Note:
This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant woman. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that Perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of PPG
The purpose of this guideline is to provide clinicians with information on how to induce labour using medical methods following diagnosis of an intrauterine fetal death after 28 weeks. It describes medical management for different clinical scenarios based on a woman’s obstetric history, medical history and her personal preferences.
## Medical Management of late IUFD

### Table: Medical methods for induction of labour after late IUFD

<table>
<thead>
<tr>
<th>Induction – no previous uterine surgery</th>
<th>Up to 34 weeks</th>
<th>Greater than 34 weeks</th>
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<tbody>
<tr>
<td>Mifepristone and misoprostol</td>
<td>Single dose 200 mg mifepristone</td>
<td>Single dose 200 mg mifepristone</td>
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<tr>
<td></td>
<td>After 36-48 hours, 200 micrograms misoprostol sublingually or vaginally every 3 hours until delivery</td>
<td>After 36-48 hours, 100 micrograms misoprostol sublingually or vaginally every 4 hours until delivery. 50 micrograms orally may be adequate beyond 36+0 weeks especially with favourable cervix</td>
</tr>
<tr>
<td></td>
<td>Consider alternatives if response (i.e. uterine contractility) is inadequate after a total of 1,200 micrograms misoprostol in 24 hours</td>
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<th>Misoprostol</th>
<th>Misoprostol</th>
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<tr>
<td></td>
<td>200 micrograms sublingually or vaginally every 3 hours until delivery</td>
<td>100 micrograms misoprostol sublingually or vaginally every 4 hours until delivery</td>
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<tr>
<td></td>
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<th>Cervical ripening (before ARM)</th>
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<td>Dinoprostone (PGE2)</td>
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<tr>
<td>Misoprostol contraindicated</td>
<td>Transcervical balloon catheter placement</td>
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<th>Oxytocin</th>
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<tr>
<td></td>
<td>High dose infusion regimen</td>
</tr>
<tr>
<td></td>
<td>Consider ARM after labour established</td>
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<th>Induction – previous uterine surgery</th>
<th>One Previous LSCS</th>
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<tbody>
<tr>
<td></td>
<td>1. Cervical ripening (before ARM)</td>
</tr>
<tr>
<td></td>
<td>Transcervical balloon catheter placement</td>
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<tr>
<td></td>
<td>Oxytocin</td>
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<tr>
<td></td>
<td>Conventional oxytocin regimen</td>
</tr>
<tr>
<td>Or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Misoprostol</td>
</tr>
<tr>
<td></td>
<td>50 micrograms sublingually or vaginally OR</td>
</tr>
<tr>
<td></td>
<td>25 micrograms orally* at every 4 hours until delivery</td>
</tr>
<tr>
<td></td>
<td>(maximum 300 micrograms in 24 hours)</td>
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</table>

<table>
<thead>
<tr>
<th>More than one Previous LSCS / atypical uterine scar</th>
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<tr>
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<td>Oxytocin</td>
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<tr>
<td>Conventional oxytocin regimen</td>
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*See Misoprostol- dosage and administration, page 10.
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Abbreviations

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<th>Definition</th>
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<tr>
<td>%</td>
<td>percent</td>
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<tr>
<td>+/-</td>
<td>Plus or minus</td>
</tr>
<tr>
<td>&gt;</td>
<td>Greater than</td>
</tr>
<tr>
<td>ARM</td>
<td>Artificial rupture of the membranes</td>
</tr>
<tr>
<td>DIC</td>
<td>Disseminated intravascular coagulopathy</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IOL</td>
<td>Induction of Labour</td>
</tr>
<tr>
<td>IUFD</td>
<td>Intrauterine fetal death</td>
</tr>
<tr>
<td>IU</td>
<td>International units</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilograms</td>
</tr>
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<td>LSCS</td>
<td>Lower segment caesarean section</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>microg</td>
<td>Micrograms</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitres</td>
</tr>
<tr>
<td>PGE₂</td>
<td>Prostaglandin E2 or dinoprostone</td>
</tr>
<tr>
<td>PO</td>
<td>Per oral</td>
</tr>
<tr>
<td>PV</td>
<td>Per vagina</td>
</tr>
<tr>
<td>SL</td>
<td>Sublingual</td>
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</tbody>
</table>

Introduction

The majority of women (over 90%) go into labour within three weeks of their baby dying in utero. The delay until the onset of labour is longer the earlier in pregnancy fetal death occurs. With an increasing delay there may be a progressive decline in platelets and fibrinogen levels increasing the risk of disseminated intravascular coagulopathy (DIC), but the latter is unlikely to occur within the first 5 weeks.

Medical Methods for Induction of Labour

Options for induction of labour at gestations > 28 weeks for intrauterine fetal death include:

- Prostaglandin analogue misoprostol alone or in combination with the anti-progesterone mifepristone
- Cervical ripening with dinoprostone (PGE₂), followed by ARM +/- oxytocin
- Cervical ripening with balloon catheter (Transcervical balloon catheter placement), followed by ARM +/- oxytocin
- High dose or conventional oxytocin infusion regimen

Mechanical methods of induction (e.g. Transcervical balloon catheter placement) may increase the risk of ascending infection in the presence of IUFD. Misoprostol alone or in combination with mifepristone or another prostaglandin analogue can be used for induction of labour following late intrauterine fetal death.
Misoprostol in combination with mifepristone is more likely to achieve successful vaginal delivery and is associated with a shorter induction to delivery interval\(^5,6\).

The average induction to delivery interval using a combination of mifepristone and misoprostol is 9.8 hours compared to 16.3 hours with misoprostol alone\(^5\).

The delay in initiation of induction to allow for effect of mifepristone may be unacceptable to some women and unsafe for others who are at risk of DIC or sepsis.

Misoprostol is more effective at achieving successful vaginal delivery and associated with shorter induction to delivery intervals than cervical priming with PGE\(_2\) followed by Oxytocin infusion\(^7,8,9\).

In women with no prior uterine surgery, induction of labour with misoprostol has a similar safety and side effect profile to PGE\(_2\) followed by oxytocin infusion\(^7,8,9\).

**Care of women with a history of uterine surgery**

There are no studies on the safety and effectiveness of induction of labour after IUFD in the third trimester in women with a caesarean scar (either one or more caesarean births)\(^3\).

Evidence regarding induction of labour with misoprostol in the second trimester in women with one previous caesarean scar has shown it to be effective but there have been conflicting findings regarding safety\(^16,17\).

Induction of labour with prostaglandins carries a higher risk of uterine rupture when compared to oxytocin\(^18,19\). It is for this reason that cervical ripening via mechanical dilatation (transcervical catheter) and uterine stimulation with oxytocin is generally recommended for induction of labour in women with a previous caesarean scar\(^12,20\).

While not without risk, induction of labour with low doses of misoprostol is thought to be safe and could be considered in a woman with one previous caesarean scar\(^3,21\).

There is no evidence regarding the safety and efficacy of induction of labour with IUFD in Women with two or more previous caesarean scars or atypical scars. These women should be advised that the safety of induction of labour is unknown\(^3\).

The maternal morbidity rates (hysterectomy, transfusion) in planned vaginal deliveries after two previous caesarean sections were only mildly increased compared to those with one prior caesarean section, and were comparable to the risks of undergoing a third (or more) caesarean section\(^20\).

Due to the higher rate of uterine rupture in women with 2 or more previous caesarean scars or atypical uterine scars, induction of labour with prostaglandins should be avoided and conventional rather than high dose oxytocin regime should be used.

The method and dose of induction agent/s in all cases of IUFD in a woman with a previous uterine scar should take into account the clinical circumstance and be determined in consultation with the obstetrician/consultant.

**Mifepristone (Mifepristone Linepharma\(^\text{®}\))**

Mifepristone is a steroid derived from norethisterone that acts by blocking the effects of progesterone, a hormone necessary for the continuation of a pregnancy\(^1\).

Mifepristone is anti-progesterone. Mifepristone sensitises the myometrium to prostaglandins, increases uterine contractility, and softens and dilates the cervix. It is not sufficient for medical termination of pregnancy when used on its own, but is effective when used synergistically with prostaglandins\(^4\).
In Australia, mifepristone has been approved by the Therapeutic Goods Administration (TGA) for: preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester general use.

Medical practitioners wishing to prescribe mifepristone and misoprostol must be registered with and certified by MS Health via the secure healthcare professional website www.ms2step.com.au. (for more information see Standards for the Management of Termination of Pregnancy in SA, www.sahealth.sa.gov.au/perinatal)

Note: Registered medical practitioners with a Fellowship of the Royal Australian New Zealand College Obstetricians Gynaecologists will not have to complete the training but are still required to register with MS Health as part of the medical termination of pregnancy Risk Management Plan.

Contraindications

- Pre-existing cardiac disease
- Renal or hepatic impairment
- Chronic adrenal failure
- Severe uncontrolled asthma
- Hereditary porphyria (disorder of enzymes in the haeme biosynthetic pathway that affects the skin, nervous system or both)
- Known sensitivity to mifepristone

Interactions

The following may interact with the action of mifepristone (note this list is not exhaustive):

- Erythromycin, rifampicin
- Itraconazole,
- Carbamazepine, phenytoin, phenobarbital
- St John’s Wort
- Grapefruit juice

The efficacy of long-term corticosteroids (including inhaled corticosteroids) may be reduced by mifepristone due to its anti-glucocorticoid activity.

Mifepristone and Misoprostol

Ensure that informed verbal consent is obtained and documented before commencing treatment

Give a single dose of oral mifepristone 200 mg following which a 36 to 48 hours interval is recommended before administration of misoprostol

The woman may go home (with medications for pain management and nausea and vomiting) with advice to return to the hospital after 48 hours for admission and misoprostol induction of labour (see below).

Side effects

- Uterine bleeding
- Gastrointestinal (nausea, vomiting, diarrhoea)
Misoprostol

Misoprostol is a synthetic prostaglandin E₁ analogue marketed for use in the prevention and treatment of peptic ulcer disease. Although not marketed for induction of labour, it is more effective for cervical ripening and induction than conventional methods. However, uterine hyperstimulation is more common¹⁰.

Sublingual / vaginal misoprostol produce uterine tone more rapidly than oral or buccal administration¹¹. Vaginal administration has a longer lasting effect on uterine tone than sublingual administration¹¹. Sublingual administration however, was found to be more successful at achieving vaginal delivery within 24 hours than vaginal administration¹².

From the limited data available, sublingual and vaginal misoprostol appear to be adequately effective¹².

Contraindications

> Known sensitivity to misoprostol or other prostaglandins

Side effects

Although there are relatively few side effects, the following may occur:

> Pyrexia
> Flushing and shivering
> Vomiting
> Diarrhoea
> Headache

Administer antiemetics, antipyretics as indicated with medical order

High doses of misoprostol can cause uterine hyperstimulation and uterine rupture⁸.

Seek medical review if:

> Temperature > 38° Celsius (may be a prostaglandin E effect or an indication of chorioamnionitis)
  - Chorioamnionitis (rising C - Reactive Protein, offensive / purulent vaginal discharge, maternal pulse > 100 bpm, uterine tenderness) requires antibiotic treatment. Give ampicillin 2 g IV initial dose, then 1g IV every 4 hours, gentamicin 5 mg / kg IV daily, metronidazole 500 mg IV every 12 hours, unless allergic to penicillin
  - If allergic to penicillin, give clindamycin 450 mg IV in 50 – 100 mL over at least 20 minutes every 8 hours OR lincomycin 600 mg IV in 100 mL over 1 hour every 8 hours AND gentamicin 5 mg / kg IV daily until delivery
  - Antipyretics such as paracetamol (1 g rectally) can be administered
> Abnormal abdominal pain or other symptoms of uterine rupture
> Dizziness
> Bronchospasm and collapse are rare but may occur when prostaglandins are administered to asthmatics.
Dosage and administration

Ensure informed verbal consent is obtained and documented

The available formulation of misoprostol is 200 micrograms tablets. The preferred route of administration is sublingual or vaginal.

> To administer a dose of 50-100 micrograms, the 200 microgram tablets can be divided in quarters or halved

> **Doses less than 50 micrograms need to be given orally.**

**Preparation of 25 micrograms for oral administration:**

1. Disperse a 200 microgram misoprostol tablet in 20 mL of water to make a 10 microgram/mL mixture (tablet may be crushed to aid dissolution)
2. Give the required dose immediately – dose is 2.5mL (25 micrograms)
3. Discard remainder of the solution. A new solution should be prepared for each dose.

Active management of third stage is recommended (e.g. with 10 IU oxytocin IM)

**Before 34⁺⁰ weeks of gestation**

Give 200 micrograms misoprostol sublingually or vaginally every 3 hours until delivery

Consider alternatives if response (i.e. uterine contractility) is inadequate after a total of 1,200 micrograms in 24 hours

> Alternatives may be to start regimen again after 24 hours, use of alternative prostaglandins, IUFD oxytocin regimen or surgical evacuation if uterine size and circumstances permit

**After 34⁺⁰ weeks**

Give 100 micrograms misoprostol sublingually or vaginally every 4 hours until delivery

At and beyond 36⁺⁰ weeks doses of 50 micrograms misoprostol orally have been found to be adequate¹³,¹⁴,¹⁵.

**One previous lower segment caesarean section**

Seek consultation with Obstetrician/consultant.

Give 25 micrograms orally every 4 hours (See Misoprostol – dosage and administration).

Assess effectiveness of contractions prior to administration of subsequent doses. Withhold further doses if uterine activity is adequate²¹.

Consider alternatives if response (i.e. uterine contractility) is inadequate after a total of 125 micrograms in 24 hours.

> Alternatives may be to start regimen again after 24 hours, conventional oxytocin regimen or surgical evacuation if uterine size and circumstances permit.

**Two or more previous lower segment caesarean sections / Atypical uterine scar.**

Avoid use of prostaglandins for induction of labour in these circumstances.
Observations

Perform the following observations before commencing procedure and hourly thereafter:

> Temperature
> Pulse
> Respiration
> Uterine activity
> Vaginal loss
> Record an accurate fluid balance chart if using oxytocin

Oxytocin

Exogenous oxytocin produces periodic uterine contractions. Myometrial responsiveness increases with advancing gestational age, from approximately 20 weeks until 34 weeks, at which time it levels off\(^2^2\). Oxytocin has been found to be less effective than misoprostol with a longer induction to delivery interval\(^7\). It should therefore be reserved for cases where misoprostol has been unsuccessful, is contraindicated or in the cases of previous uterine scar.

No previous uterine surgery

High dose infusion regimen (see Oxytocin high dose regimen for intrauterine fetal death PPG, [www.sahealth.sa.gov.au/perinatal](http://www.sahealth.sa.gov.au/perinatal)), is associated with a higher rate of vaginal delivery and shorter induction to delivery interval without increase in maternal morbidity\(^2^3\).

Previous Uterine surgery

Conventional oxytocin regimen recommended to reduce the risk of uterine rupture associated with uterine hyperstimulation\(^2^3\).

If cervix not favourable, mechanical methods for cervical dilatation (e.g. transcervical balloon catheter) to be used prior to ARM.
References


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# Medical Management of late IUFD

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