

Induction of Labour in Aotearoa New Zealand

A clinical practice guideline

2019

Acknowledgements

This guideline provides evidence-based guidance for health professionals providing care to pregnant women and for people who are pregnant. For simplicity of language, the term 'woman/women' is used throughout the guideline, but this should be taken to also include all people who are pregnant, in labour and in the postnatal period.

If you are pregnant and don't identify as a woman, please tell your Lead Maternity Carer and other health professionals the pronouns you use so that they can use them in your records and throughout your care.

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Contents

Executive summary	vii
Recommendations in brief	viii
Summary of findings	1
Consumer foreword	6
Message from the Chair	8
Purpose and scope of the guideline	10
Purpose	10
Definition of induction of labour	10
The need for the guideline	10
Scope of the guideline	11
Target audience	12
The research questions	12
Guideline development process	13
Conflicts of interest	17
Funding	17
Chapter 1 : Introduction	18
Risk factors for perinatal death	18
Principles of decision-making	18
Chapter 2 : Neonatal risks of planned birth <39 weeks' gestation	20
Summary of evidence	20
Discussion	20
Chapter 3 : Membrane sweeping at term to reduce the need for induction of labour	21
Summary of evidence	21
Discussion	22
Chapter 4 : Indications and timing of induction of labour	23
Introduction	23
Mobilisation and physical restrictions during labour and birth	24
Pregnancy lasting longer than 41 weeks' gestation	24
Pre-labour rupture of membranes at 37 weeks' or more gestation	27
Suspected small for gestational age / fetal growth restriction	29

Diabetes in pregnancy	31
Maternal obesity	35
Advanced maternal age	36
Reduced fetal movements	37
Hypertension in pregnancy	39
Antepartum haemorrhage of unknown origin	41
Assisted reproductive technology	42
Suspected fetal macrosomia	43
Multiple pregnancy	45
Reduced liquor under 41 weeks' gestation	47
Obstetric cholestasis	48
Previous stillbirth	49
No medical indication	50
Chapter 5 : Methods of cervical ripening	53
Introduction	53
PGE2 (dinoprostone) methods of administration	54
PGE1 analogue (misoprostol)	54
Discussion on prostaglandins	55
Balloon catheter	57
Methods of IOL for women with previous caesarean section	61
Chapter 6 : Methods of induction of labour	62
Introduction	62
Combining ARM with oxytocin	62
Oxytocin protocol	64
Chapter 7 : Setting for induction of labour	67
Summary of evidence	67
Abbreviations	69
Appendices	70
Appendix A: The panel that developed this clinical practice guideline	70
Appendix B: Search methods	72
Appendix C: Observational studies	82
Appendix D: Comparisons of cervical ripening and methods of induction of labour	91
Appendix E: Examples of preparation of oral misoprostol for cervical ripening	92
References	95

List of Tables

Table 1:	Summary of recommendations and practice points	1
Table 2:	NICE levels of evidence and categories of papers	14
Table 3:	GRADE quality rating for evidence and strength of recommendations	14
Table B1:	Results of searches	74
Table B2:	Recruiting trials for indications and methods of induction of labour	77
Table B3:	Recruiting trials looking at outpatient methods of induction of labour	80
Table C1:	Adjusted odds ratio for perinatal related mortality, termination of pregnancy, stillbirth and neonatal death 2011-2015 in New Zealand	82
Table C2:	Risk factors and attributable stillbirth in selected high-income countries	83
Table C3:	Population-attributable risk for stillbirth in selected high-income countries	83
Table C4:	Association of maternal factors with antepartum stillbirth (INTERGROWTH-21 Project)	84

List of Figures

Figure C1:	Association of stillbirth with gestational age, United States data	84
Figure C2:	Association of BMI and fetal death	85
Figure C3:	Association of obesity in pregnancy and stillbirth in Washington and Texas	85
Figure C4:	Association of maternal age and stillbirth in the United States	86
Figure C5:	Risk of stillbirth and neonatal complications in twin pregnancies	87
Figure C6:	Risk of perinatal death by gestational age and bile salt concentration in women with obstetric cholestasis	89

Executive summary

This guideline provides the most recent research evidence for clinical conditions where induction of labour (IOL) at term would be considered and for methods of cervical ripening and starting IOL. A multidisciplinary panel assessed the quality of the evidence and made recommendations for the New Zealand context. This guideline is meant to be used by clinicians to inform shared decision-making with women and their partners and whānau and by district health boards (DHBs) to reflect on their current practices and align local guidelines with the national guideline to help develop consistent practices.

The quality of the research evidence varied considerably. Generally, where there was sufficient level 1 evidence available, the panel made a recommendation about IOL; where there was insufficient evidence to make a recommendation (for example, suspected macrosomia) or if the evidence was rated to be of low or very low quality, then the panel made practice points.

It is important to enable and respect a woman's right to be fully informed about the quality of evidence underpinning a recommendation for IOL and to be given the opportunity to make an informed choice.

It is important to promote and support spontaneous onset of labour and physiological labour and birth. This guiding principle aligns with the International Childbirth Initiative of 2018, which states "... Every MotherBaby should be protected from unnecessary and potentially harmful interventions, practices, and procedures and from both overuse and underuse of medical technology" (Lalonde et al 2018, page 4).

It is also important to individualise all decisions about induction. Some women do not fit into a single category that in itself warrants IOL but instead have several risk factors for adverse outcomes, which can be cumulative. Clinicians should document the rationale for recommending care that does not align with the guideline.

Early term birth (37 and 38 weeks' gestation) is associated with poorer neonatal and childhood outcomes compared with babies born at 39 to 41 weeks' gestation. Unless there is an evidence-based indication supporting earlier planned birth, continue expectant management to 39 weeks' gestation or more.

The panel identified numerous research gaps and a lack of evidence for the following themes:

- The benefits and harms of IOL or expectant management for several specific conditions
- The benefits and harms of IOL or expectant management in women who have multiple risk factors for perinatal death
- Women's perspectives and experiences of IOL or expectant management
- Trials of IOL or expectant management in the New Zealand maternity health care context.

The panel recommends that all future research studies on IOL list outcomes in a core outcome set (Dos Santos et al 2018), and that academics, clinicians, consumers and policymakers undertake a research agenda priority-setting process for New Zealand.

Recommendations in brief

Membrane sweeping is the only intervention shown to reduce the need for formal IOL. Consider offering membrane sweeping at term to reduce the frequency of pregnancies continuing beyond 41 weeks' gestation.

The only clinical indication where IOL has been shown to reduce perinatal death is in pregnancy at or beyond term. Offer IOL between 41+0 and 42+0 weeks' gestation to women with uncomplicated pregnancies.

In women with pre-labour rupture of membranes (PROM) at ≥ 37 weeks' gestation, offer planned early birth (immediate intervention or intervention within 24 hours), to reduce the risks of maternal infectious morbidity, definite or probable early-onset neonatal sepsis and neonatal intensive care unit (NICU) admission.

In women with hypertension in pregnancy, the panel endorses the recommendations from the Ministry of Health clinical practice guideline, *Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in New Zealand: A clinical practice guideline* (Ministry of Health 2018).

For cervical ripening, it is reasonable to offer any of:

- prostaglandin (PG) E2 (vaginal gel or controlled-release pessary)
- PG E1 analogue (misoprostol low-dose two-hourly in oral solution)
- balloon catheter (single- or double-balloon).

Based on the reason for the IOL, maternal values and preferences, local resources and practical considerations, eg, cost, availability and clinicians skilled at using the method. For cervical ripening with single-balloon catheter, inflate greater than 30 mL to increase the chance of vaginal birth in 24 hours.

While it is recognised that cervical ripening in the setting of IOL in childbirth has not been listed as a registered indication for misoprostol use in New Zealand, it has been widely researched internationally. Should hospitals choose to use misoprostol, it is recommended they work with their pharmacy department to develop suitable local guidelines.

Summary of findings

Table 1: Summary of recommendations and practice points

Notes
<p>The GRADE system (Guyatt et al 2008) classifies the quality of evidence in one of four levels (see Table 2) and offers two grades of recommendations (see Table 3).</p> <ul style="list-style-type: none"> • Level 1 evidence: Includes meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a low risk of bias. • Recommendations: When the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not, the panel developing the clinical guideline (the panel) has offered 'strong' recommendations. When the trade-offs are less certain – either because of the low quality of the evidence or because the evidence suggests that desirable and undesirable effects are closely balanced, the panel has offered 'conditional' recommendations. • Practice points: When recommendations are based on low- or very-low-quality evidence, the panel offers practice points or important things to consider for clinical practice. <p>The guideline includes practice points aimed at encouraging further understanding and discussion about the diverse beliefs, traditions and aspirations held by many women and their partners and whānau.</p>

General principles
<p>Practice points</p> <ul style="list-style-type: none"> • Promote and support spontaneous onset of labour and physiological labour and birth. • Enable and respect a woman's right to be fully informed about the quality of evidence underpinning a recommendation for IOL and to be given the opportunity to make an informed choice. • Continue expectant management to 39 weeks' gestation or more, unless there is an evidence-based indication supporting earlier planned birth. • Inform all women about the proposed method(s) of cervical ripening and IOL, the rationale for the use of such method(s) and alternative options.

Membrane sweeping		
Recommendation	Level of evidence	Strength of recommendation
Consider offering membrane sweeping at term to reduce the frequency of pregnancies continuing beyond 41+0 weeks' gestation.	Level 1; moderate quality	Conditional
<p>Practice point</p> <ul style="list-style-type: none"> • If offering membrane sweeping, consider performing it from around 39 weeks' gestation. 		

Pregnancy ≥41 weeks' gestation		
Recommendation	Level of evidence	Strength of recommendation
Offer IOL between 41+0 and 42+0 weeks' gestation to women with uncomplicated pregnancies, to reduce the risks of perinatal death, caesarean section, 5-minute Apgar <7 and meconium aspiration syndrome.	Level 1; moderate quality	Conditional

Pre-labour rupture of membranes

Recommendation	Level of evidence	Strength of recommendation
For women with PROM at ≥ 37 weeks' gestation, offer planned early birth,* to reduce the risks of maternal infectious morbidity, definite or probable early-onset neonatal sepsis and NICU admission. * immediate intervention or intervention within 24 hours.	Level 1; low quality	Conditional

Practice points

- For women with PROM, share information with the women as early as practical after rupture of membranes to support informed decision-making.
- Unless immediate IOL is planned, avoid digital vaginal examination.
- If neonates are at risk for early-onset neonatal group B streptococcal sepsis, offer immediate IOL.
- If liquor is meconium stained, consider immediate IOL.

Suspected small for gestational age / fetal growth restriction

Practice points

- For women with a suspected SGA fetus or FGR, in settings where detailed Doppler studies are unavailable, offer IOL at around 38 weeks' gestation (or earlier if concerned).
- For women with a suspected SGA fetus with abnormal umbilical artery Dopplers, consider offering IOL at around 37 weeks' gestation (low threshold for planned birth if there is any concern about maternal or fetal wellbeing or if there is suspected cessation of fetal growth).
- For women with a suspected SGA fetus with abnormal middle cerebral artery (MCA), CPR or uterine artery Dopplers, or EFW under the 3rd centile, offer IOL at around 38 weeks' gestation (or earlier if concerned).
- For women with suspected SGA fetus with normal MCA, CPR and uterine artery Dopplers, and EFW at or over the 3rd centile, offer IOL at around 40 weeks' gestation (or earlier if concerned). These babies are likely to be constitutionally small and are at lower risk of adverse outcomes.

Diabetes in pregnancy

Practice points

- For women with gestational diabetes, continue expectant management to at least 40 weeks' gestation, in the setting of good glycaemic control, normal fetal growth and no obstetric complications.
- For women with type 2 diabetes, continue expectant management to 39 weeks' gestation, unless there are obstetric or fetal indications for earlier birth or diabetes complications, such as vascular disease.
- For women with type 1 diabetes, manage on a case-by-case basis.

Maternal obesity

Practice point

- For women with maternal obesity, in the absence of other risk factors or pregnancy complications, do not offer IOL.

Advanced maternal age

Practice point

- For women aged 40 years and over, consider offering IOL at around 40 weeks' gestation.

Reduced fetal movements

Practice point

- For women with reduced fetal movements, in the presence of normal maternal and fetal assessment, continue expectant management.

Hypertension in pregnancy

Recommendation	Level of evidence	Strength of recommendation
For women with chronic hypertension and low risk of adverse outcomes, consider expectant management beyond 37 weeks' gestation with increased monitoring.	Level 1; moderate quality	Conditional
For women with gestational hypertension diagnosed after 37 weeks' gestation, consider IOL to reduce the risks of severe hypertension, severe pre-eclampsia, HELLP syndrome, abruptio placenta, pulmonary edema, severe renal impairment and fetal growth restriction.	Level 1; moderate quality	Conditional
For women with pre-eclampsia diagnosed after 37 weeks' gestation, offer IOL.	Level 1; moderate quality	Conditional

Antepartum haemorrhage of unknown origin

Practice point

- In women with APH of unknown origin, in the presence of normal maternal and fetal assessment, consider expectant management.

Artificial reproductive technology

Practice point

- In women who conceive using ART, in the absence of other risk factors or pregnancy complications, do not offer IOL.

Suspected fetal macrosomia

Practice point

- In women with suspected macrosomia, in the absence of pregnancy complications, consider expectant management.

Multiple pregnancy

Practice points

- For women with an uncomplicated monochorionic diamniotic twin pregnancy, consider offering IOL between 36 and 37 weeks' gestation.
- For women with an uncomplicated dichorionic twin pregnancy, consider offering IOL between 37 and 38 weeks' gestation.

Reduced liquor <41 weeks' gestation

Practice point

- In women with reduced liquor as an isolated finding at <41 weeks' gestation, in the presence of normal maternal and fetal assessment, consider expectant management.

Obstetric cholestasis

Practice point

- For women with obstetric cholestasis, if symptomatic or if serum bile acid concentration ≥ 100 , consider IOL; otherwise consider expectant management.

Previous stillbirth

Practice point

- For women with previous stillbirth, consider expectant management or IOL, based on a review of risk factors for recurrence and any other antenatal risk factors, and guided by maternal choice.

No medical indication

Practice points

- Do not offer IOL in the absence of a medical indication.
- Manage maternal requests for IOL on a case-by-case basis.

Cervical ripening

Recommendation	Level of evidence	Strength of recommendation
Offer cervical ripening with PG to women with unfavourable cervix, to improve the chance of vaginal birth within 24 hours, compared with oxytocin alone.	Level 1; moderate quality	Conditional
Offer either PGE2 vaginal gel or controlled-release pessary for cervical ripening, as both methods are comparable to achieve vaginal birth in 24 hours and for risk of caesarean section.	Level 1; moderate quality	Conditional
Offer oral misoprostol for cervical ripening to reduce the risk of caesarean section.	Level 1; moderate quality	Conditional
Offer balloon catheter for cervical ripening, to reduce the risk of uterine hyperstimulation with FHR changes, compared with PG.	Level 1; moderate evidence	Conditional
For single-balloon catheter: Inflate greater than 30 mL (and not more than the manufacturer's recommendation), to increase the chance of vaginal birth in 24 hours, compared with 30 mL or less.	Level 1; moderate quality	Conditional

Practice points

- Consider offering membrane sweeping concurrent with cervical ripening.
 - For cervical ripening with PGE2 vaginal gel: Decide initial dose based on parity and Bishop score. If nulliparous and the Bishop score is ≤ 4 , consider 2 mg; otherwise consider 1 mg. Decide any subsequent dose based on cervical change – if none, consider 2 mg; otherwise consider 1 mg. Use as per the manufacturer's instructions.
 - For cervical ripening with PGE2 controlled-release vaginal pessary: Pessary may have higher risk of uterine tachysystole and hypertonus compared with vaginal gel. Use as per the manufacturer's instructions.
 - For cervical ripening with PGE1 analogue (misoprostol): Vaginal administration may have higher risk of adverse outcomes compared with oral administration. If using misoprostol, low-dose (25 mcg) two-hourly in oral solution is recommended. See also Appendix E: Examples of preparation of oral misoprostol for cervical ripening.
 - For cervical ripening with balloon catheter, consider offering either single- or double-balloon, as both are comparable to achieve vaginal birth in 24 hours and for risk of caesarean section. Use double-balloon catheter as per the manufacturer's instructions.
 - Consider using balloon catheter for cervical ripening where IOL is indicated in the setting of a previous caesarean section.
-

Induction of labour methods**Practice points**

- To start IOL once cervix is favourable, consider offering the combination of ARM and intravenous oxytocin infusion, to increase chance of vaginal birth within 24 hours.
 - The timing and order of performing ARM and starting intravenous oxytocin infusion should be individualised and negotiated between the woman, her LMC, the hospital midwife and the obstetrician.
 - Offer either low- or high-dose oxytocin protocol, as both methods are comparable in terms of achieving vaginal birth in 24 hours and risk for caesarean section.
 - The usual time interval to increase the dose of oxytocin is approximately 20 minutes.
-

Consumer foreword

Inā ora te wāhine, ka ora te whānau, ka ora te hapū, ka ora te iwi e.
When women are in good health, the whānau, hapū and iwi will flourish.

Although this guideline has been developed predominantly to guide clinical practice, good clinical practice cannot be achieved without delivering care that is respectful, mana enhancing and that supports pregnant women and their whānau to experience a pregnancy, labour and birth that honour and protect the many aspects of life that are important to them. While health care providers have distinct and influential roles in promoting and protecting physiological birth, it is important to acknowledge and understand the diverse reasons (both clinical and social) that may influence why induction of labour (IOL) may or may not be desired, requested or considered.

The panel who developed this guideline thoughtfully navigated the power dynamics between pregnant women and their whānau and health professionals and robustly explored the distinction between ‘recommending’ and ‘offering’ interventions.¹

The panel wanted to ensure that the importance of the birth experience as a whole was not lost amongst the plethora of potential clinical indications and concerns relating to the timing of labour. The loss of a physiological birth due to IOL is a significant intervention and should be treated as such. This guideline acknowledges the complexities of the birth experience whereby pregnant women and their whānau can be simultaneously grateful for medical interventions that facilitate the safe arrival of their baby/babies and experience trauma and grief at the loss of a planned birth experience.

“I appreciated the emotional support to navigate difficult decisions when facing essential interventions. [The switch] from planning a home birth to requiring an induction was quite sad for me. In the end, because I was able to negotiate every step of the way, my birth was a positive experience ... Feeling in control of the process and having my choices honoured was extremely positive.”
Respondent 168 (Women’s Health Action 2018)

The panel worked hard to develop the guideline to safeguard the health consumer rights to a reliable and fair process of informed decision-making. Health professionals have an ethical and legal responsibility to understand the differences between ‘informed choice’, ‘shared decision-making’ and ‘informed compliance and coercion’ and to facilitate the pathway to truly informed choice and consent for their patients (Gold 2014). This can only be achieved by providing individualised assessments of IOL indication(s) and giving each pregnant woman and their whānau the chance to evaluate the risks of IOL in the context of their own beliefs and meanings. Once IOL has been agreed to, a pregnant woman and their whānau must also be provided with information on what to expect and how to prepare.

¹ For further information on this survey please contact info@wha.org.nz.

“I hated the ‘informed consent’ that was given to me around the induction of my first child – it wasn’t ‘informed consent’ but ‘coerced consent’. Basically, it was made out that, if I didn’t follow their policies, then my child would die, so in order to prevent that happening, I had to consent for the induction and the ways they were inducing me. There was no discussion about the options for induction; there was no discussion about the risks involved, nor about the after-effects on both mother and baby.” Respondent 1,395 (Women’s Health Action 2018)

A lack of information and planning, delays and separation from partners during IOL have been shown to increase maternal anxiety (Jay et al 2018b) and is associated with a disparity between expectations and experience, particularly pain and duration of labour (Jay et al 2018a; Murtagh and Folan 2014).

To this end, wherever possible, this guideline has incorporated published research and first-hand accounts of individual experiences of induction of labour.

We hope that this resource will be used as a tool to assist health professionals and caregivers to work in partnership with pregnant women and their whānau; supporting them to plan for and experience the best possible labour and birth regardless of birthplace setting or mode of birth.

Message from the Chair

Induction of labour (IOL) rates are increasing in New Zealand and globally. This increase has been associated with differing opinions and practices amongst clinicians and maternity services. We need national guidance in this area, in order to educate and provide consistent recommendations around IOL that will improve the proportion of inductions performed for evidence-based reasons. This in turn will maximise the benefit, and minimise the harm, to mothers and babies.

The multidisciplinary panel that was established to develop this guideline encountered a range of challenges over the 21 months they worked on the project. Current practice for some common indications for induction, such as diabetes in pregnancy, lacks research evidence to support IOL. Yet, there is similarly no evidence to change to expectant management. Evidence that has been available for a long time, such as offering post-dates IOL from 41 weeks' gestation or oral misoprostol for cervical ripening, has not been taken up routinely in New Zealand due to a reluctance to change institutional culture ('this is how we have always done things around here'). Newly published evidence that should lead us to consider adding new indications for IOL, such as macrosomia, is challenging if results of overseas trials cannot be generalised to the New Zealand context.

The panel provided a range of perspectives, which led to robust discussion, underscoring the importance of consensus building and ensuring we 'get it right' in order to facilitate the implementation of this guideline into practice. For example, the panel spent hours on wording. The Guidelines International Network states that recommendations related to interventions should use unambiguous, active language, and guideline developers need to use such terms as 'should' or 'recommend' and avoid vague phrases such as 'may', 'can' or 'consider' (Qaseem et al 2012). Yet, the panel felt that the term 'offer' conveyed a recommendation, in that it wouldn't offer an IOL unless it recommended it.

In the end, an offer is just that, an offer. IOL decisions are value laden, reflecting individual ideology and preferences. Clinicians need to support women to make informed and shared decisions about their care. In the ideal situation, there is a three-way discussion between the woman, their lead maternity carer (LMC) and the obstetrician. However, the current reality is of two-way conversations and virtual pathways of care. In a shared decision-making model, information is provided about the different options of IOL and expectant management, preferences are discussed, and decisions are made about what is best for the woman (Elwyn et al 2010). The panel hopes to develop a decision aid to support this process.

The majority of studies reviewed provided moderate-quality evidence of the benefits of IOL, with no short-term harms. In particular, every randomised controlled trial (RCT) found women in the IOL group had lower or no difference in risk of caesarean section compared with women managed expectantly. This is not consistent with what is seen day to day. However, it is consistent across all studies for all indications in all countries. This underlies the importance of limiting IOL to those indications that have high-quality evidence and not extrapolate to clinical conditions for which IOL is not evidence based.

That being said, most studies did not measure long-term outcomes for mothers and babies. Moreover, some studies of IOL being offered under 39 weeks' gestation found some short-term neonatal risks, such as respiratory distress syndrome and admission to neonatal intensive care. A review of evidence on planned birth under 39 weeks' gestation revealed increased short- and long-term neonatal risk compared with waiting until 39 weeks' gestation or longer. The panel agreed that, in the absence of high-quality evidence, we should not offer IOL under 39 weeks' gestation – early term is not the same as full term.

The experience of an IOL in itself is another consideration. It is a medical intervention and does have an impact on choice of place of birth, time spent in hospital, experience of pain, continuity of care and emotional wellbeing. It is thus important to ensure that every induction is necessary.

Publishing a guideline does not guarantee its uptake. A Cochrane review (Chen et al 2018) found high-quality evidence of non-clinical interventions targeted at health care professionals that reduced unnecessary caesarean section: implementation of clinical practice guidelines with mandatory secondary opinion for caesarean section indication, implementation of clinical practice guidelines combined with audit and feedback, and physician education by local opinion leaders. The panel encourages maternity services to develop local systems to promote these interventions for reducing unnecessary IOL. For example, they could develop an IOL request form that aligns with the guidelines so that if the IOL were not guideline-based, then it would require a second opinion before being booked. This would drive best practice and may result in less variation.

I would like to sincerely thank the 15 panel members for their time, thoughtful consideration and respectful discussion during the development of this guideline.

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Purpose and scope of the guideline

Purpose

The purpose of this guideline is to provide a summary of the research evidence to support clinical decision-making and consistency of practice for induction of labour (IOL) at 37+0 weeks' gestation or more, in the New Zealand context. It aims to support shared decision-making within an evidence-based supportive framework.

The guideline has identified the most recent research evidence for some common potential clinical indications for IOL. An appropriate IOL is where evidence shows that the benefit to the mother and/or baby outweighs the risk.

Definition of induction of labour

IOL is commonly defined as the artificial initiation of labour (NICE 2008). The alternative is expectant management of the pregnancy, where spontaneous labour is awaited.

This guideline focuses on IOL at term. We acknowledge that 'at term' is a concept that does not have a common understanding and agreed definition. It covers a period of around five weeks, and human gestational length varies considerably. For the purposes of this guideline, 'at term' is defined as 37+0 or more weeks' gestation.

The need for the guideline

In New Zealand, the proportion of women who experience an IOL has steadily increased, from 19.4% in 2006 to 26.0% in 2017 (Ministry of Health 2019b). The most common indications for IOL at term in Auckland District Health Board (DHB) in 2016 were: pre-labour rupture of membranes (ROM) at term, diabetes in pregnancy, suspected small for gestational age fetus and post-dates (Auckland DHB 2017).

IOL is reported as one of 10 clinical maternity indicators identified by the Ministry of Health in its national quality and safety programme for maternity services (Ministry of Health 2019a). In 2017, in women expected to have an uncomplicated pregnancy and low intervention rates (defined as nulliparous, age 20–34 years, 37+0–41+6 weeks' gestation, cephalic-presenting singleton baby and no obstetric complications), the induction rate was 7.6%. Rates varied by facility of birth, from a low of 1.1% (Gisborne) to a high of 16.5% (Taranaki). This variation in IOL rate in a restricted cohort of 'low-risk' women suggests that clinician preference and institutional culture may have a more significant influence on the decision to offer IOL than clinical factors. It also highlights the need for a consistent approach using evidence-based guidance on IOL.

IOL has an impact on the woman's experience of labour and birth, with women having to reconsider their birth plans and, in some cases, their planned place of birth. Women have identified that more pain relief during labour is required, they feel less positive about their birth experience and find the induction process challenging (Coates et al 2019; Hildingsson et al 2011; Schwarz et al 2016). Therefore, it is important to only offer IOL when there is sufficient evidence of benefit. Recognising that women are active managers of their own health, providing information about induction and the different aspects of the induction process and ensuring that women participate in decision-making may help to mediate these negative experiences.

Scope of the guideline

This guideline is limited in scope to 15 common clinical indications where IOL would be considered, optimal timing of IOL and a discussion of IOL for no medical indication. The panel acknowledges that there are many risk factors and conditions during pregnancy that are associated with adverse maternal or perinatal outcome, including those reviewed in this guideline. However, the scope of this guideline is to only review research that evaluates IOL as an intervention to mitigate these risks. The evidence may suggest that IOL may be of benefit for the health of the woman and/or her baby, or there may be insufficient evidence to support the use of IOL.

The guideline provides recommendations on methods of cervical ripening and IOL, IOL in an outpatient setting and IOL for women with previous caesarean section. There is also guidance on the use of membrane sweeping to reduce the chance of needing a formal IOL and on trying to avoid planned birth before 39 weeks' gestation to optimise neonatal outcomes.

The list of indications and methods reviewed may not be comprehensive, rather it provides an overview of the more common reasons for IOL in New Zealand. There may be other situations where IOL is appropriate based on the individual clinical situation (related to the mother, the baby or the pregnancy) or several concurrent risk factors. In these situations, care should be individualised in consultation with a specialist.

The following were considered out of scope and are not covered in the guideline:

- A review of the management (apart from IOL) of included clinical conditions
- Natural methods of IOL
- Augmentation of labour
- Health care utilisation costs and resources.

Target audience

This guideline is intended for the providers of maternity care. It also has implications for health service provider organisations and funders of maternity services. The guideline may also be accessed by pregnant women and their families and whānau.

The panel included consumers who represented the views of women who had experienced pregnancies and IOL with their whānau. These and other women with experience of IOL have helped interpret the evidence and develop recommendations.

The research questions

The panel agreed on the following key questions to be addressed by this guideline.

Clinical indications for induction of labour

Population

The target population is pregnant women who develop a maternal, fetal or obstetric risk or condition where expedited labour and birth would be considered. The population includes women with cephalic presentation considering IOL at ≥ 37 weeks' gestation.

Intervention

The intervention of IOL is the artificial initiation of labour.

Comparison

The alternative is expectant management of the pregnancy where spontaneous labour is awaited.

Outcomes

Clinical outcomes are benefits to pregnant women or their babies and any complications, adverse events or side effects for pregnant women or their babies.

The primary outcome identified by the panel is perinatal death. Secondary outcomes identified are those highlighted by the core outcome set for trials on induction of labour (COSIOL) initiative (Dos Santos et al 2018) and others that are considered to be important by women, clinicians and DHBs.

Maternal outcomes include: vaginal birth within 24 hours, haemorrhage, infection, operative vaginal birth, caesarean section, reason for caesarean section, use of oxytocin, use of epidural, satisfaction with care, experience of pain, time from IOL to birth, uterine hyperstimulation, uterine rupture and 'failed' IOL.

Neonatal outcomes include: admission to the neonatal intensive care unit (NICU), 5-minute Apgar score <7, birth trauma, meconium aspiration syndrome, need for respiratory support, infection, seizures and long-term outcomes, such as neurodevelopmental impairment in childhood.

Key clinical questions for clinical conditions* where IOL or expectant management may be considered as part of a management plan are as follows.

1. Is perinatal mortality reduced (for the clinical condition*) if labour is induced or expectantly managed?
2. Is perinatal morbidity reduced (for the particular clinical condition*) if labour is induced or expectantly managed?
3. Is maternal mortality/morbidity reduced (for the clinical condition*) if labour is induced or expectantly managed?
4. What is the woman's experience of induction of labour (for the clinical condition*) or an expectantly managed labour?

* Clinical conditions where IOL may be considered include: pregnancy ≥ 41 weeks' gestation, PROM, suspected SGA, diabetes in pregnancy, maternal obesity, advanced maternal age, reduced fetal movements, hypertension in pregnancy, antepartum haemorrhage of unknown origin, ART, suspected fetal macrosomia, multiple pregnancy, reduced liquor <41 weeks' gestation, obstetric cholestasis, previous stillbirth, no medical indication.

Guideline development process

Overview

This guideline has been developed by members nominated by the New Zealand College of Midwives (NZCOM), The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and Royal Australasian College of

Physicians (RACP), along with representatives of consumer and midwifery and obstetrics groups from around New Zealand (see Appendix A).

The multidisciplinary clinical guidelines panel created a secure internet-based folder and met monthly over videoconference from February 2018 to October 2019. There was a one-day in-person meeting in Auckland in December 2018 and a two-day in-person meeting in February 2019.

The panel selected and categorised the level of evidence, including Cochrane and other meta-analyses, RCTs with IOL as the intervention, significant observational studies with IOLs the intervention, national and international guidelines and local expert advice.

Table 2: NICE levels of evidence and categories of papers

Level of evidence	Category of paper
1	Meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
2	Systematic reviews of case-control or cohort studies or well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability of causal relationship
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

Source: NICE 2008

The panel used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to rate the quality of the evidence and the strength of the recommendations (Guyatt et al 2008). The GRADE framework classifies the quality of evidence in one of four levels and offers three grades of recommendations. When the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not, the panel can offer 'strong' recommendations. On the other hand, where the trade-offs are less certain, either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced, the panel must offer 'conditional' recommendations.

The GRADE framework also offers an option for presenting a 'good practice point' (GPP). GPPs are recommendations that can be made when it is deemed they will be helpful to the clinician but where there is no direct evidence to support it.

Table 3: GRADE quality rating for evidence and strength of recommendations

GRADE rating of quality of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: Any estimate of effect is very uncertain.

Note: RCTs start at high quality, cohort and case-control studies start at low quality, and case series and expert opinion are very low quality. Confidence in the evidence may decrease for several reasons, including study limitations, inconsistency of results, indirectness of evidence, imprecision and reporting bias and may increase if the magnitude of the treatment effect is very large, if there is evidence of a dose-response relation or if all plausible biases would decrease the magnitude of an apparent treatment effect.

GRADE rating of strength of recommendations

Strong

Conditional

Good practice point (GPP)

Note: Recommendations can be in favour of or against a practice.

Source: Guyatt et al 2008

The panel discussed the evidence at length, placed it in the New Zealand context and formulated recommendations by consensus. The issues considered were sometimes complex due to the diversity of the research studies reviewed, the inconsistent reporting of outcomes and the lack of maternal experience and involvement in the research. Moreover, the evidence studied hardly ever reported the important long-term outcomes for the mother and the baby. Where evidence was insufficient, the panel flagged the research gaps.

External consultation

In July and August 2019, the panel sent out the draft guideline for extensive consultation. This involved several professional groups, including:

- Australian and New Zealand College of Anaesthetists (ANZCA)
- Clinical Directors Network New Zealand (DHB obstetrician leaders)
- DHB Midwife Leaders Group
- Health Quality & Safety Commission (HQSC)
- Maternity Services Consumer Council
- Nga Maia Māori Midwives Aotearoa
- National Maternity Monitoring Group (NMMG)
- New Zealand College of Midwives
- Perinatal Society New Zealand
- Pharmaceutical Society of New Zealand
- Royal Australasian College of Physicians (RACP)
- The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- Te Kāhui Oranga ō Nuku (formerly the New Zealand Committee).

Organisations were asked to review the guideline to verify the completeness of the literature review, ensure the guideline's clinical sensibility and judge its usefulness. Specifically, they were asked if they agreed or disagreed with the recommendations and to provide a rationale for their answer.

Individuals were also offered the opportunity to feedback via an electronic survey consisting of 10 questions with Likert-scale ratings and space for comments. There were 38 responses to the survey, some of whom indicated they were responding on behalf of a group. Formal written responses were received from five clinical directors, two individual obstetricians, ANZCA, HQSC, the New Zealand College of Midwives, the Perinatal Society New Zealand and the Maternity Services Consumer Council. During September and October 2019, the panel reviewed the external feedback and made final recommendations.

Implementation plan

The panel suggests the following plan for dissemination within the health sector, using professional and consumer networks:

- Guideline to be made available on a University of Auckland website
- Guideline to be independently assessed using the AGREE-II tool
- Written request to be sent to the Ministry of Health for ratification
- Guideline to be sent to lead maternity service providers in each DHB with a request to endorse and adapt locally
- Guideline to be presented at appropriate national fora and conferences
- PowerPoint presentation and algorithms to be developed for local clinician education
- An IOL request form to be developed that aligns with recommendations
- A decision-making aid to be developed for New Zealand pregnant women to support informed shared decision-making
- Suggestions for key maternity data to be collected at baseline and for future audit
- Funding to be sought for implementation research, such as evaluating barriers and enablers to implementing the guideline.

Primary outcomes for baseline and future audit

- IOL rate, with minimal variables such as parity, age, body mass index (BMI), gestational age, primary indication, Bishop score, first method of cervical ripening
- Vaginal birth within 24 hours
- Caesarean section
- Uterine hyperstimulation with fetal heart rate (FHR) changes
- Variation in gestational age range for post-term IOL

- Proportion of IOLs started at 39 weeks' gestation or more, overall and for standard primipara
- Proportion of IOLs that are guidelines-based in indication and timing
- Proportion of babies born at 37 or more weeks' gestation requiring respiratory support.

Updating the guidelines

These guidelines will be reviewed in three years 'from publication and updated as required.

Conflicts of interest

None of the members of the panel declared any financial or personal conflicts of interest that may affect their impartiality as a panel member.

Members of the panel involved in the ongoing OBLIGE research trial² were excluded from the development of recommendations about outpatient settings for IOL.

Funding

The Nurture Foundation for Reproductive Research that aims to promote education and research through collaboration amongst New Zealand researchers, and the Mercia Barnes Trust, RANZCOG, which seeks to help and promote research around women's and reproductive health, provided grants-in-aid to support the guideline development. The funding sources had no role in the design of the research questions, collection, analysis and interpretation of data, nor in writing of the guideline. The panel is very grateful to these organisations for their support.

² The Outpatient Balloon catheter and Inpatient prostaglandin Gel (OBLIGE) research study is a study run by The University of Auckland, with support from the Health Research Council of New Zealand in partnership with A+ Trust Auckland DHB. It compares two common ways of starting the induction of labour process. More information about the study can be found on the study's website at www.oblige.auckland.ac.nz.

Chapter 1: Introduction

Risk factors for perinatal death

The Perinatal and Maternal Mortality Review Committee (PMMRC) reviews perinatal death rates in New Zealand over time. The perinatal-related mortality rate in 2016, which includes all deaths from 20 weeks' gestation to 27 days of life, was 10.1/1000 total births. Appendix C includes tables showing stillbirth rates and associations from observational studies.

Principles of decision-making

The guideline considers women-centred care and the importance of the informed decision-making process involving the pregnant woman, her partner and whānau, her lead maternity carer (LMC) midwife and the obstetrician.

The guideline aims to both enable clinicians and to empower pregnant women to make the best decision for their specific circumstance, with awareness given to the potential power imbalance between pregnant women and clinicians.

Once recommendations have been made, it is expected that an informed decision-making process will follow, that is, a three-way conversation will take place between the pregnant woman, her LMC and the obstetrician. Clinicians need to provide clear and balanced information to pregnant women to communicate the significance of having an IOL versus awaiting spontaneous labour, including place of birth, roles and responsibilities of caregivers, length of time from start to birth and expectations. Pregnant women need time to consider the pros and cons of IOL, ask questions and be supported in their choices.

The panel acknowledges that pregnant women may have more than one risk factor, and therefore clinicians need to individualise care when making the decision for IOL. As risk factors multiply, the rate of adverse outcomes increases, though by how much is unknown. It may be appropriate for clinicians to offer IOL to women with multiple risk factors, even if the IOL does not appear to sit under any specific recommendation. The panel acknowledges that clinicians are experienced and specialised, will use their discretion appropriately and will interpret all the information available conscientiously. The panel encourage clear documentation where recommendations are not followed.

Implementation of the guideline's recommendations will vary by setting, and it is important to consult locally as each setting has its own challenges and stakeholders to consider. Resources are limited, and there is a need for clinical prioritisation. Clinicians need to set realistic expectations for the women they care for.

The panel considered the outcomes that are important to pregnant women. The guideline development process has also taken Māori and Pacific cultural considerations into account.

Research gaps

- For pregnant women where IOL is being considered, to determine effective ways to present risks and benefits as part of the three-way conversation.
 - To explore the impact of IOL on a pregnant woman's labour and her experience, such as change of planned place of birth, change of planned mode of pain relief, use of epidural analgesia in labour and the women's satisfaction with her labour and the birth.
 - To explore IOL compared with expectant management in the context of Māori health beliefs.
-

Chapter 2: Neonatal risks of planned birth <39 weeks' gestation

Summary of evidence

Babies born preterm (<37 weeks' gestational age) have a higher incidence of neonatal mortality and morbidity and long-term neurodevelopmental impairment than babies born at term (Saigal and Doyle 2008; Petrini et al 2009). Early-term birth (37–38+6 weeks' gestational age) is also associated with poorer neonatal outcomes compared with babies born at 39–41 weeks' gestational age. Babies born by planned caesarean section at early term have a higher rate of neonatal death or serious morbidity (respiratory complications, NICU admission and hypoglycaemia) compared with those born at 39 weeks' or longer gestation (Tita et al 2009). Cohort studies in Canada and New York have also shown an increased risk of NICU admission and respiratory morbidity for babies born early term compared with babies born at 39–41+6 weeks gestation (Brown et al 2013; Sengupta et al 2013).

Babies born early term are also at higher risk of long-term childhood impairments, such as cerebral palsy and special education needs (Moster et al 2010; Mackay et al 2010). New Zealand children born early term are at higher risk of requiring hospital admission in childhood and have lower National Certificate in Educational Achievement (NCEA) scores than children born at 39–40 weeks' gestation (Berry et al 2018).

Discussion

There is currently insufficient high-quality evidence to make a clear recommendation.

Practice point

- Continue expectant management to 39 weeks' gestation or more, unless there is an evidence-based indication supporting earlier planned birth.

Chapter 3: Membrane sweeping at term to reduce the need for induction of labour

Summary of evidence

One systematic review was identified.

A 2005 Cochrane review (including 22 trials of 2,797 women) comparing membrane sweeping performed in an outpatient setting at term (38–40 weeks' gestation) with no treatment or other treatment found that membrane sweeping increased the likelihood of birth within one week (RR 0.71, 95% CI 0.65–0.78), reduced the frequency of pregnancy continuing beyond 41 weeks (RR 0.59, 95% CI 0.46–0.74) and reduced the frequency of using other methods to induce labour (RR 0.60, 95% CI 0.51–0.71) (Boulvain et al 2005). Eight women need to have membrane sweeping to avoid one formal IOL (number needed to treat (NNT) = 8).

There was no difference in caesarean section (RR 0.90, 95% CI 0.70–1.15). No serious maternal morbidity/mortality was reported (including septicaemia). There was no difference in risk of maternal infection/fever (RR 1.05, 95% CI 0.68–1.65) or neonatal infection/fever (RR 0.92, 95% CI 0.3–2.82). When compared with no treatment, discomfort and other minor adverse effects were more frequently reported with membrane sweeping. They did not report on maternal satisfaction. The authors concluded that, although sweeping the membranes as a general policy from 38 to 40 weeks' gestation onwards decreased the rate of post-term pregnancy and need for formal IOL, it did not seem to improve any other clinical outcomes, was associated with some adverse effects and thus should be balanced against more formal options for IOL. Membrane sweeping does not replace a formal method of IOL.

Discussion

Studies of membrane sweeping have shown that the potential risks are minimal. Women who do not go into labour following membrane sweeping experience pregnancies of shorter duration and decreased need for formal IOL. Membrane sweeping appears to have an excellent NNT, reducing the need for a formal IOL. Women need to be reassured that although membrane sweeping may be an uncomfortable procedure, there are no associated harms. The Cochrane review refers to membrane sweeping at 38–40 weeks' gestation, whereas this guideline advocates for continuation of pregnancies until 39 weeks' gestation. The panel felt that membrane sweeping may be beneficial for women beyond 39 weeks' gestation. There is insufficient evidence to make a clear recommendation for membrane sweeping at different gestational ages.

Recommendation	Level of evidence	Strength of recommendation
Consider offering membrane sweeping at term to reduce the frequency of pregnancies continuing beyond 41 weeks' gestation.	Level 1; moderate quality	Conditional

Practice point

- If offering membrane sweeping, consider performing it from around 39 weeks' gestation.

Research gaps

- To explore women's perspectives and experiences of membrane sweeping.
- In women at term, to determine the effect of membrane sweeping compared with no treatment on maternal, perinatal and neonatal outcomes, stratifying participants by cervical status and parity.
- To explore alternative methods to encourage labour, besides membrane sweeping.

Chapter 4: Indications and timing of induction of labour

Introduction

The panel recommends offering IOL where there is clear evidence of benefit to the pregnant woman or her baby and supports clinicians offering expectant management where there is no clear evidence of benefit from IOL. If a clinician and the pregnant woman are considering IOL where evidence is insufficient to make a recommendation, then the panel recommends not offering IOL before 39 weeks' gestation in order to optimise short- and long-term outcomes for the baby.

Women may have more than one risk factor during their pregnancy. Therefore, clinicians need to individualise care when considering IOL. Clinicians should have informed discussions with women about the risks and benefits of IOL and expectant management and plan individualised care with each woman and her LMC. The panel acknowledges that even for indications where there are no reported harms in women having IOL, the intervention of IOL itself can be considered by some to be a harm. Moreover, some important or long-term outcomes have not yet been explored.

Clinicians should engage in shared decision-making that respects women's choices and autonomy. If women choose expectant management when they have been offered IOL, then the woman should be supported to revisit the decision at any time. Where clinicians do not follow guideline recommendations, then they should document their rationale adhering to the recommendation.

Mobilisation and physical restrictions during labour and birth

For many people, performing turakanga (strengthening ceremony connected with childbirth), waituhi (performing certain rites over a woman at or after childbirth), hands on healing and the ability to move freely are important aspects of whakamamae (labour) and whakawhānau (giving birth). Energy can be transferred via movement and touch, for example, rongoā māori (traditional treatments), such as mirimiri (massage), and practices such as acupressure and acupuncture. It is commonplace during IOLs to attach monitoring equipment, intravenous lines and other devices, and such equipment often restricts movement and hands-on contact. Consider less restrictive solutions where possible.

In making the recommendations for IOL, the panel considered the implications of limited resources and capacity within the current New Zealand health system if women were routinely offered IOL for clinical indications currently managed expectantly. The panel also considered the resources required for women being managed expectantly, such as specialist consultations, clinical assessments and ultrasound scans. Maternity services should accommodate requests for IOL if IOL options are available at the service. The panel acknowledges that not all services can provide IOL at all times due to limited resources. Resources and costs were beyond the scope of this guideline.

Each clinical indication listed below briefly summarises the condition and the evidence for IOL. Summaries of selected observational studies are available in Appendix C.

Pregnancy lasting longer than 41 weeks' gestation

Approximately one in four pregnancies lasts longer than 41 weeks' gestation. The risk of stillbirth or early neonatal death increases with gestational age after 40 weeks' gestation (MacDorman et al 2015). Prolonged pregnancy is one of the most common indications for IOL.

Summary of evidence

The panel identified one Cochrane review (2018), three systematic reviews (2003, 2008, 2009) and one RCT published since the most recent review. The trials included in the three earlier systematic reviews were all included in the Cochrane review and thus are not described here.

A Cochrane systematic review including 30 trials of 12,479 women from a range of upper- and lower-income countries (Middleton et al 2018) compared a policy of IOL with a policy of expectant management. IOL was undertaken at or beyond term (37–41 weeks' gestation), using a variety of methods. There was no gestational age limit imposed for expectant management in nine trials; the remaining trials identified expectant management as the provision of IOL between 41 weeks and 44 weeks of pregnancy if labour had not spontaneously occurred. Perinatal mortality was the primary outcome in 20 of the 30 studies. Significantly fewer perinatal deaths occurred in the IOL group (two deaths) than the expectant management group (16 deaths) (RR 0.33, 95% CI 0.14–0.78; 20 trials; 9,960 infants; moderate quality). The NNT with IOL in order to prevent one perinatal death was 426 (95% CI 338–1,337). For planned subgroup analysis, the authors collapsed the trials into three groups (<41 weeks' gestation, 10 trials; ≥41 weeks' gestation, 19 trials; and 37–42 weeks' gestation, 1 trial). For the primary outcome of perinatal death, no difference between timing of IOL subgroups was found.

For women in the IOL groups, there were significantly fewer caesarean sections compared with the expectant management groups (RR 0.92, 95% CI 0.85–0.99; 27 trials; 11,738 women; moderate quality). In subgroup analysis, this reduction was significant only in women induced at ≥41 weeks' gestation. There was no difference between groups for assisted vaginal birth (RR 1.07, 95% CI 0.99–1.16; 18 trials; 9,281 women). In subgroup analysis, the marginal increase was significant only in women induced <41 weeks' gestation. There was no difference between groups for postpartum haemorrhage (PPH) (RR 1.09, 95% CI 0.92–1.30; 5 trials; 3,315 women). NICU admission rate was lower when IOL was compared with expectant management (RR 0.88, 95% CI 0.77 to 1.01; 13 trials; 8,531 infants; moderate quality). Fewer babies had 5-minute Apgar score <7 in the IOL group compared with the expectant management group (RR 0.70, 95% CI 0.50–0.98; 16 trials; 9,047 infants; moderate quality), and fewer babies had meconium aspiration syndrome (RR 0.77 95% CI 0.62–0.96; 11 trials; 7,781 infants; moderate quality). Only two trials reported on maternal satisfaction. One trial had similar numbers of women indicate that they preferred the group to which they were allocated, whereas in the second trial, women allocated to induction were more likely to indicate that they would choose the same group again.

The Cochrane authors concluded that a policy of IOL at or beyond term compared with expectant management is associated with fewer perinatal deaths and fewer caesarean sections; NICU admissions were less frequent and fewer babies had low Apgar score. No important differences were seen for most of the other maternal and infant outcomes. Most of the important outcomes assessed using GRADE had a rating of moderate or low-quality evidence; with downgrading decisions generally due to study limitations, such as lack of blinding (a condition inherent in comparisons between policies of acting and waiting) or imprecise effect estimates. The authors concluded that although the absolute risk of perinatal death is small, it may be helpful to offer women appropriate counselling when considering the decision.

A multicentre RCT (INDEX) of 1,801 women from midwifery practices and hospitals in the Netherlands compared IOL at 41 weeks with expectant management (Keulen et al 2019). Women were eligible if they had a low risk, uncomplicated singleton pregnancy with cephalic presentation and certain gestational age of 40+5 to 41 weeks and no contraindications to expectant management. The IOL group was induced at 41– 41+1 weeks' gestation; the expectant management group awaited spontaneous onset of labour until 42 weeks' gestation. The primary outcome was a composite of perinatal and neonatal morbidity; defined as any one of 5-minute Apgar <7, NICU admission, arterial umbilical cord pH <7.05, meconium aspiration syndrome, brachial plexus injury or intracranial haemorrhage. Secondary outcomes included composite adverse maternal outcome (defined as any one of PPH ≥1000 mL, third- or fourth-degree perineal tear, admission to intensive care unit or manual removal of placenta). There was more risk of composite adverse perinatal outcome in the expectant management group; 28 (3.1%) compared with 15 women (1.7%) in the IOL group (risk difference - 1.4%, 95% CI -2.9%–0.0%; NNT 69; 95% CI 35–3,059). There were two perinatal deaths and eight NICU admissions in the expectant management group compared with one perinatal death and three NICU admissions in the IOL group. No neonatal deaths occurred. There was no significant difference in composite adverse maternal outcome (11.3% in the expectant group compared with 13.6% in the IOL group). The caesarean section rate was 10.8% in both groups. They did not report on maternal satisfaction.

Discussion

The evidence included in the systematic reviews is limited in quality with evidence of heterogeneity, specifically in relation to the gestational age at which IOL was offered compared with the expectant management groups. These differences make effective comparisons between groups difficult. However, 75% of participants in the Cochrane review had IOL at ≥41 weeks' gestation, and the sensitivity analysis including only these studies showed the same benefits of IOL with no harms.

A policy of routine IOL at or beyond 40 weeks' gestation was associated with fewer perinatal deaths, fewer caesarean sections and fewer babies with low Apgar scores and meconium aspiration syndrome compared with expectant management. The panel recommends that clinicians have informed discussions with women around the time of their estimated due date to discuss the benefits of IOL for women whose pregnancies may be prolonged. The panel acknowledges that women's experience of IOL for this condition has not been fully explored.

For women who choose expectant management, identify and document a plan for ongoing assessment of the woman's and baby's wellbeing and provide the opportunity to revisit the offer of IOL at any time. Consider additional maternal and fetal monitoring if clinically indicated (for example, additional antenatal risk factors or from 42 weeks' gestation). The panel has not provided specific guidance on additional monitoring because there is no evidence to support any particular method or frequency, and thus each DHB will need to identify and develop its own pathway. If any concerns about maternal or fetal wellbeing arise, then the clinician should re-discuss the benefits of IOL in light of the new context and re-offer IOL.

SWEPIS (SWEdish Post-term Induction Study) is a multicentre RCT in Sweden designed to evaluate if IOL at 41 weeks improves perinatal outcomes compared with expectant management with IOL at 42 weeks. The trial is complete, but results were not available when the panel completed its review of the evidence.

Recommendation	Level of evidence	Strength of recommendation
Offer IOL between 41 ⁺⁰ and 42 ⁺⁰ weeks' gestation to women with uncomplicated pregnancies, to reduce the risks of perinatal death, caesarean section, 5-minute Apgar <7 and meconium aspiration syndrome.	Level 1; moderate quality	Conditional

Research gap

- To explore risk profiles (including age, BMI, ethnicity, smoking), values and preferences, perspectives and experiences of women being offered IOL or expectant management at or beyond term within the New Zealand context.

Pre-labour rupture of membranes at 37 weeks' or more gestation

In approximately 1 in 12 pregnancies at term, the membranes rupture before labour starts. Approximately 79% of women will spontaneously labour within 12 hours of ruptured membranes (Middleton et al 2017). The risk of infection increases with the duration of ruptured membranes. PROM is a common indication for IOL.

Summary of evidence

One systematic review was identified.

A Cochrane systematic review including 23 RCTs of 8,615 women with PROM at ≥ 37 weeks' gestation compared planned early birth with expectant management (Middleton et al 2017). Planned early birth was defined as a decision to expedite birth through IOL or by caesarean section immediately or within 24 hours, and expectant management was defined as an intended delay of at least 24 hours. The primary maternal outcomes were infectious morbidity (chorioamnionitis and/or endometritis), caesarean section and serious morbidity or mortality. Primary neonatal outcomes were early-onset neonatal sepsis (definite or probable) and perinatal death. Women who had planned early births were at reduced risk of maternal infectious morbidity compared with women who had expectant management (RR 0.49; 95% CI 0.33–0.72; eight trials; 6,864 women; low quality), and their neonates were less likely to have early-onset neonatal sepsis (RR 0.73; 95% CI 0.58–0.92; 16 trials; 7,314 infants; low quality).

No differences were found between the planned early birth and expectant management groups for caesarean section (average RR 0.84; 95% CI 0.69–1.04; low quality); serious maternal morbidity or mortality (no events reported; three trials; 425 women; very low quality); definite early-onset neonatal sepsis (RR 0.57; 95% CI 0.24–1.33; very low quality) or perinatal death (RR 0.47; 95% CI 0.13–1.66; moderate quality). The neonates in the planned early birth group were less likely to be admitted to NICU (RR 0.75; 95% CI 0.66–0.85). No clear differences between groups were observed for endometritis, uterine rupture, postpartum haemorrhage, stillbirth, neonatal mortality or 5-minute Apgar score <7.

Only two trials reported on maternal views of care. One trial recorded responses to the question “How do you experience your plan of treatment after PROM?” by a visual analogue scale (0 = very negative to 100 = very positive) and observed that women who had planned early births had a more positive experience compared with expectant management women (mean difference 11.8 higher; 95% CI 4.36–19.24; 93 women). Another study reported that women who had planned early births were less likely to report that they liked no part of their management (RR 0.43; 95% CI 0.36–0.52; 5,041 women) and were more likely to report that there was nothing they disliked about their management (RR 1.2; 95% CI 1.10–1.30; 5,041 women) compared with expectant management women.

The authors concluded that for PROM at 37 weeks’ gestation or later, planned early birth (with IOL methods such as oxytocin or prostaglandins, PG) reduces the risk of maternal infectious morbidity and neonatal sepsis compared with expectant management, with increased maternal satisfaction.

Discussion

The evidence is based on a systematic review in which the review authors noted that “the quality of the trials and evidence was not high overall, and there was limited reporting for a number of important outcomes”. Women should be well informed of the benefits of IOL and be supported in their choice.

For women who choose expectant management, identify and document a plan for ongoing assessment of the woman and their baby’s wellbeing, and provide the opportunity to revisit the offer of IOL at any time. Consider additional maternal and fetal monitoring as time goes on. If any concerns about maternal or fetal wellbeing arise, then the clinician should re-discuss the benefits of IOL in light of the new context and re-offer IOL. Timing of IOL should be mutually agreed.

The *Referral Guidelines* for consulting obstetric and related medical services (Ministry of Health 2012) flag that an LMC should recommend the woman consults with a specialist within 24 hours following PROM at term. The management of preterm PROM was considered beyond this guideline’s scope.

Recommendation	Level of evidence	Strength of recommendation
<p>For women with PROM at ≥ 37 weeks' gestation, offer planned early birth* to reduce the risks of maternal infectious morbidity, definite or probable early-onset neonatal sepsis and NICU admission.</p> <p>* immediate intervention or intervention within 24 hours</p>	Level 1; low quality	Conditional

Practice points

- For women with PROM, share information with the women as early as practical after rupture of membranes to support informed decision-making.
- Unless immediate IOL is planned, avoid digital vaginal examination.
- If neonates are at risk of early-onset neonatal group B streptococcal sepsis (Darlow et al 2014; RANZCOG 2016), offer immediate IOL.
- If liquor is meconium stained, consider immediate IOL.

Research gaps

- In women with PROM at term, to further evaluate the effect of planned early IOL compared with expectant management on maternal, fetal, neonatal and longer-term childhood outcomes, along with the impact on maternity services.
- In women with PROM at term, to evaluate the effect of different methods of cervical ripening on outcomes.

Suspected small for gestational age / fetal growth restriction

Small for gestational age (SGA) is defined as an infant with birthweight under the 10th centile or a fetus with estimated fetal weight (EFW) under the 10th centile. Customised standards to define SGA have a stronger association with perinatal morbidity and mortality than population standards (NZMFM 2014). Fetal growth restriction (FGR) is defined as a fetus that has failed to reach its growth potential, but this is more difficult to define in practice. Identification and management of an SGA baby are essential to prevent or minimise adverse outcomes.

Summary of evidence

One systematic review was identified.

A Cochrane review (Bond et al 2015) evaluating the effects of immediate birth compared with expectant management on the neonatal, maternal and long-term outcomes for a compromised baby found three trials that met the inclusion criteria. Two trials compared outcomes for babies with intrauterine growth restriction (IUGR) (a pilot study of 33 women that became the DIGITAT study and the DIGITAT study), and one study of 54 women with pregnancies complicated by oligohydramnios. IUGR was defined as failure of a baby to reach its growth potential due to maternal, fetal or placental factors, as distinguished from SGA. The intervention was planned early birth ≥ 37 weeks' gestation initiated within 24 hours of randomisation and expectant management involved waiting 24 hours for spontaneous labour or, in the absence of other complications, IOL at >41 weeks' gestation. The primary outcomes were perinatal and maternal mortality and morbidity. They did not report on maternal satisfaction.

For the purposes of this guideline, the DIGITAT trial that contributed most of the evidence to the Cochrane review will be reviewed in more detail. The Dutch multicentre DIGITAT trial (Boers et al 2010) randomised 650 women with suspected IUGR >36 weeks' gestation to IOL (within 48 hours) or expectant management (monitoring until 41 weeks' gestation with daily fetal movement counting and twice-weekly cardiotocography (CTG), ultrasound and pre-eclampsia screening). Suspected IUGR was defined as one or more of fetal abdominal circumference (AC) under the 10th centile, EFW under the 10th centile or flattening of the growth curve in the third trimester (as judged by a clinician). Fetuses with normal and abnormal dopplers were included. The primary outcome was a composite of neonatal mortality and morbidity. There was no difference between groups in the composite neonatal outcome (difference -0.8% , 95%CI -4.3% – -2.8% ; low quality). There were no perinatal deaths. There was no difference between groups for caesarean section (difference 0.3% , 95% CI -5.0% – -5.6% ; low quality) or PPH (difference -1.5% , 95%CI -4.5% – -1.5%). There was one maternal death reported in the IOL group that occurred 10 days postpartum and was unrelated to the intervention. IOL was associated with fewer cases of pre-eclampsia (difference -4.2% , 95%CI -7.7% – -0.6%). There was no difference between groups for 5-minute Apgar score <7 (difference 1.6% , 95%CI -0.2% – -3.4%) or NICU admission (difference -1.2% , 95%CI -4.0% – -1.6% ; very low quality). There was a difference in gestational age at birth; where women induced had a shorter duration of pregnancy (266 days compared with 277 days, MD -9.9 days; 95% CI -11.3 to -8.6).

Discussion

The evidence is strongly influenced by a single trial with unclear risk of bias that was not powered to detect differences between groups for late stillbirth. In settings where detailed Doppler studies are available, the decision about IOL needs to be individualised, in consultation with an obstetrician. Factors to consider include: maternal perception of fetal movements; CTG; ultrasound findings (liquor volume, Doppler studies, severity of growth restriction) and maternal preference. The quality of the umbilical Doppler studies would appear to be important.

The 2014 New Zealand Maternal Fetal Medicine Network's (NZMFM's) *Guideline for the Management of Suspected Small for Gestational Age Singleton Pregnancies and Infants after 34 weeks' Gestation* reviewed timing of birth. The guideline differentiates management strategies based on the availability of Doppler studies to stratify risk and whether the ultrasound scan findings are normal or abnormal. This stratified plan is supported by an observational study that shows reduced maternal and neonatal morbidity with expectant management for lower risk babies (Veglia et al 2018). The panel identified the need to ensure consistency with those guideline practice points regarding timing of birth. Note: The NZMFM's guidelines refer to planned birth, whereas this guideline refers to planned IOL.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice points

- For women with suspected SGA fetus or FGR, in settings where detailed Doppler studies are unavailable, offer IOL at around 38 weeks' gestation (or earlier if concerned).
- For women with suspected SGA fetus with abnormal umbilical artery Dopplers, consider offering IOL at around 37 weeks' gestation (low threshold for planned birth if there is any concern about maternal or fetal wellbeing or if there is suspected cessation of fetal growth).
- For women with a suspected SGA fetus with abnormal middle cerebral artery (MCA), CPR or uterine artery Dopplers or EFW under the 3rd centile, offer IOL at around 38 weeks' gestation (or earlier if concerned).
- For women with suspected SGA fetus with normal MCA, CPR and uterine artery Dopplers and EFW at or over the 3rd centile, offer IOL at around 40 weeks' gestation (or earlier if concerned). These babies are likely to be constitutionally small and are at lower risk of adverse outcomes.

Research gap

- For women with suspected SGA fetus / FGR, to further evaluate planned IOL at different gestational ages, compared with expectant management with different methods of fetal monitoring, on outcomes such as perinatal death, pre-eclampsia and the women's perspectives and experiences.

Diabetes in pregnancy

Gestational diabetes mellitus (GDM) is a growing problem in New Zealand, affecting approximately 1 in 20 pregnancies. The rate varies by maternal ethnicity and by geographic region. Diabetes in pregnancy is associated with an increased risk of maternal and infant adverse outcomes. Timely diagnosis, treatment and continued follow-up are essential to prevent or minimise these adverse outcomes.

Gestational diabetes

Summary of evidence

One systematic review was identified.

A Cochrane systematic review (Biesty et al 2018a) set out to compare planned birth at or near term with expectant management in women with gestational diabetes. The intervention was planned birth at 37–40 weeks' gestation, and the control group was awaiting spontaneous labour in the absence of maternal or fetal complications. The primary outcome was maternal and perinatal mortality and morbidity.

One RCT was included in the review. The multicentre GINEXMAL trial in Italy, Slovenia and Israel (Alberico et al 2017) randomised 425 women with GDM at 38 weeks' gestation to IOL or expectant management. IOL was undertaken at 38 weeks' gestation, using dinoprostone for cervical ripening (vaginal or intracervical) followed by artificial rupture of membranes (ARM) and oxytocin. Women allocated expectant management were followed up twice a week with CTG and biophysical profile until 41 weeks' gestation and induced at that time if they had not yet spontaneously laboured. The primary outcome was caesarean section. The population was considered to be low risk, as women with EFW >4,000 g were excluded. There was no difference in caesarean section (IOL 12.6% vs expectant 11.8%, RR 1.06; 95%CI 0.63–1.77), assisted vaginal birth or PPH. There were no perinatal deaths and no difference in 5-minute Apgar <7, shoulder dystocia or NICU admission. The authors concluded that for women with GDM but no other maternal/fetal conditions, there was no difference in birth outcomes. However, the study was underpowered to detect significant difference in uncommon outcomes. It did not report on maternal satisfaction.

Discussion

Based on observational data, GDM may be associated with adverse maternal and infant outcomes. Treatment of GDM during pregnancy is associated with reduced perinatal morbidity and mortality. There is insufficient high-quality evidence to show that IOL reduces adverse outcomes. Moreover, there is insufficient evidence to make a recommendation about optimal timing of planned birth. Factors to consider in individualising timing of birth include glucose control, EFW, disproportion between fetal AC and other measurements, additional antenatal risk factors and maternal preference.

Limitations of the GINEXMAL study were identified as:

- The study did not reach its planned sample size.
- The study was underpowered to detect significant differences in uncommon outcomes.
- Women with a fetus EFW >4,000 g were excluded.
- Despite randomisation, there were more nullipara in the IOL group, and there was no adjustment for parity.

- The findings may not be generalisable to the New Zealand population (for example, in the study, mean BMI was 25, 75% were White, >50% were managed by diet alone, mean blood glucose level of 5.4 mg/dL was considered well controlled, participants had regular antenatal fetal surveillance, mean EFW was 3,200 g and different methods were used for diagnosing GDM and for cervical ripening).

However, results were reassuring in that for women with GDM induced at 38 weeks' gestation, there was no increased risk of caesarean section.

The 2014 clinical practice guideline *Screening, Diagnosis and Management of Gestational Diabetes Mellitus in New Zealand* (Ministry of Health 2014) reviewed timing of birth. It was based on low and very-low quality evidence from one RCT, one quasi-randomised RCT and one retrospective cohort study. In the executive summary, the guideline states that "Elective delivery prior to 40 weeks' gestational age is not recommended in women who have no obstetric complications (including hypertension, pre-eclampsia, large for gestational age infant \geq 90th centile, maternal age >40 years) and who have had good glucose control (>90% of glucose readings within glucose treatment targets) throughout their pregnancy" (page 34). The panel endorses this practice point.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Pre-existing diabetes mellitus

Summary of evidence

One systematic review was identified.

A Cochrane systematic review (Biesty et al 2018b) set out to compare planned birth at or near term with expectant management in women with pre-existing type 1 or 2 diabetes. The intervention was planned birth at 37–40 weeks' gestation, and the control group was awaiting spontaneous labour in the absence of maternal or fetal complications. The primary outcome was maternal and perinatal mortality and morbidity. No eligible RCTs were identified for inclusion.

Discussion

International guidelines were reviewed:

- The Australasian Diabetes in Pregnancy Society (ADIPS) consensus guideline (McElduff et al 2005) recommends that birth be at term unless there are obstetric or fetal indications. IOL should also be based on obstetric and fetal indications.
- The National Institute for Health and Care Excellence (NICE) clinical guideline (2015) recommends that women with type 1 or 2 diabetes mellitus be advised to undergo planned birth between 37 and 38+6 weeks' gestation. It also states that elective birth before 37 weeks' may be indicated if there are metabolic, maternal or fetal complications.

- The American College of Obstetricians and Gynaecologists (ACOG 2018) recommends that for women with well-controlled pre-gestational diabetes, birth should be planned at full term (39–39+6 weeks' gestation) or earlier (from 36 to 38+6 weeks' gestation) if the woman has vascular complications, poor glucose control or a previous stillbirth.

There is an increased risk of stillbirth in mothers with pre-pregnancy diabetes. There is significant disagreement between international guideline recommendations for timing of birth. There is also a need for local adaptation of international guidelines in order to take into consideration the New Zealand context and population characteristics (for example, proportion of pregnant women with poorly controlled diabetes who book late).

The panel recommends that, if pre-pregnancy diabetes is well controlled, then there is no need to offer IOL unless there are other obstetric or fetal indications present (for example, impaired renal function, changing insulin requirements, SGA, pre-eclampsia, poor adherence to treatment, etc). High-quality evidence is needed before a recommendation to offer IOL <39 weeks' gestation can be made. Individualised care should be provided based on additional risk factors or obstetric and/or fetal indications.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice points

- For women with gestational diabetes, continue expectant management to at least 40 weeks' gestation, in the setting of good glycaemic control, normal fetal growth and no obstetric complications.
- For women with type 2 diabetes, continue expectant management to 39 weeks' gestation, unless there are obstetric or fetal indications for earlier birth or diabetes complications, such as vascular disease.
- For women with type 1 diabetes, manage on a case-by-case basis.

Research gap

- For women with diabetes in pregnancy, to evaluate the effect of IOL at different gestational ages versus expectant management on maternal, perinatal and neonatal outcomes, including women's perspectives and experiences, stratified by type of diabetes.

Maternal obesity

One in four women (26.4%) who gave birth in New Zealand in 2017 were identified as having obesity (BMI $\geq 30\text{kg/m}^2$) at first registration with their primary health care provider (Ministry of Health 2019b). Women with maternal obesity (obesity in pregnancy) are at higher risk of pregnancy-related complications, such as diabetes and hypertension. Moreover, women with maternal obesity are more likely to have a caesarean section and postpartum haemorrhage and are more likely to have a stillbirth; their babies are more likely to be large for gestational age (LGA) and be admitted to NICU (CMACE 2010).

Summary of evidence

No studies were identified on IOL in the setting of maternal obesity.

Discussion

There is an association with the degree of maternal obesity and the risk of stillbirth, with increasing risk as BMI increases in a dose-dependent relationship, but there is no clear cut-off. New Zealand-specific data from the PMMRC 2016 annual report (PMMRC 2018) is limited by incomplete BMI reporting. The BMI recorded at pregnancy registration is not necessarily the pre-pregnancy BMI, is not always measured and may be based on maternal recall. The evidence for IOL for maternal obesity to improve outcomes is limited to observational data. The panel acknowledges there may be an increased risk of late stillbirth in women with obesity in pregnancy identified in observational data. There was no high-quality evidence to confirm the benefits or harms of IOL or expectant management in women with maternal obesity. Thus the panel considers there is insufficient evidence to recommend IOL when obesity is the only risk factor.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- For women with maternal obesity, in the absence of other risk factors or pregnancy complications, do not offer IOL.

Research gaps

- For women with maternal obesity, to evaluate the effect of IOL at 39 weeks or at 40 weeks versus expectant management on maternal, perinatal and neonatal outcomes stratified by category of obesity.
- To explore views and preferences of women with maternal obesity regarding IOL as a potential intervention to reduce pregnancy-related complications.

Advanced maternal age

One in five women who gave birth in New Zealand in 2015 was 35 years of age or older (Ministry of Health 2019b). Women who are older in pregnancy are at higher risk of pregnancy-related complications, such as diabetes and hypertension. The risk of stillbirth increases slightly for women who are 35 years of age or older. The PMMRC reported that, in New Zealand in 2016, there was an association between maternal age of 40 years or older and perinatal death (PMMRC 2018).

Summary of evidence

One RCT and an individual participant data (IPD) meta-analysis were identified.

An open-label RCT of 619 primigravida aged 35 years or older compared IOL with expectant management (Walker et al 2016a). The intervention was IOL at 39–39+6 weeks' gestation, and the control was expectant management defined as waiting for spontaneous labour (unless a situation developed requiring IOL earlier) with IOL offered between 41 weeks and 42 weeks' gestation. There was no difference between groups for the primary outcome of caesarean section (32% IOL, 33% expectant management; RR 1.30, 95%CI 0.96–1.77). There were no maternal or infant deaths. There was no difference between groups for NICU admission (RR 0.80, 95%CI 0.26–3.06). The authors concluded that IOL at 39–39+6 weeks' gestation had no effect on caesarean section. The trial was not powered to detect a difference in perinatal death. Eighty-three% of participants returned the Childbirth Experience Questionnaire, which showed no difference in experience between IOL and expectant management.

Walker et al (2016b) reported on an IPD meta-analysis of RCTs that compared IOL at term with expectant management (singleton or multiple pregnancy) where caesarean section was the primary outcome. The authors reported data for women aged 35 years or older. Only 5 of 31 identified trials agreed to participate in the IPD, and data from 2,526 women were included. There was no evidence of a difference between groups for the risk of caesarean section (odds ratio (OR) 1.2; 95%CI 0.74–2.0; 5 trials; 2,526 participants; high quality). There were no perinatal deaths. The authors concluded that IOL in women 35 years or older had no effect on the risk of caesarean section. They did not report on maternal satisfaction.

Discussion

There is limited evidence for IOL solely for advanced maternal age. There was no high-quality evidence from large RCTs to confirm the benefits or harms of IOL or expectant management in women of advanced maternal age. Women who are older may experience defensiveness or anxiety in their pregnancies. To support shared decision-making, inform women of the potential pregnancy complications in women aged 35 years or older, the association found in the PMMRC data on perinatal mortality in women aged 40 years or older and the lack of evidence to support IOL for age alone to improve adverse outcomes.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- For women aged 40 years and over, consider offering IOL at around 40 weeks' gestation.

Research gaps

- For women with advanced maternal age, to evaluate the effect of IOL at 39 weeks or at 40 weeks versus expectant management on maternal, perinatal and neonatal outcomes.
- To explore perspectives and experiences of women with advanced maternal age regarding IOL as a potential intervention to reduce pregnancy-related complications.

Reduced fetal movements

Approximately 1 in 10 women contact their health care provider due to concern about reduced fetal movements (RFM) during the third trimester (Gardener et al 2017). Maternal perception of fetal movement has long been used as an indicator of fetal wellbeing and reduced or decreased fetal movement is associated with adverse perinatal outcomes (Gardener et al 2017).

Summary of evidence

One RCT was identified evaluating IOL as part of a care package aimed at reducing stillbirth. A stepped-wedge cluster-randomised trial (AFFIRM) was undertaken in the United Kingdom and Ireland, evaluating a RFM care package compared with usual care across 33 maternity hospitals (Norman et al 2018). The intervention included an e-learning package for clinicians, a leaflet for pregnant women distributed around 20 weeks' gestation and a standardised management protocol for women presenting with RFM from 24 weeks' gestation. The management protocol included assessment (CTG within 2 hours of presentation, measurement of liquor volume within 12 hours and a growth scan the next working day) and planned birth at 37 weeks' gestation or more if any of the above results were abnormal (EFW <10th centile, AC <10th centile, deepest liquor pool <2 cm, abnormal CTG) or recurrent RFM. The intervention was compared with a period of usual care provided by the hospitals to women with RFMs

before the introduction of the intervention. The primary outcome was stillbirth. During the study, 409,175 women gave birth. There was no difference in stillbirth between the intervention and control periods (4.06 per 1,000 vs 4.40 per 1,000, adjusted odds ratio (aOR) 0.90 95% CI 0.75–1.07, $p=0.23$). There was no difference in perinatal death or NICU admission. IOL and caesarean section were more common during the intervention period. They did not look at maternal satisfaction. The authors concluded that the intervention package was not effective in reducing stillbirth, led to a significant increase in interventions and could not be recommended.

Discussion

The perception of RFM may be associated with stillbirth in that half of women whose pregnancies end in stillbirth recall RFM in the preceding week. Whether RFM is a symptom of inevitable stillbirth or whether it can be used as an alert to prompt action and improve outcomes is unclear (Norman et al 2018). Compared with the general population, RFM is also associated with other adverse perinatal outcomes, such as SGA. There have been no studies investigating timing of birth in women with RFM, therefore no recommendations can be made. Current evidence from the AFFIRM trial suggests that interventions increased with a programme of awareness of fetal movements and implementation of a care package to manage women with RFM but did not reduce the risk of stillbirth. There is currently no high-quality evidence to confirm the benefits or harms of IOL or expectant management for women with RFM.

The Perinatal Society of Australia and New Zealand (PSANZ) guideline on RFM (Gardener et al 2017) does not include any specific recommendations for IOL for women with RFMs from 28 weeks' gestation. The guideline provides a practice point that specialist medical opinion should be sought and further management be individualised where there is concern due to RFM.

The panel agreed that there is no evidence to support IOL for women who subjectively experience RFM when the objective assessment of the mother and baby are normal and there are no other clinical concerns. It identified a need to address the increasing practice of IOL for RFM alone. The panel emphasised that care should be individualised for women who have recurrent presentations of RFM or other antenatal risk factors.

My Baby's Movements (MBM) is a stepped wedged cluster RCT designed to test the impact of a package of interventions on the risk of stillbirth >28 weeks' gestation, at several centres across Australia and New Zealand. The trial is complete, but results were not available when the panel was completing its review of the evidence.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- For women with reduced fetal movements, in the presence of normal maternal and fetal assessment, continue expectant management.

Research gaps

- For individual women experiencing RFM, to evaluate the effect of IOL vs expectant management, on perinatal mortality and morbidity, and including other outcomes such as maternal morbidity,
- maternal anxiety, perspectives and experiences, and health care utilisation and costs.

Hypertension in pregnancy

Approximately 1 in 12 women will have high blood pressure in pregnancy. Hypertension in pregnancy includes chronic hypertension, gestational hypertension and pre-eclampsia. There is an association between hypertension in pregnancy and increased maternal morbidity and mortality (Ministry of Health 2017).

Summary of evidence

One systematic review was identified.

A 2017 Cochrane systematic review including five RCTs of 1,819 women with well-controlled chronic hypertension, gestational hypertension or non-severe pre-eclampsia >34 weeks' gestation compared planned early birth with expectant management (Cluver et al 2017). Two studies compared IOL before term, 34–36 weeks' gestation (Broekhuijsen et al 2015) and 34–37 weeks' gestation (Owens et al 2014) with a comparison group who were monitored until 37 weeks' gestation when induction began (if labour had not started spontaneously). Three studies compared IOL at term or closer to term, 37 completed weeks (Hamed et al 2014) and 36–41 weeks' gestation (Koopmans et al 2009; Majeed et al 2014) with a group monitored until 41 weeks when induction began if labour had not started spontaneously. The primary outcomes of this review were composite maternal morbidity and mortality and composite perinatal morbidity and mortality. Three trials did not report on maternal mortality, and two did not report on perinatal mortality. Two of the trials were deemed to have a low risk of bias and the other three moderate risk of bias.

For women randomised to planned early birth, there was a lower risk of a composite of maternal mortality and severe morbidity (RR 0.69; 95% CI 0.57–0.83; 2 trials; 1,459 women; high-quality evidence), haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (RR 0.4; 95% CI 0.17–0.93; 3 trials; 1,628 women) and severe renal impairment (RR 0.36; 95% CI 0.14–0.92; 1 trial; 100 women). On subgroup analysis of hypertensive condition, there was no clear difference in maternal morbidity and mortality between groups. There were no differences between planned early birth and expectant management for caesarean section (RR 0.91, 95%CI 0.78–1.07; 4 trials; 1,728 women; moderate-quality evidence). Planned early birth was associated with higher rates of NICU admission (RR 1.65; 95% CI 1.13–2.40; 4 trials; 1,585 babies)

and respiratory distress syndrome (RR 2.24, 95% CI 1.20–4.18; 3 trials; 1,511 infants). There was insufficient information to draw conclusions on neonatal mortality. No studies reported on maternal satisfaction.

For the purposes of this guideline, the HYPITAT trial is reviewed in more detail. This trial contributed most of the evidence to the Cochrane review, and included participants with hypertension >36 weeks' gestation.

The multicentre HYPITAT trial (Koopmans et al 2009) randomised 756 women in the Netherlands with gestational hypertension (diastolic blood pressure of 95 mmHg or higher) or mild pre-eclampsia >36–41 weeks' gestation to IOL within 24 hours or expectant monitoring. IOL was associated with a reduced risk of severe hypertension and a reduced risk for a composite outcome of maternal mortality and morbidity compared with expectant monitoring (RR 0.71; 95% CI 0.59–0.86). Women randomised to IOL had shorter durations of pregnancy compared with those randomised to expectant management (38.7 weeks' gestation compared with 39.9 weeks' gestation respectively). There were no cases of eclampsia or maternal or neonatal death in either group. There was no difference in caesarean section, assisted vaginal birth, PPH, NICU admission, or low 5-minute Apgar score. The authors concluded that IOL should be advised for women with gestational hypertension or mild pre-eclampsia at a gestational age beyond 37 weeks' gestation. The number of women needed to undergo IOL to prevent one woman from progressing to severe hypertension or severe pre-eclampsia was 8. This trial was well designed with low risk of bias.

Discussion

Hypertension in pregnancy is associated with adverse maternal and perinatal outcomes. The HYPITAT study found significant improvement in adverse maternal outcome when IOL was offered to women with gestational hypertension or mild pre-eclampsia, with no increase in the incidence of caesarean section. A limitation of the trial was not differentiating between gestational hypertension and pre-eclampsia. Factors to consider in individualising timing of birth include the type and degree of hypertension and its treatment, maternal and fetal wellbeing, additional antenatal risk factors and maternal preference. The woman, her LMC midwife and the obstetric team would need to discuss the optimal timing together.

The 2017 clinical practice guideline *Diagnosis and Treatment of Hypertension and Preeclampsia in Pregnancy in New Zealand* (Ministry of Health 2017) provides recommendations related to timing of birth. The guideline differentiates management strategies based on the type of hypertension in pregnancy. The panel identified the need to ensure consistency with those guideline recommendations regarding timing of birth. No new high-quality evidence has been published since 2017. Thus the following recommendations are aligned with those of the 2017 clinical practice guideline.

Recommendation	Level of evidence	Strength of recommendation
For women with chronic hypertension and low risk of adverse outcomes, consider expectant management beyond 37 weeks' gestation with increased monitoring.	Level 1; moderate quality	Conditional
For women with gestational hypertension diagnosed after 37 weeks' gestation, consider IOL, to reduce the risks of severe hypertension, severe pre-eclampsia, HELLP syndrome, abruptio placenta, pulmonary edema, severe renal impairment and fetal growth restriction.	Level 1; moderate quality	Conditional
For women with pre-eclampsia diagnosed after 37 weeks' gestation, offer IOL.	Level 1; moderate quality	Conditional

Research gaps

- For women with hypertension in pregnancy, to further evaluate the effect of IOL versus expectant management on maternal, perinatal and neonatal outcomes, stratified by type of hypertension.
- To perform an individual patient meta-analysis on current data of women with different types of hypertension to provide more information on outcomes.

Antepartum haemorrhage of unknown origin

Approximately 1 in 20 women will experience an antepartum haemorrhage (APH), defined as bleeding from the genital tract from 24 weeks' gestation and before the birth of the baby (Bhandari 2014). Causes of APH are placenta praevia, placental abruption and local causes (for example, from the cervix). When a cause is not found, it is described as unexplained APH, or APH of unknown origin.

Summary of evidence

No studies were identified on IOL in the setting of APH of unknown origin.

Discussion

APH of unknown origin is associated with adverse outcomes, such as preterm birth, stillbirth, fetal anomalies and SGA (Bhandari et al 2014). The panel identified that APH is an indication for assessment by an obstetric specialist and may require increased monitoring of the pregnancy (for example, SGA, routine enquiry for intimate partner violence). If placental abruption were clinically diagnosed, most clinicians would recommend birth. However, there is no high-quality evidence to confirm the benefits or harms of IOL or expectant management for APH of unknown origin.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- In women with APH of unknown origin, in the presence of normal maternal and fetal assessment, consider expectant management.

Research gap

- In women with APH of unknown origin, to evaluate the effect of IOL vs expectant management on maternal, perinatal and neonatal outcomes.

Assisted reproductive technology

Approximately 1 in 37 women conceive using assisted reproductive technology (ART) (Fitzgerald et al 2018). ART refers to procedures that involve the in-vitro handling of both human oocytes and sperm, or embryos, with the objective of establishing a pregnancy. Observational data suggest an increased risk of obstetric and perinatal complications in singleton pregnancies conceived through in-vitro fertilisation or intracytoplasmic sperm injection when compared with spontaneous conception (Pandey et al 2012).

Summary of evidence

No studies were identified on IOL in the setting of pregnancy using ART.

Discussion

There is no high-quality evidence to confirm the benefits or harms of IOL or expectant management in pregnancies conceived through ART. Women who conceive via ART may experience increased rates of antenatal and postnatal anxiety and depression. It is important that pregnant women and their whānau are well supported to understand their individual pregnancy risk factors rather than relying on commonly held perceptions of risks associated with ART. Women may feel that ART is not sufficient reason in an uncomplicated pregnancy to warrant having an IOL. To support shared decision-making, inform women of the lack of evidence to support IOL to improve adverse outcomes associated with ART.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- In women who conceive using ART, in the absence of other risk factors or pregnancy complications, do not offer IOL.

Research gaps

- In women who conceive using ART, to evaluate the effect of IOL compared with expectant management on maternal, perinatal and neonatal outcomes.
- To explore perspectives and experiences of women who conceive using ART regarding IOL as a potential intervention to reduce pregnancy-related complications.

Suspected fetal macrosomia

In 2017, approximately 1 in 42 women gave birth to a high birthweight baby ($\geq 4,500$ g) (Ministry of Health 2019b). Macrosomia implies fetal growth beyond a specific weight (often set at 4,000 g or 4,500 g) regardless of gestational age, however, the antenatal diagnosis is often imprecise (Chatfield 2001). Large for gestational age (LGA) is defined as birthweight above the 90th centile for population, and the rate of LGA babies is increasing. Retrospective cohort studies show an association between high birthweight and risks to baby. However, it is difficult to estimate birthweight before the birth (clinical palpation and ultrasound biometry provide an EFW) (Chatfield 2001).

Summary of evidence

One systematic review was identified.

A 2016 Cochrane review, including four trials of 1,190 women, compared IOL to expectant management for suspected fetal macrosomia (Boulvain et al 2016). Macrosomia was defined as birth weight $>4,000$ g. The intervention was IOL at or near term (37–40 weeks' gestation), and expectant management was awaiting spontaneous labour until 42 weeks' gestation then offering IOL. Primary maternity outcomes were caesarean section or instrumental birth, and primary perinatal outcomes were shoulder dystocia, brachial plexus injury, any fracture and neonatal asphyxia. There was no clear effect of IOL on the risk of caesarean section (RR 0.91, 95% CI 0.76–1.09; moderate quality) compared with expectant management. IOL reduced shoulder dystocia (RR 0.6, 95% CI 0.37–0.98; moderate quality), and any fracture (RR 0.2, 95% CI 0.05–0.79; high quality). There was no effect on mode of birth, brachial plexus injury, or low 5-minute Apgar score. There were no long-term outcomes nor maternal satisfaction reported in any trial. The authors noted that the ideal timing for IOL for macrosomia cannot be specified from these data and that further trials of induction shortly before term for suspected macrosomia are justified.

For the purposes of this guideline, the trial that contributed most of the evidence to the Cochrane review will be reviewed in more detail. For the multicentre RCT of 818 women in France (Boulvain et al 2015), women were screened at 36–38 weeks' gestation and identified as potentially eligible if they had a singleton cephalic pregnancy with an estimated LGA fetus. Women then had an ultrasound and were included if ultrasound EFW was >95th centile, defined as 3,500 g at 36 weeks' gestation; 3,700 g at 37 weeks' gestation and 3,900 g at 38 weeks' gestation. Participants were randomised to IOL between 37 and 38+6 weeks' gestation or expectant management (defined as the continuation of pregnancy until either spontaneous labour or the development of a condition that warranting delivery according to the hospital's policy).

The study population included 10% of women with GDM not on insulin, and 30% of women with previous history of macrosomia. IOL reduced the rate of the composite primary outcome (shoulder dystocia, a range of birth injuries and death) when compared with expectant management (2% vs 6%, RR 0.32, 95% CI 0.15–0.71). There was no brachial plexus injury, intracranial haemorrhage or death in either group. The likelihood of spontaneous vaginal birth was higher in the IOL group (59% vs 52%, RR 1.14, 95% CI 1.01–1.29). The risk of anal sphincter tear was infrequent and not different between groups (2% vs 1%, RR 3.03, 95% CI 0.62–14.92). The authors concluded that the exact gestation at which doctors and parents will decide on induction cannot be specified from these data. Induction between 38 and 38+6 weeks' gestation, that is, at the later gestation considered, is likely to minimise the risks of iatrogenic prematurity but may not achieve much benefit in terms of birthweight and birth injury reduction. Induction at 37 weeks' gestation may have the opposite trade-off of risks and benefits.

Discussion

The panel discussed the differences between the Boulvain et al trial and the Cochrane review. The Boulvain et al trial does not reflect current New Zealand maternity practice: because of the absolute weights at each gestational age used to estimate LGA; women were routinely screened for LGA with ultrasound at 36–38 weeks' gestation; and the mean BMI of participants was 26kg/m². Moreover, the study was underpowered to detect significant differences in uncommon outcomes. The panel considered that IOL is not justified, due to the limitations of current RCT evidence in relation to the New Zealand context and in the absence of diabetes.

Big Baby is a multicentre RCT in the United Kingdom used to determine if a policy of IOL at 38+ weeks gestation in women with babies considered LGA (>90th customised centile of EFW) will reduce the incidence of shoulder dystocia compared with expectant management. The trial is now recruiting, and the panel awaits their results to help guide future practice.

Antenatal estimates of fetal weight are often inaccurate, and identification of macrosomia can increase anxiety for the pregnant woman and for clinicians. There is emerging research on the use of customised growth charts for EFW to predict adverse neonatal outcomes. It is important to provide information to women about the difficulty of assessing fetal size and diagnosing fetal macrosomia and the benefits and harms of IOL and expectant management.

There is currently insufficient evidence to make a clear recommendation about IOL for this condition.

Practice point

- In women with suspected macrosomia, in the absence of pregnancy complications, consider expectant management.

Research gaps

- In women with suspected macrosomia, to further evaluate the effect of IOL compared with expectant management on maternal, perinatal and neonatal outcomes, in the New Zealand context.

Multiple pregnancy

In New Zealand, approximately 1 woman in 50 will have a twin pregnancy. Twin pregnancy is associated with higher rates of anomaly, preterm birth, pre-eclampsia, FGR, GDM and complicated birth. At term, the cumulative loss rate for dichorionic twins is approximately 2%; and approximately 8% for monochorionic twins, secondary to the unique placental configuration and excess anomalies (NZMFM 2015).

Summary of evidence

One systematic review was identified.

A Cochrane review included two RCTs comparing elective birth at 37 weeks' gestation with expectant management for women with an uncomplicated twin pregnancy, including both dichorionic and monochorionic twins (271 women and 542 infants) (Dodd et al 2014). Both trials showed the average gestational age at delivery was earlier in IOL compared with expectant management (Suzuki et al 2000: 37.5 ± 0.4 weeks vs 39.0 ± 1.1 weeks; Dodd et al 2012: 37.3 ± 0.4 weeks vs 37.9 ± 0.5 weeks).

There was no difference between women having IOL versus expectant management for the three primary outcomes outlined by the review: perinatal death or serious perinatal morbidity (RR 0.34; 95% CI 0.01–8.35; two studies, 542 infants; low quality); maternal death or serious maternal morbidity (RR 0.29; 95% CI 0.06–1.38; one study, 235 women; low quality); or caesarean section (RR 1.05; 95% CI 0.83–1.32; two studies, 271 women; moderate quality). There was no difference between groups for instrumental vaginal birth; 5-minute Apgar <7 or NICU admission (low to unclear risk of bias; moderate-quality evidence). They did not report on maternal satisfaction. The authors concluded that IOL at 37 weeks' gestation did not appear to be associated with increased maternal or neonatal harms for uncomplicated twin pregnancies, but there were no data available on long-term outcomes.

Discussion

Although the systematic review evidence found no differences in short-term outcomes, the analysis was underpowered for uncommon outcomes, such as perinatal death, and did not report any long-term outcomes. Due to the current lack of high-quality evidence to confirm the benefits and harms of IOL or expectant management in women with multiple pregnancy, some international guidelines were reviewed.

- In *Multiple Pregnancy* (2015), the NZMFM advises that women with monochorionic twin pregnancies should have birth considered at 36–37 weeks' gestation due to concerns of increased risk. However, it states that this is a pragmatic approach, given there is no high-quality evidence to guide care in this setting.
- The *Maternal Group B Streptococcus in Pregnancy: Screening and management* guidelines of RCOG (2016) has a consensus-based recommendation that women with monochorionic twin pregnancies give birth by 37 weeks' gestation.
- The NICE *Twin and Triplet Pregnancy* guidelines (2019) recommend offering women with uncomplicated monochorionic diamniotic twin pregnancies planned birth at 36 weeks' gestation and uncomplicated dichorionic twin pregnancies at 37 weeks' gestation. Individualised assessment is recommended for complicated twins or for triplets.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice points

- For women with an uncomplicated monochorionic diamniotic twin pregnancy, consider offering IOL between 36 and 37 weeks' gestation.
- For women with an uncomplicated dichorionic twin pregnancy, consider offering IOL between 37 and 38 weeks' gestation.

Research gap

- In women with twin pregnancy, to further evaluate the effect of IOL vs expectant management on maternal, perinatal and neonatal outcomes, stratified by type of twins.

Reduced liquor under 41 weeks' gestation

The finding of reduced liquor or decreased amniotic fluid volume (oligohydramnios) is associated with adverse perinatal outcomes, such as SGA, but is usually found in the setting of a complicated pregnancy and less commonly in isolation (Rabie et al 2017). A review of RCTs concluded that single deepest vertical pocket measurement is the method of choice for the assessing liquor volume (Nabhan 2008). Reduced liquor is thus defined in this guideline as deepest vertical pocket <2 cm.

Summary of evidence

No studies were identified on IOL in the setting of reduced liquor.

Discussion

Observational studies (Rabie et al 2017; Morris et al 2014) identify an association between reduced liquor and adverse outcome, however, this evidence is considered to be of low quality. In addition, there are limitations to the diagnosis of reduced liquor; there are different measures of liquor volume (amniotic fluid index, single deepest pocket, subjective assessment), the measures are not reproducible and reduced liquor is not specifically predictive of adverse outcome. There is no high-quality evidence to confirm the benefits or harms of IOL or expectant management in the setting of isolated reduced liquor.

The finding of reduced liquor warrants a full clinical assessment, including history and examination of the woman to exclude spontaneous rupture of membranes (SROM) and identification of other antenatal risk factors. Clinicians could consider confirming the diagnosis with a repeat ultrasound scan. Single deepest pocket appears to be the most reliable measure to predict adverse outcomes. If reduced liquor is persistent, then consider regular follow-up clinical assessment.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- In women with reduced liquor as an isolated finding at <41 weeks' gestation, in the presence of normal maternal and fetal assessment, consider expectant management.

Research gap

- In women with reduced liquor at <41 weeks' gestation, to evaluate the effect of IOL compared with expectant management on maternal, perinatal and neonatal outcomes.

Obstetric cholestasis

Approximately 1 in 100 pregnant women will have obstetric cholestasis (also called intrahepatic cholestasis of pregnancy). This is a multifactorial condition characterised by pruritus in the absence of a skin rash with abnormal liver function tests, neither of which has an alternative cause and both of which resolve after birth.

There are associated pregnancy risks, which include spontaneous preterm birth and meconium-stained liquor (Ovadia et al 2019) and maternal morbidity, such as intense itching and difficulty sleeping (RANZCOG 2011).

Summary of evidence

One RCT was identified.

One RCT of 62 women examined the timing of birth intervention and was judged to be at low risk of bias (Chappell et al 2012). There were no stillbirths or neonatal deaths in the 'early delivery' or the 'await spontaneous labour' groups. There were no significant differences between the two groups in the rates of caesarean section (RR 0.68; 95% CI 0.30–1.52; low quality) or NICU admission (RR 0.55; 95% CI 0.05–5.76; low quality).

There was no report on maternal satisfaction. Caution is advised in interpreting these data due to the small sample size.

Discussion

Based on the evidence from a Cochrane review on interventions for treating obstetric cholestasis (Gurung et al 2013), it was noted that sometimes women are induced for symptom control and that this is reasonable if other treatments are ineffective. There is no high-quality evidence to confirm the benefits or harms of IOL or expectant management for women with obstetric cholestasis.

Current practice in some places is to offer IOL for stillbirth prevention, sometimes as early as 37 weeks' gestation, but the evidence to support this approach is scarce. In the last several decades, perinatal death rate from obstetric cholestasis is comparable with whole population figures (Kenyon and Girling 2011). Two systematic reviews have found no increased risk of stillbirth in women with obstetric cholestasis (Henderson et al 2014; Ovadia et al 2019). Stratified by bile acid level, the association with stillbirth was found only in women whose bile acids were ≥ 100 (Ovadia et al 2019).

The RANZCOG guideline on obstetric cholestasis (Kenyon and Girling 2011) recommends a discussion with women regarding IOL after 37 weeks' gestation, to include: the increased risk of perinatal morbidity from early intervention; the case for intervention being possibly stronger in those with more severe biochemical abnormality; the increased risk of maternal morbidity from intervention and the inability to predict stillbirth if the pregnancy continues.

The panel suggests that the possibility of IOL be discussed with specific women and care be individualised based on clinical considerations (such as symptoms, gestational age at diagnosis and serum bile acid concentration) in consultation with an obstetrician.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- For women with obstetric cholestasis, if symptomatic or if serum bile acid concentration ≥ 100 , consider IOL; otherwise consider expectant management.

Research gap

- In women with obstetric cholestasis, to further evaluate the effect of IOL compared with expectant management on maternal, perinatal and neonatal outcomes.

Previous stillbirth

In New Zealand, approximately 1 in 500 women will experience a late stillbirth (at 28 weeks' gestation or more), and about one-third of these are unexplained (McCowan et al 2017; PMMRC 2018). The effect of a stillbirth on families can be devastating and long-term and can create anxiety in any future pregnancy. Preconceptual counselling and individualised antenatal care can assist in identifying and potentially modifying risk factors and may improve future pregnancy outcomes. The stillbirth rate in New Zealand in 2016 was 5.1/1,000 births (PMMRC 2018).

Summary of evidence

No studies were identified on IOL in the setting of previous stillbirth.

Discussion

Large population-based studies have shown an increased risk of recurrent stillbirth in a subsequent pregnancy (Lamont et al 2015; Malacova et al 2018). These studies do not identify gestation at the first or any subsequent stillbirths and therefore cannot help with decision-making around timing of induction for a stillbirth. These studies are also limited by the lack of adjustment for other known risk factors for stillbirth. There is no high-quality evidence to confirm the benefits or risks of IOL or expectant management for women with previous stillbirth.

The panel acknowledges that many of the causes of stillbirth remain unknown and stillbirth is difficult to predict or prevent. The anxiety of women who have experienced a previous stillbirth and the impact of that experience may affect decision-making in their current pregnancy. Women who have had a previous stillbirth may request IOL before the gestational age of their previous stillborn baby. Clinicians are similarly aware of increased risk, especially if maternal risk factors are still present. Therefore, the panel concluded there was a need to individualise the decision for IOL. The panel noted a preference for waiting until ≥ 39 weeks' gestation if offering IOL because it is important not to trade off the potential uncommon risk of recurrent stillbirth with the potential common risks to the neonate of an early planned birth.

There is currently insufficient high-quality evidence to make a clear recommendation about IOL for this condition.

Practice point

- For women with previous stillbirths, consider expectant management or IOL, based on a review of risk factors for recurrence and any other antenatal risk factors, and guided by maternal choice.

Research gap

- In women with previous stillbirth, to further evaluate the effect of IOL compared with expectant management on maternal, perinatal and neonatal outcomes, including women's perspectives and experiences.

No medical indication

IOL is usually offered for medical reasons, however, sometimes women request (or are offered) induction without a medical indication.

Summary of evidence

One RCT was identified.

The ARRIVE trial was an RCT that took place at 41 hospitals in the United States (Grobman et al 2018). Women considered low risk in their first pregnancy (live singleton cephalic baby with no contraindication to vaginal birth and absence of any maternal or fetal condition that would warrant induction before 40+5 weeks' gestation) were invited to participate after 34 weeks' gestation. Participants were randomised to IOL at 39–39+4 weeks' gestation or to expectant management (elective delivery after 40+5 weeks' gestation but no later than 42+2). The primary outcome was a composite of perinatal death or severe neonatal complications (including need for respiratory support after birth, 5-minute Apgar ≤ 3 , hypoxic-ischaemic encephalopathy, seizure, infection, meconium aspiration and birth trauma). The main secondary outcome was caesarean section. A two-tailed p value of less than 0.046 was deemed to be statistically significant for the primary outcome.

Of 50,581 women screened for the trial, 22,533 (44%) were eligible to take part in it, and 6,106 (27%) agreed to participate. The trial required 6,000 women to have sufficient power to demonstrate that IOL was associated with a 40% reduction in the primary adverse perinatal outcome, estimated to be 3.5% for those managed expectantly (allowing for 7.5% cross-over, that is, not all women were expected to receive the plan allocated to them).

The primary perinatal outcome was lower in the IOL group (4.3%) compared with 5.4% in the expectant management group, but this difference was not statistically significant (RR 0.80, 95%CI 0.64–1.00; $p = 0.049$). Women undergoing IOL gave birth at an earlier median gestational age (39.3 compared with 40.0 weeks' gestation; $p < 0.001$) with a lower median birthweight (3,300 g [interquartile range, 3,040–3,565] compared with 3,380 g [interquartile range, 3,110–3,650]; $p < 0.001$). Women in the IOL groups were less likely to experience hypertensive disease, complications at caesarean section and pain. The rate of caesarean section was significantly lower in the IOL group (18.6%), compared with 22.2% in the expectant group (RR 0.84; 95% CI 0.76–0.93; $p < 0.001$). About 28 women would need to have an IOL to prevent one caesarean section. The trial did not report on maternal satisfaction.

Discussion

Limitations of the Grobman et al trial were identified as:

- It does not reflect current New Zealand maternity practices because of the mostly obstetrician-led care (with only 6% midwifery led); there was a different ethnic mix in the trial population; different IOL methods were used.
- There were no long-term data on the neurodevelopmental or metabolic outcomes for the babies.

The panel considered that IOL is not justified, due to limitations of current RCT evidence in relation to the New Zealand context. Consider women's preferences, available resources and setting for IOL. However, the trial does suggest that a policy of avoiding IOL at 39 weeks' gestation to reduce caesarean section rates is not valid.

There is a difference between caesarean rates seen in RCTs and those within the New Zealand context, but the data are not comparable due to confounders. If possible, local data could be provided to women on local rates of caesarean following IOL.

The panel identified the need to ensure that information is shared with women, midwives and obstetricians, while acknowledging other factors (for example, social) that may contribute to some women requesting elective IOL at 39 weeks.

The panel discussed whether to add a further comment around what to do if a woman requested IOL at 39 weeks' gestation for no medical indication. It was considered this could lead to potential equity and access issues. Labour and birth are not only about the potential adverse outcomes but also about an important physiologic experience; where pregnancy is normal and the woman and baby are well, there needs to be a very

good reason to intervene. However, it was agreed that this should be managed on a case-by-case basis.

Practice points

- Do not offer IOL in the absence of a medical indication.
 - Manage maternal requests for IOL on a case-by-case basis.
-

Research gaps

- For women who have IOL at 39 weeks' gestation for no medical indication, to evaluate long-term outcomes for babies and maternal anxiety in next pregnancy and birth and likelihood of subsequent IOL.
 - For women with uncomplicated pregnancies, to further evaluate IOL at 39 weeks compared with expectant management on maternal, perinatal and neonatal outcomes, in the New Zealand context.
 - To explore the ethics of offering IOL for non-medical indication or for maternal request.
-

Chapter 5: Methods of cervical ripening

Introduction

When a woman has an IOL, the status, or favourability, of her cervix affects both the likely duration of the induction and the chances of achieving a vaginal birth. Unfortunately, there is no absolute consensus on how to define cervical favourability. Many clinicians use a Bishop score to assess cervical favourability, calculated on a cervical examination completed at the time of induction initiation. Regrettably, the Bishop score has limited predictability. However, no other method of cervical assessment has proven to be more useful. It is clear that higher Bishop scores are positively associated with achieving vaginal birth. A woman who has an induction with a Bishop score of nine or higher has a similar chance of achieving vaginal birth as a woman who has spontaneous labour.

Many clinicians define a favourable cervix as one with a Bishop score of six or greater. If a cervix is judged to be favourable, then ARM and/or oxytocin can be initiated without cervical ripening. However, cervical ripening with PGs probably improves the chance of vaginal birth within 24 hours for women with unfavourable cervix over oxytocin alone (Alfirevic et al 2009).

Consequently, women with an unfavourable cervix should be offered cervical ripening to increase their Bishop score and hopefully improve their chances of a successful induction. This is current practice in New Zealand, hence trials comparing cervical ripening to placebo are not reviewed in this guideline. IOL in the setting of previous caesarean section is reviewed.

Systematic reviews comparing all methods of cervical ripening and IOL are summarised in Appendix D.

In addition, some clinicians perform membrane sweeping at the same time as performing a formal IOL. This is supported by several RCTs showing that concurrent membrane sweeping increases the rate of vaginal birth, shortens the induction to birth interval and reduces the exposure of mothers and babies to oxytocin (Liu et al 2018).

The following methods of cervical ripening have been considered in this guideline:

1. PGE2 hormone (dinoprostone, PGE2)
2. PGE1 analogue (misoprostol, PGE1)
3. Mechanical methods, such as balloon catheter.

PGE2 (dinoprostone) methods of administration

Summary of evidence

One systematic review was identified that included a comparison of vaginal gel (Prostin® E2) to controlled-release pessary (CERVIDIL®). In the Cochrane review on PGs for cervix ripening (Thomas et al 2014), there were 13 trials of 1,436 women that compared PGE2 controlled-release with PGE2 any vehicle. For the primary outcomes, there was no difference between groups for vaginal birth achieved within 24 hours (43.1% vs 37.3% RR 1.15 CI 0.92–1.45; 3 trials; 450 women; moderate quality) or for caesarean section (20.4% vs 20.1% RR 1.02 CI 0.82–1.26; 11 trials; 1262 women; high quality). There was no difference in uterine hyperstimulation with FHR changes (4.9% vs 2.2% RR 2.15 CI 0.89–5.21; 5 trials; 643 women; moderate quality); in two trials, there were no events in either arm, and in three trials, the rate of this adverse outcome was higher in the controlled-release arm. For the secondary outcomes, the controlled-release was associated with a lower rate of instrumental vaginal birth and a lower chance that the cervix would remain unfavourable compared with PGE2 any vehicles. There was no difference in oxytocin augmentation or tachysystole/hypertonus (4.2% versus 2.4%, RR 1.59, 95% CI 0.81–3.14; 8 trials, 908 women).

PGE1 analogue (misoprostol)

Summary of evidence

Two systematic reviews were identified evaluating misoprostol as an induction agent.

A Cochrane systematic review of vaginal misoprostol included 121 trials (Hofmeyr et al 2010). The authors analysed 38 studies of 7,022 women comparing vaginal misoprostol with vaginal PGE2. Compared with vaginal PGE2, women who got vaginal misoprostol had a lower rate of failure to achieve vaginal birth within 24 hours (RR 0.77, 95% CI 0.66–0.89; 22 trials; low quality). There were no differences in uterine hyperstimulation with FHR changes (RR 1.43, 95% CI 0.97–2.09; 31 trials; low quality) or caesarean section (RR 0.95, 95% CI 0.87–1.03; 34 trials; moderate quality). Compared with vaginal PGE2, vaginal misoprostol was associated with less need for oxytocin augmentation (38 trials, RR 0.68, 95% CI 0.60–0.76; low quality), more uterine hyperstimulation without FHR changes (26 trials, RR 1.99, 95% CI 1.41–2.79; low quality), less epidural analgesia (8 trials, RR 0.92, 95% CI 0.85–0.99; low quality) and a higher rate of meconium stained liquor (18 trials, RR 1.35, 95% CI 1.13–1.61). No trials reported on maternal satisfaction. The authors concluded that low-dose vaginal misoprostol is similar to PGE2 in effectiveness and risks but that vaginal misoprostol should not be researched further as another Cochrane review has suggested that oral misoprostol is preferable to vaginal.

A Cochrane systematic review of oral misoprostol included 75 trials of 13,793 pregnant women in their third trimester, due for induction with a viable fetus (Alfirevic et al 2014). In the 37 trials of 6,417 women, which compared oral with vaginal misoprostol, women taking oral misoprostol had similar outcomes of vaginal birth within 24 hours (RR 1.08, 95% CI 0.86–1.36; 14 trials, 2,448 women; low quality), uterine hyperstimulation with fetal heart rate changes (RR 0.71, 95% CI 0.47–1.08; 29 trials; 5,503 women; low quality), and caesarean section (RR 0.93, 95% CI 0.81–1.07; 35 trials; 6,326 women; low quality). Women taking oral misoprostol had more meconium-stained liquor (RR 1.22, 95% CI 1.03–1.44, 24 trials; 3,634 women; moderate quality), less postpartum haemorrhage (RR 0.57, 95% CI 0.34–0.95; 10 trials; 1,478 women; low quality) and fewer babies had low 5-minute Apgar score (RR 0.60, 95% CI 0.44–0.82; 19 trials; 4,009 babies; moderate quality) compared with vaginal misoprostol. For all comparisons, the incidence of serious neonatal or maternal morbidity or death was rare. One study looked at maternal satisfaction and found that one woman in each group was dissatisfied with their treatment. The authors concluded that oral misoprostol was safer than vaginal misoprostol. The outcome of uterine hyperstimulation was dose dependent, and the authors recommend low dose 20–25 micrograms in solution if using oral misoprostol.

In the 10 trials of 3,240 women that compared oral misoprostol with vaginal PGE₂ (dinoprostone), there was similar rates of vaginal birth within 24 hours (RR 1.10, 95% CI 0.99–1.22; 5 trials; 2,128 women; moderate quality), caesarean section (RR 0.92, 95% CI 0.81–1.04; 10 trials; 3,240 women; moderate quality) and uterine hyperstimulation with FHR changes (RR 0.95, 95% CI 0.59–1.53; 7 trials; 2,352 women; low quality).

A systematic review with Bayesian network meta-analysis of IOL with PGs (Alfirevic et al 2015) included 280 RCTs of 48,068 women in their third trimester with a viable fetus who were undergoing cervical ripening or IOL. Compared with placebo, odds of failing to achieve a vaginal birth were lowest for high-dose vaginal misoprostol (≥ 50 microgram) (OR 0.06 95% CI 0.02–0.12), with a 39% absolute probability of event (95% CI 1%–94%). Compared with placebo, odds of caesarean section were lowest for low-dose (<50 microgram) titrated oral misoprostol solution (OR 0.65, 95% CI 0.49–0.83), with an absolute probability of event of 15% (3%–40%). Maternal and neonatal mortality and serious morbidity were either too rare or poorly reported to carry out meaningful analysis; when defined properly, they were rare events. Unresolved inconsistency was observed for the hyperstimulation outcome. They did not report on maternal satisfaction.

Discussion on prostaglandins

Evidence suggests that vaginal PGE₂ (dinoprostone) and oral PGE₁ analogue (misoprostol) are probably comparable in effectiveness to achieve vaginal birth in 24 hours and in safety, but oral PGE₁ is probably associated with a lower risk of caesarean section.

The panel noted that, in their experience of reviewing cases, sometimes uterine hyperstimulation is not recognised, so clinicians should consider a note of caution for any woman receiving any PG.

For vaginal PGE₂ (dinoprostone), the panel agreed that it is reasonable to continue to offer either gel or controlled-release pessary (CERVIDIL®) for cervical ripening because the limited evidence suggests both administration methods are comparable for the outcome of vaginal birth in 24 hours and for risk of caesarean section. It seems that controlled-release pessary is associated with more uterine tachysystole and hypertonus than gel, but it is not associated with more uterine hyperstimulation with FHR changes. However, this result should be interpreted with caution due to the small sample size. Specialised training in technique for positioning CERVIDIL® is required in order to ensure therapeutic and cost effectiveness. There is insufficient evidence to make recommendations regarding duration and repeat doses of controlled-release pessary nor regarding dose of vaginal gel by parity, repeat doses, total dose or time frame. In order to develop practice points, the panel consulted with the Pharmaceutical Society of New Zealand and HQSC and reviewed the protocols of the trials described above.

For PGE₁ analogue (misoprostol), it seems that vaginal administration is associated with more uterine tachysystole and hypertonus, and possibly more uterine hyperstimulation with FHR changes, than oral administration. Thus, if a decision is made to use misoprostol, the panel agreed it would be prudent to use oral misoprostol rather than vaginal. Oral administration may have the added benefit of fewer vaginal examinations. Oral misoprostol 25 microgram in solution two-hourly is widely used internationally and is recommended by the World Health Organization (WHO). The method of dissolving the misoprostol tablet in water to achieve the correct dose is easy and well described.

Although misoprostol is an approved medicine in New Zealand, it is not approved for use in childbirth. However, it can be regarded and used as a supported indication. This is similar to other medications that are not approved for the indication they are sometimes used, for example, nifedipine for tocolysis. Many clinicians or DHBs may not be comfortable using it 'off-label,' which could be a potential barrier to use. The panel has sought advice on the issue: the National Maternity Monitoring Group, in the Ministry of Health, support the use of misoprostol as an option for women undergoing IOL.

The Pharmaceutical Society of New Zealand states that, while it is recognised that cervical ripening in the setting of IOL in childbirth has not been listed as a registered indication for misoprostol use in New Zealand, the use of misoprostol in childbirth has been widely researched internationally and endorsed by the WHO. They do not believe that written informed consent for use of misoprostol for cervical ripening in IOL in childbirth is necessary but recommend referral to local policies on off-label use of medicines.

The HQSC recommends that the strength of misoprostol oral solution be standardised nationally to ensure consistency. It recommends that best evidence-based information be made available for staff making this preparation and that the same strength be prepared across all health organisations to prevent medicine dosing errors occurring due to strength mix-ups, particularly when staff work across different organisations. Any guidance on preparation should include who may prepare the solution, where it may be prepared, how to prepare it and the expiry (for example, for product prepared 'at the bedside' compared with in a pharmacy). HQSC has kindly provided two protocols that are listed in Appendix E.

The panel suggests that DHBs consult locally and develop local guidelines based on those provided, in cooperation with their local pharmacy, should they choose to use misoprostol. MidCentral DHB implemented misoprostol in 2018 and are another resource to assist with this.

Balloon catheter

Summary of evidence

One systematic review was identified evaluating mechanical methods, and two RCTs have been published since the meta-analysis.

A Cochrane systematic review (Jozwiak et al 2012a) of 71 RCTs of 9,722 women compared mechanical methods for IOL with any PG. In the 21 studies of 3,202 women comparing balloon catheter specifically with PGs, balloon catheter resulted in similar caesarean section rates (RR 1.01, 95% CI 0.9–1.13; 21 trials; moderate quality), assisted vaginal births (RR 0.99, 95% CI 0.79–1.24; 6 trials; moderate quality) and vaginal birth not achieved in 24 hours (RR 1.26, 95% CI 0.94–1.68; 7 trials; low quality) compared with any PG. For balloon catheter induction, more women needed oxytocin augmentation (RR 1.51, 95% CI 1.15–1.97; 6 studies; low-quality evidence), and there was less risk of uterine hyperstimulation with FHR changes (RR 0.19, 95% CI 0.08–0.43; 9 studies; moderate quality).

Compared with PGE2 alone, PGE2 plus balloon catheter resulted in a decreased rate of not achieving vaginal birth at 24 hours (RR 0.45, 95% 0.28–0.71; 3 trials; moderate quality), similar caesarean section rate (0.92, 95% 0.79–1.08; 3 trials; moderate quality) and less uterine hyperstimulation with FHR changes (RR 0.53, 95% 0.35–0.78; 1 trial; low quality). Only one trial measured patient satisfaction and discomfort. Women reported less discomfort with the single balloon catheter compared with the double balloon and PGE2 but a comparable overall satisfaction with the three methods.

PROBAAT-II was a multicentre randomised controlled non-inferiority trial in the United Kingdom (Eikelder et al 2016) of 1,859 women with an unfavourable cervix and intact membranes having IOL at term, comparing oral misoprostol with a single balloon catheter left in situ from 12 up to 48 hours. The composite primary outcome (neonatal asphyxia or post-partum haemorrhage) occurred in 12.2% of participants in the misoprostol group compared with 11.5% in the balloon group (adjusted relative risk (aRR) 1.06, 90% CI 0.–1.31), and caesarean section occurred in 16.8% compared with 20.1% (RR 0.84, 95% CI 0.69–1.02; $p=0.07$). They did not have maternal satisfaction as an outcome. There were 27 adverse events reported in the misoprostol group compared with 25 in the balloon group, none of which was related to the intervention. Both balloon catheter and misoprostol were considered to be of equivalent effectiveness and safety.

INFORM was an RCT in India of 602 women with hypertension in pregnancy, comparing oral misoprostol with a single balloon catheter left in situ for 12 hours (Mundle et al 2017). Women in the misoprostol group were more likely to have a vaginal birth within 24 hours compared with women in the balloon group (57% vs 47% women; absolute risk difference 10%, 95% CI 2.0–17.9; $p=0.01$). Uterine hyperstimulation was uncommon (two cases (0.7%) vs one (0.3%); absolute risk difference 0.3%, 95% CI -0.8–1.5; $p=0.57$). There were 17 serious adverse events (3%): one case of intrapartum convulsion and one case of disseminated intravascular coagulation (both in the balloon group); two stillbirths (both in the balloon group); eight neonatal deaths (five in the misoprostol group and three in the balloon group); three cases of birth asphyxia and one case each of septicaemia and neonatal convulsion. Most women found their method of induction (and its duration) to be acceptable and the pain as slight or moderate. Women undergoing induction with misoprostol were more likely to report that they would use the same method in the future, compared with the balloon catheter.

Single versus double balloon catheters

One systematic review was identified.

A systematic review of five RCTs of 996 women compared single- versus double-balloon catheters for IOL (Salim et al 2018). There may be little or no difference between groups for the time from insertion of the catheter to birth nor mode of birth (primary outcomes). There may be little or no difference between groups for caesarean section, birth within 24 hours, intrapartum fever or chorioamnionitis, and 5-minute Apgar score <7. Women who were induced with the single-balloon catheter were more satisfied ($p = 0.03$; WMD 0.56; 95% CI: 0.06–1.06) and less likely to report pain scores >4 compared with double-balloon catheter (36% vs 55%, $p < 0.001$). Note that, in the balloon arm of these trials, the balloon remained in situ for up to 12 hours.

Single-balloon catheters and volume of inflation

One systematic review, and one RCT published since the review, were identified.

The systematic review (Berndl et al 2014) of three trials of 575 women compared high- or low- volume single-balloon catheters (left in situ for 12 hours) for IOL. High-volume inflation was associated with a lower rate of failure to deliver within 24 hours (RR 0.70, 95% CI 0.54–0.90; moderate quality) and a more favourable cervix at time of balloon removal (RR 1.72, 95% CI 1.46–2.04; very low quality), compared with low-volume inflation. There was no difference in caesarean section (RR 0.82, 95% CI 0.48–1.41; moderate quality) or epidural use. The authors did not report on maternal satisfaction.

An RCT of 174 women comparing single-balloon catheters filled with 30 mL with catheters filled with 60 mL (Sandberg et al 2017) found no difference between groups for birth within eight hours after ARM (40.7% vs 48.8%; moderate quality). The 60 mL catheter was associated with higher spontaneous labour (OR 2.35, 95% CI 1.1–5.1), shorter time interval for cervical ripening (OR 4.5, 95% CI 1.2–16.7) and less blood loss ($p=0.002$). Subgroup analysis was performed by parity. For multipara, more women in the 60 mL group gave birth within eight hours (93.1% vs 65.2%, OR 7.2, 95% CI 1.4–38.4); for nullipara, the 30 mL catheter was associated with increased caesarean section (31.8% vs 15.5%; OR 2.53, 95% CI 1.1–6.2). The 60 mL catheter ruptured 12 times compared with none in the 30 mL group. There were no differences in neonatal outcomes or maternal satisfaction.

Discussion on balloon catheters

For balloon catheters, the panel agreed that it is reasonable to continue to offer either single- or double-balloon catheter for cervical ripening, because the limited evidence suggests there may be no difference in mode of birth. There is a 50-mL single-balloon foley catheter available in New Zealand, and DHBs may wish to consider cost and clinician preference in deciding which to offer.

Evidence suggests that balloon catheter and vaginal PGE2 are comparable in effectiveness to achieve vaginal birth in 24 hours and in risk for caesarean section, but that balloon catheter has less risk of uterine hyperstimulation with FHR changes. On the other hand, PGs have less need for oxytocin augmentation. Evidence further suggests that oral misoprostol is more effective than balloon catheter in achieving vaginal birth in 24 hours. Balloon catheters and oral misoprostol are comparable in risk for caesarean section, PPH and neonatal asphyxia.

The panel agreed that it is reasonable to offer any of balloon catheter, vaginal PGE2 or oral PGE1 analogue (misoprostol) for cervical ripening. Balloon catheter may be more appropriate in circumstances where the risk of uterine hyperstimulation has more consequences, such as severe SGA. The panel suggests that DHBs decide which cervical ripening options to offer to women, including one (or more) pharmacological method and one (or more) mechanical method, based on values and preferences, local resources and practical considerations.

Recommendation	Level of evidence	Strength of recommendation
Offer cervical ripening with PG to women with unfavourable cervix, to improve the chance of vaginal birth within 24 hours, compared with oxytocin alone.	Level 1; moderate quality	Conditional
Offer either PGE2 vaginal gel or controlled-release pessary for cervical ripening, as both methods are comparable to achieve vaginal birth in 24 hours and for risk of caesarean section.	Level 1; moderate quality	Conditional
Offer oral misoprostol for cervical ripening, to reduce the risk of caesarean section.	Level 1; moderate quality	Conditional
Offer balloon catheter for cervical ripening, to reduce the risk of uterine hyperstimulation with FHR changes, compared with PG.	Level 1; moderate quality	Conditional
For single-balloon catheter: Inflate greater than 30 mL (and not more than the manufacturer's recommendation), to increase the chance of vaginal birth in 24 hours, compared with 30 mL or less.	Level 1; moderate quality	Conditional

Practice points

- Consider offering membrane sweeping concurrent with cervical ripening.
- For cervical ripening with PGE2 vaginal gel: Decide initial dose based on parity and Bishop score. If nulliparous and the Bishop score is ≤ 4 , consider 2 mg; otherwise consider 1 mg. Decide any subsequent dose based on cervical change – if none, consider 2 mg; otherwise consider 1 mg. Use as per the manufacturer's instructions.
- For cervical ripening with PGE2 controlled-release vaginal pessary: Pessary may have higher risk of uterine tachysystole and hypertonus compared with vaginal gel. Use as per the manufacturer's instructions.
- For cervical ripening with PGE1 analogue (misoprostol): Vaginal administration may have higher risk of adverse outcomes compared with oral administration. If using misoprostol, low-dose (25 microgram) two-hourly in oral solution is recommended. See also Appendix EAppendix E: Examples of preparation of oral misoprostol for cervical ripening.
- For cervical ripening with balloon catheter, consider offering either single- or double-balloon, as both are comparable to achieve vaginal birth in 24 hours and for risk of caesarean section. Use double-balloon catheter as per the manufacturer's instructions.

Research gaps

- For women having cervical ripening, to evaluate timing of starting IV Luer (routinely at start of IOL compared with as needed), on maternal satisfaction and potential harms.
- For cervical ripening with CERVIDIL®, to evaluate the effect of leaving it in situ for 24 versus 12 hours, and to evaluate the effect of a 2nd dose compared with one dose only, on chance of vaginal birth and on potential harms.
- For cervical ripening with Prostin®, to evaluate the effect of the number and dose of application/s on chance of vaginal birth and on potential harms, stratified by parity.
- After how much time do you consider changing to a second method of cervical ripening?
- For cervical ripening with single-balloon catheter, to evaluate the effect of leaving it in situ for 12 compared with 24 hours, and to further evaluate the effect of low- vs high-volume inflation, on chance of vaginal birth, maternal satisfaction and comfort, and potential harms, stratified by parity.
- To perform an economic analysis comparing mechanical methods with PG.

Methods of IOL for women with previous caesarean section

Summary of evidence

One systematic review was identified.

A Cochrane review of eight RCTs of 707 women reported on methods of IOL at term in women with a previous caesarean section (West et al 2017). All methods of cervical ripening or IOL (vaginal or oral PGs, mifepristone, mechanical methods, oxytocin or placebo) that were compared with placebo or any other method were included. Primary outcomes were: vaginal birth within 24 hours, uterine hyperstimulation with FHR changes, caesarean section, serious neonatal morbidity or perinatal death and serious maternal morbidity or death. No studies were found that looked at vaginal birth within 24 hours or uterine hyperstimulation. The other outcomes were considered of low-quality evidence. Meta-analysis could not be undertaken due to multiple interventions with limited studies and variable quality. The authors concluded that RCT data on women with previous caesarean are underpowered and inadequate.

Discussion

Prospective and retrospective cohort studies have shown an increased risk of uterine rupture in women who have had a previous caesarean section following IOL, especially when PGs are used for cervical ripening (Landon 2004; Lydon-Rochelle 2001; Smith 2004). The risk of uterine rupture following mechanical methods for cervical ripening is lower than with PGs (Bujold 2004; Landon 2004; Ravasia 2000), approximating the risk after spontaneous onset of labour. A UK national case-control study has shown that the use of oxytocin to induce labour in women who have had a previous caesarean section is associated with an increased risk of uterine rupture (Fitzpatrick et al 2012).

There is insufficient high-quality evidence to make a clear recommendation for method of IOL in women with a previous caesarean section.

Practice point

- Consider using balloon catheter for cervical ripening where IOL is indicated in the setting of a previous caesarean section.

Research gap

- To evaluate different methods of cervical ripening in women with previous caesarean section, such as mifepristone and balloon catheter.

Chapter 6: Methods of induction of labour

Introduction

In this chapter, amniotomy or artificial rupture of membranes (ARM) and intravenous oxytocin infusion are considered.

Combining ARM with oxytocin

One systematic review and one RCT published since that review were identified evaluating the combination of ARM with oxytocin.

In a Cochrane review (Howarth and Botha 2001) of 17 clinical trials (2,566 women), amniotomy with oxytocin for third-trimester IOL was compared with a placebo or other treatments. The primary outcomes were: vaginal birth not achieved in 24 hours, uterine hyperstimulation with FHR changes, caesarean section, serious neonatal morbidity or perinatal death, and serious maternal morbidity or death. Secondary outcomes included instrumental delivery, epidural, perinatal death, PPH and fever.

Comparing ARM/oxytocin with ARM alone, fewer women in the ARM/oxytocin group failed to achieve vaginal birth within 24 hours (RR 0.13, CI 0.04–0.41; two trials; 296 women; low quality). Rates of caesarean section were similar between the groups (RR 0.45, CI 0.16–1.30; two trials; 510 women; low quality). There were fewer instrumental deliveries in the ARM/oxytocin group compared with ARM alone (RR 0.65, 95% CI 0.49–0.85, two trials; 510 women; low quality) and no difference in PPH (RR 0.44, 95% CI 0.2–1.0; 2 trials; 500 women; low quality) or fever (RR 0.25, 95% CI 0.03–2.16; 1 trial; 100 women; low quality). One trial of 100 women reported on perinatal death, where there was one event in the oxytocin/ARM group. There was no estimable effect for epidural. In women with a favourable cervix, use of amniotomy alone is an option for IOL if the head is well opposed to the cervix; however, the combination of ARM and intravenous oxytocin administration is more effective. This combination resulted in at least a 60% reduction in women undelivered at 24 hours compared with ARM alone.

Comparing ARM/oxytocin with oxytocin alone, there was no difference between the groups for caesarean section (RR 1.05 95% CI 0.64–1.70; two trials; 511 women; low quality). The Cochrane authors concluded that research was limited and clinical practice should not be guided based on this review.

Gagnon-Gervais et al (2012) performed an RCT of 143 women, comparing oxytocin with early ARM (performed within one hour of starting oxytocin) to oxytocin with late ARM (performed four hours after starting oxytocin). The primary outcome was caesarean section; secondary outcomes were duration of labour and intrapartum fever. Caesarean section rates were similar in early and late ARM groups for nullipara (17.6% (early) vs 16.6% (late); RR 1.06, 95% CI 0.38–2.97) and multipara (2.7% (early) vs 0% (late), $p=0$). Nullipara who had early ARM had a shorter labour (12.1 (6.7) vs 15.4 (5.6) hours, $p = 0.03$) and were less likely to have intrapartum fever (RR 0.24, 95% CI 0.05–1.01), compared with late ARM.

Timing of ARM

Three RCTs, with a total of 1 073 women, were identified comparing early ARM (at start of IOL) with late ARM (>4 hours or >4 cm or at clinician discretion). Makarem et al (2013) performed an RCT of 320 women, comparing vaginal misoprostol with early ARM to vaginal misoprostol with delayed ARM. Vaginal misoprostol was administered every six hours until regular contractions were established or maximum of four doses. Early ARM was performed in the early active phase of labour (where the cervix was 3 cm dilated), and late ARM was defined as either spontaneous rupture of membranes (SROM) or as judged by the senior clinician. The primary outcome was vaginal birth within 24 hours. Early ARM was more likely to achieve vaginal birth in 24 hours compared with late ARM (117 (73.13%) vs 105 (65.63), $p = 0.15$) and shorter labour duration (9.72 (4.61) vs 13.61 (5.61) hours, $p = 0.002$). There were no significant differences in other secondary outcomes.

Macones et al (2012) performed an RCT of 585 women, comparing any method of cervical ripening with ARM to any method with delayed ARM. Early ARM was defined as ARM occurring at cervical dilatation ≤ 4 cm and late ARM at dilatation >4 cm. The primary outcomes were time from start of IOL to birth and the proportion of women who gave birth within 24 hours from start of IOL. Secondary outcomes included: caesarean section, indications for caesarean section, chorioamnionitis (maternal temperature $>38^{\circ}\text{C}$), post-partum fever, wound infection, endometritis, NICU admission and suspected neonatal sepsis. Most women had misoprostol, and others had a single-balloon catheter; 73% of women in both groups received more than one method of cervical ripening. Early ARM was associated with shorter IOL to delivery time (19.0 (9.1) vs 21.3 (10.1) hours; $p = 0.04$) and increased birth within 24 hours (RR 0.72, 95% CI 0.59–0.89; $p = 0.02$) compared with late ARM. There was no difference in caesarean section (RR 1.03, 95% CI 0.85–1.25), chorioamnionitis (1.35, 95% CI 0.83–2.21), NICU admission (RR 0.90; 95% CI 0.61–1.35) or neonatal sepsis (RR 0.87; 95% CI 0.54–1.41).

Levy et al (2002) performed an RCT of 211 women who had cervical ripening with a balloon catheter and, once expelled, were then randomised to early ARM (80 women) or intravenous oxytocin with late ARM once regular contractions were established or change in cervical dilatation/effacement (88 women). The primary outcomes were caesarean section, chorioamnionitis and immediate neonatal complications (5-minute Apgar score <7 or cord pH <7.0). There was a significant increase in caesarean section (RR 1.74, 95% CI 1.30–2.34) and maternal fever in labour (RR 1.69; 95% CI 1.15–2.5) with early ARM compared with late ARM. There were no immediate neonatal complications.

Oxytocin protocol

One systematic review was identified evaluating oxytocin protocols.

A Cochrane review comparing high- versus low-dose oxytocin protocols included nine RCTs of 2,391 women (Budden et al 2014). 'High dose' was defined by Cochrane authors as at least 100 milliunits in the first 40 minutes, with increments delivering at least 600 milliunits in the first two hours; 'low dose' as <100 milliunits oxytocin in the first 40 minutes, with increments delivering <600 milliunits total in the first two hours. There were probably few or no differences in most clinical outcomes, such as perinatal death, caesarean section, vaginal birth within 24 hours, severe acute maternal morbidity (SAMM) or uterine hyperstimulation with FHR changes. After removing high-risk-of-bias studies, the remaining trials of 489 women showed that high-dose protocols may shorten the time from IOL to birth compared with low-dose protocols but may be associated with a higher rate of tachysystole/hypertonus. No trial assessed maternal satisfaction. The authors concluded that there was no evidence to support the use of high-dose oxytocin for IOL.

Discussion

The panel discussed the fact that individualising care is important when discussing the timing of ARM and starting oxytocin. It is usual practice in New Zealand to start oxytocin once the cervix is favourable and after ruptured membranes. There is no evidence to support the hypothetical concern for amniotic fluid embolism if oxytocin is started before ARM, and there may be benefits, such as fetal descent and rotation to occiput anterior and reduced risk of fever.

When considering ARM, it is important to acknowledge the emotional and spiritual aspects of 'rupturing membranes.' For many cultures (including te ao Māori), the membranes are āhuru mōwai (safe haven) and are considered a taonga. The waters hold more significance than just liquid surrounding the pēpi. They facilitate a transmission of knowledge through taonga puoro (musical instruments), vibrations and korero; transferring the hopes, dreams and aspirations from māmā, pāpā and whānau and making connections to tūpuna. Discuss where, when and how the waters are ruptured. This understanding of āhuru mōwai is explored in the video Membranes Matter³ (Farry and Mellor 2008).

³ <https://vimeo.com/316244298>

The different approaches to IOL have pros and cons. The panel noted that it depends on the outcome that is valued in terms of interpreting these data. If achieving vaginal birth within 24 hours is of high value, then the current evidence supports the combination of early ARM and oxytocin to start an IOL. If shortening the time from start of IOL to birth is important, then limited evidence supports high-dose oxytocin protocol. However, other outcomes are not yet known, such as patient satisfaction, experience, pain scores, use of epidural and neonatal outcomes. There is a lot of qualitative evidence on the experience of women having oxytocin for induction. The panel agreed that the decision on the approach to be taken should be determined by the woman, her clinicians and the DHB protocols.

DHBs can decide their own oxytocin protocol. There is no evidence to support a different protocol for nullipara and multipara, different protocol for induction and augmentation, nor maximal dose for women with previous caesarean section. For safety, it may be prudent to have one protocol only and for an individual clinician to document any change to the protocol on a case-by-case basis. It is important that women are provided with information about the different methods of IOL and the factors that affect clinician decisions about which methods to offer.

The panel noted that, in their experience of reviewing cases, sometimes uterine hyperstimulation is not recognised, so the guideline should include a note of caution for any woman receiving oxytocin. If PGs are used for cervical ripening and a decision is made to induce or augment labour with oxytocin, then there is an increased risk of causing uterine hyperstimulation. The CERVIDIL® manufacturer recommends oxytocin not be administered for at least 30 minutes after removal, and the Prostin® manufacturer recommends six hours between the time of most recent application of gel and the administration of oxytocin.

There is currently insufficient high-quality evidence to make a clear recommendation about method of IOL.

Practice points

- To start IOL once the cervix is favourable, consider offering the combination of ARM and intravenous oxytocin infusion, to increase the chance of vaginal birth within 24 hours.
- The timing and order of performing ARM and starting intravenous oxytocin infusion can be individualised and negotiated between the woman, her LMC, the hospital midwife and the obstetrician.
- Offer either low- or high-dose oxytocin protocol, as both methods are comparable in terms of achieving vaginal birth in 24 hours and risk for caesarean section.
- The usual time interval to increase the dose of oxytocin is approximately 20 minutes.

Research gaps

- To explore New Zealand women's experience of oxytocin infusion and of ARM.
 - To further evaluate high- vs low-dose oxytocin protocols and to evaluate time interval to increase dose and by how much, to maximise benefit and minimise harm.
 - For women with Bishop scores >6, to evaluate the effect of combination of ARM/oxytocin vs ARM alone with delayed oxytocin by 4–6 hours on maternal, perinatal, neonatal and long-term childhood outcomes.
 - For women with Bishop scores >6, to evaluate the effect of combination of ARM/oxytocin vs oxytocin alone with delayed ARM until cervix >4 cm dilated on maternal, perinatal, neonatal and long-term childhood outcomes.
 - To develop a national oxytocin protocol.
-

Chapter 7: Setting for induction of labour

Summary of evidence

One systematic review, and one RCT published since the review, were identified.

A Cochrane review published in 2013 (Kelly et al 2013) included four trials of 1,439 women and compared inpatient versus outpatient IOL. Three used PGs, and one used balloon catheter. A meta-analysis was not able to be performed due to study heterogeneity. The authors noted that uterine hyperstimulation may prevent a woman from going or remaining at home, so PGs may not be the best outpatient induction agent. The four trials included in this review are detailed below.

Wilkinson et al (2012) conducted an RCT in Australia of 827 women, and Ryan et al (1998) conducted an RCT in Canada of 201 women, evaluating outpatient versus inpatient IOL with vaginal PGE₂. There may be little or no difference between groups in the primary outcomes of oxytocin use, total length of hospital stay or serious neonatal morbidity/death, nor in secondary outcomes of caesarean section, use of epidural, 5-minute Apgar <7 or NICU admission. Patient satisfaction was studied, but not reported.

Biem et al (2003) conducted an RCT in Canada of 300 women, evaluating outpatient versus inpatient controlled-release PGE₂ insert. There was probably no difference between groups in the primary outcomes of vaginal birth at 24 hours, oxytocin use or total length of hospital stay, nor in secondary outcomes of mode of birth, abnormal FHR pattern or NICU admission. Women in the outpatient group were more likely to report high levels of satisfaction about their care during the induction process, but there was no difference during labour and birth.

Sciscione et al (2001) randomised 111 women in the United States to outpatient vs inpatient single-balloon catheter and found no differences between the groups in the primary outcome of change in Bishop score nor in secondary outcomes. There were no adverse events or maternal morbidity. Women in the outpatient group spent 10 fewer hours in hospital.

Wilkinson et al (2015a) performed a pilot RCT of 48 women evaluating outpatient versus inpatient double-balloon catheter. Women in the outpatient group were less likely to require oxytocin, had a lower caesarean section rate and a higher instrumental birth rate, but differences were not statistically significant (small sample size). There were no serious maternal or neonatal morbidities. Women in the outpatient group spent an average of 12 hours out of hospital and were more likely to report they got a good night's rest. Women in the outpatient group felt more emotionally supported, and midwives/doctors said they felt more comfortable sending their patients home

with the balloon compared with PG. The authors concluded that the possibility of cervical ripening with balloon catheters in an outpatient setting should be explored in an adequately powered trial.

Discussion

The Cochrane authors concluded that, on the basis of the available data, it is not possible to determine whether these methods of IOL are effective and safe within an outpatient setting. The included trials were of varying quality, and all were underpowered for the outcomes assessed. The trials do report high satisfaction levels in women who spent some time during their IOL out of hospital.

There are two ongoing RCTs evaluating this research question. The OBLIGE study⁴ in New Zealand is comparing inpatient PGE2 with outpatient single-balloon catheter, and the primary outcome is caesarean section rate; the PINC Balloon study in Australia is comparing inpatient PGE2 with outpatient double-balloon catheter, and the primary outcome is a composite neonatal adverse outcome.

It would seem sensible to have women at home with balloon-catheter inductions rather than PGs, given that studies show almost no adverse events during the cervical ripening phase of IOL with balloon catheters (Diederens et al 2018). If offering outpatient IOL, it is imperative that safety measures and support be in place. Women should be encouraged to communicate with the hospital midwives if they have any questions or concerns and be given written instructions to return to hospital if they have contractions or ROM or at a pre-specified time for reassessment.

There is insufficient high-quality evidence to make a clear recommendation regarding outpatient IOL.

Research gap

- For women who need cervical ripening, to evaluate the effect of initiating labour away from a hospital setting compared with inpatient care, on chance of vaginal birth, potential harms, and maternal satisfaction, experience and perspectives.

⁴ See www.oblige.auckland.ac.nz.

Abbreviations

AFI	Amniotic fluid index
ANZCTR	Australian New Zealand Clinical Trials Registry
aOR	Adjusted odds ratio
APH	Antepartum haemorrhage
ARM	Artificial rupture of membranes
ART	Assisted reproductive technology
BMI	Body mass index
CTG	Cardiotocography
DHB	District health board
EFW	Estimated fetal weight
FHR	Fetal heart rate
FGR	Fetal growth restriction
GDM	Gestational diabetes mellitus
HELLP	Haemolysis, elevated liver enzymes, and low platelet count
HQSC	Health Quality & Safety Commission
ICSI	Intracytoplasmic sperm injection
IOL	Induction of labour
IUGR	Intrauterine growth restriction
IVF	In vitro fertilisation
LGA	Large for gestational age
LMC	Lead maternity carer
MCA	Middle cerebral artery
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NNT	Number needed to treat
PG	Prostaglandin
PMMRC	Perinatal and Maternal Mortality Review Committee
PPH	Postpartum haemorrhage
PROM	Pre-labour rupture of membranes
RANZCOG	The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RFM	Reduced fetal movements
ROM	Rupture of membranes
SGA	Small for gestational age
SROM	Spontaneous rupture of membranes
WHO	World Health Organization

Appendices

Appendix A: The panel that developed this clinical practice guideline

Member	Affiliation / representing organisation	Role
Dr Michelle Wise	Senior Lecturer, Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, The University of Auckland; Obstetrician and Gynaecologist, Auckland DHB	Chair
Dr Jane Alswailer	Consultant Neonatologist, NICU, Auckland DHB; Senior Lecturer, Department of Paediatrics: Child and Youth Health, The University of Auckland; Honorary Senior Lecturer, Liggins Institute, The University of Auckland	Representing RACP
Jacqui Anderson	Midwifery Advisor: Quality Assurance	Representing New Zealand College of Midwives
Lesley Ansell	Associate Clinical Charge Midwife Manager, Counties Manukau Health	
Dr Sue Belgrave	Obstetrician and Gynaecologist, Waitematā DHB; former Chair of the Perinatal and Maternal Mortality Review Committee (PMMRC)	Representing RANZCOG
Dr Isabel Camano	Clinical Director, Obstetrics, Waikato DHB	
Dr Lesley Dixon	Midwifery Advisor: Practice advice and research development	Representing New Zealand College of Midwives
Emma Farmer	Head of Midwifery, Waitematā DHB	
Dr Charlotte Farrant	Obstetrician and Gynaecologist, Northland DHB	
Dr Per Kempe	Medical Lead, Obstetrician and Gynaecologist, MidCentral DHB	
Dr Jenny McDougall	Service Clinical Director – Secondary Maternity, Auckland DHB	
Isis McKay	General Manager: Women’s Health Action (WHA); Co-founder: Health Promotion in Partnership	Representing consumer perspectives

Member	Affiliation / representing organisation	Role
Deborah Pittam	Midwifery Leader, Auckland DHB; Previously midwife in Northland DHB	
Dr Sean Pocock	Obstetrician and Gynaecologist, Tairāwhiti DHB	
Rose Swindells	–	Representing consumer perspectives
Juliette Wotton	Clinical Educator in Midwifery, Auckland University of Technology (AUT)	

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Helena Trollope, Research Assistant and Project Manager

Julie Brown, Research Assistant

Tash Wharerau, Wahine Ora Health Promoter, Women's Health Action (WHA)

Appendix B: Search methods

Methods

Searches for indications and methods for induction of labour (Table B1) were conducted using the Cochrane Database of Systematic Reviews, and databases PubMed, MeSH and Google Scholar. Search dates were limited from 01/01/2014 to 03/12/2018 to ensure any updated information from the 2014 National Consensus IOL Guideline was identified. If searching new terms, the timeline was open. In addition, the registries clinicaltrials.gov and ANZCTR were searched to identify any ongoing clinical trials focused on IOL.

Searches

Terms used in all searches included: 'induction of labour', 'labour, induced', 'expectant management'. Each indication was searched for using a variety of keywords. The initial search was for Cochrane reviews. If not found, the search was limited to systematic reviews and meta-analyses, followed by RCTs. If not found, then observational studies were used.

Search terms (in alphabetical order)

Advanced maternal age; antepartum haemorrhage; antepartum haemorrhage of unknown origin; artificial reproduction; artificial reproduction techniques; artificial rupture of membrane; artificial rupture of membranes; assisted reproduction; awareness of fetal movements; body mass index; carboprost; catheter; cervical ripening; cervidil; cholestasis of pregnancy; controlled release; decreased fetal movements; DFM; Diabetes, Gestational; diabetes mellitus; dinoprostone; double balloon; double balloon catheter; early amniotomy; early artificial rupture of membranes; elective induction; elective procedure; Fertilization in Vitro; fetal growth retardation; gestational diabetes; gestational hypertension; Hemorrhage; high dose oxytocin; history of stillbirth; Hypertension; hypertension in pregnancy; Hypertension, Pregnancy-Induced; increased BMI; Infant, Small for Gestational Age; inpatient; intracytoplasmic sperm injection; intrahepatic cholestasis of pregnancy; intrauterine growth restriction; in-vitro fertilisation; IUGR; IVF; large for gestational age; LGA; late amniotomy; late artificial rupture of membranes; low dose oxytocin; macrosomia; Maternal Age; maternal outcome; membrane sweeping; misoprostol; multiple pregnancy; neonatal outcome; Obesity; Obesity, Morbid; Oligohydramnios; outpatient; oxytocin; oxytocin protocol; oxytocin regimen; perinatal outcome; PGE2; PGE2 gel; policy induction of labour; post-term; Pre-Eclampsia; Pregnancy, Multiple; Pregnancy, Prolonged; pregnancy stillbirth;

pregnancy, Twin; Pre-labour rupture of membranes; Prolonged pregnancy; PROM; prostaglandins; prostin; prostin gel; raised BMI; recurrent stillbirth; reduced fetal movements; RFM; Reproductive Techniques; single balloon; Sperm Injections, Intracytoplasmic; Stillbirth; stillborn; suspected SGA; suspected small for gestational age; twin gestation; type 1 diabetes, type 2 diabetes, pre-existing diabetes.

MeSH search terms (in alphabetical order)

amniotomy; carboprost; catheters; diabetes, gestational; diabetes mellitus; diabetes mellitus, type 1; diabetes mellitus, type 2; dinoprostone; fertilisation, in-vitro; fetal growth retardation; fetal macrosomia; fetal membranes; hemorrhage; hypertension; hypertension, pregnancy-induced; infant; inpatients; intracytoplasmic sperm injection; intrahepatic cholestasis of pregnancy (supplementary concept); Labor, induced; maternal age; obesity; obesity, morbid; oligohydramnios; outpatient, hospital clinic; outpatients; oxytocin; pre-eclampsia; pregnancy; pregnancy, multiple; pregnancy outcomes; outcome assessment (healthcare); pregnancy, twin; premature rupture; prolonged; reduced fetal movements; reproductive techniques; small for gestational age; stillbirth; treatment outcome.

Selection criteria

Selection criteria included papers written in English, where the ideal countries for published material were from populations most similar to that of New Zealand (Australia, United Kingdom, Canada, United States of America). Papers were selected if they evaluated IOL versus expectant management for the specific indication and had full texts available to assess.

Quality of evidence

Papers were categorised into the levels of evidence for intervention studies provided by the National Institute for Health and Care Excellence (NICE 2008) (see Table 2 under Guideline development process above). The panel aimed to provide the highest level of evidence available for each indication in order to provide the most evidence-based guidance on IOL. The Cochrane Database of Systematic Reviews was the primary search as it provides the highest-quality evidence (level 1). If a Cochrane review was found, database searches were performed to assess any level-1 evidence published after the review. If a Cochrane review was not found, the PubMed and Google Scholar were searched for level-1 evidence; if none was found, high-quality level-2 evidence was sought. If level-2 evidence was not found, international guidelines were identified.

Results

Table B1: Results of searches

Indication	Cochrane Review	PubMed / Google Scholar
Pregnancy \geq 41 weeks' gestation* Δ	1 review (2018) 30 trials	19 results: 5 reviews, 4 clinical trials
Pre-labour rupture of membranes* Δ	1 review (2017) 23 trials	19 results: 7 reviews, 4 clinical trials
Advanced maternal age* Δ	No results	5 results 1 review, 1 clinical trial
Obesity in pregnancy* Δ	No results	7 results: 1 review, 0 clinical trials Wider search (remove e): 15 reviews, 2 clinical trials; none of level-1 quality
Gestational diabetes* Δ	1 review (2018) 1 trial	19 results: 5 reviews; 2 clinical trials
Hypertension in pregnancy* Δ	1 review (2017) 5 trials	28 results: 10 reviews, 6 clinical trials
Suspected SGA \geq 34 weeks* Δ	1 review (2015) 3 trials	17 results: 3 reviews, 3 clinical trials
Suspected macrosomia* Δ	1 review (2016) 4 trials	24 results: 11 reviews, 2 clinical trials
Multiple pregnancy* Δ	1 review (2014) trials	5 results: 4 reviews, 0 clinical trials Wider search (remove e): 183 results: 20 reviews, 6 clinical trials
Assisted reproductive technology* Δ	No results	2 results: 1 review, 0 clinical trials Wider search (remove e): 98 results: 9 reviews, 10 clinical trials
Antepartum haemorrhage of unknown origin* Δ	No results	4 results: 0 reviews, 2 clinical trials Wider search (remove e): 30 results: 3 reviews, 4 clinical trials
Previous stillbirth* Δ	No results	20 results: 10 reviews, 2 clinical trials Wider search (remove e): 133 results: 22 reviews, 8 clinical trials
Cholestasis of pregnancy* Δ	1 review (2013) 21 trials	0 results Wider search (remove e): 17 results: 4 reviews, 1 clinical trial
Reduced fetal movements Δ	No results	15 results: 8 reviews, 2 clinical trials Wider search (remove e): 534 results: 92 reviews, 48 clinical trials
Oligohydramnios	No results	529 results: 82 reviews, 59 clinical trials Wider search (remove e): 626 results: 75 reviews, 53 clinical trials
Pre-existing diabetes mellitus Δ	1 review (2018) No trials	36 results: 11 reviews, 6 clinical trials
IOL with no medical indication / elective IOL Δ	No results	35 results: 12 reviews, 2 clinical trials

Indication	Cochrane Review	PubMed / Google Scholar
Methods		
Mechanical IOL	2 reviews (2012, 2017) 2012: 71 trials 2017: 8 trials	492 results: 64 reviews, 147 clinical trials
PGE2 gel – dinoprosotone vs cervidil; cervical vs vaginal	2 reviews (2008, 2014) 2008: 56 trials 2014: 70 trials	38 results: 2 reviews, 12 clinical trials
Pharmacological IOL / cervical ripening	2 reviews (2014, 2017) 2014: 75 trials 2017: 8 trials	1,045 results: 175 reviews, 431 clinical trials
Artificial rupture of membranes timing (early vs late)	1 review (2013) 14 trials	22 results: 4 reviews, 10 clinical trials
Oxytocin protocol (low vs high; timing to increasing dose)	2 reviews (2009, 2014) 2009: 61 trials 2014: 9 trials	3,923 results: 353 reviews, 724 clinical trials
Membrane sweeping for reduction in need for IOL	1 review (2005) 22 trials	50 results: 17 reviews, 23 clinical trials
Outpatient IOL	2 reviews (2013, 2017) 2013: 4 trials 2017: 34 studies	48 results: 9 reviews, 15 clinical trials

Note:

* = restricted dates 01/01/2014–03/12/2018; Δ = expectant management included in search terms

Searches for ongoing clinical trials

Searches on clinicaltrials.gov⁵ and ANZCTR yielded a total of 253 trials. Studies were not included if they were observational or if they combined methods and indications (for example, methods of IOL for obesity).

⁵ The web-based library of publicly and privately supported clinical studies of diseases and conditions, maintained by the National Library of Medicine and the National Institutes of Health of the United States and open to patients, their families, health care professionals, researchers and the public.

Indications

Eleven trials focused on IOL versus expectant management for an indication. Three trials were found on GDM; two trials were completed (one published – Alberico 2017; one not published), one trial not yet recruiting. Two trials were found on macrosomia; one completed (no publication), one not yet recruiting. Two trials were found for no medical indication; one published (Grobman et al 2018), one unknown status. One trial was found for post-dates; completed (no publication). Two trials were found for term PROM; one recruiting (Table B2), one unknown status. One study was for 'risks associated with c-section' and was terminated.

Methods and setting

One hundred and thirty-eight trials were found for methods or setting of IOL.

Of the 138 trials, 69 were completed; 37 were recruiting; 5 were active, not recruiting; 5 were not yet recruiting; 4 were terminated and 28 were 'unknown status'. Of the 69 completed trials, 17 were published. Of the 37 recruiting, 23 were relevant (Table B2), 3 were not; 8 were related to methods for specific indications; 3 were for methods not researched in this guideline and 7 were for outpatient. Of the 138 trials, 16 were found with methods not included in this guideline. Five stated they were going to assess maternal satisfaction.

Of the 138 trials, 12 were evaluating outpatient versus inpatient care. Two of these were completed, 2 were not yet recruiting, 7 were recruiting (Table B3), 2 had an 'unknown status' and 1 was terminated. No publications were available. One trial that was not found in our search comparing inpatient with outpatient inductions is currently recruiting.

Table B2: Recruiting trials for indications and methods of induction of labour

Identifier	Inclusion criteria	Primary outcome
Indications		
Premature rupture of membranes with a Bishop score <6; comparison of medical induction / expectant management, NCT02825641	Women with term (>37 weeks' gestation), singleton, vertex presentation pregnancies, with no obstetric or clinical contraindications for labour induction, Bishop score <6, and reactive non-stress test on presentation.	Percentage of participants that achieve vaginal delivery (up to 7 days from the time of the presentation with PROM).
Methods		
An RCT of a synthetic osmotic cervical dilator for IOL in comparison to dinoprostone vaginal insert (SOLVE), NCT03001661	Women ≥16 years of age with a singleton pregnancy and able to provide informed consent.	Failure to achieve vaginal delivery within 36 hours from randomisation.
Efficacy of induction of labor on term using a double balloon catheter compared to dinoprostone vaginal-insert, NCT01720394	Medical indication for IOL, aged 18 years, signed informed consent, cephalic presentation, no PROM, 37–42 weeks' gestation, Bishop score ≤6, no contraindication for medical induction and no clinical sign of infection.	Time interval from primary treatment to delivery.
Early amniotomy vs delayed amniotomy following Foley catheter ripening in nulliparous labor induction, NCT03039036	Women, aged ≥18 years who are nulliparous, pregnant with a singleton gestation (≥37 weeks gestation) undergoing induction with Foley catheter, English speaking and can provide informed consent.	Time interval from Foley catheter removal to delivery.
What after the first proppess (PRODUCT), NCT02956785	Women with a viable singleton pregnancy with no antenatal fetal concerns, cephalic presentation with intact membranes and no prior c-section, booked for IOL at 37–42 weeks' gestation.	Rate of achieving spontaneous or artificial rupture of membranes.
Foley bulb with oral misoprostol for induction of labor, NCT03407625	Women with a live singleton fetus with no major fetal malformations, cephalic presentation at ≥37 weeks gestation, with cervical dilatation of ≤2 cm, no previous uterine scar, intact fetal membranes and who have an indication for induction or attempted IOL and qualify for PG administration (according to current Parkland protocol).	Vaginal delivery.

Identifier	Inclusion criteria	Primary outcome
Outpatient Foley for starting induction of labor at term in nulliparous women (OFFSITE III), NCT03472937	Nulliparous women aged ≥ 18 years with a singleton, vertex presentation pregnancy with gestation between 39 and 42 weeks' gestation, a modified Bishop score < 5 and cervical dilatation < 2 cm, no previous uterine surgery, reside within 30 minutes of the hospital and have access to a telephone and reliable transportation.	Total time from admission to delivery.
Comparing Foley catheter balloon with early amniotomy for induction of labor at term, NCT03629548	Women with singleton, cephalic presentation pregnancy ≥ 37 weeks' gestation, with intact membranes, Bishop score < 5 , obstetric indications for IOL and less than three uterine contractions in every 10 minutes.	Induction-to-delivery time.
A comparison of oral misoprostol and vaginal misoprostol for cervical ripening and induction of labor, NCT02777190	Women aged ≥ 18 years with a single live cephalic presenting intrauterine pregnancy (≥ 37 weeks' gestation) undergoing IOL, with 20 minutes reassuring fetal heart rate, Bishop score ≤ 6 (cervical dilatation ≤ 2 cm), and three or fewer uterine contractions over 10 minutes.	Time interval from start of IOL (first misoprostol administration) to active phase of labor (≥ 6 cm cervical dilation).
Cervical ripening with the double balloon device (DBD) for 6 hours compared with 12 hours (DoubleCRIB), NCT03045939	Parous women aged ≥ 18 years with an indication for IOL, with a singleton pregnancy in vertex presentation with intact membranes and no significant regular uterine contraction (≥ 37 weeks' gestation) with a Bishop score of ≤ 5 , willingness to comply with the protocol for the duration of the study and signed informed consent.	Time from insertion of the DBD to delivery.
Is there an interest in repeating the vaginal administration of dinoprostone (Propess®), to promote induction of labor of pregnant women at term? (RE-DINO), NCT02888041	Women ≥ 18 years old with a term cephalic presentation pregnancy ≥ 37 weeks' gestation, undergoing a medically indicated IOL with intact membranes, unfavourable cervical conditions (Bishop score < 6 , 1 hour before inclusion), who have had the establishment of a first Propess® within 24–36 hours (before signing consent), have signed the consent form and are affiliated with a social security number.	Rate of deliveries vaginally.

Identifier	Inclusion criteria	Primary outcome
Labour induction with a combined method (pharmacologic and mechanical): randomized controlled trial, NCT03928600	Women with singleton, vertex-presenting pregnancies at term (≥ 37 weeks' gestation), with no contraindication to vaginal delivery, intact membranes and Bishop score < 7 and cervical dilatation ≤ 2 cm.	Time to delivery.
Oral misoprostol solution in labour induction, NCT03927807	Nulliparous women with a singleton live pregnancy, cephalic presentation at term (≥ 37 weeks' gestation), with a Bishop score < 6 , reassuring FHR pattern, not in labour (no contractions), and a clinically adequate pelvis.	Mode of delivery.
Efficacy and safety of hourly titrated misoprostol versus vaginal dinoprostone and misoprostol for cervical ripening and labour induction, NCT02902653	Women aged > 18 years with a single cephalic presenting pregnancy with intact membranes, unfavourable cervix (Bishop score < 6), CTG normal and signed informed consent from the patient.	Compare the percentage of women in each group who achieved vaginal delivery within 24 hours after the beginning of administration in each group (oral misoprostol, vaginal misoprostol and vaginal dinoprostone).
Comparison of misoprostol ripening efficacy with dilapan (COMRED), NCT03670836	Women undergoing IOL with a single live fetus in cephalic presentation with ≥ 37 weeks' gestation and able to provide informed consent.	Proportion of women achieving vaginal delivery.
Cervical ripening using misoprostol vs dinoprostone: a randomised, triple-blinded, interventional study comparing safety and efficacy in primiparous women, ACTRN12616000522415, www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370551&isReview=true	Pregnant women aged ≥ 18 years with BMI < 50 at booking, between 37 and 41+4 weeks' gestation, having first baby undergoing medically indicated IOL, with Bishop score ≤ 4 .	<p>Number of women requiring further cervical ripening with balloon following treatment as assessed by Bishops' score ≤ 7 following removal of treatment drug (at 24 hours).</p> <p>Number of women requiring IOL with oxytocin as assessed by the number of women who have not achieved spontaneous labour following treatment at 48 hours).</p> <p>Number of women requiring intervention for uterine hyperstimulation that is assessed by the number of women having 6 or more contractions in 10 minutes who require tocolysis or other intervention for fetal cardiotocography changes.</p>

Identifier	Inclusion criteria	Primary outcome
Tension versus no tension with Foley bulb induction, NCT03588585	Nulliparous women aged ≥ 18 years with a singleton live intrauterine pregnancy, cephalic presenting, with intact fetal membranes, undergoing IOL at Kapi'olani Medical Center for Women and Children, Hawaii Pacific Health with a Bishop score ≤ 6 .	Time to delivery.

Table B3: Recruiting trials looking at outpatient methods of induction of labour

Identifier	Inclusion criteria	Primary outcome
Outpatient cervical preparation to reduce induction duration in NTSV women (OCPRID), NCT03934918	Nulliparous women aged > 18 years with a singleton live pregnancy with vertex presentation, scheduled for IOL between 37 and 42 weeks' gestation and a Bishop score < 6 .	Duration of time from admission for IOL to delivery.
Comparison of low-risk pregnant women undergoing induction of labour at term by outpatient balloon or inpatient prostaglandin in order to assess caesarean section rate; an randomized controlled trial, ACTRN12616000739415, www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370330&isReview=true	Women with a live singleton cephalic presentation and IOL planned at ≥ 37 weeks' gestation.	Caesarean section.
Comparing outpatient to inpatient cervical ripening using Dilapan-S® (HOMECARE), NCT03665688	Pregnant women aged between 18–45 years with live singleton, cephalic presentation ≥ 37 weeks' gestation with intact membranes, a pelvic exam of ≤ 3 cm and at most 60% effaced, with understanding and can sign informed consent.	Rate of hospital stay > 48 hours (from admission to discharge). Health care cost impact (assessed based on direct hospital costs or Medicaid charges).
Outpatient Foley for starting induction of labor at term (OFFSITE), NCT02756689	Multiparous women aged ≥ 18 years with singleton, vertex presentation 39–42 weeks' gestation with cervix ≤ 3 cm (if 2–3 cm must be $< 80\%$ effaced), no previous caesarean section or uterine scar, resides local and has access to a phone and reliable transportation.	Total time from admission to delivery.
Patient satisfaction during outpatient versus inpatient Foley catheter induction of labor, NCT02975167	Women aged > 18 years with a singleton vertex presenting fetus at ≥ 39 weeks' gestation.	Patient satisfaction scores.
Sleep and depression in induction of labour, NCT03380897	Women with an uncomplicated singleton pregnancy ≥ 37 – $\leq 41+5$ weeks' gestation, patient lives within half an hour of the hospital.	Pain after double-balloon catheter insertion, measured by visual analogue scale (VAS).

Identifier	Inclusion criteria	Primary outcome
Comparison of two mechanical methods of outpatient ripening of the cervix (CORC), NCT03752073	Women between 39 and 41 weeks' gestational age who desire elective IOL, based on reliable estimated gestational age.	Time from start of cervical ripening to delivery.
Prostaglandin inpatient induction of labour compared with balloon outpatient induction of labour: a randomised controlled trial, ACTRN12614000039684, www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365522	All women, aged 18–52 years, with live singleton ≥37 weeks' gestation, booked for IOL because of post-term and/or social/elective reasons, and requiring cervical priming will be suitable for inclusion in this study.	Composite measure of neonatal outcome comprising one or more of: admission to NICU; need for intubation and/or external cardiac compressions; neonatal academia (cord arterial pH <7.10); hypoxic ischemic encephalopathy (HIE); neonatal seizure; infection (needing neonatal antibiotics); persistent pulmonary hypertension of the newborn.

Appendix C: Observational studies

Tables of national and international stillbirth risk factors

Table C1: Adjusted odds ratio for perinatal related mortality, termination of pregnancy, stillbirth and neonatal death 2011–2015 in New Zealand

	Fetal deaths											
	Perinatal related mortality n=494,210			Termination of pregnancy n=494,210			Stillbirth n=494,210			Neonatal mortality n=490,578		
	OR adjusted	95%CI		OR adjusted	95%CI		OR adjusted	95%CI		OR adjusted	95%CI	
Ethnicity*												
Māori	0.90	0.83	0.97	0.53	0.44	0.64	0.93	0.83	1.03	1.18	1.02	1.36
Pacific	1.09	1.00	1.20	0.65	0.52	0.82	1.17	1.03	1.33	1.32	1.11	1.57
Indian	1.50	1.32	1.71	1.36	1.04	1.78	1.46	1.21	1.75	1.74	1.36	2.22
Other Asian	0.94	0.84	1.05	1.30	1.07	1.57	0.76	0.64	0.90	0.91	0.72	1.15
Other	0.69	0.62	0.77	0.76	0.62	0.93	0.69	0.59	0.81	0.62	0.49	0.78
New Zealand European	1.00			1.00			1.00			1.00		
Age*												
<20	1.62	1.45	1.81	1.62	1.25	2.12	1.49	1.28	1.75	1.81	1.49	2.20
20–24	1.11	1.01	1.21	1.18	0.97	1.43	1.11	0.98	1.25	1.05	0.89	1.23
25–29	1.00			1.00			1.00			1.00		
30–34	0.97	0.89	1.05	1.03	0.87	1.23	1.00	0.89	1.12	0.85	0.73	1.00
35–39	1.19	1.09	1.30	1.29	1.07	1.55	1.16	1.02	1.31	1.17	0.99	1.38
≥40	1.51	1.32	1.72	1.80	1.38	2.34	1.47	1.22	1.78	1.34	1.03	1.74
Deprivation decile* (per unit)	1.05	1.03	1.06	0.99	0.97	1.02	1.05	1.03	1.07	1.08	1.06	1.11
Year of birth*	0.99	0.98	1.01	1.00	0.97	1.03	0.99	0.97	1.00	1.00	0.98	1.03
Sex*												
Male	1.00			1.00			1.00			1.00		
Female	0.95	0.90	1.00	1.03	0.91	1.16	0.97	0.90	1.05	0.85	0.76	0.94
Multiple pregnancy*	4.28	3.91	4.69	2.07	1.60	2.67	4.01	3.52	4.56	6.73	5.80	7.81

* Data for numerator from the PMMRC dataset.
 * Data for numerator from the MAT dataset.
 † Data for numerator from the MAT dataset, then the PMMRC dataset if MAT data are missing.
 OR = odds ratio.
 CI = confidence interval.

Source: PMMRC 2017

Table C2: Risk factors and attributable stillbirth in selected high-income countries

	aOR (95% CI)	Australia (n=1236 SB)			Canada (n=1885 SB)			USA (n=20 416 SB)			UK (n=4898 SB)			Netherlands (n=1153 SB)			Total preventable SB for five study HIC	Total preventable SB for all HIC
		P (%)	PAR	SB (n)	P (%)	PAR	SB (n)	P (%)	PAR	SB (n)	P (%)	PAR	SB (n)	P (%)	PAR	SB (n)		
BMI (kg/m²)																		
<25	1.0	57.6	12.3%	178	52.3	13.9%	304	41.6	17.6%	4056	57.4	12.2%	705	72.5	7.7%	108	5352	8064
25–30	1.2 (1.09–1.38)	28.7	31.3	34.2	29	20.5
>30	1.6 (1.35–1.95)	13.7	16.4	24.2	13.5	7.1
Maternal age (years)																		
<35	1.0	77.7	82	85.8	79.9	78.2
35–39	1.5 (1.22–1.73)	18.7	11.1%	99	15.1	9.1%	123	11.6	7.5%	1116	16.4	10.2%	367	19	10.6%	86	1790	4226
40–44	1.8 (1.4–2.3)	3.4	2.8	2.4	3.5	2.7
≥45	2.9 (1.9–4.4)	0.2	0.1	0.2	0.2	0.1
Anysmoking	1.4 (1.27–1.46)	16.6	6.2%	77	13.4	5.1%	96	14.2	5.4%	1097	19	7.1%	346	10	3.9%	44	1660	2852
Primiparity	1.4 (1.42–1.33)	41.6	14.3%	176	44.4	15.1%	284	42.6	14.6%	2972	43	14.7%	719	45.1	15.3%	176	4328	7434
Medical disease																		
Pre-existing hypertension	2.6	4.6	6.9%	85	5.4	8.0%	151	4.8	7.1%	1451	9.8	13.6%	665	7.1	10.2%	118	2470	4242
Pre-existing diabetes	2.9	2.6	4.7%	58	2.1	3.9%	74	2.5	4.5%	914	2.2	4.0%	193	1.8	3.3%	39	1277	2194
Abruption	18.9	1	15.2%	188	1	15.2%	286	1	15.2%	3100	1	15.2%	744	1	15.2%	175	4492	7716

Five study HIC were those with the highest numbers of stillbirths and all relevant data for analysis available. aOR=adjusted odds ratio. SB=stillbirths. HIC=high-income countries. P=prevalence. PAR=population-attributable risk. SB (n)=number of SB attributed. BMI=body-mass index. The sources used to generate the data of this table are referenced in webappendix pp 34–35.

Table 1: Most important potentially modifiable risk factors and attributable stillbirth across selected HIC

Source: Flenady et al 2011

Table C3: Population-attributable risk for stillbirth in selected high-income countries

	aOR (95% CI)	Prevalence (%)	PAR (%)
Illicit drug use	1.9 (1.2–3.0)*	2.4	2.1
Low education	1.7 (1.4–2.0)*	6.9	4.9
Low socioeconomic status	1.2 (1.0–1.4)	49.6	9.0
No antenatal care	3.3 (3.1–3.6)	0.3	0.7
Assisted reproductive technology singleton pregnancy	2.7 (1.6–4.7)*	3.1	3.1
Hypertension			
Pregnancy-induced	1.3 (1.1–1.6)*	6.3	1.9
Pre-eclampsia	1.6 (1.1–2.2)*	5.3	3.1
Eclampsia	2.2 (1.5–3.2)	0.1	0.1
Small size for gestational age (<10th centile)	3.9 (3.0–5.1)*	10.0	23.3
Post-term pregnancy (≥42 weeks)	1.3 (1.1–1.7)*	0.9	0.3
Previous stillbirth	2.6 (1.5–4.6)*	0.5	0.8

aOR=adjusted odds ratio. PAR=population-attributable risk. HIC=high-income countries.*aOR results from meta-analysis. The sources used to generate the data of this table are referenced in webappendix p 35–36.

Table 2: PAR for stillbirth in HIC, according to maternal demographic and pregnancy factors

Source: Flenady et al 2011

Table C4: Association of maternal factors with antepartum stillbirth (INTERGROWTH-21 Project)

Table 1. Association of maternal factors with antepartum stillbirth in a population of 60 121 babies in the INTERGROWTH-21st Project

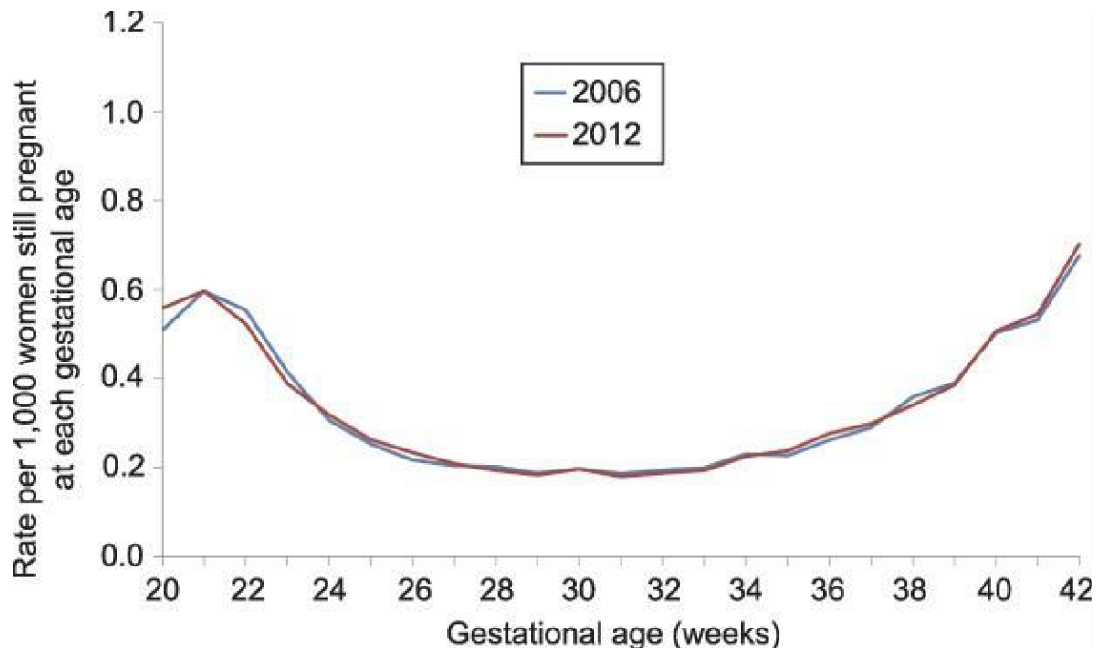
Variable	Adjusted hazard ratio (95% CI)	Population-attributable percentage (%)
Low socio-economic standing	1.6 (1.2–2.1)*	9.7
Single marital status	2.0 (1.4–2.8)*	4.8
Maternal age (years)		
<18	0.8 (0.4–1.6)**	
18–25	Ref	
26–34	1.1 (0.9–1.4)**	
35–39	1.2 (0.8–1.7)**	
≥40	2.2 (1.4–3.7)**	3.0
Prior history of hypertension	4.0 (2.7–5.9)***	5.5
HIV/AIDS diagnosed before pregnancy	4.3 (2.0–9.1)***	0.3
Last two pregnancies ended in miscarriage	1.8 (1.1–3.0)***	4.3
Pre-eclampsia	1.6 (1.1–3.8)****	1.4
Severe pre-eclampsia/eclampsia/HELLP without antepartum haemorrhage	2.8 (1.5–5.1)****	1.6
Severe pre-eclampsia/eclampsia/HELLP with antepartum haemorrhage	4.2 (1.3–13.6)****	2.2
Antepartum haemorrhage without severe pre-eclampsia	3.3 (2.5–4.5)****	9.0
Multiple pregnancy	3.3 (2.0–5.6)****	7.4
Fetal distress suspected in pregnancy	2.1 (1.3–2.7)*****	3.4

All models adjusted for country of birth and fetal gender. In addition, the following stepwise adjustments were made: *Model 1, socio-economic deprivation and marital status; **Model 2, $P < 0.2$ in Model 1 + maternal age, body mass index, height, weight, parity + smoking, illicit drug use, >5 units of alcohol per week + high-risk occupation; ***Model 3, $P < 0.2$ in Model 2 + pre-existing maternal medical conditions and past obstetric outcomes; ****Model 4, $P < 0.2$ in Model 3 + maternal illnesses and conditions that develop during in pregnancy; *****Model 5, $P < 0.2$ in Model 4 + fetal-related conditions.

Source: Hirst et al 2018

Pregnancy 41 weeks' gestation or more

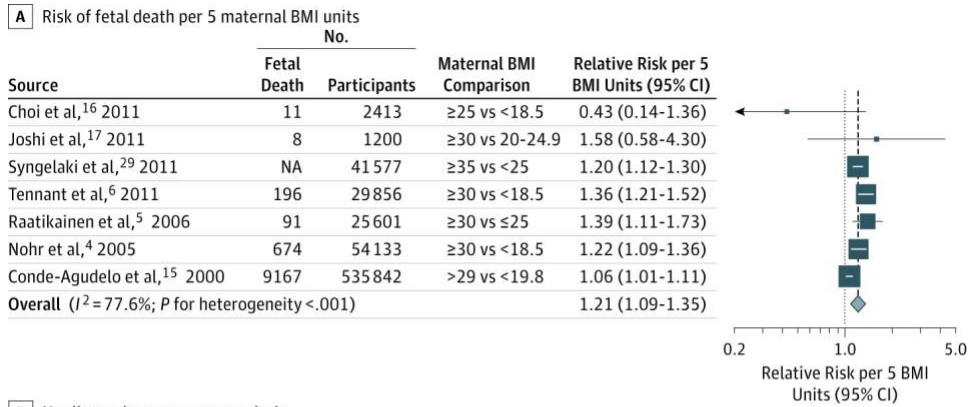
Figure C1: Association of stillbirth with gestational age, United States data



Source: MacDorman et al 2015

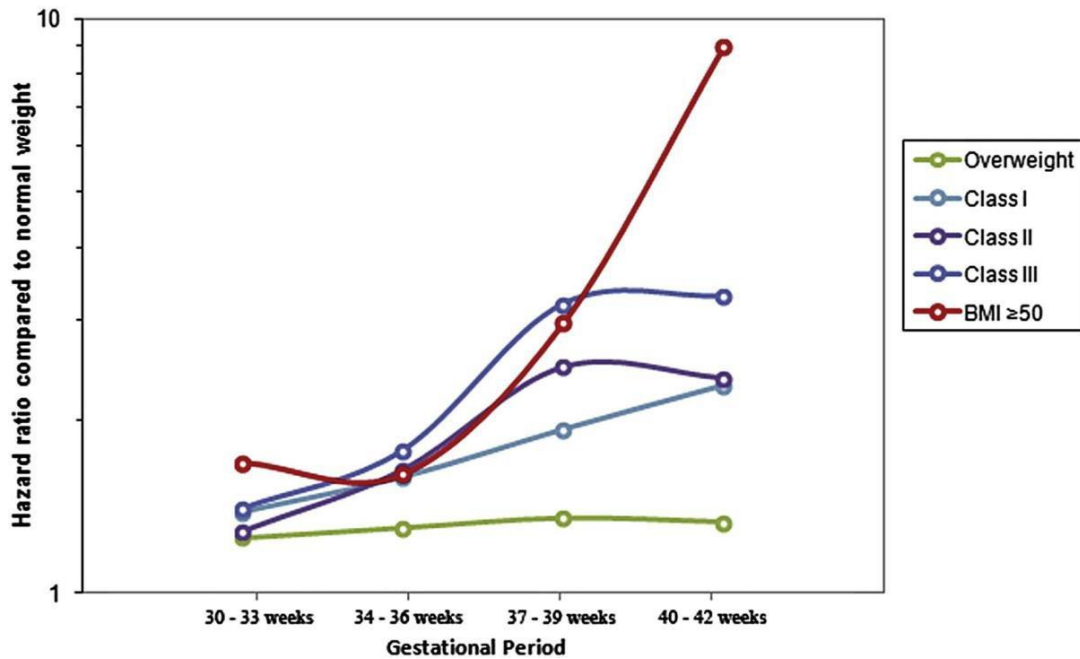
Obesity in pregnancy

Figure C2: Association of BMI and fetal death



Source: Aune et al 2014

Figure C3: Association of obesity in pregnancy and stillbirth in Washington and Texas



Source: Yao et al 2014

Advanced maternal age

Figure C4: Association of maternal age and stillbirth in the United States

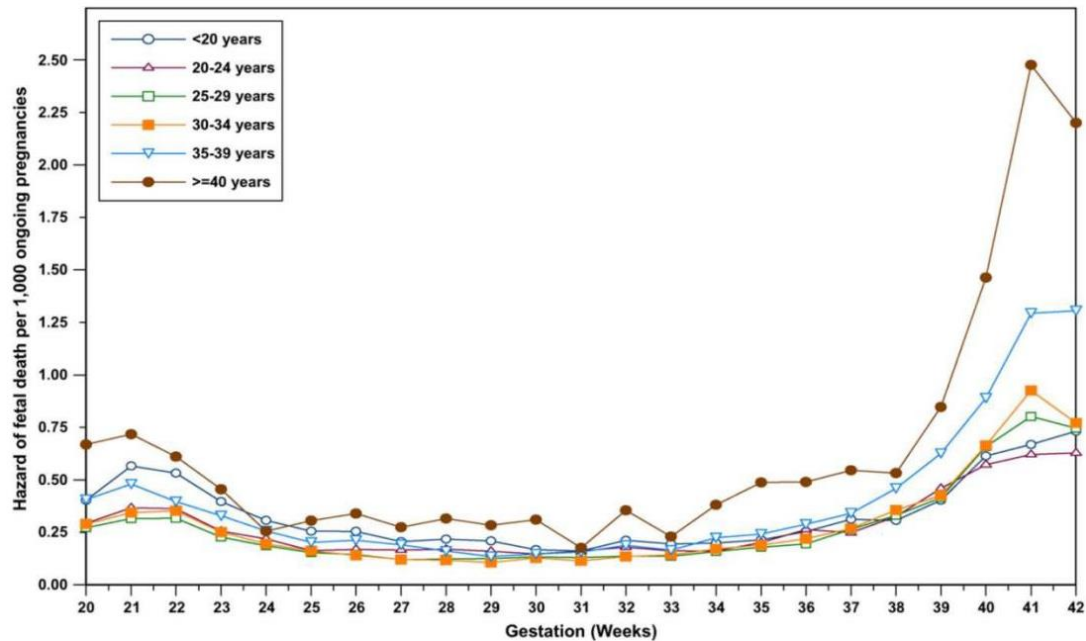


Figure Hazard (risk) of stillbirth for singleton births without congenital anomalies by gestational age, 2001-2002.

Reproduced with permission from Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. *Am J Obstet Gynecol* 2006; 195(3): 764-770.

Source: Reddy and Ko 2006.

Antepartum haemorrhage of unknown origin

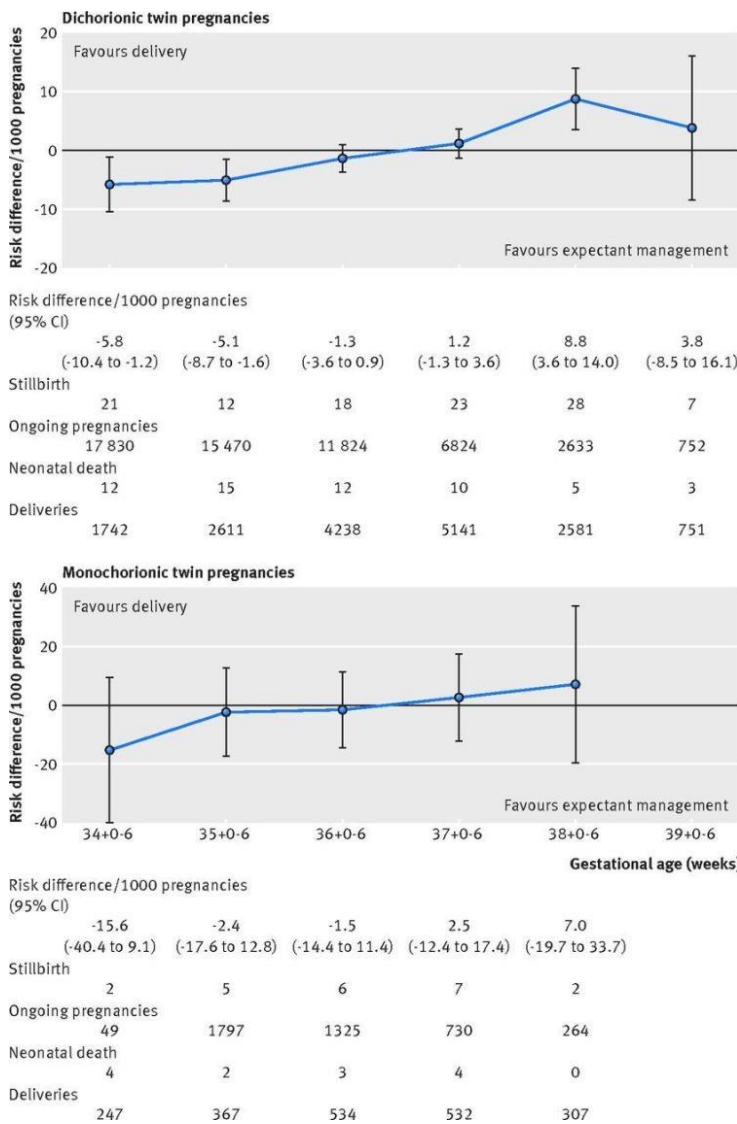
A retrospective cohort study (Bhandari et al 2014) reported on all primigravidae giving birth between 1976 and 2010, using the Aberdeen Maternity and Neonatal Databank (University of Aberdeen, Scotland). There were 7,517 women with APH of unknown origin and 68,423 without. Social class, smoking, marital status and a higher BMI were associated with APH of unknown origin. On multivariable analysis, pregnancies affected by APH of unknown origin were not associated with risk of preterm birth or PPH. There was no increase seen in perinatal death after adjusting for preterm birth.

Pregnancy following assisted reproductive technology

A systematic review of 30 observational studies compared obstetric and perinatal outcomes for singletons born after in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) compared with those of spontaneous conceptions (Pandey et al 2012). IVF/ICSI singleton pregnancies were associated with a higher risk for caesarean section (RR 1.56, 95% CI 1.51–1.60), admission to NICU (RR 1.58, 95% CI 1.42–1.77) and perinatal death (RR 1.87, 95% CI 1.48–2.37). Observational studies were of moderate quality but of high risk of bias due to non-randomised evidence.

Multiple pregnancy

Figure C5: Risk of stillbirth and neonatal complications in twin pregnancies



Source: Cheong-See et al 2016

Oligohydramnios

A systematic review of 15 observational studies (n=35,593 women) reported on adverse pregnancy outcomes in singleton pregnancies diagnosed with oligohydramnios (defined as amniotic fluid index (AFI) <5 cm) (Rabie 2017). For the six low risk of bias studies, women with isolated oligohydramnios had higher risk of caesarean section for fetal distress (RR 2.16; 95% CI 1.64–2.85) and higher NICU admission (RR 1.71; 95% CI, 1.20–2.42) compared to normal AFI. In women with oligohydramnios in the setting of co-morbidities, there was no difference in 5-minute Apgar score <7 (RR 1.85; 95% CI, 0.69–4.96), admission to NICU (RR, 2.09; 95% CI 0.80–5.45) or caesarean section for fetal distress (RR 1.65; 95% CI 0.81–3.36). Stillbirth rates were too low to analyse. The review provided insufficient data to determine the optimal timing of birth in low-risk cases with oligohydramnios. In a high-risk pregnancy, management of timing of birth should be based on the co-morbid condition and not the presence of oligohydramnios.

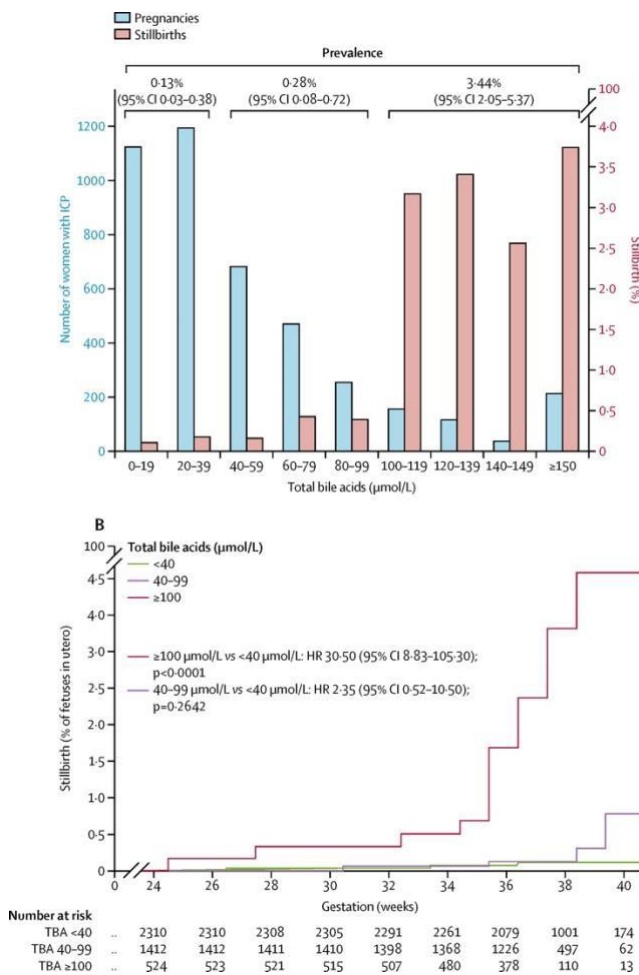
A systematic review of 43 observational studies (n=244,493) evaluated the association and predictive value of ultrasound measurements of amniotic fluid volume for adverse pregnancy outcome (Morris 2014). The review found a strong association between oligohydramnios (varying definitions) and neonatal death (OR 8.72, 95% CI 2.43–31.26); and in a subset of high-risk women, an association between oligohydramnios and perinatal death (OR 11.54, 95% CI 4.05–32.9). The authors of the review noted that despite increased risk for poor outcomes, oligohydramnios was not a predictor for individual risk.

Obstetric cholestasis

Ovadia et al (2019) published a systematic review and individual patient data meta-analysis of 23 studies (5,557 intrahepatic cholestasis of pregnancy cases; 165,136 controls; 27 studies of 269 women provided data for the individual patient data), which focused on reporting perinatal outcomes for women with intrahepatic cholestasis of pregnancy where serum bile acids were available.

Stillbirth occurred in 45 of 4 936 (0.9%) obstetric cholestasis cases vs 519 of 163,947 (0.3%) control cases (OR 1.46 CI 0.73–2.89) (no difference). Obstetric cholestasis was associated with spontaneous preterm birth and with meconium stained liquor. Stratified by bile acid level, they found an association with stillbirth with bile acids ≥ 100 but no association if <100. This risk of stillbirth increased as gestational age progressed. They did not see associations between stillbirth and level of aspartate transaminase (AST), alanine transaminase (ALT) or bilirubin.

Figure C6: Risk of perinatal death by gestational age and bile salt concentration in women with obstetric cholestasis



Source: Ovadia et al 2019

Previous stillbirth

A systematic review and meta-analysis of cohort ($n = 13$) and case control ($n = 3$) studies from high-income countries investigated the association between stillbirth in the initial pregnancy and risk of stillbirth in subsequent pregnancies (Lamont et al 2015). Data were available on 3,412,079 women, where in an initial pregnancy (>20 weeks' gestation), 3,387,538 (99.3%) had a live birth and 24,541 (0.7%) had a stillbirth. A total of 14,283 stillbirths occurred in the subsequent pregnancy, 606 (2.5%) in women with a history of stillbirth and 13,677 (0.4%) in women with no such history (pooled OR 4.83, 95% CI 3.77–6.18). Twelve studies specifically assessed the risk of stillbirth in second pregnancies. Compared with women who had a live birth in their first pregnancy, those who experienced a stillbirth in the first pregnancy were at an increased risk of a stillbirth in their second pregnancy (OR 4.77, 95% CI 3.70–6.15). The pooled odds ratio using the adjusted effect measures from the primary studies was 3.38 (95% CI 2.61–4.38).

Four studies examined the risk of recurrent unexplained stillbirth. Methodological differences between these studies precluded pooling the results. Two of the studies conducted prospective analyses looking at explained and unexplained stillbirth recurrence after a previous unexplained stillbirth. The reported risk for stillbirth in a subsequent pregnancy after a previously unexplained stillbirth was OR 3.10 (95% CI 0.98–9.76) and aOR 1.0 (95% CI 0.23–4.30). A retrospective analysis looked at the risk of unexplained stillbirth after any previous stillbirth; the reported risk was aOR 4.18 (95% CI 1.36–12.89). The final study reported the adjusted risk for unexplained stillbirth after any stillbirth as aOR 3.20 (95% CI 1.59–6.45).

The review authors concluded that the risk of stillbirth in subsequent pregnancies is higher in women who experience a stillbirth in their first pregnancy. This increased risk remained after adjusted analysis. Evidence surrounding the recurrence risk of unexplained stillbirth remains controversial due to limitations of observational data, and the studies included in the review were low quality due to study design and heterogeneity.

Another systematic review (Malacova et al 2018) evaluated the risk of stillbirth, preterm birth and SGA following exposure to one or more of these factors in a previous birth. The risk of stillbirth, preterm birth or SGA was moderately elevated in women who had previously experienced a single exposure but increased when two previous adverse outcomes were combined. The risk of stillbirth varied with prematurity, increasing threefold following preterm birth <34 weeks' gestation (pooled OR 2.98; 95% CI 2.05–4.34) and sixfold following preterm SGA <34 weeks' gestation (pooled OR 6.00; 95% CI 3.43–10.49). The authors concluded that the risk of adverse birth outcomes in a subsequent pregnancy increases with the combined number of previous adverse events.

Appendix D: Comparisons of cervical ripening and methods of induction of labour

Comparing all cervical ripening methods to each other

A systematic review and meta-analysis included 96 RCTs of 17,387 women, evaluating different cervical ripening methods during IOL (Chen et al 2016). In women with intact membranes >28 weeks' gestation, vaginal misoprostol was the most effective method to achieve birth within 24 hours, followed by vaginal PGE2. However, vaginal misoprostol was associated with higher rates of uterine hyperstimulation with FHR changes. In contrast, mechanical IOL using single-balloon catheter was the least effective method, along with oral misoprostol, but had the lowest incidence of uterine hyperstimulation with FHR changes.

Oral misoprostol was the best method of IOL in terms of reducing the likelihood of delivery by caesarean section, and it caused less uterine hyperstimulation with FHR changes compared with vaginal misoprostol.

All methods of IOL

A systematic review and network meta-analysis included 611 RCTs of 103,041 women (Alfirevic 2016). Of these 611 RCTs, 77 were post-term, 333 were >37 weeks' gestation and 149 were mixed (some preterm). The interventions most likely to achieve vaginal birth within 24 hours were intravenous oxytocin with ARM (for women with favourable cervix) and higher-dose (≥ 50 mg) vaginal misoprostol. The ranking according to safety of different methods was less clear. For uterine hyperstimulation, double-balloon catheter compared with placebo had the highest probability of being among the safest three treatments, whereas vaginal misoprostol (≥ 50 mg) compared with placebo was most likely to increase the odds of uterine hyperstimulation. For other safety outcomes, there were insufficient data, or too much uncertainty, to identify which treatments performed 'best'. Data on women's perspectives were poorly reported in the included studies.

Appendix E: Examples of preparation of oral misoprostol for cervical ripening

A standardised strength of misoprostol oral suspension is recommended to ensure that consistent and best evidence-based information is available for staff making this preparation. Using a standardised suspension strength across all health organisations will reduce the risk of dosing error due to strength mix-ups, particularly when staff work across different organisations.

Two example methods are provided for preparation outside a pharmacy. It is anticipated that misoprostol suspension will be required out of hours when pharmacy-based preparations are not available.

Method A⁶

Ingredient	Quantity
Pair of non-sterile examination gloves	1
20 mL oral syringe	1
3 mL oral syringe	1
Mixing cannula	1
Oral medicine measure (eg, a 40 mL conical medicine measure or plastic medicine pot)	1
Water for injection 20 mL ampoule	1
Misoprostol 200 microgram tablet	1

Preparation instructions

- The solution may be prepared by a midwife, a registered nurse, a doctor or a pharmacist.
- Prepare in a clean area on the ward (eg, in the same area where intravenous medicines are prepared).
- A new suspension must be prepared for every dose.
- Administer the dose of misoprostol immediately after preparation.
- To prepare a dose of misoprostol 25 microgram:
 - 1 Put on the gloves.
 - 2 Empty the contents of the 20 mL water for injection ampoule into the oral medicine measure (this should be slightly more than 20 mL).
 - 3 Using the 20 mL oral syringe, draw up 20 mL water for injection.
 - 4 Discard any remaining water in the medicine measure (but keep the measure for the next step).
 - 5 Place the misoprostol 200 microgram tablet in the empty medicine measure.
 - 6 Add the 20 mL water for injection from the oral syringe into the medicine measure with the misoprostol tablet.
 - 7 Use the mixing cannula, mix until the tablet is fully dispersed. This gives a suspension of misoprostol 200 microgram in 20 mL (10 microgram/mL).
 - 8 Using the 3 mL oral syringe, draw up 2.5 mL of the suspension. Make sure the suspension is fully dispersed by mixing vigorously with the mixing cannula and drawing up the 2.5 mL immediately, before the suspension settles.
 - 9 Label the oral syringe as per local requirements (eg, drug name, dose, patient's name, etc).
 - 10 Shake the oral syringe well immediately before administering the dose.
 - 11 Discard the remaining suspension in the medicine measure.
 - 12 Keep the medicine measure, 20 mL oral syringe and mixing cannula in case another dose is required. If a further dose is not required, discard the oral syringe and mixing cannula.

⁶ Based on the method developed by MidCentral DHB Hospital Pharmacy Services – Whare Rongoā te Pūtake. To facilitate the preparation of the misoprostol suspension, Hospital Pharmacy Services provide a 'Misoprostol Kit for Induction of Labour' with enough components for six doses. Unused components are returned for re-using in a new kit.

Method B⁷

Ingredient	Quantity
Pair of non-sterile examination gloves	1
20 mL oral syringe with syringe cap	1
Water for injection 20 mL ampoule	1
Misoprostol 200 microgram tablet	1

Preparation instructions

- The solution may be prepared by a midwife, a registered nurse, a doctor or a pharmacist.
- Prepare in a clean area on the ward (eg, in the same area where intravenous medicines are prepared).
- A new suspension must be prepared for every dose.
- Administer the dose of misoprostol immediately after preparation.
- To prepare a dose of misoprostol 25 microgram:
 - 1 Put on the gloves.
 - 2 Remove the plunger from the oral syringe.
 - 3 Ensure the tip of the oral syringe is capped.
 - 4 Drop the misoprostol tablet directly into the syringe. Do not crush it.
 - 5 Reinsert the plunger in the syringe barrel. Note: You may need to loosen the cap to allow air to exit the oral syringe.
 - 6 Remove the syringe cap and draw up exactly 20 mL of water into the oral syringe.
 - 7 Draw up extra air into the oral syringe.
 - 8 Cap the syringe and allow the misoprostol tablet to disintegrate over 3–5 minutes. Shake the syringe a few times during this period until no large particles of medication remain in the syringe. Note: The medication may not completely dissolve, and a fine powder may be present in the syringe, but you may still give the medicine.
 - 9 Shake the syringe and remove the cap.
 - 10 Discard the unneeded misoprostol suspension until only 2.5 mL of suspension remains in the syringe.
 - 11 Recap the syringe.
 - 12 Label the syringe as per local requirements (eg, drug name, dose, patient's name, etc).
 - 13 Shake the syringe well immediately before administering the dose.
 - 14 Discard the unneeded misoprostol suspension remaining in the medicine measure and the 20 mL oral syringe. Discard the gloves.

⁷ Adapted from the method used reported in Winnipeg Regional Health Authority. 2017. *Clinical Practice Guideline: Induction and Augmentation of Labour and Cervical Ripening of Labour*. November 2016, revised March 2017. Winnipeg: Winnipeg Regional Health Authority.

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