

Induction of Labour in Aotearoa New Zealand

A clinical practice guideline

2019

Table of Contents

Table of Contents	2
Executive summary	7
Summary of findings	9
Table 1. Summary of Recommendations and Practice Points	9
Consumer foreword	14
Note from the Chair	16
Scope and purpose of the guideline	18
Purpose	18
Definitions	18
The need for the guideline	18
Scope of the guideline	19
Target Audience	19
The Research Questions	19
Clinical Indications for IOL	19
Population	19
Intervention	20
Comparison	20
Outcomes	20
Guideline development process	20
Overview	20
Table 2. National Institute of Clinical Health and Excellence levels of evidence and categories of papers (NICE 2008)	21
Table 3. GRADE quality rating for evidence and strength of recommendations (Guyatt 2008)	21
External consultation	22
Implementation plan	22
Primary outcomes for baseline and future audit	22
Updating the guidelines	23
Conflicts of interest	23
Funding	23
Chapter 1 - Introduction	24
Risk factors for perinatal death	24
Principles of decision-making	24
Chapter 2 - Neonatal risks of planned birth < 39 weeks' gestation	25

Summary of evidence	25
Discussion	25
Chapter 3 - Membrane sweeping at term for reducing the need for induction of labour	26
Summary of evidence	26
Discussion	26
Chapter 4 - Indications and timing of induction of labour	27
Introduction	27
4.1 Pregnancy \geq 41 weeks' gestation	27
Summary of evidence	28
Discussion	29
4.2 Pre-labour rupture of membranes \geq 37 weeks' gestation	30
Summary of evidence	30
Discussion	31
4.3 Suspected small for gestational age (SGA)/fetal growth restriction (FGR)	31
Summary of evidence	32
Discussion	32
4.4 Diabetes in pregnancy	33
Gestational diabetes	33
Summary of evidence	33
Discussion	34
Pre-existing diabetes mellitus	35
Summary of evidence	35
Discussion	35
4.5 Maternal obesity	36
Summary of evidence	36
Discussion	36
4.6 Advanced maternal age	36
Summary of evidence	36
Discussion	37
4.7 Reduced fetal movements	37
Summary of evidence	37
Discussion	38
4.8 Hypertension in pregnancy	39
Summary of evidence	39

Discussion	40
4.9 Antepartum haemorrhage of unknown origin	41
Summary of evidence	41
Discussion	41
4.10 Assisted Reproductive Technology (ART)	41
Summary of evidence	41
Discussion	41
4.11 Suspected fetal macrosomia	42
Summary of evidence	42
Discussion	43
4.12 Multiple pregnancy	43
Summary of evidence	44
Discussion	44
4.13 Reduced liquor < 41 weeks' gestation	45
Summary of evidence	45
Discussion	45
4.14 Obstetric cholestasis	45
Summary of evidence	45
Discussion	46
4.15 Previous stillbirth	46
Summary of evidence	47
Discussion	47
4.16 No medical indication	47
Summary of evidence	47
Discussion	48
Chapter 5 - Methods of cervical ripening	49
Introduction	49
5.1 PGE2 (dinoprostone) methods of administration	49
Summary of evidence	49
5.2 PGE1 analogue (misoprostol)	50
Summary of evidence	50
Discussion on PGs	51
5.3 Balloon catheter	52
Summary of evidence	52

Single versus double balloon catheters	53
Single balloon catheters and volume of inflation	53
Discussion on balloon catheters	53
5.4 Methods of IOL for women with previous caesarean section	55
Summary of evidence	55
Discussion	55
Chapter 6 - Methods of induction of labour	56
Introduction	56
6.1 Combination ARM with oxytocin	56
6.2 Timing of ARM	56
6.3 Oxytocin protocol	57
Discussion	57
Chapter 7 - Setting for induction of labour	60
Summary of evidence	60
Discussion	60
ABBREVIATIONS	62
APPENDIX A - Clinical Guidelines Panel	63
APPENDIX B - Search Methods	64
Methods	64
Searches	64
Search terms	64
Selection Criteria	64
Quality of Evidence	65
Results	65
Table 4. Results of searches	65
Searches for Ongoing Clinical Trials	67
Indications	67
Methods and Setting	67
Table 5. Recruiting trials for indications and methods of induction of labour.	67
Table 6. Recruiting trials looking at outpatient methods of induction of labour	70
APPENDIX C - Observational studies	71
C.1 Tables of national and international stillbirth risk factors	71
Table 7. Adjusted odds ratio for perinatal related mortality, termination of pregnancy, stillbirth and neonatal death 2011-2015 in New Zealand (PMMRC 2017)	71

Table 8. Risk factors and attributable stillbirth in selected high-income countries (Flenady 2011)	72
Table 9. Population-attributable risk for stillbirth in selected high-income countries (Flenady 2011)	72
Table 10. Association of maternal factors with antepartum stillbirth (INTERGROWTH-21 Project) (Hirst 2018)	73
C.2 Pregnancy \geq 41 weeks' gestation or more	73
Figure 1: Association of stillbirth with gestational age, USA data (MacDorman 2015)	73
C.3 Obesity in Pregnancy	74
Figure 2: Association of BMI and fetal death (Aune 2014)	74
Figure 3: Association of obesity in pregnancy and stillbirth in Washington and Texas (Yao 2014)	74
C.4 Advanced Maternal Age	75
Figure 4: Association of maternal age and stillbirth in the USA (Reddy 2006)	75
C.5 Antepartum Haemorrhage (APH) of Unknown Origin	75
C.6 Pregnancy Following Assisted Reproductive Technology	75
C.7 Multiple pregnancy	76
Figure 5: Risk of stillbirth and neonatal complications in twin pregnancies (Cheong-See 2016)	76
C.8 Oligohydramnios	76
C.9 Obstetric Cholestasis	77
Figure 6: Risk of perinatal death by gestational age and bile salt concentration in women with obstetric cholestasis (Ovadia 2019)	77
C.10 Previous Stillbirth	78
APPENDIX D - Comparisons of cervical ripening and methods of induction of labour	79
D.1 Comparing all cervical ripening methods to each other	79
D.2 All methods of IOL	79
APPENDIX E - Examples of preparation of oral misoprostol for cervical ripening	80
REFERENCES	82

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 induction of labour. A multidisciplinary Panel assessed quality of evidence and made recommendations, considering the Aotearoa New Zealand (NZ) context. This guideline is meant to be used by clinicians to inform shared decision-making with women and their whānau, and by district health boards to reflect on their current practice and align local guidelines with the national guideline to facilitate consistent practice.

The quality of research evidence varied considerably. Generally, where there was sufficient Level 1 evidence available, then the Panel made a recommendation about induction of labour; where there was insufficient evidence to make a recommendation, or if the evidence was rated to be of low or very low quality, then the Panel made practice points. In some conditions where Level 1 evidence was reviewed, such as suspected macrosomia, and no medical indication, the Panel debated at length a recommendation to offer IOL, but decided by consensus that the evidence was insufficient for the NZ context (different population, different intervention, or outcomes not of sufficient effect) and made practice points instead. Practice points are designed to help guide clinical practice, and encourage further understanding and discussion about the diverse beliefs, traditions and aspirations held by many women, their partners, family and whānau.

It is important to enable and respect a woman's right to be fully informed about the quality of evidence underpinning a recommendation for induction of labour and 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 which states *“maternal and newborn health benefits from an evidence-based approach to care. Every MotherBaby should be protected from unnecessary and potentially harmful interventions, practices, and procedures and from both overuse and underuse of medical technology.”*

It is important to individualise all decisions about induction. Some women do not fit into any one 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 guidelines.

Early term birth (37 and 38 weeks' gestation) is associated with poorer neonatal and childhood outcomes compared to 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 have identified that there is 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 NZ maternity healthcare context

The Panel recommends that all future research studies on IOL include outcomes listed in the Core Outcome Set on IOL (Dos Santos 2018), and that academics, clinicians, policy-makers and consumers undertake a research agenda priority setting process for NZ.

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 pregnancy 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 an uncomplicated pregnancy.

In women with pre-labour rupture of membranes 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 NICU admission.

In women with hypertension in pregnancy, the Panel endorses the recommendations from the NZ Ministry of Health clinical practice guideline.

For cervical ripening, it is reasonable to offer any of: prostaglandin E2 (vaginal gel or controlled-release pessary), prostaglandin E1 analogue (misoprostol low-dose two-hourly in oral solution) or balloon catheter (single- or double-balloon), based on reason for IOL, maternal values and preferences, local resources, and practical considerations. For cervical ripening with single-balloon catheter, inflate greater than 30mL to increase the chance of vaginal birth in 24 hours, compared to 30mL or less.

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 NZ, it has been widely researched internationally. Should hospitals choose to use misoprostol, it is recommended they develop local guidelines in cooperation with their Pharmacy department.

Summary of findings

Table 1. Summary of Recommendations and Practice Points

Notes

The GRADE system (Guyatt 2008) classifies the quality of evidence in one of four levels (see Table 2), and offers two grades of recommendations (see Table 3).

- **Level 1 evidence:** Includes meta-analyses, systematic reviews of randomized 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, guideline panels offer ‘strong’ recommendations. When the trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced— they offer ‘conditional’ recommendations.
- **Practice Points:** When recommendations are based on low or very low quality evidence, the guideline panel offers practice points, or important things to consider for clinical practice.

Throughout this guideline, the Clinical Guidelines Panel has included practice points aimed at encouraging further understanding and discussion about the diverse beliefs, traditions and aspirations held by many women, their partners, family and whānau.

General principles

Practice points
<i>Promote and support spontaneous onset of labour and physiological labour and birth.</i>
<i>Enable and respect woman’s right to be fully informed about the quality of evidence underpinning a recommendation for induction of labour and be given the opportunity to make an informed choice.</i>
<i>Continue expectant management to 39 weeks’ gestation or more, unless there is an evidence-based indication supporting earlier planned birth.</i>
<i>Inform women about the proposed method(s) of cervical ripening and induction of labour, the rationale, and alternative options.</i>

Membrane sweeping

Recommendation	Level of evidence	Strength of recommendation
Consider offering membrane sweeping at term to reduce the frequency of pregnancy continuing beyond 41 weeks’ gestation.	Level 1; Moderate quality	Conditional
Practice Point		
<i>If offering membrane sweeping, consider performing from around 39 weeks’ gestation.</i>		

Pregnancy ≥ 41 weeks’ gestation

Recommendation	Level of evidence	Strength of recommendation
Offer induction of labour between 41 ⁺⁰ and 42 ⁺⁰ weeks’ gestation to women with an uncomplicated pregnancy, 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
In women with pre-labour rupture of membranes 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		
<i>For women with prelabour rupture of membranes, share information with women as early as practical after rupture of membranes to support informed decision making.</i>		
<i>If neonates are at risk for early-onset Group B Streptococcus neonatal sepsis, offer immediate induction of labour.</i>		
<i>If liquor is meconium-stained, consider immediate induction of labour.</i>		
<i>Unless immediate induction of labour is planned, avoid digital vaginal examination.</i>		

Suspected small for gestational age/fetal growth restriction

Practice Points
<i>For women with suspected small for gestational age fetus or fetal growth restriction, in settings where detailed Doppler studies are unavailable, offer induction of labour at around 38 weeks' gestation (or earlier if concern).</i>
<i>For women with suspected small for gestational age fetus with abnormal umbilical artery Dopplers, consider offering induction of labour at around 37 weeks' gestation (low threshold for planned birth if there is any concern about maternal or fetal well-being or if there is suspected cessation of fetal growth).</i>
<i>For women with suspected small for gestational age fetus with abnormal MCA, CPR or uterine artery Dopplers, or EFW $<3^{\text{rd}}$ centile, offer induction of labour at around 38 weeks' gestation (or earlier if concern).</i>
<i>For women with suspected small for gestational age fetus with normal MCA, CPR and uterine artery Dopplers, and EFW 3^{rd} centile or more, offer induction of labour at around 40 weeks' gestation (or earlier if concern). These babies are likely to be constitutionally small and are at lower risk of adverse outcome.</i>

Diabetes in pregnancy

Practice Points
<i>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.</i>
<i>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.</i>
<i>The management of women with Type 1 diabetes is to be individualised.</i>

Maternal obesity

Practice Point
<i>For women with maternal obesity, in the absence of other risk factors or pregnancy complications, do not offer induction of labour.</i>

Advanced maternal age

Practice Point

For women age 40 years and over, consider offering induction of labour 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

Recommendations	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+0 weeks' gestation, consider induction of labour, to reduce the risks of severe hypertension, severe preeclampsia, HELLP syndrome, abruptio placenta, pulmonary edema, severe renal impairment, and fetal growth restriction.	Level 1; Moderate quality	Conditional
For women with preeclampsia diagnosed after 37+0 weeks' gestation, offer induction of labour.	Level 1; Moderate quality	Conditional

Antepartum haemorrhage of unknown origin

Practice Point

In women with antepartum haemorrhage 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 assisted reproductive technology, in the absence of other risk factors or pregnancy complications, do not offer induction of labour.

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 induction of labour between 36 and 37 weeks' gestation.

For women with an uncomplicated dichorionic twin pregnancy, consider offering induction of labour 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 induction of labour; otherwise consider expectant management.

Previous stillbirth

Practice point

For women with previous stillbirth, consider expectant management or induction of labour, 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 induction of labour in the absence of a medical indication.

The management of induction of labour for maternal request is to be individualised.

Cervical ripening

Recommendations	Level of evidence	Strength of recommendation
Offer cervical ripening with prostaglandins to women with unfavourable cervix, to improve the chance of vaginal birth within 24 hours, compared to oxytocin alone.	Level 1; moderate quality	Conditional
For PGE2 for cervical ripening, offer either vaginal gel or controlled-release pessary, 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 fetal heart rate changes, compared to prostaglandins.	Level 1; moderate evidence	Conditional
For single-balloon catheter, inflate greater than 30 mL (and not more than manufacturer recommendation), to increase the chance of vaginal birth in 24 hours, compared to 30mL or less.	Level 1; moderate quality	Conditional
Practice Points		
<i>Consider offering membrane sweeping concurrent with cervical ripening.</i>		
<i>For cervical ripening with PGE2 vaginal gel: Decide initial dose based on parity and Bishop score. If nulliparous and $BS \leq 4$, consider 2mg; otherwise consider 1mg. Decide subsequent dose based on cervical change – if none, consider 2mg; otherwise consider 1mg. Use as per manufacturer's instructions.</i>		
<i>For cervical ripening with PGE2 controlled-release vaginal pessary: Pessary may have higher risk of uterine tachysystole and hypertonus compared to vaginal gel. Use as per manufacturer's instructions.</i>		
<i>For cervical ripening with PGE1 analogue (misoprostol): Vaginal administration may have higher risk of adverse outcomes compared to oral administration. If using misoprostol, low-dose (25 micrograms) two-hourly in oral solution is recommended. See Appendix E for suggested protocols.</i>		

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 manufacturer's instructions.

Consider using balloon catheter for cervical ripening where induction of labour is indicated in setting of previous caesarean section.

Induction of labour methods

Practice Points

To start induction of labour once cervix is favourable, consider offering the combination of artificial rupture of membranes and intravenous oxytocin infusion, to increase chance of vaginal birth within 24 hours.

The timing and order of performing artificial rupture of membranes and starting intravenous oxytocin infusion to be individualised and negotiated between the woman, her Lead Maternity Carer, the hospital midwife and the obstetrician.

Offer either low- or high-dose oxytocin protocol, as both methods are comparable to achieve vaginal birth in 24 hours, and risk for caesarean section.

Usual time interval to increase dose of oxytocin is approximately 20 minutes.

Consumer foreword

Inā ka ora te wahine, ka ora te whānau, ka ora te hapū, ka ora te iwi

When Women are in good health, the Whānau, Hapū and Iwi will flourish

Although this guideline has been developed to guide clinical practice, ‘good practice’ cannot be achieved without delivery of care that is respectful, mana enhancing and supports pregnant women and their whānau to experience a pregnancy, labour and birth that honours and protects the many aspects that are important to them. While health care providers have distinct and influential roles in the promotion and protection of 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.

During the development of this guideline we have thoughtfully navigated the power dynamics between consumers and health professionals and have robustly explored the distinction between ‘recommending’ and ‘offering’ interventions.

As consumers who have experienced birth and induction of labour multiple times, we 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. We wanted this guideline to reflect the complexities of 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.

“The emotional support to navigate difficult decisions when facing essential interventions was appreciated. From planning a home birth then 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)

While developing this guideline, we have worked hard to safeguard health consumer rights to the process of informed decision making. Health professionals have an ethical and legal responsibility to ensure they understand the differences between ‘informed choice’, ‘shared decision-making’ and ‘informed compliance and coercion’ and facilitate the pathway to truly informed choice and consent (Gold 2014). This can only be achieved by providing individualised assessment of IOL indication(s), and the opportunity for pregnant women and their whānau to evaluate risk in the context of their own beliefs and meanings. Once IOL has been agreed to, pregnant women and their whānau must also be provided with information on what to expect and how to prepare.

“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 that 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 has been shown to increase maternal anxiety (Jay 2018 A) and is associated with a disparity between expectations and experience, particularly pain and duration of labour (Jay 2018 B; Murtagh 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 birth place setting or mode of birth.

Note from the Chair

Induction of labour (IOL) rates are increasing in New Zealand (NZ) and globally, associated with variation in opinion and practice amongst clinicians and maternity services. A need was identified for national guidance in this area, in order to provide education and recommendations around IOL. The purpose was to collectively improve the proportion of inductions performed for evidence-based reasons, in order to maximise benefit, and minimise harm, to mothers and babies.

Over the last 21 months, the Clinical Guidelines Panel has encountered several challenges. Current practice for some common indications for induction, such as diabetes in pregnancy, lacks research evidence to support IOL, however, 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⁺⁰ weeks' gestation, or oral misoprostol for cervical ripening, has not been taken up routinely in NZ due to a reluctance to change institutional culture ("this is how we do things around here" or "this is how we have always done it"). Newly published evidence that should lead us to consider adding new indications for IOL, such as macrosomia, is challenging if results of overseas trials are not externally generalisable to the NZ context.

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

In the end, an offer is just that, an offer. IOL decisions are value-laden, reflecting individual values and preferences. Clinicians need to support women to make informed and shared decisions about their care. In the ideal situation, there is a 3-way discussion between the woman, the LMC, and the obstetrician. However, the current reality is of 2-way conversations and virtual pathways of care. In a shared decision-making model, information is provided about options of IOL and expectant management, preferences are discussed, and decisions made about what is best for the woman. (Elwyn and Frosch 2010) The Panel hopes to develop a decision aid to support this process.

The majority of studies reviewed provided moderate-quality evidence of benefits of IOL, with no short-term harms. In particular, every RCT found women in the IOL group had lower risk of caesarean section (CS) compared to women managed expectantly, or no difference in risk. This is not consistent with what we observe day-to-day. However, this finding 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, the majority of studies did not measure long-term outcomes for mothers and babies. Moreover, some of the studies where IOL was offered < 39 weeks' gestation did find some short-term neonatal risks, such as respiratory distress syndrome and admission to neonatal intensive care. In review of evidence on planned birth < 39 weeks' gestation, there are increased short- and long-term neonatal risks compared to waiting until 39 weeks' gestation

or more. The Panel agreed that in the absence of high-quality evidence we should not be offering IOL < 39 weeks' gestation. Early term is not the same as full term.

The experience of an IOL in itself can be considered a “harm.” 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 well-being. It is thus important to ensure that every induction is necessary.

Publishing a guideline does not guarantee its uptake. A Cochrane review (Chen 2019) found high quality evidence of non-clinical interventions targeted at healthcare professionals that reduced unnecessary CS: implementation of clinical practice guidelines (CPG) with mandatory 2nd opinion for CS indication, implementation of CPG 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, an IOL request form aligned with the guidelines such that if the IOL was not guideline-based, then it requires a 2nd opinion prior to it 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. Hopefully updating it in three years will not take nearly as much time as developing this first iteration!

Dr Michelle Wise

Senior Lecturer, Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, University of Auckland

Scope and purpose 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 Aotearoa New Zealand context.

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

This guideline has been developed to provide guidance for health professionals, to support shared decision-making within an evidence-based supportive framework. It should be used alongside best judgement, taking into account the individualised needs and preferences of the woman.

Definitions

IOL is 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 about which there is not a common understanding and agreement as to its definition. “At term” 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 NZ, the proportion of women who experience an IOL has steadily increased, from 19.4% in 2006 to 26.0% in 2017 (Ministry of Health 2019). The most common indications for IOL at term in one tertiary unit in NZ were: pre-labour rupture of membranes at term, diabetes in pregnancy, suspected small for gestational age fetus, and post-dates (Auckland DHB 2017).

IOL is reported as one of ten clinical maternity indicators identified by the NZ Ministry of Health, in its national quality and safety programme for maternity services (Ministry of Health 2019). 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 do clinical factors. This variation 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 2019; Hildingsson 2011; Schwarz 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, along with

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, and optimal timing of IOL, and a discussion of IOL for no medical indication. The Panel acknowledges that there are many risk factors and conditions recognised 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 may be insufficient to support IOL.

This 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 prior to 39 weeks' gestation to optimise neonatal outcomes.

The list of indications and methods reviewed may not be comprehensive, rather an overview of the more common reasons for IOL in NZ. 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. This guideline may be accessed by pregnant women and their families and whānau.

The Clinical Guidelines Panel has been committed to including consumers in the development process. Consumers are an integral part of the Panel and have helped with the interpretation of the evidence and development of recommendations.

The Research Questions

The Clinical Guidelines Panel agreed on the following key questions to be addressed by this guideline.

Clinical Indications for IOL

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 by the Panel are those identified by the core outcome set for trials on induction of labour (COSIOL) initiative for IOL research studies (Dos Santos 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 management plan:

1. Is perinatal mortality reduced (for the clinical condition*) if labour is induced or if pregnancy is 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, prelabour rupture of membranes, suspected small for gestational age, diabetes in pregnancy, maternal obesity, advanced maternal age, reduced fetal movements, hypertension in pregnancy, antepartum haemorrhage of unknown origin, assisted reproductive technology, 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 New Zealand College of Midwives (NZCOM), Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG), and Royal Australasian College of Physicians, along with representatives of consumer groups and Midwifery and Obstetrics from around NZ (see Appendix A). The multidisciplinary Clinical Guidelines Panel created a secure internet-based folder and met monthly over video-conference 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 IOL as the intervention, national and international guidelines, and local expert advice.

Table 2. National Institute of Clinical Health and Excellence levels of evidence and categories of papers (NICE 2008)

Level of evidence	Category of paper
1	Meta-analyses, systematic reviews of randomized controlled trials (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 that the relationship is causal
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used to rate the quality of the evidence and the strength of the recommendations (Guyatt 2008). The GRADE system classifies the quality of evidence in one of four levels, and offers two grades of recommendations. When the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not, guideline panels offer ‘strong’ recommendations. On the other hand, when the trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced—‘conditional’ recommendations become mandatory.

Table 3. GRADE quality rating for evidence and strength of recommendations (Guyatt 2008)

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
<i>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 be decreased for several reasons including study limitations, inconsistency of results, indirectness of evidence, imprecision and reporting bias; and may be increased 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.</i>
GRADE rating of strength of recommendations
Strong
Conditional
Good practice point (GPP)
<i>Note: Recommendations can be in favour of or against a practice</i>

The Panel discussed the evidence at length, placed it in the local NZ context, and formulated recommendations by consensus. The issue is complex due to differing heterogeneity of the research studies reviewed, the inconsistent reporting of outcomes, and the lack of maternal experience and involvement in the research. Moreover, the important long-term outcomes for the mother and the baby are hardly ever reported. Where evidence is insufficient, research gaps are identified.

External consultation

In July and August 2019, the draft guideline was sent for extensive consultation involving several professional groups, including Australia NZ College of Anaesthetists (ANZCA), Clinical Directors Network (DHB Obstetrician leaders), DHB Midwife Leaders group, Health Quality and Safety Commission (HQSC), Nga Maia, National Maternity Monitoring Group, NZ College of Midwives (NZCOM), Perinatal Society of NZ, Pharmaceutical Society of NZ, RACP, RANZCOG Te Kāhui Oranga ō Nuku. 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, NZCOM, Perinatal Society of NZ, and the Maternity Services Consumer Council. During September and October 2019, feedback was reviewed at length by the Panel, and final recommendations made.

Implementation plan

The Clinical Guidelines Panel suggests the following plan for dissemination within the 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 (MoH) for ratification
- Guideline to be sent to lead maternity service providers in each District Health Board (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
- "IOL Request Form" to be developed that aligns with recommendations
- Decision aid to be developed for NZ 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, 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 primip'
- 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' time and updated as required.

Conflicts of interest

Members of the Clinical Guidelines Panel were asked if they had conflicts of interest to declare. None of the members declare 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 Trial (www.oblige.auckland.ac.nz) were excluded from the development of recommendations about outpatient setting for IOL.

Funding

The Nurture Foundation, and the Mercia Barnes Trust, RANZCOG, 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 enabling this process to occur.

Chapter 1 - Introduction

Risk factors for perinatal death

The Perinatal Mortality and Morbidity Review Committee (PMMRC) reviews perinatal death rates in NZ 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 shows tables of 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 with the woman, her partner and family/whānau, her Lead Maternity Carer (LMC) midwife and the obstetrician.

The guideline is meant to both enable clinicians and to empower women to make the best decision for that specific circumstance, being aware of the potential power imbalance between women and clinicians.

After recommendations are made, it is expected that informed decision-making follows i.e. 3-way conversation between the woman, her LMC and the obstetrician. Clinicians need to provide clear and balanced information to 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. Women need time to consider the pros and cons of IOL, ask questions, and be supported in their choices.

The Clinical Guidelines Panel acknowledge that 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 outcome increases, though by how much is unknown. Women with multiple risk factors may be appropriately offered IOL by the clinician, even if it does not appear to come under any one recommendation. The Panel acknowledges that clinicians are experienced and specialised, and are meant to use discretion, and interpret all the information available. We encourage clear documentation where recommendations are not followed.

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

The Panel considered outcomes important to women. The guideline development process has also taken Māori and Pacific cultural considerations into account when making recommendations.

Research gaps
For pregnant women where IOL is being considered, to determine effective ways to present risks and benefits as part of the 3-way conversation
To explore the impact of IOL on the 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 women's satisfaction with labour and birth.
To explore IOL compared to expectant management in the context of Maori 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 2008; Petrini 2009). Early term birth (37⁺⁰ to 38⁺⁶ weeks' gestational age) is also associated with poorer neonatal outcomes compared to 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 to those born at 39 weeks' gestation or more (Tita 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 to babies born at 39 to 41⁺⁶ weeks gestation (Brown 2013; Sengupta 2013).

Babies born early term are also at higher risk of long-term childhood impairment such as cerebral palsy and special education needs (Moster 2010; Mackay 2010). New Zealand children born early term are at higher risk of requiring hospital admission in childhood and have lower National Certificate of Educational Achievement scores than children born at 39 to 40 weeks' gestation (Berry 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 for reducing 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 to 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 to 0.78), reduced the frequency of pregnancy continuing beyond 41 weeks (RR 0.59, 95% CI 0.46 to 0.74), and reduced the frequency of using other methods to induce labour (RR 0.60, 95% CI 0.51 to 0.71) (Boulvain 2005). Eight women need to have sweeping of membranes 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 to 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 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 for 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 to 40 weeks' gestation, whereas, this guideline is advocating for continuation of pregnancies until 39 weeks' gestation. The Clinical Guidelines 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 pregnancy continuing beyond 41 weeks' gestation.	Level 1; moderate quality	Conditional

Practice Point

If offering membrane sweeping, consider performing 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 vs 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 Clinical Guidelines Panel recommends offering IOL where there is clear evidence of benefit to the woman or her baby, and supports clinicians to offer expectant management where there is no clear evidence of benefit for IOL. If a clinician and woman are considering IOL where evidence is insufficient to make a recommendation, then the Panel recommends not offering IOL prior to 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 with women. Clinicians should ensure informed discussions with women about the risks and benefits of IOL and expectant management, and plan her care with the 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 were not explored.

Clinicians should engage in shared decision-making which 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.

Mobilisation and physical restrictions during labour and birth: For many people, performing turakanga, waituhi, hands on healing, and the ability to move freely is an important part of whakamamae, whakawhānau and the birthing process. This includes the transfer of energy via movement and touch, for example rongoā māori practices such as mirimiri and other common practices such as acupressure and acupuncture. Attachment of monitoring equipment, intravenous lines and any other devices are common during induction of labour, this 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 NZ health system if women were routinely offered IOL for clinical indications currently managed expectantly. Resources required for women being managed expectantly, such as specialist consultations, clinical assessments and ultrasound scans, were also considered. Maternity services should accommodate request for IOL if offered. The Panel acknowledges that not all services can provide this at all times due to limited resources. The Panel agreed that resources and costs were beyond the scope of this guideline.

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

4.1 Pregnancy ≥ 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 2015). Prolonged pregnancy is one of the most common indications for IOL.

Summary of evidence

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

A Cochrane systematic review including 30 trials spanning upper- and lower-income countries of 12 479 women (Middleton 2018) compared a policy of IOL to a policy of expectant management. IOL was undertaken at or beyond term (37 to 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 to 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 to 1337). For planned subgroup analysis, the authors collapsed the trials into three groups (<41 weeks' gestation 10 trials, ≥ 41 weeks' 19 trials, and 37-42 weeks' 1 trial). For the primary outcome of perinatal death, no difference between timing of IOL subgroups was found.

For women in the policy of IOL arms of trials, there were significantly fewer caesarean sections compared with expectant management (RR 0.92, 95% CI 0.85 to 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 to 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 to 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 expectant management (RR 0.70, 95% CI 0.50 to 0.98; 16 trials, 9 047 infants; moderate quality), and fewer babies had meconium aspiration syndrome (RR 0.77 95% CI 0.62 to 0.96; 11 trials, 7 781 infants; moderate quality). Only two of the thirty 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 arm 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 a policy of acting and of 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 1801 women from midwifery practices and hospitals in the Netherlands compared IOL at 41 weeks with expectant management (Keulen 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+0 weeks' and no contraindications to

expectant management. The IOL group was induced at 41+0 to 41+1 weeks' gestation; expectant management group awaited spontaneous onset of labour until 42+0. The primary outcome was a composite outcome 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, intracranial haemorrhage. Secondary outcome included composite adverse maternal outcome (defined as any one of PPH \geq 1000mL, 3rd or 4th degree perineal tear, admission to intensive care unit, manual removal of placenta). There was an increased risk of composite adverse perinatal outcome in the expectant management group; 15 women (1.7%) in the IOL group and 28 (3.1%) in the expectant management group (risk difference -1.4%, 95% CI -2.9% - 0.0%; NNT 69, 95% CI 35 to 3059). There was one perinatal death and three NICU admissions in the IOL group; two perinatal deaths and eight NICU admissions in the expectant management group. No neonatal deaths occurred. There was no significant difference in composite adverse maternal outcome (13.6% in the IOL group vs 11.3% in the expectant group). 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 \geq 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 score and meconium aspiration syndrome compared with expectant management. The Clinical Guidelines Panel recommends that clinicians have an informed discussion 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 is not fully explored.

For women who choose expectant management, identify and document a plan for ongoing assessment of the woman and baby's well-being 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 pathways. If any concerns about maternal or fetal well-being arise, then the clinician should re-discuss the benefits of IOL in light of new context, and re-offer IOL.

SWEPIS is a multi-centre RCT in Sweden designed to evaluate if IOL at 41+0 weeks improves perinatal outcome compared to expectant management with IOL at 42+0 weeks. The trial is complete but results were not available at the time of completing our review of the evidence.

Recommendation	Level of evidence	Strength of recommendation
Offer induction of labour between 41 ⁺⁰ and 42 ⁺⁰ weeks' gestation to women with an uncomplicated pregnancy, 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 NZ context

4.2 Pre-labour rupture of membranes ≥ 37 weeks' gestation

In approximately one in 12 pregnancies at term, the membranes rupture prior to labour starting. Approximately 79% of women will spontaneously labour within 12 hours of ruptured membranes (Middleton 2017). The risk of infection increases with duration of ruptured membranes. Pre-labour rupture of 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 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 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 birth were at reduced risk of maternal infectious morbidity compared with women who had expectant management (RR 0.49; 95% CI 0.33 to 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 to 0.92; sixteen 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 to 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 to 1.33; very low quality) or perinatal death (RR 0.47; 95% CI 0.13 to 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 to 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 birth had a more positive experience compared to expectant management (mean difference 11.8 higher; 95% CI 4.36 - 19.24; 93 women). Another study reported that women who had planned early birth 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 to expectant management.

The authors concluded that for PROM at 37 weeks' gestation or later, planned early birth (with IOL methods such as oxytocin or prostaglandins) 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 “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 baby’s well-being, 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 well-being arise, then the clinician should re-discuss the benefits of IOL in light of new context, and re-offer IOL. Timing of IOL should be mutually agreed.

The Referral Guidelines for consultation with obstetric and related medical services (Ministry of Health 2012) identify that a LMC should recommend the woman has a consultation with a specialist before 24 hours following PROM at term.

The Clinical Guidelines Panel acknowledges that the management of preterm PROM was considered to be outside the scope of this guideline.

Recommendation	Level of evidence	Strength of recommendation
For women with pre-labour rupture of membranes 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 prelabour rupture of membranes, share information with 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 (Darlow 2015, RANZCOG 2016), offer immediate IOL.

If liquor is meconium-stained, consider immediate IOL.

Research Gaps

In women with pre-labour rupture of membranes 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 pre-labour rupture of membranes at term, to evaluate the effect of different methods of cervical ripening on outcomes.

4.3 Suspected small for gestational age (SGA)/fetal growth restriction (FGR)

SGA is defined as an infant with birthweight <10th centile or a fetus with EFW <10th centile. Customised standards to define SGA have a stronger association with perinatal morbidity and mortality than population standards (NZMFM 2014). FGR is defined as a fetus that has failed to reach its growth potential but 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 2015) evaluating the effects of immediate birth compared to 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) (pilot study of 33 women that became the DIGITAT study, and the DIGITAT study), and one study of 54 women for 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 from 37 weeks' gestation or greater 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 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 CTG, ultrasound and preeclampsia screening). Suspected IUGR was defined as one or more of fetal AC <10th centile, EFW <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% to 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% to 5.6%; low quality) or PPH (difference -1.5%, 95%CI -4.5% to 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 preeclampsia (difference -4.2%, 95%CI -7.7% to -0.6%). There was no difference between groups for 5-minute Apgar score <7 (difference 1.6%, 95%CI -0.2% to 3.4%) or NICU admission (difference -1.2%, 95%CI -4.0% to 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 to 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; cardiotocograph (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 NZ Maternal Fetal Medicine Network guideline "Management of babies with suspected SGA/FGR diagnosed after 34 weeks' gestation" (NZMFM Network 2014) reviewed timing of birth. The guideline differentiates management strategies based on the availability of Doppler studies to stratify risk, and if 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 2018). The Clinical Guidelines Panel identified the need to ensure consistency with those guideline practice points regarding timing of birth. Note the MFM 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
<i>For women with suspected small for gestational age fetus or fetal growth restriction, in settings where detailed Doppler studies are unavailable, offer IOL at around 38 weeks' gestation (or earlier if concern).</i>
<i>For women with suspected small for gestational age fetus with abnormal umbilical artery Dopplers, consider offering induction of labour at around 37 weeks' gestation (low threshold for planned birth if there is any concern about maternal or fetal well-being or if there is suspected cessation of fetal growth).</i>
<i>For women with suspected small for gestational age fetus with abnormal MCA, CPR or uterine artery Dopplers, or EFW <3rd centile, offer IOL at around 38 weeks' gestation (or earlier if concern).</i>
<i>For women with suspected small for gestational age fetus with normal MCA, CPR and uterine artery Dopplers, and EFW 3rd centile or more, offer IOL at around 40 weeks' gestation (or earlier if concern). These babies are likely to be constitutionally small and are at lower risk of adverse outcome.</i>

Research Gaps
For women with suspected small for gestational age fetus/fetal growth restriction, to further evaluate planned IOL at different gestational ages, compared to expectant management with different methods of fetal monitoring, on outcomes such as perinatal death, preeclampsia, and women's perspectives and experiences.

4.4 Diabetes in pregnancy

Gestational diabetes (GDM) is a growing problem in NZ, affecting approximately one 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 2018) 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 to 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 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 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 estimated fetal weight (EFW) > 4000 g were excluded. There was no difference in caesarean section (IOL 12.6% vs. expectant 11.8%, RR 1.06; 95%CI 0.63 to 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. They 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, estimated fetal weight, disproportion between fetal abdominal circumference (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 > 4000g 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 NZ population (for example, in the study, mean body mass index (BMI) was 25, 75% were White, >50% were managed by diet alone, mean blood glucose level of 5.4mg/dL was considered well-controlled, participants had regular antenatal fetal surveillance, mean EFW was 3200g, different methods of diagnosing GDM, and different methods of 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 NZ Ministry of Health "Screening, diagnosis and management of GDM in New Zealand; a CPG" (NZ 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' gestation is not recommended in women with GDM who have no obstetric complications (including hypertension, preeclampsia, LGA \geq 90%, maternal age > 40 years) and who have had good glucose control (> 90% of blood glucose readings within treatment targets) throughout their pregnancy." The Clinical Guidelines 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 2018) 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 to 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 Australian Diabetes in Pregnancy Society consensus guideline (McElduff 2005) recommends that birth should be at term unless there are obstetric or fetal indications. IOL should also be based on obstetric and fetal indications.
- The NICE clinical guideline (2015) recommends that women with type 1 or 2 diabetes mellitus should be advised to undergo planned birth between 37+0 and 38+6 weeks' gestation. They also state that elective birth before 37 weeks' may be indicated if there are metabolic, maternal or fetal complications.
- The American College of Obstetricians and Gynaecologists (2018) recommends that for women with well-controlled pre-gestational diabetes, birth should be planned at full term (39+0 to 39+6 weeks' gestation); or earlier (from 36+0 to 38+6 weeks' gestation) if the women has vascular complications, poor glucose control, or prior 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 NZ local context and population characteristics (e.g. proportion of pregnant women with poorly controlled diabetes who are late bookers).

The Clinical Guidelines 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 (e.g. impaired renal function, changing insulin requirements, small for gestational age (SGA), preeclampsia, 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.

The management of women with Type 1 diabetes is to be individualised.

Research Gaps

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.

4.5 Maternal obesity

One in four women (26.4%) who gave birth in NZ in 2017 were identified as having obesity (BMI ≥ 30 kg/m²) at first registration with their primary care provider (NZ Ministry of Health, 2019). 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/RCOG, 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. NZ specific data from the PMMRC 2018 report is limited by incomplete BMI reporting (PMMRC, 2018). 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 Clinical Guidelines 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 induction of labour.

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.

4.6 Advanced maternal age

One in five women who gave birth in NZ in 2015 was ≥ 35 years of age (NZ Ministry of Health, 2019). 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 old. In NZ in 2016, the PMMRC reported an association between maternal age ≥ 40 years 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 compared IOL with expectant management (Walker 2016a). The intervention was IOL at 39+0 to 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+0 weeks and 42+0 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 to 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 to 3.06). The authors concluded that IOL at 39+0 to 39+6 weeks' gestation had no effect on caesarean section. The trial was not powered to detect a difference in perinatal death. Eighty-three percent of participants returned the Childbirth Experience Questionnaire, which showed no difference in experience between IOL and expectant management.

Walker (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. Only five 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 (OR 1.2; 95%CI 0.74 to 2.0; 5 trials, 2526 participants; high quality). There were no perinatal deaths. The authors concluded that IOL in women ≥ 35 years 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 ≥ 35 , the association found in the PMMRC data on perinatal mortality in women ≥ 40 , 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
<i>For women age 40 years and over, consider offering IOL at around 40 weeks' gestation.</i>

Research Gaps
For women with advanced maternal age, to evaluate the effect of IOL at 39 weeks or at 40 weeks vs 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.

4.7 Reduced fetal movements

Approximately one in 10 women contact their health care provider due to concern about reduced fetal movements (RFMs) during the third trimester (Gardener 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 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 done in the UK and Ireland evaluating a RFM care package compared to usual care across 33 maternity hospitals (Norman

2018). The intervention included an e-learning education 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 two 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 <2cm, abnormal CTG) or recurrent RFM. The intervention was compared to a period of usual care provided by the hospitals to women with RFMs prior to 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 1000 vs 4.40 per 1000, 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 outcome is unclear (Norman et al. 2018). Compared to 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 program 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 NZ guideline on RFM (Gardener 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 Clinical Guidelines 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. There was a need identified 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 NZ. The trial is complete but results were not available at the time of completing our review of the evidence.

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

Practice Point
<i>For women with reduced fetal movements, in the presence of normal maternal and fetal assessment, continue expectant management.</i>

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.

4.8 Hypertension in pregnancy

Approximately one in 12 women will have high blood pressure in pregnancy. Hypertension in pregnancy includes chronic hypertension, gestational hypertension and preeclampsia. There is an association between hypertension in pregnancy and increased maternal morbidity and mortality (NZ Ministry of Health - CPG, 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 preeclampsia >34 weeks' gestation compared planned early birth versus expectant management (Cluver 2017). Two studies compared IOL before term (34-36 weeks' gestation (Broekhuijsen 2015), 34-37 weeks' gestation (Owens 2014)) with a comparison group who were monitored until 37 weeks' gestation when induction began (if labour had not started spontaneously). Three studies compared induction of labour at term or closer to term [37 completed weeks (Hamed), 36-41 weeks' gestation (Koopmans 2009, Majeed 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 be 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 to 0.83; 2 trials, 1 459 women; high quality evidence), HELLP syndrome (RR 0.4; 95% CI 0.17 to 0.93; 3 trials, 1 628 women) and severe renal impairment (RR 0.36; 95% CI 0.14 to 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 to 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 to 2.40; 4 trials, 1 585 babies) and respiratory distress syndrome (RR 2.24, 95% CI 1.20 to 4.18; three trials, 1511 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 2009) randomised 756 women in the Netherlands with gestational hypertension (diastolic blood pressure of 95mmHg or higher) or mild preeclampsia >36 to 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 to 0.86). Women randomised to IOL had shorter durations of pregnancy compared to those randomised to expectant management (38.7 weeks' gestation vs 39.9 weeks' gestation). 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 preeclampsia at a gestational age beyond 37 weeks' gestation. The number of women needed to undergo IOL to prevent one woman from progression to severe hypertension or severe preeclampsia 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 is offered to women with gestational hypertension or mild preeclampsia, with no increase in the incidence of caesarean section. A limitation of the trial was not differentiating between gestational hypertension and preeclampsia. Factors to consider in individualising timing of birth include the type and degree of hypertension and its treatment, maternal and fetal well-being, additional antenatal risk factors, and maternal preference. The woman, her LMC midwife and the obstetric team would need to discuss together the optimal timing.

The 2017 Diagnosis and treatment of hypertension and preeclampsia in pregnancy in New Zealand; a Clinical Practice Guideline” (NZ Ministry of Health 2017) provide recommendations related to timing of birth. The guideline differentiates management strategies based on the type of hypertension in pregnancy. The Clinical Guidelines 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 NZ clinical practice guideline.

Recommendations	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 ⁺⁰ weeks' gestation, consider IOL, to reduce the risks of severe hypertension, severe preeclampsia, HELLP syndrome, abruptio placenta, pulmonary edema, severe renal impairment, and fetal growth restriction.	Level 1; Moderate quality	Conditional
For women with preeclampsia diagnosed after 37 ⁺⁰ weeks' gestation, offer IOL.	Level 1; Moderate quality	Conditional

Research Gaps
For women with hypertension in pregnancy, to further evaluate the effect of IOL vs 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.

4.9 Antepartum haemorrhage of unknown origin

Approximately one in 20 women will experience an antepartum haemorrhage (APH), defined as bleeding from the genital tract from 24 weeks' gestation and prior to the birth of the baby (Bhandari 2014). Causes of APH are placenta praevia, placental abruption and local causes (e.g. 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 2014). The Clinical Guidelines Panel identified that APH is an indication for assessment by an obstetric specialist and may require increased monitoring of the pregnancy (e.g. SGA, routine enquiry for intimate partner violence). If placental abruption was 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 antepartum haemorrhage of unknown origin, in the presence of normal maternal and fetal assessment, consider expectant management.

Research Gaps

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

4.10 Assisted Reproductive Technology (ART)

Approximately one in 37 women conceive using ART (Fitzgerald 2018). ART refers to procedures that involve the in vitro handling of both human oocytes and sperm, or of 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 fertilization or intracytoplasmic sperm injection when compared with spontaneous conception (Pandey 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. People 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 assisted reproductive technology, in the absence of other risk factors or pregnancy complications, do not offer induction of labour.

Research Gaps

In women who conceive using assisted reproductive technology, to evaluate the effect of IOL vs expectant management on maternal, perinatal and neonatal outcomes.

To explore perspectives and experiences of women who conceive using artificial reproductive technology regarding IOL as a potential intervention to reduce pregnancy-related complications.

4.11 Suspected fetal macrosomia

Approximately one in 42 women gave birth to a high birthweight baby ($\geq 4500\text{g}$) in 2017 (NZ Ministry of Health 2019). Macrosomia implies fetal growth beyond a specific weight (often set at 4000g or 4500g) regardless of gestational age, however, the antenatal diagnosis is often imprecise (Chatfield, 2001). Large for gestational age (LGA) is defined as birthweight above 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 prior to the birth (clinical palpation and ultrasound biometry provide an estimated fetal weight) (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 2016). Macrosomia was defined as birth weight $>4000\text{ g}$. The intervention was IOL at or near term (37 to 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 to 1.09; moderate quality), compared to expectant management. IOL reduced shoulder dystocia (RR 0.6, 95% CI 0.37 to 0.98; moderate quality), and any fracture (RR 0.2, 95% CI 0.05 to 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 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 $>95\text{th}$ percentile, defined as 3500g at 36 weeks', 3700g at 37 weeks', and 3900g at 38 weeks' gestation. Participants were randomised to IOL between 37+0 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% 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+0 and 38+6 weeks' gestation, i.e. 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 Clinical Guidelines Panel discussed the differences between the Boulvain trial and the Cochrane review. The Boulvain trial does not reflect current NZ 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 NZ context and in the absence of diabetes.

Big Baby is a multi-centre RCT in the United Kingdom 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 to expectant management. The trial is now recruiting, and we await their results to help guide future practice.

Antenatal estimates of fetal weight are often inaccurate and identification of macrosomia can increase anxiety for the 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 assessment of fetal size and diagnosis of 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 vs expectant management on maternal, perinatal and neonatal outcomes, in the NZ context.

4.12 Multiple pregnancy

In New Zealand, approximately one woman in 50 will have a twin pregnancy. Twin pregnancy is associated with higher rates of anomaly, preterm birth, preeclampsia, 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 2014). Both trials showed the average gestational age at delivery was earlier in IOL compared to 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 to 8.35; two studies, 542 infants; low quality); maternal death or serious maternal morbidity (RR 0.29; 95% CI 0.06 to 1.38; one study, 235 women; low quality); or caesarean section (RR 1.05; 95% CI 0.83 to 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.

- The NZ Maternal Fetal Medicine Network (2015) advises that women with monochorionic twin pregnancies should have birth considered at 36 to 37 weeks' gestation, due to concerns of increase risk. However, they state that this is a pragmatic approach, given there is no high-quality evidence to guide care in this setting.
- The RCOG (2016) has a consensus-based recommendation that women with monochorionic twin pregnancies give birth by 37 weeks' gestation.
- The NICE guidelines (2019) recommend offering women with uncomplicated monochorionic diamniotic twin pregnancies planned birth at 36 weeks' gestation, and uncomplicated dichorionic twins at 37 weeks' gestation. Individualised assessment 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 induction of labour between 36 and 37 weeks' gestation.

For women with an uncomplicated dichorionic twin pregnancy, consider offering induction of labour between 37 and 38 weeks' gestation.

Research Gaps

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.

4.13 Reduced liquor < 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 2017). A review of RCTs concluded that single deepest vertical pocket measurement is the method of choice for the assessment of liquor volume (Nabhan 2014). Reduced liquor is thus defined in this guideline as deepest vertical pocket <2cm.

Summary of evidence

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

Discussion

Observational studies (Rabie, 2017; Morris 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; 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 ROM 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 persistent reduced liquor, 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 Gaps

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

4.14 Obstetric cholestasis

Approximately one in 100 pregnant women will have obstetric cholestasis (also called intrahepatic cholestasis of pregnancy). It 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 2019), and maternal morbidity, such as intense itching and difficulty sleeping (RCOG 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 2012). There were no stillbirths or neonatal deaths in 'early delivery' or

the 'await spontaneous labour' group. There were no significant differences between the two groups in the rates of caesarean section (RR 0.68; 95% CI 0.30 to 1.52; low quality) or NICU admission (RR 0.55; 95% CI 0.05 to 5.76; low quality). They did not 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 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 to whole population figures (Kenyon 2011). Two systematic reviews have found no increased risk of stillbirth in women with obstetric cholestasis (Henderson 2014; Ovadia 2019). Stratified by bile acid level, the association with stillbirth was found only in women whose bile acids were ≥ 100 (Ovadia 2019).

The RCOG guideline on obstetric cholestasis (Kenyon 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 may be 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 Clinical Guidelines Panel suggests that the possibility of IOL be discussed with the woman, 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
<i>For women with obstetric cholestasis, if symptomatic or if serum bile acid concentration ≥ 100, consider induction of labour; otherwise consider expectant management.</i>

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

4.15 Previous stillbirth

In NZ, approximately one in 500 women will experience a late stillbirth (at 28 weeks' gestation or more), and about one third of these are unexplained (McCowan 2017, PMMRC 2018). The effect of a stillbirth on parents is devastating and long-term, and creates 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 NZ in 2016 was 5.1/1000 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 2015; Malacova 2018). These studies do not identify gestation at first or subsequent stillbirth and therefore cannot help with decision making around timing of induction for a previous 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 Clinical Guidelines Panel acknowledges that many of the causes of stillbirth remain unknown and stillbirth is difficult to predict or prevent. The anxiety of women with a previous stillbirth and the impact of their prior experience may affect decision-making in their current pregnancy. Women who have had a previous stillbirth may request IOL prior to 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 stillbirth, consider expectant management or induction of labour, based on a review of risk factors for recurrence and any other antenatal risk factors, and guided by maternal choice.

Research Gaps

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

4.16 No medical indication

Induction of labour 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 at 41 hospitals in the United States (Grobman 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+0 to 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, 22 533 (44%) were eligible 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, i.e. 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 to 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 vs 40.0 weeks' gestation; p<0.001) with a lower median birthweight (3300g [interquartile range, 3040 to 3565] vs. 3380 g [interquartile range, 3110 to 3650]; 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 to 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. They did not report on maternal satisfaction.

Discussion

Limitations of the Grobman trial were identified as:

- does not reflect current NZ maternity practice 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;
- no long-term data on the neurodevelopmental or metabolic outcomes for the babies.

The Clinical Guidelines Panel considered that IOL is not justified, due to limitations of current RCT evidence in relation to the NZ context. Consider women's preferences, resources available, and setting for IOL. This 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 NZ context but the data are not comparable due to confounders. If possible, local data could be provided to women on local rate of caesarean following IOL. The Panel identified the need to ensure that information is shared with women, midwives and obstetricians, while acknowledging other factors (e.g. 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 is not only about the potential adverse outcomes but is 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.

<i>Practice points</i>
<i>Do not offer induction of labour in the absence of a medical indication.</i>
<i>The management of induction of labour for maternal request is to be individualised.</i>

Research Gaps
For women who have IOL at 39 weeks' 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 pregnancy, to further evaluate IOL at 39 weeks vs expectant management on maternal, perinatal and neonatal outcomes, in the NZ 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 done at the time of the initiation of the induction. Unfortunately, the predictability of the Bishop score is limited. 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 greater has a similar chance of achieving vaginal birth as someone 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 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 NZ, hence trials comparing cervical ripening to placebo are not reviewed in this document. IOL in the setting of previous caesarean section is reviewed. Systematic reviews comparing all methods to each other are summarized in Appendix D.

In addition, some clinicians perform membrane sweeping at the same time as performing a formal labour induction. 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 2017).

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

1. Prostaglandin E2 hormone (dinoprostone)
2. Prostaglandin E1 analogue (misoprostol)
3. Mechanical methods, such as balloon catheter

5.1 PGE2 (dinoprostone) methods of administration

Summary of evidence

One systematic review was identified that included a comparison of vaginal gel (Prostin) to controlled-release pessary (Cervidil). In the Cochrane review on PGs for cervix ripening (Thomas 2014), there were 13 trials of 1436 women that compared PGE2 (controlled-release) vs. 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 the cervix would remain unfavourable, compared to other PGE2 vehicles. There was no difference in oxytocin augmentation, or tachysystole/hypertonus (4.2% versus 2.4%, RR 1.59, 95% CI 0.81 to 3.14, eight trials, 908 women).

5.2 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 2010). The authors analysed 38 studies of 7022 women comparing vaginal misoprostol to vaginal PGE2. Compared to vaginal PGE2, women who got vaginal misoprostol had 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 to 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 the third trimester due for induction with a viable fetus (Alfirevic 2014). In the 37 trials of 6417 women which compared oral to vaginal misoprostol, women taking oral misoprostol had similar outcomes of vaginal birth within 24 hours (RR 1.08, 95% CI 0.86 to 1.36; 14 trials, 2 448 women; low quality), uterine hyperstimulation with fetal heart rate changes (RR 0.71, 95% CI 0.47 to 1.08; 29 trials, 5 503 women; low quality), and caesarean section (RR 0.93, 95% CI 0.81 to 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 to 1.44, 24 trials, 3 634 women; moderate quality), less postpartum haemorrhage (RR 0.57, 95% CI 0.34 to 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 to 0.82, 19 trials, 4 009 babies; moderate quality) compared to 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. The outcome of uterine hyperstimulation was dose dependent, and the authors suggested that if using oral misoprostol, then low dose 20—25 micrograms in solution was recommended.

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

A systematic review with Bayesian network meta-analysis of IOL with PGs (Alfirevic 2015) included 280 RCTs of 48 068 women in their third trimester with a viable fetus who were undergoing cervical ripening or labour induction. Compared to placebo, odds of failing to achieve a vaginal birth were lowest for high-dose vaginal misoprostol (≥ 50 micrograms) (OR 0.06 (95% CI 0.02 to 0.12), with a 39% absolute probability of event (95% CI 1% to 94%). Compared to placebo, odds of caesarean section were lowest for low-dose (< 50 micrograms) titrated oral misoprostol solution (OR 0.65, 95% CI 0.49 to 0.83), with an absolute probability

of event of 15% (3% to 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 PGs

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 that oral PGE1 is probably associated with a lower risk of caesarean section.

The Clinical Guidelines Panel noted that in their experience of reviewing cases, sometimes uterine hyperstimulation is not recognised, so we should have a note of caution for any woman receiving any prostaglandin.

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 not 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, we have consulted with the Perinatal Society of NZ and the Health Quality and Safety Commission, and reviewed protocols of trials included 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 micrograms in solution two-hourly is widely used internationally and is recommended by the World Health Organisation (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 NZ, 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 which 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. We have sought advice on this issue:

The National Maternity Monitoring Group (NZ MoH) supports the use of misoprostol as an option for women undergoing IOL.

The Pharmaceutical Society of NZ 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 NZ, 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 [Health Quality and Safety Commission](#) recommends that the strength of misoprostol oral solution is standardised nationally to ensure consistency. HQSC recommends that best evidence-based information is available for staff making this preparation and that the same strength is 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 (eg, for product prepared ‘at the bedside’ vs. in a pharmacy). HQSC has kindly provided two protocols that can be found 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.

5.3 Balloon catheter

Summary of evidence

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

A Cochrane systematic review (Jozwiak 2012) of 71 RCTs of 9 722 women compared mechanical methods for IOL to any PG. In the 21 studies of 3 202 women comparing balloon catheter specifically to 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 to 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 fetal heart rate changes (RR 0.19, 95% CI 0.08-0.43; 9 studies; moderate quality).

Compared with PGE2 alone, PGE2 plus balloon catheter resulted in decreased rate of not achieving vaginal birth at 24 hours (RR 0.45, 95% 0.28 to 0.71; 3 trials; moderate quality), similar caesarean section rate (0.92, 95% 0.79 to 1.08; 3 trials; moderate quality), and less uterine hyperstimulation with FHR changes (RR 0.53, 95% 0.35 to 0.78; 1 trial; low quality). Only one trial measured patient satisfaction and discomfort. Women reported less discomfort with the single balloon catheter compared to 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 2016) of 1 859 women with an unfavourable cervix and intact membranes having IOL at term, comparing oral misoprostol versus 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 versus 11.5% in the balloon group (aRR 1.06, 90% CI 0.86 to 1.31), and caesarean section occurred in 16.8% versus 20.1% (RR 0.84, 95% CI 0.69 to 1.02, p=0.07). They did not have maternal satisfaction as an outcome. There were 27 adverse events reported in the misoprostol group versus 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 versus a single balloon catheter left in situ for 12 hours (Mundle 2017). Women in

the misoprostol group were more likely to have a vaginal birth within 24 hours compared to women in the balloon group (57% vs 47% women; absolute risk difference 10%, 95% CI 2.0 to 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 to 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 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 to 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 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% 0.54 to 0.90; moderate quality) and a more favourable cervix at time of balloon removal (RR 1.72, 95% 1.46 to 2.04; very low quality), compared to low-volume. There was no difference in caesarean section (RR 0.82, 95%CI 0.48 to 1.41; moderate quality) or epidural use. They did not report on maternal satisfaction.

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

Discussion on balloon catheters

For balloon catheters, the Clinical Guidelines 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 50mL single balloon

foley catheter available in NZ, 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.

Recommendations	Level of evidence	Strength of recommendation
Offer cervical ripening with prostaglandins to women with unfavourable cervix, to improve the chance of vaginal birth within 24 hours, compared to 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 fetal heart rate changes, compared to prostaglandins.	Level 1; moderate quality	Conditional
For single-balloon catheter: Inflate greater than 30 mL (and not more than manufacturer recommendation), to increase the chance of vaginal birth in 24 hours, compared to 30mL 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 BS≤4, consider 2mg; otherwise consider 1mg. Decide subsequent dose based on cervical change – if none, consider 2mg; otherwise consider 1mg. Use as per manufacturer’s instructions.

For cervical ripening with PGE2 controlled-release vaginal pessary: Pessary may have higher risk of uterine tachysystole and hypertonus compared to vaginal gel. Use as per manufacturer’s instructions.

For cervical ripening with PGE1 analogue (misoprostol): Vaginal administration may have higher risk of adverse outcomes compared to oral administration. If using misoprostol, low-dose (25 micrograms) two-hourly in oral solution is recommended. See Appendix E for suggested protocols.

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 manufacturer’s instructions.

Research Gaps
For women having cervical ripening, to evaluate timing of starting IV luer (routinely at start of IOL vs as needed), on maternal satisfaction and potential harms.
For cervical ripening with Cervidil, to evaluate the effect of leaving it in situ for 24 vs 12 hours, and to evaluate the effect of a 2 nd dose vs 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 vs 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 prostaglandins.

5.4 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 2017). All methods of cervical ripening or IOL (prostaglandins (vaginal or oral), mifepristone, mechanical methods, oxytocin or placebo) that was 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 nor 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 prostaglandins 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. Studies have 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 (Landon 2005; Fitzpatrick 2012). Without the use of oxytocin, 36/10,000 women experienced rupture, compared with 87/10,000 women following oxytocin (Landon 2005). Fitzpatrick noted an increase in the risk of rupture with oxytocin use (aOR 3.92).

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 induction of labour is indicated in the setting of previous caesarean section.

Research Gaps

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.

6.1 Combination ARM with oxytocin

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

In a Cochrane review (Howarth 2001) of 17 clinical trials (2 566 women), amniotomy with oxytocin for third trimester IOL was compared to 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, post-partum haemorrhage and fever.

Comparing ARM/oxytocin to ARM alone, fewer women in the ARM/oxytocin group failed to achieve vaginal birth within 24 hours (RR 0.13, CI 0.04 to 0.41, two trials, 296 women; low quality). Rates of caesarean section were similar between the groups (RR 0.45, CI 0.16 to 1.30, two trials, 510 women; low quality). There were fewer instrumental deliveries in the ARM/oxytocin group compared to 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 at least a 60% reduction in women undelivered at 24 hours compared with ARM alone.

Comparing ARM/oxytocin to oxytocin alone, there was no difference between the groups for caesarean section (RR 1.05 95% CI 0.64 to 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 (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 to late ARM.

6.2 Timing of ARM

Three RCTs, with a total of 1 073 women, were identified comparing early ARM (at start of IOL) vs 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 3cm dilated), and late ARM was defined as either 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% 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.

6.3 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 little or no differences in most clinical outcomes, such as perinatal death, caesarean section, vaginal birth within 24 hours, Serious Adverse Maternal Morbidity, 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 to low-dose, 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 Clinical Guidelines Panel discussed that individualising care is important when discussing the timing of ARM and starting oxytocin. It is usual practice in NZ 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 prior to 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 (a ‘safe haven’) and are considered a taonga. The ‘waters’ hold more significance than just liquid surrounding the pepi. The waters facilitate a transmission of knowledge through taonga pūoro , vibrations and kōrero , transferring the hopes, dreams and aspirations from māmā, pāpā ,whānau and connections to tūpuna. Discuss where, when, how the waters are ruptured. This understanding of āhuru mōwai is explored in the following video <https://vimeo.com/316244298> (Farry 2008).

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 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 we should have a note of caution for any woman receiving oxytocin. If prostaglandins 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 that oxytocin is not 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
<i>To start induction of labour once the cervix is favourable, consider offering the combination of artificial rupture of membranes and intravenous oxytocin infusion, to increase chance of vaginal birth within 24 hours.</i>
<i>The timing and order of performing ARM and starting intravenous oxytocin infusion can to be individualised and negotiated between the woman, her Lead Maternity Carer, the hospital midwife and the obstetrician.</i>
<i>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.</i>
<i>Usual time interval to increase dose of oxytocin is approximately 20 minutes.</i>

Research Gaps

To explore NZ 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 score > 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 score > 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 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 the 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 (2012) conducted an RCT in Australia of 827 women, and Ryan (1998) 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 (2003) conducted an RCT in Canada of 300 women evaluating outpatient (150 women) versus inpatient controlled-release PGE₂ insert (150 women). 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 of their care during the induction process, but there was no difference during labour and birth.

Sciscione (2001) randomised 111 women in the USA 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. (2015) 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 nights' 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 to PGs. 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 study in New Zealand is comparing inpatient PGE2 with outpatient single balloon catheter and the primary outcome is caesarean section rate (www.oblige.auckland.ac.nz); 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 (<https://www.materresearch.org.au/Our-research/Research-projects/Project-Detail?project=462>). Details of both studies can be found on the Australia New Zealand Clinical Trial Registry website.

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 (Mol 2018). If offering outpatient IOL, it is imperative that safety measures and support are 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 rupture of membranes, or at a pre-specified time for reassessment.

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

Research Gaps

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

ABBREVIATIONS

AC	Abdominal circumference
AFI	Amniotic fluid index
APH	Antepartum haemorrhage
ART	Assisted reproductive technology
aOR	Adjusted Odds Ratio
aRR	Adjusted Relative Risk
CPG	Clinical practice guidelines
CPR	Cerebro-placental ratio
CTG	Cardiotocography
DHB	District Health Board
EFW	Estimated fetal weight
FGR	Fetal growth restriction
GBS	Group B streptococcus
GDM	Gestational diabetes mellitus
HELLP	Haemolysis, elevated liver enzymes, and low platelet count
IOL	Induction of labour
IUGR	Intrauterine growth restriction
LGA	Large for gestational age
LMC	Lead maternity carer
MCA	Middle cerebral artery
MOH	Ministry of Health
NICE	National Institute for Clinical Evaluation
NICU	Neonatal intensive care unit
NNT	Number needed to treat
NZ	New Zealand
NZCOM	New Zealand College of Midwives
OR	Odds Ratio
PG	Prostaglandin
PMMRC	Perinatal Morbidity and Mortality Review Committee
PROM	Pre-labour rupture of membranes
RANZCOG	Royal Australia and New Zealand College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RFM	Reduced fetal movements
ROM	Rupture of membranes
RR	Relative Risk
SGA	Small for gestational age
WHO	World Health Organisation

APPENDIX A - Clinical Guidelines Panel

Member	Affiliation /representing organisation	Role
Dr Michelle Wise	Senior Lecturer, Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, University of Auckland; Obstetrician and Gynaecologist, Auckland DHB	Chair
Dr Jane Alsweiler	Consultant Neonatologist, NICU, Auckland DHB; Senior Lecturer, Department of Paediatrics: Child and Youth Health, University of Auckland; Honorary Senior Lecturer, Liggins Institute, University of Auckland	Representing Royal Australasian College of Physicians
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, Waitemata DHB; former Chair of PMMRC	Representing RANZCOG
Dr Isabel Camano	Clinical Director, Obstetrics, Waikato DHB	
Lesley Dixon	Midwifery Advisor: Practice advice & research development	Representing New Zealand College of Midwives
Emma Farmer	Head of Midwifery, Waitemata 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 Trust; Co-Founder: Health Promotion in Partnership	Representing consumer perspectives
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	

Acknowledgements:

Helena Trollope, Research Assistant and Project Manager

Julie Brown, Research Assistant

Tash Wharerau – Wahine Ora Health Promoter - Women’s Health Action

APPENDIX B - Search Methods

Methods

Searches for indications and methods for induction of labour (Table 4) were conducted using the Cochrane Database of Systematic Reviews, and databases PubMed, MeSH and Google Scholar. Search dates were limited from 01/01/2014 - 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 had a variety of keywords searched. 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

Prolonged pregnancy; Pregnancy, Prolonged; post-term; Pre-labour rupture of membranes; PROM; advanced maternal age; Maternal Age; Obesity; Obesity, Morbid; increased BMI; raised BMI; body mass index; gestational diabetes; Diabetes, Gestational; diabetes mellitus; Hypertension; Hypertension, Pregnancy-Induced; Pre-Eclampsia; gestational hypertension; hypertension in pregnancy; fetal growth retardation; intrauterine growth restriction; Infant, Small for Gestational Age; suspected small for gestational age; suspected SGA; IUGR; macrosomia; large for gestational age; LGA; pregnancy, Twin; twin gestation; Pregnancy, Multiple; multiple pregnancy; artificial reproduction techniques; artificial reproduction; Reproductive Techniques; assisted reproduction; IVF; Fertilization in Vitro; in-vitro fertilisation; intracytoplasmic sperm injection; Sperm Injections, Intracytoplasmic; antepartum haemorrhage; Hemorrhage; antepartum haemorrhage of unknown origin; history of stillbirth; pregnancy stillbirth; stillborn; Stillbirth; recurrent stillbirth; intrahepatic cholestasis of pregnancy; cholestasis of pregnancy; reduced fetal movements; RFM; decreased fetal movements; awareness of fetal movements; decreased fetal movements; DFM; Oligohydramnios; type 1 diabetes, type 2 diabetes, pre-existing diabetes; membrane sweeping; elective induction; elective procedure; policy induction of labour; inpatient; outpatient; double balloon catheter; double balloon; catheter; single balloon; misoprostol; PGE2; PGE2 gel; cervical ripening; late amniotomy; late artificial rupture of membranes; early artificial rupture of membranes; early amniotomy; artificial rupture of membranes; artificial rupture of membrane; misoprostol; prostaglandins; dinoprostone; cervidil; controlled release; prostin; prostin gel; carboprost; oxytocin; oxytocin protocol; oxytocin regimen; low dose oxytocin; high dose oxytocin; maternal outcome; perinatal outcome; neonatal outcome.

MeSH

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

Selection Criteria

Selection criteria included papers written in English, where the ideal countries for published material were from populations most similar to NZ (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 Clinical Excellence (NICE 2008) (Table 2). We aimed to provide the highest level of evidence available for each indication as to provide the most evidence based guidance on induction of labour. The Cochrane Database of Systematic Reviews was the primary search as it provided 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 4. Results of searches

Indication	Cochrane Review	PubMed
Pregnancy \geq 41 weeks' gestation* Δ	1 review (2018) 30 trials	19 results: 5 review, 4 clinical trial
Pre-labour rupture of membranes* Δ	1 review (2017) 23 trials	19 results: 7 review, 4 clinical trial
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; <i>None of level 1 quality</i>
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) 2 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	Results: 4: 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 movementsΔ	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
Preexisting diabetes mellitusΔ	1 review (2018) No trials	36 results: 11 reviews, 6 clinical trials
Induction of labour with no medical indication/elective IOLΔ	No results	35 results: 12 reviews, 2 clinical trials
Methods		
Mechanical induction of labour	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 induction of labour/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 induction of labour	1 review (2005) 22 trials	50 results: 17 reviews, 23 clinical trials
Outpatient induction of labour	2 reviews (2013, 2017) 2013; 4 trials 2017; 34 studies	48 results: 9 reviews, 15 clinical trials

(*restricted dates 01/01/2014 - 03/12/2018; Δexpectant management included in search terms)

Searches for Ongoing Clinical Trials

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

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 2018), one unknown status. One trial was found for post-dates; completed (no publication). Two trials were found for term PROM; one recruiting (Table 5), 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 5), 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 6), 2 had an ‘unknown status’, and 1 was terminated. No publications were available. One trial that was not found in our search comparing inpatient to outpatient inductions is currently recruiting.

Table 5. 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 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 IOL on term using a double balloon catheter compared to dinoprostone vaginal insert NCT01720394	Medical indication for IOL, 18 years of age, signed informed consent, cephalic presentation, no PROM, 37+0 - 42+0 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 labour induction NCT03039036	Women, aged 18 or over who are nulliparous, pregnant with a singleton gestation (>=37 weeks gestation) undergoing induction with Foley catheter, who is English speaking and can provide informed consent.	Time interval from Foley catheter removal to delivery

What after the first proposs 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 IOL NCT03407625	Women with a live singleton fetus with no major fetal malformations, cephalic presentation at ≥ 37 weeks gestation, with cervical dilatation of 2cm or less, no previous uterine scar, intact fetal membranes and who have an indication for induction or attempted IOL and qualify for prostaglandin administration (according to current Parkland protocol)	Vaginal delivery
Outpatient foley for starting IOL at term in nulliparous women NCT03472937	Nulliparous women ≥ 18 years with a singleton, vertex presentation pregnancy with gestation between 39+0 - 42+0, a modified Bishop score < 5 and cervical dilatation < 2 cm, no prior uterine surgery, and reside within 30mins 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 IOL at term NCT03629548	Women with singleton, cephalic presentation pregnancy ≥ 37 weeks with intact membranes, Bishop score < 5 , with obstetric indications for IOL and had 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 IOL NCT02777190	Women ≥ 18 years with a single live cephalic presenting intrauterine pregnancy (≥ 37 weeks) undergoing IOL, with 20 minutes reassuring fetal heart rate, Bishop score ≤ 6 (cervical dilatation ≤ 2 cm), and 3 or less uterine contractions over 10 minutes.	Time interval from start of IOL (first misoprostol administration) to active phase of labor (greater than or equal to 6 cm cervical dilation).
Cervical ripening with the double balloon device (DBD) for 6 hours compared with 12 hours (DoubleCRIB) NCT03045939	Parous women ≥ 18 years old with an indication for IOL, with a singleton pregnancy in vertex presentation with intact membranes and no significant regular uterine contraction (≥ 37 completed weeks gestation) with a Bishop score of 5 or less, 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 administration of dinoprostone (Propess), to promote IOL of pregnant women at term? NCT02888041	Women ≥ 18 years old with a term cephalic presentation pregnancy ≥ 37 weeks, undergoing a medically indicated IOL with intact membranes, unfavourable cervical conditions (Bishop score < 6 1 hr prior to 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
Labour induction with a combined method	Women with singleton, vertex-presenting pregnancies at term (≥ 37 weeks'	Time to delivery

(pharmacologic and mechanical): randomised controlled trial NCT03928600	gestation), with no contraindication to vaginal delivery, intact membranes and Bishop score <7 and cervical dilatation </=2cm.	
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 fetal heart rate pattern, not in labour (no contractions), and a clinically adequate pelvis.	Mode of delivery
Efficacy and safety of hourly titrated misoprostol vs vaginal dinoprostone and misoprostol for cervical ripening and labour induction NCT02902653	Women over 18 years old with a single cephalic presenting pregnancy with intact membranes, unfavourable cervix (Bishop <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 NCT03670836	Women undergoing IOL with a single live fetus in cephalic presentation with a gestation of ≥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 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370551&isReview=true)	Pregnant women ≥18 years old with BMI <50 at booking, between 37+0 - 41+4 weeks gestation, having first baby undergoing medically indicated IOL, with Bishop score </=4.	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) 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) 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
Tension vs no tension with foley bulb induction NCT03588585	Nulliparous women (≥18 years old) with a singleton live intrauterine pregnancy, cephalic presenting, with intact fetal membranes, undergoing IOL at Kapiolani Medical Center for Women and Children with a Bishop score </= 6.	Time to Delivery

Table 6. Recruiting trials looking at outpatient methods of induction of labour

Identifier	Inclusion criteria	Primary outcome
Outpatient cervical preparation to reduce induction to delivery in NTSV women (OCPRID) NCT03934918	Nulliparous women >18 years of age 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 IOL at term by outpatient balloon or inpatient prostaglandin in order to assess caesarean section rate; an RCT. ACTRN12616000739415 (https://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 between 18 - 45 years of age with live, singleton, cephalic presentation ≥37 weeks' gestation with intact membranes, a pelvic exam of </=3cm and at most 60% effaced, with understanding and can sign informed consent.	Rate of hospital stay > 48 hours (from admission to discharge) Healthcare cost impact (assessed based on direct hospital costs or Medicaid charges)
Outpatient foley for starting IOL at term (OFFSITE) NCT02756689	Multiparous women ≥18 years of age with singleton, vertex presentation 39+0 to 42+0 with cervix </=3cm (if 2-3cm must be <80% effaced), no prior 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 IOL NCT02975167	Women >18 years old with a singleton vertex presenting fetus at ≥39 weeks' gestation.	Patient satisfaction scores
Sleep and Depression in IOL NCT03380897	Women with an uncomplicated singleton pregnancy ≥37 - </= 41+5 weeks gestation, patient lives within half an hour of the hospital.	Pain after double-balloon catheter insertion, measured by VAS
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 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365522)	All women, aged 18-52 years, with live singleton pregnancies greater than or equal to 37 weeks 0 days, 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 acidemia (cord arterial pH <7.10); HIE; Neonatal seizure; Infection (needing neonatal antibiotics); Persistent pulmonary hypertension of the newborn

APPENDIX C - Observational studies

C.1 Tables of national and international stillbirth risk factors

Table 7. Adjusted odds ratio for perinatal related mortality, termination of pregnancy, stillbirth and neonatal death 2011-2015 in New Zealand (PMMRC 2017)

	Fetal deaths											
	Perinatal related mortality			Termination of pregnancy			Stillbirth			Neonatal mortality		
	n=494,210			n=494,210			n=494,210			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.

Table 8. Risk factors and attributable stillbirth in selected high-income countries (Flenady 2011)

	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
Any smoking	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

Table 9. Population-attributable risk for stillbirth in selected high-income countries (Flenady 2011)

	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

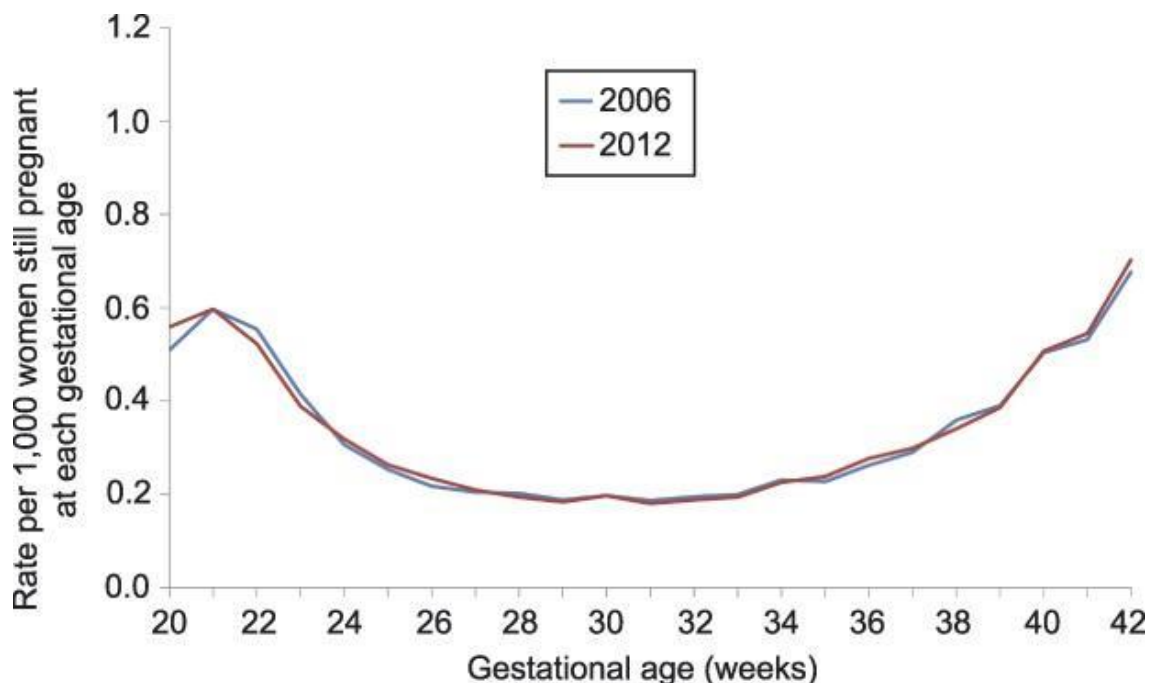
Table 10. Association of maternal factors with antepartum stillbirth (INTERGROWTH-21 Project) (Hirst 2018)

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, $I < 0.2$ 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.

C.2 Pregnancy ≥41 weeks' gestation or more

Figure 1: Association of stillbirth with gestational age, USA data (MacDorman 2015)



C.3 Obesity in Pregnancy

Figure 2: Association of BMI and fetal death (Aune 2014)

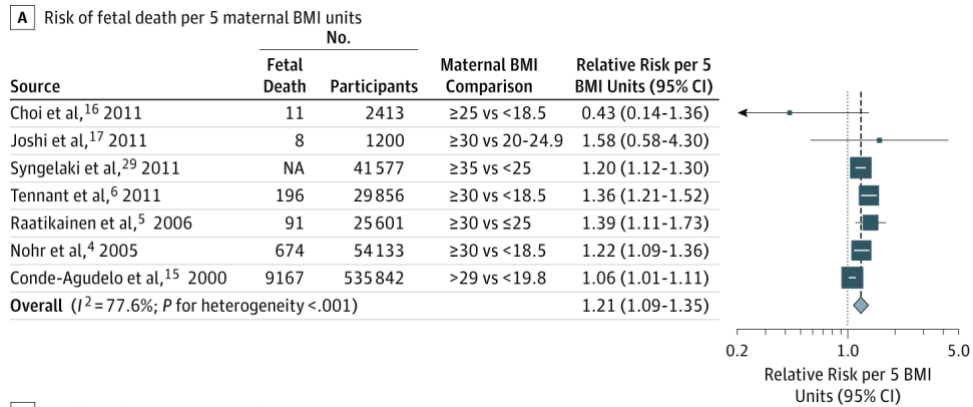
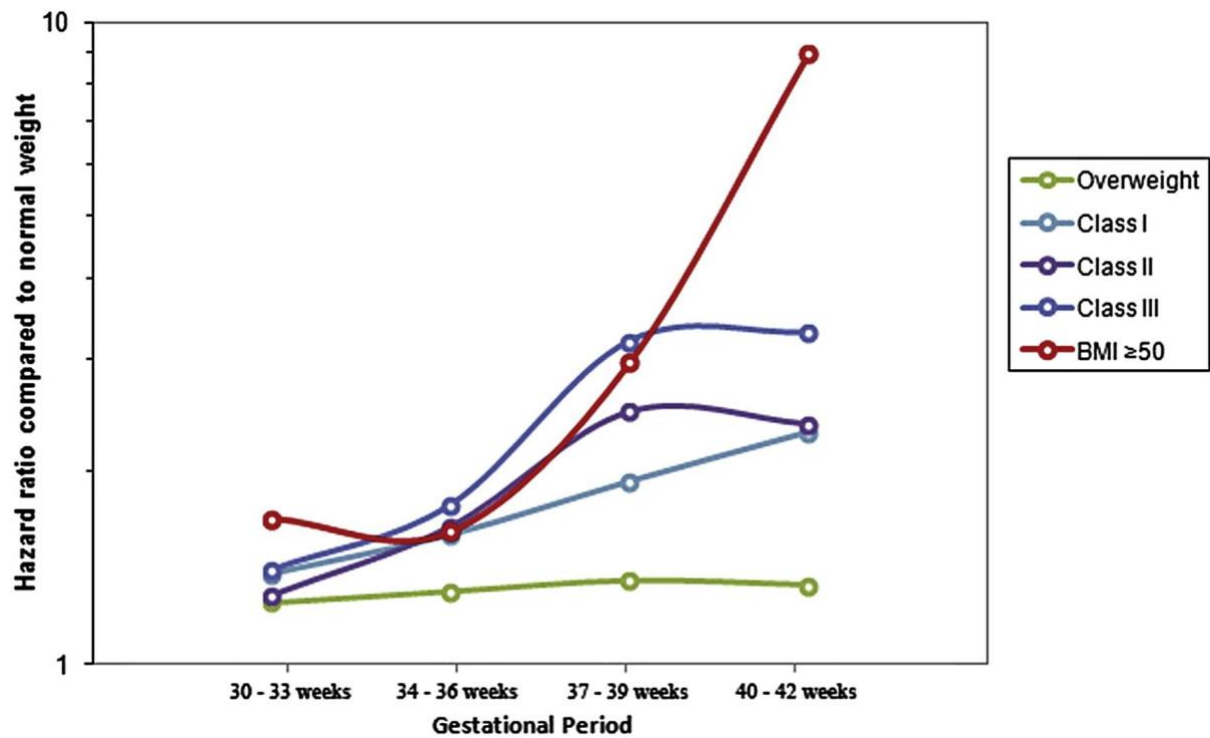
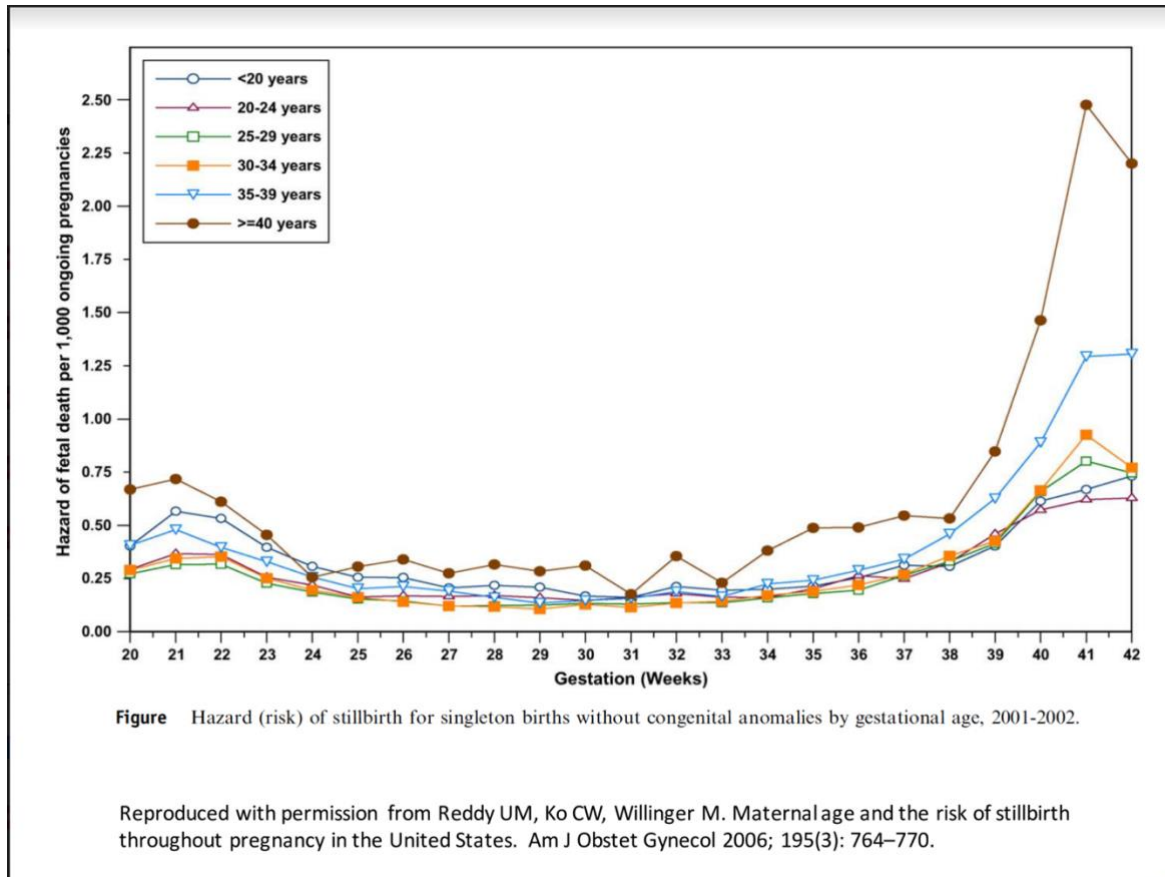


Figure 3: Association of obesity in pregnancy and stillbirth in Washington and Texas (Yao 2014)



C.4 Advanced Maternal Age

Figure 4: Association of maternal age and stillbirth in the USA (Reddy 2006)



C.5 Antepartum Haemorrhage (APH) of Unknown Origin

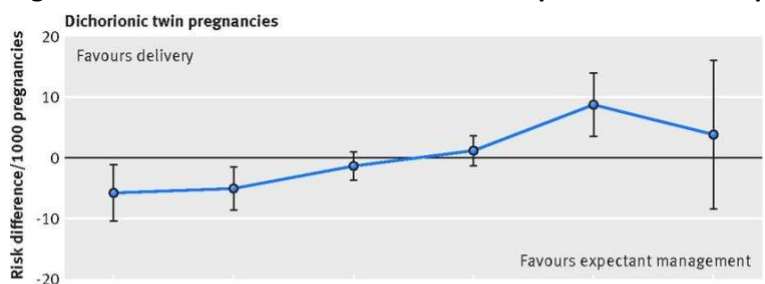
A retrospective cohort study (Bhandari 2014) reported on all primigravidae giving birth between 1976 and 2010 using the Aberdeen Maternity and Neonatal Databank (Scotland). There were 7,517 women with APH of unknown origin and 68,423 without. Social class, smoking, marital status and a higher BMI were 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 postpartum haemorrhage. There was no increase seen in perinatal death after adjusting for preterm birth.

C.6 Pregnancy Following Assisted Reproductive Technology

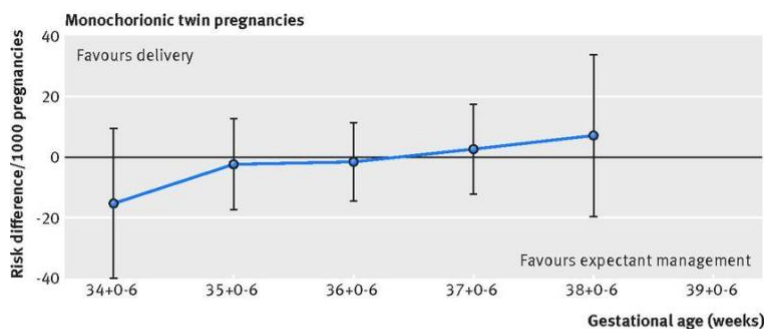
A systematic review of 30 observational studies compared obstetric and perinatal outcomes for singletons born after in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) compared with those of spontaneous conceptions (Pandey 2012). IVF/ICSI singleton pregnancies were associated with 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 to 1.77) and perinatal death (RR 1.87, 95% CI 1.48 to 2.37). Observational studies were of moderate quality; however high risk of bias due to non-randomised evidence.

C.7 Multiple pregnancy

Figure 5: Risk of stillbirth and neonatal complications in twin pregnancies (Cheong-See 2016)



Risk difference/1000 pregnancies (95% CI)	34+0-6	35+0-6	36+0-6	37+0-6	38+0-6	39+0-6
Stillbirth	-5.8 (-10.4 to -1.2)	-5.1 (-8.7 to -1.6)	-1.3 (-3.6 to 0.9)	1.2 (-1.3 to 3.6)	8.8 (3.6 to 14.0)	3.8 (-8.5 to 16.1)
Ongoing pregnancies	21 17 830	12 15 470	18 11 824	23 6824	28 2633	7 752
Neonatal death	12	15	12	10	5	3
Deliveries	1742	2611	4238	5141	2581	751



Risk difference/1000 pregnancies (95% CI)	34+0-6	35+0-6	36+0-6	37+0-6	38+0-6
Stillbirth	-15.6 (-40.4 to 9.1)	-2.4 (-17.6 to 12.8)	-1.5 (-14.4 to 11.4)	2.5 (-12.4 to 17.4)	7.0 (-19.7 to 33.7)
Ongoing pregnancies	2 49	5 1797	6 1325	7 730	2 264
Neonatal death	4	2	3	4	0
Deliveries	247	367	534	532	307

C.8 Oligohydramnios

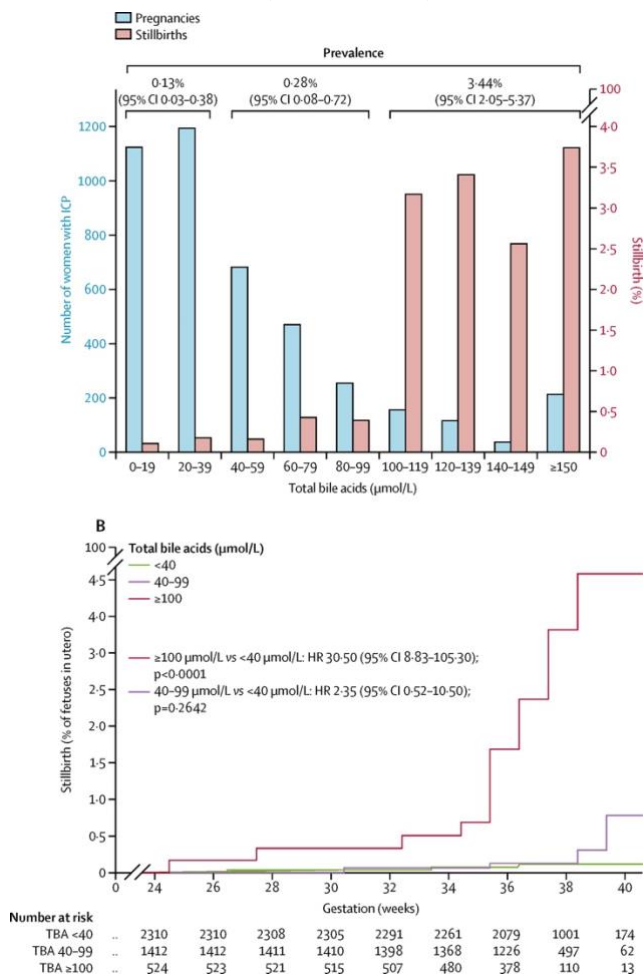
A systematic review of 15 observational studies (n=35,593 women) reported on adverse pregnancy outcomes in singleton pregnancies diagnosed with oligohydramnios (defined as amniotic fluid index (AFI) < 5cm) (Rabie 2017). For the six low risk of bias studies, women with isolated oligohydramnios had higher risk of caesarean section for fetal distress (RR 2.16; 95% CI 1.64 to 2.85) and higher NICU admission (RR 1.71; 95% CI, 1.20 to 2.42) compared to normal AFI. In women with oligohydramnios in the setting of co-morbidities, there was no difference in 5-min Apgar score <7 (RR 1.85; 95% CI, 0.69 to 4.96), admission to NICU (RR, 2.09; 95% CI 0.80 to 5.45) or caesarean section for fetal distress (RR 1.65; 95% CI 0.81 to 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 to 31.26); and in a subset of high-risk women, an association between oligohydramnios and perinatal death (OR 11.54, 95% CI 4.05 to 32.9). The authors of the review noted that despite increased risk for poor outcomes, oligohydramnios was not a predictor for individual risk.

C.9 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 IPD) 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 AST, ALT or bilirubin.

Figure 6: Risk of perinatal death by gestational age and bile salt concentration in women with obstetric cholestasis (Ovadia 2019)



C.10 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 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 to 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 were at an increased risk of a stillbirth in their second pregnancy (OR 4.77, 95% CI 3.70 to 6.15). The pooled odds ratio using the adjusted effect measures from the primary studies was 3.38 (95% CI 2.61 to 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 were OR 3.10 (95% 0.98 to 9.76), and aOR 1.0 (95% CI 0.23 to 4.30). A retrospective analysis looked at the risk of unexplained stillbirth after any previous stillbirth; the reported risk was aOR 4.18 (95% 1.36 to 12.89). The final study reported the adjusted risk for unexplained stillbirth after any stillbirth as aOR 3.20 (95% CI 1.59 to 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 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 previously experienced a single exposure, but increased when two prior adverse outcomes were combined. The risk of stillbirth varied with prematurity, increasing three-fold following preterm birth <34 weeks' gestation (pooled OR 2.98; 95% CI 2.05 to 4.34) and six-fold following preterm SGA <34 weeks' gestation (pooled OR 6.00; 95% CI 3.43 to 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

D.1 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 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 rate 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 caused less uterine hyperstimulation with FHR changes compared to vaginal misoprostol.

D.2 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 pre-term). 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 micrograms) 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 micrograms) compared with placebo was most likely to increase the odds of uterine hyperstimulation. For other safety outcomes there were insufficient data, or there was too much uncertainty, to identify which treatments performed 'best'. Data for 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 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 of a pharmacy. It is anticipated that misoprostol suspension will be required out of hours when pharmacy-based preparation is not available.

Method A₁

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
<p>Preparation instruction:</p> <ul style="list-style-type: none"> • 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 that 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: <ol style="list-style-type: none"> 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 prior to 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. 	

Method B₂

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 instruction:

- 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 that 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 name, etc.).
 13. Shake the syringe well immediately prior to administering the dose.
 14. Discard the unneeded misoprostol suspension remaining in the medicine measure and the 20 mL oral syringe. Discard the gloves.

1. Based on the method developed by MidCentral hospital pharmacy service. To facilitate the preparation of the misoprostol suspension, MidCentral hospital pharmacy provide a 'Misoprostol Kit for Induction of Labour' with enough components for six doses. Unused components are returned for re-use in a new kit.
2. Adapted from the method used reported in Winnipeg Regional Health Authority: Winnipeg Regional Health Authority. Clinical Practice Guideline: Induction and Augmentation of Labour and Cervical Ripening of Labour. November 2016, revised March 2017.

REFERENCES

ACOG Committee Opinion Summary. No. 764. Medically indicated late-preterm and early-term deliveries. *Obstet Gynecol.* 2019; 133(2):400-402.

ACOG Practice Bulletin No. 107: Induction of labor. *Obstet Gynecol.* 2009;114(2):386-397.

ACOG Practice Bulletin No. 201: Pre-gestational Diabetes Mellitus. *Obstet Gynecol.* 2018; 132: e228-e248.

Alberico S, Erenbourg A, Hod M, et al. Immediate delivery or expectant management in gestational diabetes at term: the GINEXMAL randomised controlled trial. *BJOG.* 2017;124:669–677.

Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD001338. DOI: 10.1002/14651858.CD001338.pub3.

Alfirevic, Z., Keeney, E., Dowswell, T., Welton, N.J., Dias, S., Jones, L.V., Navaratnam, K., Caldwell, D.M. Labour induction with prostaglandins: a systematic review and network meta-analysis. *BMJ.* 2015;350:h217

Alfirevic Z, Keeney E, Caldwell D, Welton N, Medley N, Dias S, et al. Which method is best for induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis. *Health Technol Assess* 2016;20(65)

Alfirevic Z, Kelly A, Dowswell T. Intravenous oxytocin alone for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews.* 2009. Issue 4, Art.No.:CD003246.

Auckland District Health Board. 2017. National Women’s Annual Clinical Report 2016. Auckland, ADHB.

Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal Body Mass Index and the Risk of Fetal Death, Stillbirth, and Infant Death A Systematic Review and Meta-analysis. *JAMA.* 2014;311(15):1536–1546. doi:10.1001/jama.2014.2269

Berndl A, El-Chaar D, Murphy K, Macdonald S. Does cervical ripening at term using a high volume foley catheter result in a lower caesarean section rate than a low volume foley catheter? A systematic review and meta-analysis. *J Obstet Gynaecol Can.* 2014;36(8):678–687.

Berry M, Foster T, Rowe K, et al. Gestational Age, health and educational outcomes in adolescents. *Pediatrics.* 2018;142 (5):e20181016.

Bhandari S, Raja EA, Shetty A, Bhattacharya S. Maternal and perinatal consequences of antepartum haemorrhage of unknown origin. *BJOG* 2014;121:44–52.

Biem SRD, Turnell RW, Olatunbosun O, Tauh M, Biem HJ. A randomized controlled trial of outpatient versus inpatient labour induction with vaginal controlled-release prostaglandin-E2: effectiveness and satisfaction. *J Obstet Gynaecol Can.* 2003;25(1):23-31.

Biesty LM, Egan AM, Dunne F, Dempsey E, Meskell P, Smith V, Ni Bhuinneain GM, Devane D. Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants. *Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD012910. DOI: 10.1002/14651858.CD012910

Biesty LM, Egan EM, Dunne F, Smith V, Meskell P, Dempsey E, Bhuienneian GM, Devane D. Planned birth at or near term for improving health outcomes for pregnant women with pre-existing diabetes and their infants. *Cochrane Database of Systematic Reviews*. 2018. Issue 2, Art.No.:CD012948.

Boers K E, Vijgen S M C, Bijlenga D, van der Post J A M, Bekedam D J, Kwee A et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). *BMJ* 2010; 341:c7087.

Bond DM, Gordon A, Hyett J, de Vries B, Carberry AE, Morris J. Planned early delivery versus expectant management of the term suspected compromised baby for improving outcomes. *Cochrane Database of Systematic Reviews*. 2015. Issue 11.Art.No.:CD009433. DOI: 10.1002/14651858.CD009433.pub2.

Boulvain M, Irion O, Dowswell T, Thornton JG. Induction of labour at or near term for suspected fetal macrosomia. *Cochrane Database of Systematic Reviews* 2016, Issue 5.Art.No.:CD000938. DOI: 10.1002/14651858.CD000938.pub2.

Boulvain M, Senat MV, Perrotin F, Winer N, Beucher G, Subtil D, et al. Induction of labour versus expectant management for large-for-date fetuses: a randomised controlled trial. *Lancet* 2015;385(9987):2600–5.

Boulvain M, Stan CM, Irion O. Membrane sweeping for induction of labour. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD000451. DOI: 10.1002/14651858.CD000451.pub2.

Broekhuijsen K, van Baaren G-J, van Pampus M-G, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label randomised controlled trial. *Lancet*. 2015;385:2492-501.

Brown HK, Speechley KN, et.al. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. *Int J Epidemiol*. 2013: 1-13

Budden et al. High vs Low dose oxytocin for induction of labour. *Cochrane Database of Systematic Reviews*. 2014.

Caughey AB, Sundaram V, Kaimal AJ, Cheng YW, Gienger A, Little SE, Lee JF, Wong L, Shaffer BL, Tran SH, Padula A, McDonald KM, Long EF, Owens DK, Bravata DM. Maternal and neonatal outcomes of elective induction of labor. *Evid Rep Technol Assess (Full Rep)*. 2009;(176):1-257.

Center for Maternal and Child Enquiries, Royal College of Obstetricians and Gynaecologists. CMACE and RCOG Joint Guideline - Management of Women with Obesity in Pregnancy. 2010

Chappell LC, Gurung V, Seed PT, Chambers J, Williamson C, Thornton JG. Ursodeoxycholic acid versus placebo, and early term delivery versus expectant management, in women with intrahepatic cholestasis of pregnancy: semifactorial randomised clinical trial. *BMJ* 2012;344:e3799.

Chatfield J. ACOG issues guidelines on fetal macrosomia. American College of Obstetricians and Gynecologists. *Amer Fam Phys* 2001;64(1):169-70.

Chen I, Opiyo N, Tavender E, et al. Non-clinical interventions for reducing unnecessary caesarean section. *Cochrane Database of Systematic Reviews* 2018, Issue 9. Art. No.: CD005528. DOI: 10.1002/14651858.CD005528.pub3.

Chen W, Xue J, Peprah MK, Wen SW, Walker M, Gao Y, Tang Y. A systematic review and network meta-analysis comparing the use of Foley catheters, misoprostol, and dinoprostone for cervical ripening in the induction of labour. *BJOG*. 2016; 123(3):346-54. doi: 10.1111/1471-0528.13456.

Cheong-See Fiona, Schuit Ewoud, Arroyo-Manzano David, Khalil Asma, Barrett Jon, Joseph K S et al. Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. *BMJ* 2016; 354 :i4353

Cluver C, Novikova N, Koopmans CM, West HM. Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD009273. DOI: 10.1002/14651858.CD009273.pub2.

Coates, R., Cupples, G., Scamell, A., & McCourt, C. (2019). Women's experiences of induction of labour: Qualitative systematic review and thematic synthesis. *Midwifery*, 69, 17-28. doi:10.1016/j.midw.2018.10.013

Darlow B, Campbell N, Austin N, Chin A, Grigg C, Skidmore C, Voss L, Walls T, Wise M, Werno A. The prevention of early-onset neonatal group B streptococcus infection: New Zealand Consensus Guidelines 2014. *N Z Med J*. 2014; 128:69-76.

Darney BG, Snowden JM, Cheng YW, Jacob L et al. Elective Induction of Labor at Term Compared With Expectant Management: Maternal and Neonatal Outcomes. *Obstet Gynecol*. 2013;122(4):761–9.

Dodd et al. Elective birth at 37 weeks' gestation for women with an uncomplicated twin pregnancy. *Cochrane Database of Systematic Reviews*. 2014; 2. Art. No.: CD003582.

Dodd J, Crowther C, Haslam R, Robinson J, for the Twins Timing of Birth Trial Group. Elective birth at 37 weeks of gestation versus standard care for women with an uncomplicated twin pregnancy at term: the Twins Timing of Birth Randomised Trial. *Brit J Obstet Gynaecol* 2012;119(8):964-74.

Dos Santos F et al. Development of a core outcome set for trials on induction of labour: an international multistakeholder Delphi study. *BJOG*. 2018; 125 (13):1673-1680.

Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, Kroll J, Jones RL, Sibley CP, Frøen JF, Heazell AEP. Prediction of poor perinatal outcomes after maternal perception of reduced fetal movements - a prospective cohort study. *PLoS One*. 2012; 7: e39784.

Eikelder M, et al. Induction of labour at term with oral misoprostol versus a Foley catheter (PROBAAT-II): a multicentre randomised controlled non-inferiority trial. *Lancet*. 2016. 16;387(10028):1619-28. doi: 10.1016/S0140-6736(16)00084-2.

Elwyn G, Frosch D, Volandes AE, et al. Investing in Deliberation: A Definition and Classification of Decision Support Interventions for People Facing Difficult Health Decisions. *Med Decis Making* 2010; 30(6): 701–11.

Farry A, Mellor C. HALO Tool - Artificial Rupture of Membranes [Poster]. Retrieved from <https://www.v2.i3-uat.nz/our-work/resources/halo-tool-artificial-rupture-of-membranes-poster/> 2008.

Fitzgerald O, Paul RC, Harris K, Chambers GM 2018. Assisted reproductive technology in Australia and New Zealand 2016. Sydney: National Perinatal Epidemiology and Statistics Unit, the University of New South Wales Sydney

Fitzpatrick KE, Kurinczuk JJ, Alfirevic Z, Spark P, Brocklehurst P, et al. (2012) Uterine Rupture by Intended Mode of Delivery in the UK: A National Case-Control Study. *PLoS Med* 9(3): e1001184. doi:10.1371/journal.pmed.1001184

Flenady et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet*. 2011; 377:1331-1340.

Gagnon-Gervais K, Bujold E, Iglesias M, Duperron L, Masse A, Mayrand M, Sansregret A, Fraser W, Audibert F. Early versus late amniotomy for labour induction: a randomized controlled trial. *J Mat-Fet Neonat Med*. 2012;11: 2326-2329.

Gardener G, Daly L, Bowring V, Burton G, Chadha Y, Ellwood D, Frøen F, Gordon A, Heazell A, McDonald S, Mahomed K, Norman JE, Oats J, Flenady V. Clinical practice guideline for the care of women with decreased fetal movements. Centre of Research Excellence in Stillbirth. Brisbane, Australia, August 2017.

Gibbs Pickens et al. Term elective induction of labour and pregnancy outcomes among obese women and their offspring. *Obstet Gynaecol*. 2018;131:12-22.

Gibson K, Waters T. Measures of success: Prediction of successful labor induction. *J Perinatol*. 2018; 38:217-225

Gibson KS, Waters TP, Bailit JL. Maternal and neonatal outcomes in electively induced low-risk term pregnancies. *Am J Obstet Gynecol*. 2014;211:249e1-16.

Gold RB. Guarding against coercion while ensuring access: a delicate balance. *Guttmacher Policy Review*. 2014;17(3).

Grobman et al. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. *NEJM*. 2018; 379:513-523

Gülmezoglu AM, Crowther CA, Middleton P, Heatley E. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database of Systematic Reviews* 2012, Issue 6. Art. No.: CD004945. DOI: 10.1002/14651858.CD004945.pub3.

Gurung V, Stokes M, Middleton P, Milan SJ, Hague W, Thornton JG. Interventions for treating cholestasis in pregnancy. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD000493. DOI: 10.1002/14651858.CD000493.pub2.

Guyatt G, Oxman A, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008; 336: 924-926. <https://doi-org.ezproxy.auckland.ac.nz/10.1136/bmj.39489.470347.AD>

Henderson CE, Shah RR, Gottimukkala S, et al. Primum non nocere: how active management became modus operandi for intrahepatic cholestasis of pregnancy. *Am J Obstet Gynecol* 2014

Hildingsson I, Karlstrom A, Nystedt A. Women's experiences of induction of labour--findings from a Swedish regional study. *Aust N Z J Obstet Gynaecol* 2011; 51(2): 151-157.

Hirst et al. The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from the INTERGROWTH-21st Project. *BJOG*. 2018;125(9):1145-1153

Hofmeyr GJ, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD000941. DOI: 10.1002/14651858.CD000941.pub2.

Howarth G, Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour. *Cochrane Database of Systematic Reviews* 2001, Issue 3. Art. No.: CD003250. DOI: 10.1002/14651858.CD003250.

Jay A, Thomas H, Brooks F. (2018 A). Induction of labour: How do women get information and make decisions? Findings of a qualitative study. *Br J Midwifery*, 26(1); 22-29.

Jay A, Thomas H, Brooks F. (2018 B). In labor or in limbo? The experiences of women undergoing induction of labor on hospital: Findings of a qualitative study. *Birth*. 45(1): 64-70. doi:10.1111/birt.12310Epub2017Sep17

Jozwiak M, Bloemenkamp KWM, Kelly AJ, Mol BWJ, Iriion O, Boulvain M. Mechanical methods for induction of labour. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No.: CD001233. DOI: 10.1002/14651858.CD001233.pub2.

Jozwiak M, Rengerink KO, Bentherm M, et al. Foley catheter versus vaginal prostaglandin E2 gel for induction of labour at term (PROBAAT trial): an open-label randomised controlled trial. *Lancet* 2012;378:2095-103.

Kelly AJ, Alfirevic Z, Ghosh A. Outpatient versus inpatient induction of labour for improving birth outcomes. *Cochrane Database of Systematic Reviews* 2013, Issue 11

Kenyon AP, Girling JC on behalf of the Royal College of Obstetricians and Gynaecologists. Obstetric Cholestasis; Green-Top Guideline No. 43. 2011: e1-e14.

Keulen JKJ, Bruinsma A, Kortekaas JC, van Dillen J, Bossuyt PMM, Oudijk MA et al. Induction of labour at 41 weeks versus expectant management until 42 weeks (INDEX): multicentre, randomised non-inferiority trial. *BMJ*. 2019; 364: I344

Kilby MD, Bricker L on behalf of the Royal College of Obstetricians and Gynaecologists. Management of monochorionic twin pregnancy. *BJOG*. 2016; 124: e1-e45

Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label, randomised controlled trial. *Lancet*. 2009; 374:979-98.

Lamont K, Scott NW, Jones GT, Bhattacharya S. Risk of recurrent stillbirth: A systematic review and meta-analysis. *BMJ*. 2015;350:h3080.

Lean et al. Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis. *PLoS One*. 2017;12: e0186287.

Lee et al. Term elective induction of labour and perinatal outcomes in obese women: retrospective cohort study. *BJOG*. 2016; 123:271-278.

Levy, R. , Ferber, A. , Ben-Arie, A. , Paz, B. , Hazan, Y. , Blickstein, I. and Hagay, Z. J. A randomised comparison of early versus late amniotomy following cervical ripening with a Foley catheter. *BJOG: An Int J Obstet Gynaecol*. 2002; 109: 168-172. doi:[10.1111/j.1471-0528.2002.01137.x](https://doi.org/10.1111/j.1471-0528.2002.01137.x)

Liu J, Song G, Meng T *et al*. Membrane sweeping added to formal induction method to increase the spontaneous vaginal delivery: a meta-analysis. *Arch Gynecol Obstet*. 2018;297: 623. <https://doi.org/10.1007/s00404-017-4643-y>

MacDorman MF, Reddy UM, Silver RM. Trends in Stillbirth by Gestational Age in the United States, 2006-2012. *Obstet Gynecol*. 2015;126:1146-1150

Mackay DF, Smith GCS, Dobbie R, Pell JP. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 school children. *PLOS*. 2010; 7(6)

Macones GA, Cahill A, Stamilio DM, Odibo AO. The efficacy of early amniotomy in nulliparous labor induction: a randomized controlled trial. *Am J Obstet Gynecol*. 2012; 403e.1-403.e5.

Majeed A, Kundu S, Singh P. Study on induction of labour versus expectant management in gestational hypertension or mild preeclampsia after 36 weeks of gestation. *BJOG: Int J Obstet Gynaecol* 2014;121(Suppl 2):118.

Makarem MH, Zahran KM, Abdellah MS, Karen MA. Early amniotomy after vaginal misoprostol for induction of labor: a randomized clinical trial. *Arch Gynecol Obstet*. 2013; 288:261–265.

Malacova E, Regan A, Nassar N, Raynes-Greenow C, Leonard H, Srinivasjois R, Shand A, Lavin T, Pereira G. Risk of stillbirth, preterm delivery, and fetal growth restriction following exposure in a previous birth: systematic review and meta-analysis. *BJOG* 2018;125:183–192.

McCarthy CM, Meaney S, O'Donoghue K. Perinatal outcomes after reduced fetal movements: a cohort study. *BMC Preg Childbirth*. 2016;16:169.

McCowan L, Thompson J, Cronin R, et al. Going to sleep in the supine position is a modifiable risk factor for late pregnancy stillbirth; Findings from the New Zealand multicentre stillbirth case-control study. *PLoS One* 2017; 12: e0179396.

McElduff A, Cheung NW, McIntrye HD, Lagström JA, Oats JJN, Ross GP, Simmons D, Walters BNJ, Wein P. The Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy. *MJA*. 2005; 138: 373-377.

Middleton P. et al. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). *Cochrane Database of Systematic Reviews*. 2017. <http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD005302.pub3/full>

Middleton P, Shepherd E, Crowther CA. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database Syst Rev*. 2018 May 9;5:CD004945. doi: 10.1002/14651858.CD004945.pub4.

Ministry of Health. 2012. Guidelines for Consultation with Obstetric and Related Medical Services (Referral Guidelines). Wellington: Ministry of Health.

Ministry of Health. 2019. Report on Maternity 2017. Wellington: Ministry of Health.

Ministry of Health. 2019. New Zealand Maternity Clinical Indicators 2017. Wellington: Ministry of Health.

Mishanina E, Rogozinska E, Thatthi T et al. Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. *Can Med Assoc J*. 2014. DOI:10.1503/cmaj.130925

Morris RK, Meller CH, Tamblyn J, Malin GM, Riley RD, Kilby MD, Robson SC, Khanh KS. Association and prediction of amniotic fluid measurements for adverse pregnancy outcome: systematic review and meta-analysis. *BJOG* 2014;121:686–699.

Moster D, Wilcox AJ, et al. Cerebral Palsy Among Term and Post-term Births. *JAMA* 2010; 304(9): 976-982.

Mundle S, et al. Foley catheterisation versus oral misoprostol for induction of labour in hypertensive women in India (INFORM): a multicentre, open-label, randomised controlled trial. *Lancet*. 2017. 12;390(10095):669-680. doi: 10.1016/S0140-6736(17)31367-3.

Murtagh M, Folan M. Women's experiences of induction of labour for post- date pregnancy. *Brit J Midwifery*. 2014;22(2): 105-110.

Nabhan AF, Abdelmoula YA. Amniotic fluid index versus single deepest vertical pocket as a screening test for preventing adverse pregnancy outcome. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD006593. DOI: 10.1002/14651858.CD006593.pub2.

National Institute for Health and Care Excellence. Induction of labour. NICE Clinical Guideline 70; 2008.

National Institute for Health and Care Excellence. Twin and triplet pregnancy. NICE guideline [NG137]. 2019.

National Institute of Health Care and Excellence. NICE Guideline NG3: Diabetes in pregnancy: management from preconception to the postnatal period; 2015.

New Zealand Maternal Fetal Medicine Network (NZMFM). Guideline for the management of suspected small for gestational age singleton pregnancies and pregnancies after 34 weeks' gestation. 2014.

New Zealand Maternal Fetal Medicine Network (NZMFM). Multiple Pregnancy. 2015.

New Zealand Ministry of Health. Diagnosis and treatment of hypertension and preeclampsia in pregnancy in New Zealand; a CPG. 2017. Wellington: New Zealand.

New Zealand Ministry of Health. Screening, diagnosis and management of Gestational Diabetes Mellitus in NZ; a CPG. 2014. Wellington: New Zealand.

Norman JE, *et al*. Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial. *Lancet*. 2018; 392: 1629-1638

Ovadia et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. *Lancet*. 2019; 393: 899-909.

Owens MY, Thigpen B, Parrish MR, Keiser SD, Sawardecker S, Wallace K, et al. Management of preeclampsia when diagnosed between 34-37 weeks' gestation: deliver now or deliberate until 37 weeks? *J Mississippi State Med Assoc*. 2014;55(7):208-11.

Pandey et al. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update*. 2012; 18: 485-503.

Petrini et al. Increased risk of adverse neurological development for late preterm infants. *J Pediatr*. 2009; 154: 169-76

PMMRC. 2017. Eleventh Annual Report of the Perinatal and Maternal Mortality Review Committee: Reporting mortality 2015. Wellington: Health Quality & Safety Commission.

PMMRC. 2018. Twelfth annual report of the Perinatal and Maternal Mortality Review Committee. Reporting mortality 2016. Health, Quality and Safety Commission. Wellington: New Zealand.

Puljic, *et al*. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. *Am J Obstet Gynaecol*. 2015. <https://doi.org/10.1016/j.ajog.2015.02.012>

Qaseem A, Forland F, Macbeth F. et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med.* 2012; 156: 525-531.

Rabie N, Magann E, Steelman S, Ounpraseuth S. Oligohydramnios in complicated and uncomplicated pregnancy: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2017; 49: 442-449.

Reddy et al. Maternal age and the risk of stillbirth throughout pregnancy in the United States. *Am J Obstet Gynecol.* 2006; 195:764-770

Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Maternal Group B Streptococcus in pregnancy: screening and management. 2016.

Royal College of Obstetricians and Gynaecologists. Obstetric Cholestasis; Green-top Guideline No. 43. 2011.

Ryan G, Oskamp M, Seaward PGR, Barrett J, Barrett H, O'Brien K, et al. Randomized controlled trial of inpatient vs. outpatient administration of prostaglandin E2, gel for induction of labour at term [SPO Abstract 303]. *Am J Obstet Gynecol.* 1998; 178(1 Pt 2): S92.

Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet.* 2008; 371 (9608): 261-9

Salemi JL, Pathak EB, Salihu HM. Infant outcomes after elective early-term delivery compared with expectant management. *Obstet Gynecol.* 2016; 127: 657–66.

Salim R, Schwartz N, Zafran N, Suarez-Easton S, Garmi G, Romano S. Comparison of single and double balloon catheters for labour induction: a meta-analysis and systematic review of randomised controlled trials. *J Perinatol.* 2018; 38: 217-225.

Sanchez-Ramos L, Olivier F, Delke I et al. Labor Induction Versus Expectant Management for Postterm Pregnancies: A Systematic Review With Meta-analysis. *Obstet Gynecol.* 2003; 101: 1312–8.

Sandberg et al. Foley catheter for induction of labour filled with 30mL or 60mL: a randomised controlled trial. *Eur J Obstet Gynaecol Reprod Biol.* 2017; 211: 150-155.

Schwarz, C., Gross, M. M., Heusser, P., & Berger, B. (2016). Women's perceptions of induction of labour outcomes: Results of an online-survey in Germany. *Midwifery*, 35, 3-10. doi:10.1016/j.midw.2016.02.002

Sciscione AC, Muench M, Pollock M, Jenkins TM, Tildon-Burton J, Colmorgen GHC. Transcervical foley catheter for preinduction cervical ripening in an outpatient versus inpatient setting. *Obstet Gynecol.* 2001; 98: 751-6.

Sengupta S, Carrion V, et.al. Adverse neonatal outcomes associated with early term birth. *JAMA Pediatr.* 2013; 167(11): 1053-1059

Sharma PP, Salihu HM, Kirby RS. Stillbirth recurrence in a population of relatively low-risk mothers. *Paediatr Perinat Epidemiol.* 2007; 21(Suppl1): 24-30.

Snowden JM, Muoto I, Darney BG, Quigley B, Tomlinson MW, Neilson D, Friedman SA, Rogovoy J, Caughey AB. Oregon's Hard-Stop policy limiting elective early-term deliveries: association with obstetric procedure use and health outcomes. *Obstet Gynecol.* 2016; 128(6): 1389–1396.

Suzuki S, Otsubo Y, Sawa R, Yoneyama Y. Clinical trial of induction of labor versus expectant management in twin pregnancy. *Gynecol Obstet Investig.* 2000; 49: 24-7.

- Teixeira C, Lunet N, Rodrigues T, Barros H. The Bishop score as determinant of labour induction success: a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2012; 286: 739-753
- Thomas, J., Fairclough, A., Kavanagh, J., Kelly, A.J. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. *Cochrane Database of Systematic Reviews*. 2014; 6. Art. No.: CD003101
- Tita AT, et.al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *NEJM* 2009; 360(2): 111-120
- Vahratian A, Zhang J, Troendle JF, Sciscione AC, Hoffman MK. Labor progression and risk of caesarean delivery in electively induced nulliparas. *Obstet Gynecol*. 2005; 105: 698-704.
- Vaknin Z, Kurzweil Y, Sherman D. Foley catheter balloon vs locally applied prostaglandins for cervical ripening and labor induction: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2010; doi:10.1016/j.ajog.2010.04.038
- Veglia M, Cavallaro A, Papageorghiou A, Black R, Impey L. Small-for-gestational-age babies after 37 weeks: impact study of risk-stratification protocol. *Ultrasound Obstet Gynecol* 2018; 52: 66-71. doi:10.1002/uog.17544
- Vrouenraets F, Roumen F, Dehing C, van den Akker E, Aarts M, Scheve E. Bishop score and risk of caesarean delivery after induction of labor in nulliparous women. *Obstet Gynaecol*. 2005; 105:690-697.
- Walker et al. Randomised trial of labour induction in women 35 years of age or older. *NEJM*. 2016a; 34: 813-822
- Walker, et al. Induction of labour versus expectant management at term by subgroups of maternal age: an individual patient data meta-analysis. *Eur J Obstet Gynaecol Reprod Bio*. 2016b; 197: 1-5.
- Wennerholm U-B, Hagberg H, Brorsson B, Bergh C. Induction of labor versus expectant management for post-date pregnancy: Is there sufficient evidence for a change in clinical practice? *Acta Obstetrica et Gynecologica*. 2009; 88: 617.
- West HM, Jozwiak M, Dodd JM. Methods of term labour induction for women with a previous caesarean section. *Cochrane Database of Systematic Reviews* 2017, Issue 6. Art. No.: CD009792. DOI: 10.1002/14651858.CD009792.pub3.
- Wilkinson C, Bryce R, Adelson P, Coffey J, Coombas J, Ryan P, et al. Two center RCT of outpatient versus inpatient cervical ripening for induction of labour with PGE2. *Am J Obstet Gynecol*. 2012;206(Suppl 1):S137.
- Wilkinson *et al*. A randomised controlled trial of outpatient compared with inpatient cervical ripening with prostaglandin E2 (OPRA study). *BJOG*. 2015; 122: 94-104.
- Wilkinson C, Adelson P, Turnbull D. A comparison of inpatient with outpatient balloon catheter cervical ripening: a pilot randomized controlled trial. *BMC Preg Childbirth*. 2015;15:126. doi:10.1186/s12884-015-0550-z
- Yao *et al*. Obesity and the risk of stillbirth: a population-based cohort study. *Am J Obstet Gynecol*. 2014;210:457e.1-457e.9