The use of nifedipine in obstetrics

This statement has been developed and reviewed by the Women’s Health Committee and approved by the RANZCOG Board and Council.

A list of Women’s Health Committee Members can be found in Appendix A.

Disclosure statements have been received from all members of this committee.

Disclaimer This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.

First endorsed by RANZCOG: July 2002
Current: July 2014
Review due: July 2017

Background: This statement was first developed by Women’s Health Committee in July 2002 and reviewed in July 2014.

Values: The evidence was reviewed by the Women’s Health Committee (RANZCOG), and applied to local factors relating to Australia and New Zealand.

Funding: The development and review of this statement was funded by RANZCOG.
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1. **Patient summary**

Preterm birth is a leading contributor to death and long term disability in newborns. Outcomes in women presenting in preterm labour can be improved if delivery can be delayed, in order for (i) medications to be given that improve outcomes for preterm newborns and (ii) enable transfer to a hospital with facilities to manage the preterm newborn. There are a variety of medications given to reduce contractions. The most commonly used medication for this purpose is nifedipine tablets. This is a drug most commonly used for high blood pressure, but using nifedipine to stop uterine contractions has been shown to be very effective, reducing the risk of preterm birth, and improving outcomes for the baby with reduced side effects for the mother. If you have any questions about the use of this medication in pregnancy, or the dose and duration of treatment you will receive, please discuss this with your obstetrician.

2. **Discussion and recommendations**

There is considerable evidence in published studies concerning the use of nifedipine in obstetrics for the treatment of threatened preterm labour and for hypertension in pregnancy.

2.1 What is the role of nifedipine in the management of preterm labour?

Nifedipine appears to be at least as effective as other tocolytic agents (perhaps more effective) with the advantage of less maternal side effects. The currently available evidence supports the view that it is safe for both mother and baby, and suggests that when used for tocolysis it may be associated with improved neonatal outcomes when compared with other tocolytic drugs.

The most recent Cochrane meta-analysis on the use of nifedipine in preterm labour in 26 trials involving 2511 women was published in 2014. This review reported that calcium channel blockers (CCBs) resulted in an increase in interval between trial entry and birth, and gestational age at delivery. CCBs decreased preterm and very preterm birth (RR 0.89, 95% CI 0.80 to 0.98 and RR 0.78, 95% CI 0.66 to 0.93); respiratory distress syndrome (RR 0.64, 95% CI 0.48 to 0.86); necrotising enterocolitis (RR 0.21, 95% CI 0.05 to 0.96); intraventricular haemorrhage (RR 0.53, 95% CI 0.34 to 0.84); neonatal jaundice (RR 0.72, 95% CI 0.57 to 0.92); and admissions to neonatal intensive care unit (NICU) (average RR 0.74, 95% CI 0.63 to 0.87).

This review concluded that calcium channel blockers (mainly nifedipine) for women in preterm labour have benefits over placebo or no treatment in terms of postponement of birth. Calcium channel blockers were shown to have benefits over betamimetics with respect to prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects.

The place of nifedipine as a maintenance therapy was addressed in a Cochrane review published in 2013, which concluded that maintenance treatment did not reduce preterm birth, or improve maternal/fetal outcomes. There were no significant differences in the incidence of preterm birth, birth within 48 hours of treatment or neonatal mortality, although it needs to be acknowledged the numbers were small.

2.2 What is the role of nifedipine in the management of hypertension in pregnancy?

Nifedipine is sometimes used as an effective antihypertensive agent for the management of both the acute and chronic hypertension in pregnancy. Current available evidence shows no suggestion of teratogenicity with first trimester use and demonstrates safety for both mother and baby in the both second and third trimesters. The use of nifedipine in pregnancy is associated with a small risk of serious maternal side effects.

2.3 What are the precautions?

In accordance with usual practice, Fellows should be familiar with the published literature and drug information provided before prescribing the drug.
Serious maternal side effects have been reported with nifedipine; however they are uncommon (1-2%). The most common serious side effects are pulmonary oedema and severe hypotension. Particular attention is drawn to concerns with the use of nifedipine in combination with magnesium sulphate, and it is recommended that its use in combination with other tocolytic drugs should be avoided. Caution should be exercised when nifedipine is used in the presence of multiple pregnancy, ruptured membranes, sepsis, diabetes mellitus and underlying cardiac disease.

There is no clear consensus on the most appropriate dosage regimen for nifedipine in the treatment of preterm labour. Higher doses appear to be associated with an increased risk of serious side effects. It is suggested these occur more frequently when the maintenance doses of > 60mg per day. The references cited below include information about evaluated regimens.

2.4 What is the attitude of the pharmaceutical industry regarding the use of nifedipine in pregnancy?
Despite the wealth of published studies demonstrating the safety and efficacy of nifedipine for management of preterm labour, the current product information for nifedipine lists its use in pregnancy as a contraindication. It is classified as Category C. As the use of nifedipine in pregnancy is therefore "off-label", no liability would be accepted by the company for any adverse events.

3. Conclusion
As with all therapeutic agents, practitioners should take particular care to use nifedipine according to regimens for which evidence is available. Where nifedipine is the most appropriate therapeutic option, it should be available for use according to established medical evidence.

Where trainees and junior medical staff are involved in care, it is reasonable to expect that consultants will accept responsibility for the use of nifedipine in any given clinical situation.

4. Other suggested reading


Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database of Systematic Reviews 2006, Issue 3.

Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 2007, Issue 1.


NSW Department of Health Circular, File No 02/1303, Circular No 2002/49, Issued 23 April 2002 ‘Protocols for Administration of tocolytic agents (intravenous salbutamol or oral nifedipine) for threatened preterm labour’.

5. Links to other College statements
Consent and the Provision of Information to Patients in Australia regarding Proposed Treatment (C-Gen 02a)

Consent and Provision of Information to Patients in New Zealand regarding Proposed Treatment (C-Gen 02b)

Evidence-based Medicine, Obstetrics and Gynaecology (C-Gen 15)

6. Patient information

A range of RANZCOG Patient Information Pamphlets can be ordered via:

https://www.ranzcog.edu.au/Womens-Health/Patient-Information-Guides/Patient-Information-Pamphlets
Appendices

Appendix A Women’s Health Committee Membership

<table>
<thead>
<tr>
<th>Name</th>
<th>Position on Committee</th>
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<tbody>
<tr>
<td>Associate Professor Stephen Robson</td>
<td>Chair</td>
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<tr>
<td>Professor Susan Walker</td>
<td>Deputy Chair - Obstetrics</td>
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<tr>
<td>Dr Gina Pecoraro</td>
<td>Deputy Chair - Gynaecology</td>
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<tr>
<td>Professor Yee Leung</td>
<td>Member</td>
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<tr>
<td>Associate Professor Anuschirawan Yazdani</td>
<td>Member</td>
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<tr>
<td>Dr Simon Craig</td>
<td>Member</td>
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<tr>
<td>Associate Professor Paul Duggan</td>
<td>Member</td>
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<tr>
<td>Dr Vijay Roach</td>
<td>Member</td>
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<td>Dr Stephen Lyons</td>
<td>Member</td>
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<td>Dr Ian Page</td>
<td>Member</td>
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<td>Dr Donald Clark</td>
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<td>Dr Amber Moore</td>
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<td>Dr Martin Ritossa</td>
<td>Member</td>
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<td>Dr Benjamin Bopp</td>
<td>Member</td>
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<td>Dr James Harvey</td>
<td>Member</td>
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<td>Dr John Tait</td>
<td>Member</td>
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<tr>
<td>Dr Anthony Frumar</td>
<td>Member</td>
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<tr>
<td>Associate Professor Kirsten Black</td>
<td>Member</td>
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<tr>
<td>Dr Jacqueline Boyle</td>
<td>Chair of IWHC</td>
</tr>
<tr>
<td>Dr Louise Sterling</td>
<td>GPOAC representative</td>
</tr>
<tr>
<td>Ms Catherine Whitby</td>
<td>Council Consumer representative</td>
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<tr>
<td>Ms Susan Hughes</td>
<td>Consumer representative</td>
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<tr>
<td>Ms Sherryn Elworthy</td>
<td>Midwifery representative</td>
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<tr>
<td>Dr Scott White</td>
<td>Trainee representative</td>
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<tr>
<td>Dr Agnes Wilson</td>
<td>RANZCOG Guideline developer</td>
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Appendix B Overview of the development and review process for this statement

i. Steps in developing and updating this statement

This statement was originally developed in July 2002 and was most recently reviewed in July 2014. The Women’s Health Committee carried out the following steps in reviewing this statement:

- Declarations of interest were sought from all members prior to reviewing this statement.
- Structured clinical questions were developed and agreed upon.
- An updated literature search to answer the clinical questions was undertaken.
- At the July 2014 face-to-face committee meeting, the existing consensus-based recommendations were reviewed and updated (where appropriate) based on the available body of evidence and clinical expertise. Recommendations were graded as set out below in Appendix B part iii)

ii. Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of the Women’s Health Committee.
A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. The Women’s Health Committee members were required to declare their relevant interests in writing on this form prior to participating in the review of this statement.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this statement.

### iii. Grading of recommendations

Each recommendation in this College statement is given an overall grade as per the table below, based on the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades of Recommendations for Developers of Guidelines. Where no robust evidence was available but there was sufficient consensus within the Women’s Health Committee, consensus-based recommendations were developed or existing ones updated and are identifiable as such. Consensus-based recommendations were agreed to by the entire committee. Good Practice Notes are highlighted throughout and provide practical guidance to facilitate implementation. These were also developed through consensus of the entire committee.

<table>
<thead>
<tr>
<th>Recommendation category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Evidence-based</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation(s) but care should be taken in its application</td>
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<tr>
<td>D</td>
<td>The body of evidence is weak and the recommendation must be applied with caution</td>
</tr>
<tr>
<td>Consensus-based</td>
<td>Recommendation based on clinical opinion and expertise as insufficient evidence available</td>
</tr>
<tr>
<td>Good Practice Note</td>
<td>Practical advice and information based on clinical opinion and expertise</td>
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Appendix C Full Disclaimer

This information is intended to provide general advice to practitioners, and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient.

This information has been prepared having regard to general circumstances. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual patient and the particular circumstances of each case.

This information has been prepared having regard to the information available at the time of its preparation, and each practitioner should have regard to relevant information, research or material which may have been published or become available subsequently.

Whilst the College endeavours to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available.