South Australian Perinatal Practice Guidelines

Medical management of late intrauterine fetal death

Medical methods for induction of labour after late IUFD

	Up to 34 weeks	Greater than 34 weeks
Induction – no previous uterine surgery	**Misoprostol (Cytotec®)** > 200 micrograms sublingually or vaginally at 3 hourly intervals until delivery	**Misoprostol (Cytotec®)** > 100 micrograms misoprostol sublingually or orally at 4 hourly intervals until delivery > 50 micrograms orally may be adequate beyond 36^{+0} weeks especially with favourable cervix
	Consider alternatives if response (i.e. uterine contractility) is inadequate after a total of 1200 micrograms misoprostol in 24 hours	
	Mifepristone (Mifegyne®) and misoprostol (Cytotec®) > Single dose 200 mg mifepristone After 24-48 hours > 200 micrograms sublingually or vaginally at 3 hourly intervals until delivery	**Mifepristone (Mifegyne®) and misoprostol (Cytotec®)** > Single dose 200 mg mifepristone After 24-48 hours > 100 micrograms misoprostol sublingually or orallly at 4 hourly intervals until delivery > 50 micrograms orally may be adequate beyond 36^{+0} weeks especially with favourable cervix
	Consider alternatives if response (i.e. uterine contractility) is inadequate after a total of 1200 micrograms misoprostol in 24 hours	
	Cervical ripening (before ARM) > Dinoprostone (PGE_2) > Balloon catheter - Transcervical Foley catheter placement (see PPG 'IOL techniques/cervical ripening' for further information)	
	Syntocinon® > High dose infusion regimen (see PPG 'Syntocinon® high dose infusion regimen for IUFD')	**Syntocinon®** > Conventional Syntocinon® regimen > Consider ARM after labour established > (see in PPG 'Induction of labour techniques/intravenous oxytocin')
Induction – previous uterine surgery	**Discuss the dosage / regimen with the obstetrician / consultant if the woman has had previous uterine surgery**	

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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[1]. With an increasing delay there may be a progressive decline in platelets and fibrinogen levels increasing the risk of disseminated intravascular coagulopathy, but the latter is unlikely to occur within the first 5 weeks[2]

Medical methods

- 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 (PGE_2), followed by ARM +/- Syntocinon®
  - Cervical ripening with balloon catheter (Transcervical Foley catheter placement), followed by ARM +/- Syntocinon®
  - High dose Syntocinon infusion regimen
- Mechanical methods of induction (e.g. Transcervical Foley catheter placement) may increase the risk of ascending infection in the presence of IUFD[5]
- Misoprostol alone or in combination with mifepristone or another prostaglandin (analogue) can be used for induction of labour following late intrauterine fetal death[3]
- The average induction to delivery interval using a combination of mifepristone and misoprostol is 8.5 hours[4]

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 women with a caesarean scar (either one or more caesarean births)[5]
- The method and / or dose of induction agent/s should take into account the clinical circumstances, availability of preparations and local guidelines and be determined in consultation with the obstetrician / consultant. It would be wise to use the lower dose regimens
- Women with a single lower segment scar should be advised that, in general, induction of labour with prostaglandin is safe but not without risk[5]
- Women with two previous LSCS should be advised that, in general, the absolute risk of induction of labour with prostaglandin is only a little higher than for women with a single previous LSCS[5]
- Women with more than two LSCS deliveries or atypical scars should be advised that the safety of induction of labour is unknown[5]

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Mifepristone (Mifegyne®)

- Mifepristone is a steroid derived from norethisterone that acts by blocking the effects of progesterone, a hormone necessary for the continuation of a pregnancy[3]
- 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[3]
- In Australia, mifepristone has not been approved for general use by the Therapeutic Goods Administration (TGA). Practitioners may apply for authorised prescriber status (section 19 [5] of the Therapeutic Goods Act 1989) or on a case by case basis through the Special Access Scheme (SAS)[6]
- The administration of mifepristone must be carried out by the nominated practitioner to the consented patient as specified on the SAS Category B Form[6]

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

Precautions

The following may interact with the action of mifepristone:

- Erythromycin, rifampicin
- Ketoconazole,
- Carbamazepine, Phenytoin, phenobarbitol
- Corticosteroids
- St John's Wort
- Grapefruit juice

Mifepristone (Mifegyne®) and misoprostol (Cytotec®)

- Ensure that informed verbal consent is obtained and documented before commencing treatment
- Give a single dose of oral mifepristone 200 mg following which a 24 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 (mifepristone)

- Uterine bleeding and gastrointestinal (nausea, vomiting, diarrhoea)

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Misoprostol (Cytotec®)

- Misoprostol is a synthetic prostaglandin E_1 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 common[7]
- Oral and sublingual Misoprostol produce uterine action more rapidly than vaginal administration. Sublingual (also known as buccal) administration also achieves higher serum concentrations because it avoids the first pass intestinal-hepatic circulation[8]
- From the limited data available, sublingual and oral misoprostol appear to be equally effective[7]

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 rupture[7]

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 lincomycin 600 mg IV in 100 mL over 1 hour every 8 hours or clindamycin 450 mg IV in 50 – 100 mL over at least 20 minutes until delivery
  - Antipyretics such as Panadol (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

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Dosage and administration

- Ensure that informed verbal consent is obtained and documented
- The available dose of misoprostol is 200 micrograms. To administer a dose of 100 micrograms, the 200 microgram tablets can be divided in half or dissolved in water **by pharmacists** and administered as measured aliquots prepared[5]
    - The preferred route of administration is sublingual, however, doses < 100 micrograms may need to be given orally
- Active management of third stage is recommended (e.g. with 10 IU Syntocinon® IV)

Before 34^{+0} weeks of gestation

- Give 200 micrograms misoprostol sublingually or vaginally at 3 hourly intervals until delivery
- Consider alternatives if response (i.e. uterine contractility) is inadequate after a total of 1200 micrograms in 24 hours
    - Alternatives may be to start regimen again after 24 hours, use of alternative prostaglandins, IUFD Syntocinon® regimen or surgical evacuation if uterine size and circumstances permit
- Doses of 400 micrograms may be needed under 24 weeks of gestation
- Discuss the dosage with a consultant if the woman has a history of uterine surgery

After 34^{+0} weeks

- Give 100 micrograms misoprostol sublingually or orally at 4 hourly intervals until delivery[11]
- Discuss the dosage with a consultant if the woman has a history of uterine surgery
- At and beyond 36^{+0} weeks doses of 50 micrograms misoprostol orally (prepared by the pharmacist) may be adequate especially in the presence of a favourable cervix.[11]

Observations

- Perform the following observations before commencing procedure and hourly thereafter:
    - Temperature
    - Pulse
    - Respirations
    - Uterine activity
    - Vaginal loss
    - Record an accurate fluid balance chart if using oxytocin

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Abbreviations

ACOG	American College of Obstetrics and Gynecology
bpm	Beats per minute
et al	And others
g	Gram(s)
i.e.	That is
IV	Intravenous
mg	Milligram(s)
mL	Millilitre(s)
IU	International units
IUFD	Intrauterine fetal death

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