Maternity - Tocolytic Agents for Threatened Preterm Labour Before 34 Weeks Gestation

Summary
Public Health Organisations are required to have procedures for the detection and management of threatened preterm labour before 34 weeks gestation, and to ensure that staff have the knowledge and skills necessary to implement the policy.

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Audience All clinicians working in maternity services; including Aboriginal Infant Health; Emergency Depts

Secretary, NSW Health
This Policy Directive may be varied, withdrawn or replaced at any time. Compliance with this directive is mandatory for NSW Health and is a condition of subsidy for public health organisations.
MATERNITY - TOCOLYTIC AGENTS FOR THREATENED PRETERM LABOUR BEFORE 34 WEEKS GESTATION

PURPOSE
This policy provides direction to NSW maternity services, clinicians and emergency patient transport services regarding the use of tocolytic agents for threatened preterm labour before 34 weeks gestation. Preterm birth remains a major cause of perinatal morbidity and mortality and this policy will help inform maternity care providers in the development and implementation of local clinical practice guidelines and protocols.

MANDATORY REQUIREMENTS
All NSW Public Health Organisations providing maternity services and all emergency patient transport services involved in obstetric transfers must have clinical practice guidelines and protocols for the use of tocolytic agents in threatened preterm labour before 34 weeks.

This policy should only be used in consultation with specialists who are familiar with the management of threatened and established preterm labour and the care of preterm infants.

IMPLEMENTATION
• Chief Executives of Local Health Networks are ultimately responsible for the implementation of this policy directive within the Network’s facilities.
• The Chief Executive of the Ambulance Service of NSW is responsible for the implementation of this policy directive in the NSW Ambulance Service.
• The NSW Aeromedical and Medical Retrieval Service (AMRS), a unit of the NSW Ambulance Service, provides statewide coordination of adult medical retrieval services for critically ill patients in collaboration with the Regional Retrieval Services. Similarly, the Regional Retrieval Services liaise with AMRS regarding all retrieval activity.

REVISION HISTORY

<table>
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<tr>
<th>Version</th>
<th>Approved by</th>
<th>Amendment notes</th>
</tr>
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<tr>
<td>May 2011 (PD2011_025)</td>
<td>Deputy Director-General Strategic Development</td>
<td>Updates and Replaces PD2005_249</td>
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</table>

ATTACHMENTS
1. Maternity – Tocolytic agents for threatened preterm labour before 34 weeks gestation: Procedures
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1 BACKGROUND

1.1 About this document
Preterm birth remains a major cause of perinatal morbidity and mortality\(^1\). Although preterm birth is defined as being birth before 37 weeks gestation, most mortality and morbidity is experienced by babies born before 34 weeks\(^2\). For many women in preterm labour it may not be appropriate to consider tocolysis, but where it is appropriate and safe to do so, tocolysis aims to delay preterm birth to allow time for in-utero transfer to a tertiary perinatal centre for multidisciplinary management, and/or maternal administration of corticosteroids to enhance fetal lung maturity.

It is outside of the scope of this document to discuss screening for risk factors associated with and/or prevention of preterm birth. It is also outside of the scope of this document to discuss the use of predictive tests for preterm labour. The resources available at individual sites will vary and if such screening or predictive tests are available at a particular site then these should be incorporated into local evidence-based clinical algorithms for the management of threatened preterm labour.

1.2 Related Documents
This Policy Directive should be read in conjunction with the following policy directives:

* PD2010_040 Maternity – Fetal Heart Rate Monitoring*
* PD2010_069 Critical Care Tertiary Referral Networks (Perinatal)*

1.3 Key definitions

**Preterm birth** means birth after 20 weeks and before 37 weeks gestation.

**Preterm labour** means labour that occurs after 20 weeks and before 37 weeks.

**Threatened preterm labour** means the presence of uterine activity (contractions) after 20 weeks and before 37 weeks gestation. Only a minority of women who present with preterm contractions will progress to actual labour and birth.

For the purposes of this document, the administration of tocolytic agents should be restricted to those pregnancies that are at a gestation where benefit may be gained by delaying preterm delivery to allow time for in-utero transfer to a tertiary perinatal centre for multidisciplinary management, and/or maternal administration of corticosteroids to enhance fetal lung maturity. Generally this is between 24 and 34 weeks gestation.

2 KEY POINTS

2.1 Tocolysis
The aim of tocolysis is to delay preterm birth to allow time for maternal administration of corticosteroids and in-utero transfer to a tertiary perinatal centre, thereby reducing neonatal morbidity and mortality. There is no clear evidence that tocolytic drugs in themselves improve outcomes following preterm labour\(^2\). The women most likely to benefit from tocolysis are those needing in-utero transfer to a tertiary perinatal centre and/or those who have not yet completed a full course of corticosteroids to promote fetal lung maturation. Discussions with women and their families should include these points.
2.1.1 Choice of tocolytic agent

Before pharmacotherapy with tocolytic agents was introduced, maternal bed rest, sedation or analgesia, and maternal hydration were used to reduce uterine activity. Maternal hydration promotes a diuresis by causing a reduction in vasopressin (antidiuretic hormone) secretion with less stimulation of V1a and oxytocin receptors for which there is crossover affinity. Alcohol, which inhibits both the secretion of oxytocin and vasopressin, was used until the 1980’s but had unacceptable maternal side-effects. β-sympathomimetic agents (β-agonists) were introduced in the 1980’s and became established as first line tocolytics. During the 1990’s there were increasing concerns about the potentially serious side-effects of β-agonists and other agents with tocolytic effect were explored. Currently there are a number of tocolytic agents in use each with differing strengths of evidence base for their safety and efficacy. There is insufficient evidence to recommend exclusive use of one tocolytic agent. Oxytocin receptor antagonists are not available for use in Australia. The tocolytic agents available in Australia are not utero-specific and as such have potential fetomaternal side-effects. Therefore the choice of tocolytic agent should be based on the available evidence base for efficacy and fetomaternal safety (table 1).

Table 1:

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Efficacy</th>
<th>Fetomaternal safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers (e.g. nifedipine)</td>
<td>No placebo-controlled trials. Randomised trials comparing nifedipine with ritodrine, magnesium sulphate and terbutaline. Meta-analyses show similar efficacy to ritodrine with decreased incidence of maternal side-effects.</td>
<td>Maternal flushing, headache, dizziness, nausea, transient hypotension, transient tachycardia, palpitations. Fetal hypoxia associated with maternal hypotension</td>
</tr>
<tr>
<td>β-agonists (e.g. salbutamol)</td>
<td>Randomised placebo-controlled trials. Efficacy demonstrated in a number of systematic reviews.</td>
<td>Maternal tachycardia, headache, palpitations, sweating, tremor, dyspnoea, cardiac arrhythmias, myocardial ischaemia, pulmonary oedema, hyperglycaemia, hypokalaemia. Tachycardia, hypoglycaemia in neonate</td>
</tr>
<tr>
<td>Nitric oxide donors (e.g. GTN patches)</td>
<td>Randomised placebo-controlled trial demonstrated that transdermal nitroglycerin may reduce neonatal morbidity and mortality as a result of decreased risk of birth before 28 weeks. However randomised trial comparing transdermal nitroglycerin and β2 sympathomimetics demonstrated GTN is a less efficacious tocolytic compared with β2 sympathomimetics.</td>
<td>Maternal headache, hypotension. Neonatal hypotension</td>
</tr>
<tr>
<td>Prostaglandin synthetase inhibitors (e.g. indomethacin)</td>
<td>Randomised placebo-controlled trials. Meta-analysis showing demonstrated efficacy and reduced maternal side-effects.</td>
<td>Maternal gastro-intestinal side-effects, renal impairment, headache, dizziness, depression. Fetus/neonate – constriction of ductus arteriosus, pulmonary hypertension, reversible decrease in renal function (oligohydramnios).</td>
</tr>
<tr>
<td>Magnesium sulphate</td>
<td>Two systematic reviews demonstrate magnesium sulphate to be ineffective as a tocolytic</td>
<td>Maternal flushing, sweating, nausea, loss of deep tendon reflexes, respiratory depression, bradycardia, myocardial depression, neuromuscular blockade.</td>
</tr>
</tbody>
</table>
Broadly speaking, there are 5 classes of tocolytic agents available in Australia currently: calcium channel blockers, ß-agonists, nitric oxide donors, prostaglandin synthetase inhibitors, and magnesium sulphate. The evidence to support the use of magnesium sulphate as a first line tocolytic is poor so it is not recommended for this purpose.

The use of ß-agonists (like salbutamol) or multiple tocolytics is associated with a high incidence of serious adverse drug reactions\(^5\). Both nitric oxide donors (like GTN patches) and prostaglandin synthetase inhibitors (like indomethacin) may have a role prior to 28 weeks gestation.

2.1.2 Preferred tocolytic - Nifedipine

Given the efficacy and fetomaternal safety of the various tocolytic agents currently available nifedipine appears to be the preferred tocolytic (see Appendix 1 for example administration protocol).

The use of nifedipine is well established in clinical practice across NSW having been approved for use through local Drug Committees.

**NOTE:** Tocolysis is not an approved indication for use for nifedipine. Prior to using any drug for an unapproved (off-label) indication, approval should be sought from the local hospital or Local Health Network Drug Committee and informed patient consent obtained. In the context of this Policy Directive, this means that any drug approvals required should be sought prior to an emergency - i.e. at the time of developing local hospital policies for tocolysis.

2.1.3 Combined tocolytics

The incidence of serious adverse drug reactions in women receiving combined courses of tocolytics is high (1.6 – 2.5\%)\(^5\). There is no evidence that treatment with combined tocolytics is superior to single or sequential treatment.

2.1.4 Maintenance tocolysis

There is insufficient evidence for any firm conclusions about whether or not maintenance tocolytic therapy following threatened preterm labour is worthwhile\(^6\). As such, maintenance therapy cannot be recommended for routine practice.

2.1.5 Contraindications to tocolysis

The administration of tocolytic agents should be restricted to those pregnancies that are at a gestation where benefit may be gained by delaying preterm delivery to allow time for in-utero transfer to a tertiary perinatal centre for multidisciplinary management and/or maternal administration of corticosteroids to enhance fetal lung maturity. Attempts at tocolysis are less likely to be successful with advanced cervical dilatation, particularly in the presence of ruptured membranes. The presence of certain maternal or fetal risk factors may make tocolysis unwise e.g. active bleeding, evidence of chorioamnionitis, documented intrauterine growth restriction.

Tocolysis is not indicated where delivery is required because of immediate risk to the life of mother or fetus. Tocolysis is not indicated where labour is advanced or where the fetus is sufficiently mature that the fetomaternal risks of tocolysis outweigh the benefits i.e. > 34 weeks gestation. Tocolysis is indicated where benefit may be gained by delaying preterm delivery to allow time for in-utero transfer to a tertiary perinatal centre
2.2 Diagnosis of threatened preterm labour

The diagnosis of suspected threatened preterm labour on clinical grounds should include uterine contractions that are painful, palpable, last more than 30 seconds and occur with a frequency of at least 2 every 10 minutes. There may or may not be evidence of cervical change (position, consistency, length or dilatation). Maternal anxiety often causes difficulty with the diagnosis and the absence of cervical change does not mean that the patient’s complaints of pain or the possibility that she is in early labour may be ignored.

On admission a thorough assessment must be made. This includes a detailed history, particularly with respect to uterine activity and any vaginal loss particularly in relation to rupture of the membranes and antepartum haemorrhage. The gestational age must be confirmed by the best available information. Maternal examination must include temperature, uterine tone and tenderness, and clinical assessment of liquor volume, fetal size and presentation.

A speculum examination should be performed utilising an aseptic technique. Genital tract swabs should be taken for microbiological assessment. Digital examination should be avoided unless the cervix cannot be adequately visualised.

Urine microbiology should be undertaken. Cardiotocography (CTG) should also be undertaken if appropriate for the period of gestation.

If the woman is admitted to a non-tertiary hospital and is less than 34 weeks gestation, consideration should be given to transfer. There is clear evidence that neonatal outcomes are improved with in-utero rather than ex-utero transfer. Hospitals must be appropriately networked so that in-utero transfer is both appropriate and timely. In-utero transfer should not be undertaken where there is significant risk of birth occurring during transfer. Consultation with a perinatal advisor through the NSW Newborn & Paediatric Emergency Transport Service (NETS) is available.

Corticosteroids should be administered to accelerate fetal lung maturation. If transfer is indicated because of significant uterine activity or if cervical change has been demonstrated then tocolysis should be commenced unless contraindicated. Abnormalities of the maternal or fetal condition that may contraindicate the use of tocolysis include antepartum haemorrhage, pre-eclampsia, chorioamnionitis, pathological fetal heart rate pattern. Intravenous antibiotics should be given to women with established preterm labour with significant urinary tract sepsis or overt sepsis.
2.3 Algorithm for tocolytic agent use for threatened preterm labour

Repeat cervical assessment prior to transfer should only be undertaken if the clinical condition changes or if uterine activity is unable to be suppressed by tocolysis.

**Maternal Assessment:**
History – check EDC, ? APH, ?PPROM
Examination – temperature, uterus, fetus, liquor
Speculum examination
+ Digital vaginal examination (if cervix not visualised)

**Microbiology:**
Lower genital tract swab
Mid stream urine

**Establish IV access and commence IV fluids. If no contraindication to tocolysis, then**

**Nifedipine protocol (Appendix 1).**

Contraindication to nifedipine or failed nifedipine tocolysis may need to consider alternate tocolytic agent (Appendix 2). Where in-utero transfer is required discussion regarding further tocolysis should occur with the Perinatal Advisor (available through NETS*).

*Any clinician can contact a perinatal advisor on the NETS Hot Line (1300 36 2500). Call cost are at local call rates from within Australia. Calls to the NETS Line are answered immediately. A list of options is presented and callers are reminded about the fact that calls to NETS are recorded. Option 1 (for emergency retrieval) is answered by the duty ’clinical coordinator’ who connects the caller (in conference mode) to the duty consultant and then other specialists as required.*
3 REFERENCES


4 LIST OF ATTACHMENTS

1. Appendix 1
2. Appendix 2
3. Implementation checklist.
4.1 Appendix 1: Nifedipine administration protocol - example

| Nifedipine Administration Protocol – Example |

**NOTE:**
- *Nifedipine carries the potential for fetal hypoxia associated with maternal hypotension.*
- *The blood pressure lowering effect of nifedipine may be potentiated by other antihypertensives.*
- *Do not use in women who are hypotensive or in women with established cardiac disease including conduction defects and left ventricular failure.*
- *Extreme caution should be exercised if Nifedipine and magnesium sulphate are used concomitantly.*

**PRESENTATION:**
20mg Tablets

**ADMINISTRATION:**
Nifedipine tablets should be swallowed whole. Dose may vary with clinical situation & should be titrated against tocolytic effect. Nifedipine is highly light sensitive.

**INITIAL DOSE:**
20mg Nifedipine orally stat (N.B. onset of tocolysis is at 30-60 minutes.)

**If uterine contractions persist after 30 minutes:**
Further 20mg Nifedipine orally may be given at 30 minute intervals for two further doses if required.

**If contractions cease:**
- A maintenance dose of 20 to 40mg Nifedipine 6 hourly may be given, depending on uterine activity and other clinical circumstances, to a maximum of 160mg in 24 hours
- Decisions about cessation of treatment will be on an individual basis and need to take into account location, steroid cover and gestational age

**MAXIMUM DOSE:**
160mg in 24 hours

**Side effects:**
- Hypotension, especially in hypertensive patients
- Tachycardia, palpitations
- Flushing
- Headaches, dizziness
- Nausea

**MATERNAL and FETAL OBSERVATION AND MONITORING:**
- Maternal blood pressure, temperature, pulse and respiratory rate hourly during the acute stabilisation phase. Observations may then be recorded less frequently but at least 4 hourly during treatment
- Report systolic BP less than 100 mmHg, temperature greater than 37.5 degrees Celsius or pulse greater than 100
- Report side effects listed above
- If initial cardiotocograph is reactive, record fetal heart rate hourly with doppler during the acute stabilisation phase, then at least 6 hourly for first 48 hrs

**Overdosage symptoms (observed in cases of severe nifedipine intoxication):**
- Disturbed consciousness to the point of coma
- A drop in blood pressure
- Tachycardic/bradycardic heart rhythm disturbances
- Hyperglycaemia
- Metabolic acidosis
- Hypoxia
- Cardiogenic shock with pulmonary oedema
### 4.2 Appendix 2: Salbutamol infusion protocol - example

<table>
<thead>
<tr>
<th><strong>Salbutamol Infusion Regimen – Example</strong></th>
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<tbody>
<tr>
<td><strong>NOTE:</strong></td>
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<tr>
<td>- To prevent hypotension due to aorto-caval compression, the patient should lie on her side during infusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PRESENTATION:</strong></th>
<th>Ventolin Obstetric 5mg ampoules (1mg per ml)</th>
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</thead>
<tbody>
<tr>
<td><strong>ADMINISTRATION:</strong></td>
<td>Salbutamol should be given by controlled infusion to control dose and fluid volume; a syringe or volumetric infusion pump is the equipment of choice. Caution is required when changing to Salbutamol from a vasodilator such as Nifedipine, which has a half-life of 6 to 12 hours. In these circumstances, frequent maternal and fetal observations (as described below) are required.</td>
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<tr>
<th><strong>DOSE:</strong></th>
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<tbody>
<tr>
<td>- Draw up 10ml (10mg) of Obstetric Salbutamol in a 10ml syringe</td>
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<tr>
<td>- Withdraw 10ml from a 100ml bag of Normal Saline and replace with the 10ml of Salbutamol. The resulting solution will contain 100 micrograms per ml</td>
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<tr>
<td>- Start the infusion at 6ml per hour</td>
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<tr>
<td>- Increase the rate by 3ml per hour every 10 minutes until there is a suitable response, either cessation of contractions or a reduction in frequency and strength of contractions</td>
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<tr>
<td>- Do not exceed 30ml per hour (equivalent to 50 micrograms per minute). However, the maximum dose is determined by the individual’s response and may be much less than this in some cases.</td>
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If maternal pulse greater than 140 bpm or sustained fetal tachycardia (greater than 180 bpm)

| • Slow infusion rate until pulse or fetal heart rate return below these levels |

**Side effects:**

| • Tremor, anxiety, nausea and palpitations are likely and the woman should be warned |
| • CEASE INFUSION if chest pain, dyspnoea or vomiting occurs |

If contractions cease

| • Maintain infusion rate for the next 6 hours and then reduce by 3 ml per hour each hour until a maintenance level is reached (3ml per hour) |
| • Decisions about cessation of treatment will be on an individual basis and need to take into account location, steroid cover and gestational age. |

**MATERNAL and FETAL OBSERVATION AND MONITORING**

| • Maternal blood pressure, pulse and respiratory rate following each increase in the infusion rate during the acute stabilisation phase. Observations may then be recorded less frequently, but at least 4 hourly during treatment |
| • If initial cardiotocograph is reactive, record fetal heart rate with doppler after each increase in the infusion rate during the acute stabilisation phase, then at least 6 hourly for first 48 hrs. |

**NB:** Abnormalities detected in the fetal heart rate and/or ongoing uterine activity may require ongoing continuous CTG monitoring.
### 4.3 Attachment 3: Implementation checklist

<table>
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<tr>
<th>IMPLEMENTATION REQUIREMENTS</th>
<th>Not commenced</th>
<th>Partial compliance</th>
<th>Full compliance</th>
<th>Notes</th>
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<tr>
<td>2. Development of local protocols for the administration of tocolytic agents</td>
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<tr>
<td>3. Compliance with <em>PD2010_069 Critical Care Tertiary Referral Networks (Perinatal)</em></td>
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<tr>
<td>4. Compliance with <em>PD2010_040 Fetal Heart Rate Monitoring</em></td>
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Assessed by:  
Date of Assessment: