The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Excellence in Women's Health

The use of misoprostol in obstetrics and gynaecology

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: November 2001
Current: March 2016
Review due: March 2019

Objectives: To provide advice on the use of misoprostol in obstetrics and gynaecology.

Target audience: All health practitioners providing maternity care.

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

Background: This statement was first developed by Women's Health Committee in November 2001 and reviewed in March 2016.

Funding: The development and review of this statement was funded by RANZCOG.

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1. Patient summary

Misoprostol is a medication that is available in Australia and New Zealand. It is used as part of the treatment for miscarriage (early pregnancy loss) and where termination of a pregnancy is undertaken. When used in these settings Misoprostol is safe and effective, and can provide important benefits for women. These should be discussed with the doctor providing care.

2. Summary of recommendations

Recommendation 1	Grade
Misoprostol is appropriate for use, and demonstrates advantages over available alternatives, in the medical management of miscarriage and in combination with mifepristone for termination of pregnancy in the first trimester.	Consensus-based recommendation
Recommendation 2	**Grade**
Under current TGA guidelines in Australia misoprostol is registered for use in a composite pack with mifepristone for termination of pregnancy up to 63 days. There is no approved use beyond 63 days gestation or for other obstetric or gynaecological procedures. Any "off-label" use should only occur in the clinical situation after obtaining and documenting informed consent from the woman.	Consensus-based recommendation
Recommendation 3	**Grade**
Misoprostol is used in combination with mifepristone for termination of pregnancy. Detailed information about this indication can be found in the College statement *The use of mifepristone for medical termination of pregnancy (C-Gyn 21).*	Consensus-based recommendation

3. Introduction

There is considerable evidence in published studies about the use of misoprostol in obstetrics. There are in excess of 200 randomised controlled trials included in Cochrane Systematic Reviews, involving more than 35,000 women where misoprostol has been administered for obstetric or gynaecological indications.

4. Discussion and recommendations

Recommendation 1	Grade
Misoprostol is appropriate for use, and demonstrates advantages over available alternatives, in the medical management of miscarriage and in combination with mifepristone for termination of pregnancy in the first trimester.	Consensus-based recommendation

4.1 Use in first and second trimesters

In general, the evidence demonstrates advantages of misoprostol over available alternatives for use in medical management of miscarriage and termination of pregnancy in the first and second trimesters. The advantages are that it is at least as effective as alternatives, has fewer side effects, is more practical to use and is cheaper. Recent research reports suggest that alternatives to misoprostol are used with diminishing frequency. The occurrence of maternal side effects is reduced when using lower doses of misoprostol, when compared with higher cumulative doses.
In 2012 misoprostol was registered in Australia for use orally or buccally in combination with mifepristone for termination of pregnancy up to 49 days gestation. From February 2015 a composite pack containing both misoprostol and mifepristone was introduced with a new indication of termination of pregnancy up to 63 days gestation.

The Therapeutic Goods Administration approved product information and evidence based guidelines should be consulted for detailed information about appropriate regimens.[1]

4.2 Use in third trimester

4.2.1 Induction of labour

Misoprostol is used extensively in the third trimester in countries other than Australia. Advantages include that it is relatively inexpensive, can be stored at room temperature and has a long shelf life. However, in Australia, use of misoprostol is less common after the first trimester and, under current TGA guidelines, the use of misoprostol after 63 days gestation other than for termination of pregnancy, or for other obstetric or gynaecological procedures, is not an approved indication.

There is considerable literature evaluating the use of misoprostol for cervical ripening and induction of labour. Both vaginal and oral administration of misoprostol are effective methods for cervical ripening and for induction labour. As with other prostaglandins, misoprostol can cause uterine hypertonicity. Misoprostol is an effective uterotonic and can achieve sustained uterine contraction in the third stage.

4.2.2 Third stage management [2-6]

There is insufficient evidence to recommend misoprostol over conventional injectable uterotonics in prophylaxis management in the third stage of labour, particularly in women considered to be at low risk.

Misoprostol may be used for the management of post partum haemorrhage. This is covered in more detail in the College statement *Postpartum Haemorrhage (C-Obs 43).* However there is insufficient evidence to recommend its use over injectable uterotonics at this stage.

4.3 Registration status of misoprostol

In Australia misoprostol is now only registered for use in obstetrics and gynaecology in a composite pack with Mifepristone and solely for the purpose of termination of pregnancy up to 63 days gestation.
Use of misoprostol after 63 days gestation or for other obstetric or gynaecological indications is not an approved indication.

Misoprostol is included in the regimen for early medical abortion in the New Zealand Medsafe datasheet for mifepristone, but misoprostol itself is not registered there for obstetric and gynaecological indications and therefore is used as not an approved indication.

The company which markets the widely used formulation of misoprostol which is registered for gastrointestinal indications has not researched, and does not support its use, in pregnancy, and has not expressed any intention to do so.

4.4 Use in clinical practice

Recommendation 2	Grade
Under current TGA guidelines in Australia misoprostol is registered for use in a composite pack with mifepristone for termination of pregnancy up to 63 days. There is no approved use beyond 63 days gestation or for other obstetric or gynaecological procedures. Any "off-label" use should only occur in the clinical situation where there is published supporting evidence and after obtaining and documenting informed consent from the woman.	Consensus-based recommendation
Recommendation 3	**Grade**
Misoprostol is used in combination with mifepristone for termination of pregnancy. Detailed information about this indication can be found in the College statement *The use of mifepristone for medical termination of pregnancy (C-Gyn 21).*	Consensus-based recommendation

Particular caution is recommended with the use of misoprostol for cervical ripening and induction of labour. The potential risks and benefits in each individual case should be carefully evaluated and attention paid to the published information regarding minimization of dosage. As with all prostaglandin preparations, caution is recommended with the use of misoprostol in the presence of a uterine scar.

5. Conclusion

There is abundant evidence from peer reviewed literature attesting to the efficacy of Misoprostol as a therapeutic agent in treating a number of conditions in Obstetrics and Gynaecology. Practitioners should be aware that when they prescribe it, they will be generally be using it 'off label' and should only use it in clinical situations after obtaining and documenting informed consent from the woman.

The references which follow include information about dosage regimens evaluated.

6. References

1. (TGA) TGA. Product Information- MS-2 Step Mifepristone Linepharma 200 mg Tablet Packhttps://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-CMI-01028-1&d=201511121611462241 2Product Information – GyMiso misoprostol 200 microgram tablet. 2012.

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3. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. BJOG : an international journal of obstetrics and gynaecology. 2001;108(9):952-9.

4. Dallenbach P, Boulvain M, Viardot C, Irion O. Oral misoprostol or vaginal dinoprostone for labor induction: a randomized controlled trial. American journal of obstetrics and gynecology. 2003;188(1):162-7.

5. Moodley J, Venkatachalam S, Songca P. Misoprostol for cervical ripening at and near term--a comparative study. S Afr Med J. 2003;93(5):371.

6. Muzonzini G, Hofmeyr GJ. Buccal or sublingual misoprostol for cervical ripening and induction of labour. The Cochrane database of systematic reviews. 2004(4):CD004221.

7. Other suggested reading

National Consensus Guideline for Treatment of Postpartum Haemorrhage
http://www.health.govt.nz/publication/national-consensus-guideline-treatment-postpartum-haemorrhage

New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) Data Sheet – MIFEGYNE Mifepristone micronised 200 mg tablets. June 2012. Available at:
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Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD004901. DOI: 10.1002/14651858.CD004901.pub2.

Dodd JM, Crowther CA. Misoprostol versus cervagem for the induction of labour to terminate pregnancy in the second and third trimester for women with a fetal anomaly or after intra-uterine fetal death: A systematic review. Eur J Obstet Gyn Reprod Biol 2005.

Goldberg AB, Greenberg MB, Darney PD. Drug Therapy: Misoprostol and Pregnancy. New England Journal of Medicine 2001; 344: 38-47 (95 references).

Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. The Cochrane Database of Systematic Reviews 2003, Issue 1 Art. No.: CD000941. DOI: 10.1002/14651858.CD000941.

Kulier R, Gülmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. The Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD002855. DOI: 10.1002/14651858.CD002855.pub3.

Royal College of Obstetricians and Gynaecologists. The Care of Women Requesting Induced Abortion. Evidence-based Clinical Guideline Number 7. RCOG Press November 2011. Available at: http://www.rcog.org.uk/files/rcog-corp/Abortion%20guideline_web_1.pdf

Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 55. Late Intrauterine Fetal Death and Stillbirth. October 2010. Available at: http://www.rcog.org.uk/files/rcog-corp/GTG%2055%20Late%20Intrauterine%20fetal%20death%20and%20stillbirth%2010%2011%2010.pdf

Weeks A, Fiala C, Safar P. Misoprostol and the debate over off-label (not an approved indication) drug use. BJOG 2005 Mar; 112 (3): 269-72.

8. Links to other College statements

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

The use of mifepristone for medical termination of pregnancy (C-Gyn 21)

Birth after previous Caesarean Section (C-Obs 38)

Management of postpartum haemorrhage (C-Obs 43)

Appendices

Appendix A Women's Health Committee Membership

Name	Position on Committee
Professor Stephen Robson	Chair and Board Member
Dr James Harvey	Deputy Chair and Councillor
Associate Professor Anusch Yazdani	Member and Councillor
Associate Professor Ian Pettigrew	Member and Councillor
Dr Ian Page	Member and Councillor
Professor Yee Leung	Member of EAC Committee
Professor Sue Walker	General Member
Dr Lisa Hui	General Member
Dr Joseph Sgroi	General Member
Dr Marilyn Clarke	General Member
Dr Donald Clark	General Member
Associate Professor Janet Vaughan	General Member
Dr Benjamin Bopp	General Member
Associate Professor Kirsten Black	General Member
Dr Jacqueline Boyle	Chair of the ATSIWHC
Dr Martin Byrne	GPOAC representative
Ms Catherine Whitby	Community representative
Ms Sherryn Elworthy	Midwifery representative
Dr Nicola Quirk	Trainee representative

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 November 2001 and was most recently reviewed in November 2015. 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 November 2015 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.

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

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.