evaluated the effect of inducing labour at 37–42 weeks, <41 weeks, and ≥41 weeks. The intervention was compared with expectant management with fetal monitoring at varying intervals. Trials were conducted in either hospitals or large medical centres in Austria (1), Canada (1), China (3), Finland (1), France (1), India (2), the Netherlands (1), Norway (3), Spain (1), Sweden (2), Thailand (2), Tunisia (1), Turkey (1), United Kingdom (4), and United States (6).

The trials used a combination of methods of induction: most trials used oxytocin infusion in some or all of the women in the intervention group, with or without artificial rupture of membranes, and with or without additional methods. Some trials used prostaglandin E2 in gel or pessary form and one used laminaria tents. Some trials used only prostaglandin E2, without oxytocin infusion. One trial had three treatment arms (vaginal misoprostol, oxytocin, and Foley catheter). Two trials did not report the method used. For the majority of trials, expectant management protocols included various combinations of fetal heart rate monitoring, ultrasound for amniotic fluid measurements and, in earlier studies, biochemical tests.

#### ► Labour induction compared to expectant management for improving birth outcomes for women at or beyond term (all trials)

#### Effects of interventions

##### *Maternal outcomes*

**Caesarean section:** Moderate-certainty evidence suggests that induction between 37-42 weeks of gestation probably slightly reduces the caesarean section rate compared with expectant management (27 trials, 11 738 women; 980/6004 vs 1056/5734; RR 0.92, 95% CI 0.85 to 0.99).

**Instrumental vaginal birth:** Moderate-certainty evidence suggests that induction probably makes little or no difference to the number of women with an operative vaginal birth (forceps or ventouse) (18 trials, 9281 women; 984/4775 vs 869/4506; RR 1.07, 95% CI 0.99 to 1.16).

**Postpartum haemorrhage:** Low-certainty evidence suggests that induction may make little or no difference to the number of women with postpartum haemorrhage (five trials, 3315 women; 218/1649 vs 203/1666; RR 1.09, 95% CI 0.92 to 1.30).

**Maternal satisfaction with the care related to induction of labour:** Two outcomes were indicators of maternal satisfaction. In one trial, moderate-certainty evidence suggests that women who

had an induction are probably more likely to want to be randomized to the same trial arm in future trials (one trial, 496 women; 184/250 vs 94/246; RR 1.93, 95% CI 1.62 to 2.30). In another trial, it is uncertain whether women in the induction or expectant management group preferred their allocation because the certainty of evidence is very low.

### *Infant outcomes*

**Serious neonatal morbidity:** Low-certainty evidence suggests induction may make little or no difference to **neonatal trauma** (three trials, 4255 neonates; 26/2128 vs 22/2127; RR 1.18, 95% CI 0.68 to 2.05) or **neonatal convulsions** (three trials, 4365 neonates; 3/2178 vs 6/2187; RR 0.54, 95% CI 0.15 to 1.97). Moderate-certainty evidence suggests induction probably slightly reduces the number of neonates with **meconium aspiration syndrome** (11 trials, 7781 neonates; 133/3887 vs 173/3894; RR 0.77, 95% CI 0.62 to 0.96).

**Perinatal death:** Moderate-certainty evidence suggests that induction between 37-42 weeks of gestation probably slightly reduces the number of **perinatal deaths** (20 trials, 9960 neonates; 2/4988 vs 16/4972; RR 0.33, 95% CI 0.14 to 0.78) and **stillbirths** (20 trials, 9960 neonates; 1/4988 vs 10/4972; RR 0.33, 95% CI 0.11 to 0.96). Low-certainty evidence suggests little or no difference in the number of **neonatal deaths** (19 trials, 9776 neonates; 1/4896 vs 6/4880; RR 0.37, 95% CI 0.10 to 1.38).

**Apgar score less than 7 at 5 minutes:** Moderate-certainty evidence suggests that induction probably slightly reduces the number of neonates with Apgar scores of less than 7 at 5 minutes (16 trials, 9047 neonates; 52/4523 vs 76/4524; RR 0.70, 95% CI 0.50 to 0.98).

**Admission to neonatal intensive care unit:** Moderate-certainty evidence suggests that induction probably makes little or no difference to the number of neonates admitted to intensive care (13 trials, 8531 neonates; 320/4271 vs 363/4260; RR 0.88, 95% CI 0.77 to 1.01).

## ► Labour induction compared to expectant management for improving birth outcomes for women at or beyond term (gestational age at induction < 41 weeks and ≥ 41 weeks)

### Effects of interventions

#### *Maternal outcomes*

**Caesarean section < 41 weeks:** Moderate-certainty evidence suggests that induction before 41 weeks probably makes little or no difference to the caesarean section rate (nine trials, 2806 women; 191/1532 vs 175/1274; RR 1.04, 95% CI 0.87 to 1.24).

**Caesarean section ≥ 41 weeks:** Moderate-certainty evidence suggests that induction after and including 41 weeks probably slightly reduces the caesarean section rates (17 trials, 8803 women; 774/4407 vs 857/4396; RR 0.90, 95% CI 0.83 to 0.98).

**Instrumental vaginal birth < 41 weeks:** Moderate-certainty evidence suggests that induction before 41 weeks probably increases operative vaginal birth (forceps or ventouse) (seven trials, 2401 women; 304/1327 vs 198/1074; RR 1.27, 95% CI 1.08 to 1.48).

**Instrumental vaginal birth ≥ 41 weeks:** Moderate-certainty evidence suggests that induction after and including 41 weeks probably makes little or no difference to operative vaginal birth (forceps or ventouse) (10 trials, 6751 women; 668/3383 vs 665/3368; RR 1.00, 95% CI 0.91 to 1.10).

*Infant outcomes*

**Perinatal death < 41 weeks:** It is uncertain whether induction before 41 weeks reduces perinatal death because the certainty of evidence is very low.

**Perinatal death ≥ 41 weeks:** Moderate-certainty evidence suggests that induction after and including 41 weeks probably slightly reduces perinatal mortality (15 trials, 8408 neonates; 2/4217 vs 13/4191; RR 0.33, 95% CI 0.13 to 0.87).

**Stillbirth < 41 weeks:** It is uncertain whether induction before 41 weeks reduces stillbirth because the certainty of evidence is very low.

**Stillbirth ≥ 41 weeks:** Low-certainty evidence suggests that induction after and including 41 weeks might make little or no difference to stillbirth (15 trials, 8408 neonates; 1/4217 vs 7/4191; RR 0.34, 95% CI 0.09 to 1.24).

**Admission to neonatal intensive care unit < 41 weeks:** It is uncertain whether induction before 41 weeks reduces admission to neonatal intensive care units because the certainty of evidence is very low.

**Admission to neonatal intensive care unit ≥ 41 weeks:** Moderate-certainty evidence suggests that induction after and including 41 weeks probably makes little or no difference to admissions to neonatal intensive care (nine trials, 7397 neonates; 307/3704 vs 350/3693; RR 0.88, 95% CI 0.76

► **Desirable effects**

How substantial are the desirable anticipated effects of induction of labour at <41 weeks?

*Judgement*

|                          |                          |                                     |                          |                          |                          |
|--------------------------|--------------------------|-------------------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Don't know               | Varies                   | Trivial                             | Small                    | Moderate                 | Large                    |

How substantial are the desirable anticipated effects of induction of labour at ≥41 weeks?

*Judgement*

|                          |                          |                          |                          |                          |                                     |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| Don't know               | Varies                   | Trivial                  | Small                    | Moderate                 | Large                               |

► **Undesirable effects**

How substantial are the undesirable anticipated effects of induction of labour at <41 weeks?

*Judgement*

|                          |                          |                          |                          |                                     |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> |
| Don't know               | Varies                   | Large                    | Moderate                 | Small                               | Trivial                  |

How substantial are the undesirable anticipated effects of induction of labour at ≥41 weeks?

*Judgement*

|                          |                          |                          |                          |                          |                                     |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| Don't know               | Varies                   | Large                    | Moderate                 | Small                    | Trivial                             |

### ► Certainty of the evidence

What is the overall certainty of the evidence of the effects of induction of labour at <41 weeks?

|                          |                                     |                          |                          |                          |
|--------------------------|-------------------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| No included studies      | Very low                            | Low                      | Moderate                 | High                     |

What is the overall certainty of the evidence of the effects of induction of labour at ≥41 weeks?

|                          |                          |                                     |                          |                          |
|--------------------------|--------------------------|-------------------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| No included studies      | Very low                 | Low                                 | Moderate                 | High                     |

#### Additional considerations

None.

### ► Values

Is there important uncertainty about, or variability in, how much women value the main outcomes associated with induction of labour?

#### Research evidence

We did not identify any evidence that addressed this question directly.

#### Additional considerations

Evidence from a qualitative systematic review of what women want from antenatal care showed that healthy pregnant women from high-, medium- and low-resource settings valued maintenance of optimal health for mother and baby (17). Evidence from a separate qualitative systematic review found that while women place a high value on a physiological labour and birth experience, they also acknowledge that birth can be unpredictable. Even where an intervention (such as induction of labour) is needed or wanted, women usually wish to retain a sense of personal achievement and control by being involved in decision-making (18). The GDG considered it likely that women in different settings would consider the outcomes of stillbirth and perinatal mortality very important.

A 2011 systematic review assessed women's preferences for caesarean section and included 38 studies (19 403 women) from a range of countries (19). The overall pooled preference for caesarean section was 15.6% (95% CI 12.5 – 18.9) – only a minority of women in a wide variety of countries expressed a preference for caesarean section.

#### Judgement

|                                      |   |  |   |
|--------------------------------------|---|--|---|
| <input type="checkbox"/>             | <input type="checkbox"/>                      | <input checked="" type="checkbox"/>              | <input type="checkbox"/>                |
| Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | No important uncertainty or variability |

### ► Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison (for induction of labour at <41 weeks)?

#### Judgement

|                          |                          |                                     |                                 |  |                                   |                          |
|--------------------------|--------------------------|-------------------------------------|---------------------------------|--|-----------------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/>        | <input type="checkbox"/>                           | <input type="checkbox"/>          | <input type="checkbox"/> |
| Don't know               | Varies                   | Favours the comparison              | Probably favours the comparison | Does not favour the intervention or the comparison | Probably favours the intervention | Favours the intervention |

Does the balance between desirable and undesirable effects favour the intervention or the comparison (for induction of labour at ≥41 weeks)?

#### Judgement

|                          |                          |                          |                                 |  |                                   |                                     |
|--------------------------|--------------------------|--------------------------|---------------------------------|--|-----------------------------------|-------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>        | <input type="checkbox"/>                           | <input type="checkbox"/>          | <input checked="" type="checkbox"/> |
| Don't know               | Varies                   | Favours the comparison   | Probably favours the comparison | Does not favour the intervention or the comparison | Probably favours the intervention | Favours the intervention            |



## 2. RESOURCES

How large are the resource requirements (costs) of induction of labour at ≥41 weeks?

#### Research evidence

A 2011 cost-effectiveness analysis from the USA compared induction of labour at 41 weeks vs expectant management in nulliparous women (20). The authors reported that induction of labour was cost-effective, with an incremental cost of \$10 945 per quality-adjusted life year gained.

A trial in Canada (included in the Cochrane review) randomly assigned 3418 women with uncomplicated pregnancies of 41 or more weeks gestation to induction of labour or serial antenatal monitoring (21). While the trial did not show clear differences in perinatal mortality and neonatal morbidity, the mean cost per patient with a post-term pregnancy managed through monitoring was \$3132 (95% CI \$3090 to \$3,174) compared to \$2939 (95% CI \$2898 to \$2981), a difference of \$193 per patient (22). Additional costs in the monitoring arm were due mainly to the costs of additional monitoring and higher caesarean section rates.



*Main resource requirements*

| Resource       | Description   |
|----------------|---|
| Staff training | <ul style="list-style-type: none"> <li>If ultrasound is available, trained providers who can assess gestational age accurately using obstetric ultrasound</li> <li>Training in performance and monitoring of labour induction</li> </ul>    |
| Supplies       | <ul style="list-style-type: none"> <li>Induction agents (e.g. misoprostol or prostaglandin E2) (12)</li> <li>Ultrasound gel</li> </ul>  |
| Equipment      | <ul style="list-style-type: none"> <li>Tools to accurately estimate gestational age (e.g. antenatal ultrasound, gestational age wheel)</li> <li>Clinical protocol for safe labour induction</li> <li>Equipment for vaginal birth</li> </ul> |
| Infrastructure | <ul style="list-style-type: none"> <li>Capacity to perform caesarean section (if required)</li> <li>Availability of appropriate space, beds or both for women undergoing induction</li> </ul>   |
| Staff time     | <ul style="list-style-type: none"> <li>20 minutes for initial assessment</li> <li>After administration of misoprostol, 40 minutes additional monitoring</li> </ul>  |

*Additional considerations*

A 2016 systematic review assessed the effectiveness, safety and cost-effectiveness of different labour induction methods (23). The cost-effectiveness analysis compared only 20 induction interventions. Findings suggest that most interventions have similar utility but differ in cost. The authors report that titrated misoprostol solution and buccal or sublingual misoprostol have the highest likelihood of being cost-effective, though this is uncertain.

► **Resources required***Judgement*

|                          |                          |                          |                                     |                             |                          |                          |
|--------------------------|--------------------------|--------------------------|-------------------------------------|-----------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/>    | <input type="checkbox"/> | <input type="checkbox"/> |
| Don't know               | Varies                   | Large costs              | Moderate costs                      | Negligible costs or savings | Moderate savings         | Large savings            |

► **Certainty of evidence on required resources**

What is the certainty of evidence on costs?

*Judgement*

|                          |                          |                                     |                          |                          |
|--------------------------|--------------------------|-------------------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| No included studies      | Very low                 | Low                                 | Moderate                 | High                     |

► **Cost-effectiveness***Judgement*

|                          |                          |                          |                                 |   |                                     |                          |
|--------------------------|--------------------------|--------------------------|---------------------------------|---|-------------------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>        | <input type="checkbox"/>                                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |
| Don't know               | Varies                   | Favours the comparison   | Probably favours the comparison | Does not favour either the intervention or the comparison | Probably favours the intervention   | Favours the intervention |

### 3. EQUITY

What would be the impact of induction of labour at >41 weeks on health equity?

#### Research evidence

No direct evidence was identified to address this question.

#### Additional considerations

In LMICs, women who are poor, least educated, and residing in rural areas have lower health intervention coverage and worse health outcomes than more advantaged women (24). Safe, effective, equitable implementation of this intervention to prevent perinatal mortality and morbidity could therefore reduce health inequities.

#### Judgement

|                          |                          |                          |                          |                          |                                     |                          |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> |
| Don't know               | Varies                   | Reduced                  | Probably reduced         | Probably no impact       | Probably increased                  | Increased                |



### 4. ACCEPTABILITY

Is the intervention acceptable to key stakeholders?

#### Research evidence

In one trial of 496 women (25) that was included in the Cochrane review, more women in the induction group said that they would choose the same arm in a future trial, compared with women in the expectant management group (RR 1.93, 95% CI 1.62 to 2.30). In an older trial of 184 women, similar numbers of women indicated that they preferred the group they had been allocated to (RR 0.90, 95% CI 0.72 to 1.13) (26).

#### Additional considerations

A 1991 survey of 500 pregnant women in the UK showed that at 37 weeks of gestation, 45% of women preferred conservative management. Of women undelivered by 41 weeks, 31% desired conservative management (27).

In a 2009 study, 23 primigravid women in Australia (18 of whom were induced) were interviewed before and after induction (28). The women described feeling that induction was being imposed externally, with hospital policy defining “when time was up”. Being booked for induction required a shift in women’s expectations on what would happen during labour and birth. Women reported a lack of meaningful information given to them and some were afraid of the increased interventions. After birth, induced women were generally positive about the outcome of a healthy baby, if not necessarily positive about the induction experience.

*Judgement*

|  |   |                                |   |  |                                 |
|--|---|--------------------------------|---|--|---------------------------------|
| <input type="checkbox"/><br>Don't know | <input checked="" type="checkbox"/><br>Varies | <input type="checkbox"/><br>No | <input type="checkbox"/><br>Probably No | <input type="checkbox"/><br>Probably Yes | <input type="checkbox"/><br>Yes |
|--|---|--------------------------------|---|--|---------------------------------|



**5. FEASIBILITY**

Is the intervention feasible to implement?

*Research evidence*

No direct evidence was identified to address this question.

*Additional considerations*

Labour induction is a common practice worldwide. Induction rates exceed 20% in some high-income countries, however it is also widely used in hospitals in lower-income countries. A WHO multi-country, facility-based survey reported hospital induction rates of 11.4% in eight Latin American countries, 4.4% in seven African countries and 12.1% in nine Asian countries. Hospitals in some low-income countries (such as Sri Lanka and Cuba) had induction rates comparable to high-income countries.(29)

*Judgement*

|  |                                    |                                |   |  |  |
|--|------------------------------------|--------------------------------|---|--|--|
| <input type="checkbox"/><br>Don't know | <input type="checkbox"/><br>Varies | <input type="checkbox"/><br>No | <input type="checkbox"/><br>Probably No | <input type="checkbox"/><br>Probably Yes | <input checked="" type="checkbox"/><br>Yes |
|--|------------------------------------|--------------------------------|---|--|--|



**C) SUMMARY OF JUDGEMENTS – LABOUR INDUCTION < 41 WEEKS**

|   |                                 |             |                                    |   |  |  |  |
|---|---------------------------------|-------------|------------------------------------|---|--|--|--|
| Desirable effects                           | —<br>Don't know                 | —<br>Varies |                                    | ✓<br><b>Trivial</b>                       | —<br>Small   | —<br>Moderate  | —<br>Large                                   |
| Undesirable effects                         | —<br>Don't know                 | —<br>Varies |                                    | —<br>Large                                | —<br>Moderate  | ✓<br><b>Small</b>  | —<br>Trivial                                 |
| Certainty of the evidence                   | —<br>No included studies        |             |                                    | ✓<br><b>Very low</b>                      | —<br>Low   | —<br>Moderate  | —<br>High                                    |
| Values                                      |                                 |             |                                    | —<br>Important uncertainty or variability | —<br>Possibly important uncertainty or variability             | ✓<br><b>Probably no important uncertainty or variability</b> | —<br>No important uncertainty or variability |
| Balance of effects                          | —<br>Don't know                 | —<br>Varies | ✓<br><b>Favours the comparison</b> | —<br>Probably favours the comparison      | —<br>Does not favour either the intervention or the comparison | —<br>Probably favours the intervention                       | —<br>Favours the intervention                |
| Resources required                          | ✓<br><b>Don't know</b>          | —<br>Varies | —<br>Large costs                   | —<br>Moderate costs                       | —<br>Negligible costs or savings                               | —<br>Moderate savings  | —<br>Large savings                           |
| Certainty of evidence of required resources | ✓<br><b>No included studies</b> |             |                                    | —<br>Very low                             | —<br>Low   | —<br>Moderate  | —<br>High                                    |
| Cost-effectiveness                          | ✓<br><b>Don't know</b>          | —<br>Varies | —<br>Favours the comparison        | —<br>Probably favours the comparison      | —<br>Does not favour either the intervention or the comparison | —<br>Probably favours the intervention                       | —<br>Favours the intervention                |
| Equity                                      | ✓<br><b>Don't know</b>          | —<br>Varies | —<br>Reduced                       | —<br>Probably reduced                     | —<br>Probably no impact  | —<br>Probably increased                                      | —<br>Increased                               |
| Acceptability                               | ✓<br><b>Don't know</b>          | —<br>Varies |                                    | —<br>No                                   | —<br>Probably No   | —<br>Probably Yes  | —<br>Yes                                     |
| Feasibility                                 | ✓<br><b>Don't know</b>          | —<br>Varies |                                    | —<br>No                                   | —<br>Probably No   | —<br>Probably Yes  | —<br>Yes                                     |

**C) SUMMARY OF JUDGEMENTS – LABOUR INDUCTION ≥ 41 WEEKS**

|   |                          |             |                             |   |  |  |  |
|---|--------------------------|-------------|-----------------------------|---|--|--|--|
| Desirable effects                           | —<br>Don't know          | —<br>Varies |                             | —<br>Trivial                              | —<br>Small   | —<br>Moderate  | ✓<br><b>Large</b>                            |
| Undesirable effects                         | —<br>Don't know          | —<br>Varies |                             | —<br>Large                                | —<br>Moderate  | —<br><b>Small</b>  | ✓<br><b>Trivial</b>                          |
| Certainty of the evidence                   | —<br>No included studies |             |                             | —<br>Very low                             | ✓<br><b>Low</b>  | —<br>Moderate  | —<br>High                                    |
| Values                                      |                          |             |                             | —<br>Important uncertainty or variability | —<br>Possibly important uncertainty or variability             | ✓<br><b>Probably no important uncertainty or variability</b> | —<br>No important uncertainty or variability |
| Balance of effects                          | —<br>Don't know          | —<br>Varies | —<br>Favours the comparison | —<br>Probably favours the comparison      | —<br>Does not favour either the intervention or the comparison | —<br>Probably favours the intervention                       | ✓<br><b>Favours the intervention</b>         |
| Resources required                          | —<br>Don't know          | —<br>Varies | —<br>Large costs            | ✓<br><b>Moderate costs</b>                | —<br>Negligible costs or savings                               | —<br>Moderate savings  | —<br>Large savings                           |
| Certainty of evidence of required resources | —<br>No included studies |             |                             | —<br>Very low                             | ✓<br><b>Low</b>  | —<br>Moderate  | —<br>High                                    |
| Cost-effectiveness                          | —<br>Don't know          | —<br>Varies | —<br>Favours the comparison | —<br>Probably favours the comparison      | Does not favour either the intervention or the comparison      | ✓<br><b>Probably favours the intervention</b>                | —<br>Favours the intervention                |
| Equity                                      | —<br>Don't know          | —<br>Varies | —<br>Reduced                | —<br>Probably reduced                     | —<br>Probably no impact  | ✓<br><b>Probably increased</b>                               | —<br>Increased                               |
| Acceptability                               | ✓<br><b>Don't know</b>   | —<br>Varies |                             | —<br>No                                   | —<br>Probably No   | —<br>Probably Yes  | —<br>Yes                                     |
| Feasibility                                 | —<br>Don't know          | —<br>Varies |                             | —<br>No                                   | —<br>Probably No   | —<br>Probably Yes  | ✓<br><b>Yes</b>                              |

## ANNEX 5. GRADE TABLES

**Question:** Labour induction compared to expectant management (all trials) for improving birth outcomes for women at or beyond term

**Setting:** Hospital or medical centres in Austria, Canada, China, Finland, France, India, Netherlands, Norway, Spain, Sweden, Thailand, Tunisia, Turkey, UK, US

| Certainty assessment   |                   |                      |               |              |                           |                      | № of patients    |                                   | Effect                           |   | Certainty        | Importance |
|--|-------------------|----------------------|---------------|--------------|---------------------------|----------------------|------------------|-----------------------------------|----------------------------------|---|------------------|------------|
| № of studies   | Study design      | Risk of bias         | Inconsistency | Indirectness | Imprecision               | Other considerations | Labour induction | Expectant management (all trials) | Relative (95% CI)                | Absolute (95% CI)   |                  |            |
| Caesarean section  |                   |                      |               |              |                           |                      |                  |                                   |                                  |   |                  |            |
| 27   | randomized trials | serious <sup>a</sup> | not serious   | not serious  | not serious               | none                 | 980/6004 (16.3%) | 1056/5734 (18.4%)                 | <b>RR 0.92</b><br>(0.85 to 0.99) | <b>15 fewer per 1,000</b><br>(from 2 fewer to 28 fewer)   | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Operative vaginal birth (forceps or ventouse)  |                   |                      |               |              |                           |                      |                  |                                   |                                  |   |                  |            |
| 18   | randomized trials | serious <sup>a</sup> | not serious   | not serious  | not serious               | none                 | 984/4775 (20.6%) | 869/4506 (19.3%)                  | <b>RR 1.07</b><br>(0.99 to 1.16) | <b>91 fewer per 1,000</b><br>(from 21 fewer to 137 fewer) | ⊕⊕⊕○<br>MODERATE | IMPORTANT  |
| Postpartum haemorrhage   |                   |                      |               |              |                           |                      |                  |                                   |                                  |   |                  |            |
| 5  | randomized trials | serious <sup>a</sup> | not serious   | not serious  | serious <sup>b</sup>      | none                 | 218/1649 (13.2%) | 203/1666 (12.2%)                  | <b>RR 1.09</b><br>(0.92 to 1.30) | <b>11 more per 1,000</b><br>(from 10 fewer to 37 more)    | ⊕⊕○○<br>LOW      | CRITICAL   |
| Maternal satisfaction (Hoping to be randomized to the same trial arm as they had been in this study) |                   |                      |               |              |                           |                      |                  |                                   |                                  |   |                  |            |
| 1  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | not serious               | none                 | 184/250 (73.6%)  | 94/246 (38.2%)                    | <b>RR 1.93</b><br>(1.62 to 2.30) | <b>355 more per 1,000</b><br>(from 237 more to 497 more)  | ⊕⊕⊕○<br>MODERATE | IMPORTANT  |
| Maternal satisfaction (Preferred their allocation)   |                   |                      |               |              |                           |                      |                  |                                   |                                  |   |                  |            |
| 1  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | very serious <sup>d</sup> | none                 | 55/92 (59.8%)    | 61/92 (66.3%)                     | <b>RR 0.90</b><br>(0.72 to 1.13) | <b>66 fewer per 1,000</b><br>(from 86 more to 186 fewer)  | ⊕○○○<br>VERY LOW | IMPORTANT  |

| Certainty assessment         |                   |                      |               |              |                      |                      | No of patients     |                                   | Effect                           |   | Certainty        | Importance |
|------------------------------|-------------------|----------------------|---------------|--------------|----------------------|----------------------|--------------------|-----------------------------------|----------------------------------|---|------------------|------------|
| No of studies                | Study design      | Risk of bias         | Inconsistency | Indirectness | Imprecision          | Other considerations | Labour induction   | Expectant management (all trials) | Relative (95% CI)                | Absolute (95% CI)                                       |                  |            |
| Neonatal trauma              |                   |                      |               |              |                      |                      |                    |                                   |                                  |   |                  |            |
| 3                            | randomized trials | serious <sup>a</sup> | not serious   | not serious  | serious <sup>b</sup> | none                 | 26/2128 (1.2%)     | 22/2127 (1.0%)                    | <b>RR 1.18</b><br>(0.68 to 2.05) | <b>2 more per 1,000</b><br>(from 3 fewer to 11 more)    | ⊕⊕○○<br>LOW      | CRITICAL   |
| Neonatal convulsions         |                   |                      |               |              |                      |                      |                    |                                   |                                  |   |                  |            |
| 3                            | randomized trials | serious <sup>a</sup> | not serious   | not serious  | serious <sup>b</sup> | none                 | 3/2178 (0.1%)      | 6/2187 (0.3%)                     | <b>RR 0.54</b><br>(0.15 to 1.97) | <b>1 fewer per 1,000</b><br>(from 2 fewer to 3 more)    | ⊕⊕○○<br>LOW      | CRITICAL   |
| Meconium aspiration syndrome |                   |                      |               |              |                      |                      |                    |                                   |                                  |   |                  |            |
| 11                           | randomized trials | serious <sup>a</sup> | not serious   | not serious  | not serious          | none                 | 133/3887<br>(3.4%) | 173/3894 (4.4%)                   | <b>RR 0.77</b><br>(0.62 to 0.96) | <b>10 fewer per 1,000</b><br>(from 2 fewer to 17 fewer) | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Perinatal death              |                   |                      |               |              |                      |                      |                    |                                   |                                  |   |                  |            |
| 20                           | randomized trials | serious <sup>a</sup> | not serious   | not serious  | not serious          | none                 | 2/4988 (0.0%)      | 16/4972 (0.3%)                    | <b>RR 0.33</b><br>(0.14 to 0.78) | <b>2 fewer per 1,000</b><br>(from 1 fewer to 3 fewer)   | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Stillbirth                   |                   |                      |               |              |                      |                      |                    |                                   |                                  |   |                  |            |
| 20                           | randomized trials | serious <sup>a</sup> | not serious   | not serious  | not serious          | none                 | 1/4988 (0.0%)      | 10/4972 (0.2%)                    | <b>RR 0.33</b><br>(0.11 to 0.96) | <b>1 fewer per 1,000</b><br>(from 0 fewer to 2 fewer)   | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Neonatal death               |                   |                      |               |              |                      |                      |                    |                                   |                                  |   |                  |            |
| 19                           | randomized trials | serious <sup>a</sup> | not serious   | not serious  | serious <sup>b</sup> | none                 | 1/4896 (0.0%)      | 6/4880 (0.1%)                     | <b>RR 0.37</b><br>(0.10 to 1.38) | <b>1 fewer per 1,000</b><br>(from 0 fewer to 1 fewer)   | ⊕⊕○○<br>LOW      | CRITICAL   |

| Certainty assessment                      |                   |                      |               |              |             |                      | No of patients   |                                   | Effect                           |  | Certainty        | Importance |
|---|-------------------|----------------------|---------------|--------------|-------------|----------------------|------------------|-----------------------------------|----------------------------------|--|------------------|------------|
| No of studies                             | Study design      | Risk of bias         | Inconsistency | Indirectness | Imprecision | Other considerations | Labour induction | Expectant management (all trials) | Relative (95% CI)                | Absolute (95% CI)                                      |                  |            |
| Apgar score less than 7 at 5 minutes      |                   |                      |               |              |             |                      |                  |                                   |                                  |  |                  |            |
| 16  | randomized trials | serious <sup>a</sup> | not serious   | not serious  | not serious | none                 | 52/4523 (1.1%)   | 76/4524 (1.7%)                    | <b>RR 0.70</b><br>(0.50 to 0.98) | <b>5 fewer per 1,000</b><br>(from 0 fewer to 8 fewer)  | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Admission to neonatal intensive care unit |                   |                      |               |              |             |                      |                  |                                   |                                  |  |                  |            |
| 13  | randomized trials | serious <sup>a</sup> | not serious   | not serious  | not serious | none                 | 320/4271 (7.5%)  | 363/4260 (8.5%)                   | <b>RR 0.88</b><br>(0.77 to 1.01) | <b>10 fewer per 1,000</b><br>(from 1 more to 20 fewer) | ⊕⊕⊕○<br>MODERATE | CRITICAL   |

**CI:** Confidence interval; **RR:** Risk ratio

### Explanations

- All studies have design limitations (-1)
- Wide 95% CI crossing the line of no effect (-1)
- Single study with design limitations (-1)
- Wide 95% CI crossing the line of no effect, and small sample size (-2)



**Question:** Labour induction compared to expectant management (gestational age at induction) for improving birth outcomes for women at or beyond term

**Setting:** Hospital or medical centres in Austria, Canada, China, Finland, France, India, Netherlands, Norway, Spain, Sweden, Thailand, Tunisia, Turkey, UK, US

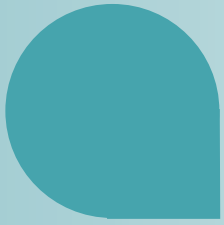
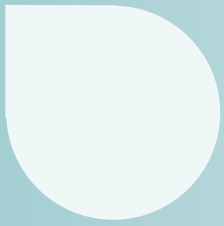
| Certainty assessment                                     |                   |                      |               |              |                           |                      | No of patients   |   | Effect                           |   | Certainty        | Importance |
|--|-------------------|----------------------|---------------|--------------|---------------------------|----------------------|------------------|---|----------------------------------|---|------------------|------------|
| No of studies  | Study design      | Risk of bias         | Inconsistency | Indirectness | Imprecision               | Other considerations | Labour induction | Expectant management (gestational age at induction) | Relative (95% CI)                | Absolute (95% CI)                                       |                  |            |
| Caesarean section < 41 weeks                             |                   |                      |               |              |                           |                      |                  |   |                                  |   |                  |            |
| 9  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | not serious               | none                 | 191/1532 (12.5%) | 175/1274 (13.7%)                                    | <b>RR 1.04</b><br>(0.87 to 1.24) | <b>5 more per 1,000</b><br>(from 18 fewer to 33 more)   | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Caesarean section ≥ 41 weeks                             |                   |                      |               |              |                           |                      |                  |   |                                  |   |                  |            |
| 17   | randomized trials | serious <sup>c</sup> | not serious   | not serious  | not serious               | none                 | 774/4407 (17.6%) | 857/4396 (19.5%)                                    | <b>RR 0.90</b><br>(0.83 to 0.98) | <b>19 fewer per 1,000</b><br>(from 4 fewer to 33 fewer) | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Operative vaginal birth (forceps or ventouse) < 41 weeks |                   |                      |               |              |                           |                      |                  |   |                                  |   |                  |            |
| 7  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | not serious               | none                 | 304/1327 (22.9%) | 198/1074 (18.4%)                                    | <b>RR 1.27</b><br>(1.08 to 1.48) | <b>50 more per 1,000</b><br>(from 15 more to 88 more)   | ⊕⊕⊕○<br>MODERATE | IMPORTANT  |
| Operative vaginal birth (forceps or ventouse) ≥ 41 weeks |                   |                      |               |              |                           |                      |                  |   |                                  |   |                  |            |
| 10   | randomized trials | serious <sup>c</sup> | not serious   | not serious  | not serious               | none                 | 668/3383 (19.7%) | 665/3368 (19.7%)                                    | <b>RR 1.00</b><br>(0.91 to 1.10) | <b>0 fewer per 1,000</b><br>(from 18 fewer to 20 more)  | ⊕⊕⊕○<br>MODERATE | IMPORTANT  |
| Perinatal death < 41 weeks                               |                   |                      |               |              |                           |                      |                  |   |                                  |   |                  |            |
| 5  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | very serious <sup>d</sup> | none                 | 0/771 (0.0%)     | 3/781 (0.4%)  | <b>RR 0.33</b><br>(0.05 to 2.06) | <b>3 fewer per 1,000</b><br>(from 4 fewer to 4 more)    | ⊕○○○<br>VERY LOW | CRITICAL   |

| Certainty assessment                                 |                   |                      |               |              |                           |                      | No. of patients  |   | Effect                           |  | Certainty        | Importance |
|--|-------------------|----------------------|---------------|--------------|---------------------------|----------------------|------------------|---|----------------------------------|--|------------------|------------|
| No. of studies                                       | Study design      | Risk of bias         | Inconsistency | Indirectness | Imprecision               | Other considerations | Labour induction | Expectant management (gestational age at induction) | Relative (95% CI)                | Absolute (95% CI)                                      |                  |            |
| Perinatal death ≥ 41 weeks                           |                   |                      |               |              |                           |                      |                  |   |                                  |  |                  |            |
| 15   | randomized trials | serious <sup>c</sup> | not serious   | not serious  | not serious               | none                 | 2/4217 (0.0%)    | 13/4191 (0.3%)                                      | <b>RR 0.33</b><br>(0.13 to 0.87) | <b>2 fewer per 1,000</b><br>(from 0 fewer to 3 fewer)  | ⊕⊕⊕○<br>MODERATE | CRITICAL   |
| Stillbirth < 41 weeks                                |                   |                      |               |              |                           |                      |                  |   |                                  |  |                  |            |
| 5  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | very serious <sup>d</sup> | none                 | 0/771 (0.0%)     | 3/781 (0.4%)  | <b>RR 0.33</b><br>(0.05 to 2.06) | <b>3 fewer per 1,000</b><br>(from 4 fewer to 4 more)   | ⊕○○○<br>VERY LOW | CRITICAL   |
| Stillbirth ≥ 41 weeks                                |                   |                      |               |              |                           |                      |                  |   |                                  |  |                  |            |
| 15   | randomized trials | serious <sup>c</sup> | not serious   | not serious  | serious <sup>e</sup>      | none                 | 1/4217 (0.0%)    | 7/4191 (0.2%)                                       | <b>RR 0.34</b><br>(0.09 to 1.24) | <b>1 fewer per 1,000</b><br>(from 0 fewer to 2 fewer)  | ⊕⊕○○<br>LOW      | CRITICAL   |
| Admission to neonatal intensive care unit < 41 weeks |                   |                      |               |              |                           |                      |                  |   |                                  |  |                  |            |
| 3  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | very serious <sup>d</sup> | none                 | 11/502 (2.2%)    | 12/503 (2.4%)                                       | <b>RR 0.92</b><br>(0.41 to 2.05) | <b>2 fewer per 1,000</b><br>(from 14 fewer to 25 more) | ⊕○○○<br>VERY LOW | CRITICAL   |
| Admission to neonatal intensive care unit ≥ 41 weeks |                   |                      |               |              |                           |                      |                  |   |                                  |  |                  |            |
| 9  | randomized trials | serious <sup>c</sup> | not serious   | not serious  | not serious               | none                 | 307/3704 (8.3%)  | 350/3693 (9.5%)                                     | <b>RR 0.88</b><br>(0.76 to 1.01) | <b>11 fewer per 1,000</b><br>(from 1 more to 23 fewer) | ⊕⊕⊕○<br>MODERATE | CRITICAL   |

**CI:** Confidence interval; **RR:** Risk ratio

### Explanations

- Single study with design limitations (-1)
- Wide 95% CI crossing the line of no effect, and small sample size (-2)
- All studies have design limitations (-1)
- Wide 95% CI crossing the line of no effect, and low event rate (-2)
- Wide 95% CI crossing the line of no effect (-1)



**For more information, please contact the following departments:**

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