Category: Clinical Statement

C-Obs 29b Progesterone: Use in the second and third trimester

This statement has been updated in response to changes in available evidence, including an updated meta-analysis that excludes data from a retracted study. The interim update of the statement provides guidance on the use of progesterone in the second and third trimesters, approved by the Women's Health Committee, RANZCOG Council and Board.

A list of the Women's Health Committee membership can be found in Appendix A.

Conflict of Interest disclosures were received from all members of this Committee (Appendix C)

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 (Appendix D)

First developed by RANZCOG: March 2010
Current version: July 2017, with interim update November 2023
Review due: July 2024

Objectives:	To provide advice on the use of progesterone to prevent preterm birth.
Target audience:	This statement was developed primarily for use by registered health practitioners providing care to women[1] in maternity care.
Background:	The statement was first published in March 2010 and reviewed in July 2017. The most recent interim update of this statement is in response to an updated meta-analysis on vaginal progesterone reducing the chances of preterm birth <33 weeks' gestation among women with a twin pregnancy. The statement draws on earlier evidence-based methodology (i.e. not GRADE methodology). (Appendix C).
Funding:	The development and review of this statement was funded by RANZCOG.

[1] *RANZCOG currently uses the term 'woman' in its documents to include all individuals needing obstetric and gynaecological healthcare, regardless of their gender identity. The College is firmly committed to inclusion of all individuals needing O&G care, as well as all its members providing care, regardless of their gender identity.*

Contents

1. Plain language summary

Preterm birth is the leading cause of neonatal mortality, and so prevention of preterm birth is a high priority in obstetric care. Approximately two thirds of all preterm births occur spontaneously, with the other third being so-called 'indicated preterm births', usually where there is concern about fetal growth, or maternal medical conditions, such as pre-eclampsia.

2. Purpose and scope

The purpose of this document is to provide guidance to registered health practitioners on the evolving function of progesterone in reducing the risk of spontaneous preterm birth, and to assist them in making clinical decisions regarding patient care.

3. Terminology

The statement has been updated using contemporary terminology that is identified as being acceptable to consumers (Re:Birth survey UK, 2023).

4. Table of recommendations

Recommendation 1	Grade
Vaginal progesterone therapy is recommended for asymptomatic women with a short cervix (<25 mm) on transvaginal cervical length assessment in the midtrimester.	Consensus-based recommendation
Recommendation 2	**Grade**
Progesterone therapy should be considered for women with a singleton pregnancy with a history of previous spontaneous preterm singleton birth.	Consensus-based recommendation

5. Introduction

The role of progesterone in the prevention of preterm birth has been the subject of several randomised controlled trials in the last decade, both for women with a previous spontaneous preterm birth or for those with a sonographically confirmed short cervix at the time of routine midtrimester ultrasound. These trials have re-ignited interest in the use of progesterone to reduce the risk of preterm birth. These studies have contributed to recent meta-analyses [1-3], suggesting that progesterone reduces the risk of preterm birth in women with a previous history of spontaneous preterm birth. A recent large randomised controlled trial however published in 2016 [4], showing no benefit, was not included.

These meta-analyses do however confirm that progesterone reduces the risk of preterm birth in women found to have a short cervix using a standardised transvaginal technique at the time of the routine anomaly scan.

6. Discussion and recommendations

Recommendation 1	Grade
Vaginal progesterone therapy is recommended for asymptomatic women with a short cervix (<25 mm) on transvaginal cervical length assessment in the midtrimester.	Consensus-based recommendation
Recommendation 2	**Grade**
Progesterone therapy should be considered for women with a singleton pregnancy with a history of previous spontaneous preterm singleton birth.	Consensus-based recommendation

6.1. What are the management considerations for patients with a history of spontaneous preterm birth?

Systematic review and meta-analysis of five randomised trials in women with a history of spontaneous preterm birth suggest a significant risk reduction in both preterm birth, perinatal mortality and major morbidity among women receiving progesterone. [1, 3-9] However, this meta-analysis does not include the OPPTIMUM trial published in 2016, that shows no reduction in preterm birth with the use of progesterone in women with a previous history of preterm birth. [4] An updated meta-analysis including this trial is awaited.

It needs to be appreciated that there are many potential contributors to spontaneous preterm birth, which may account for significant heterogeneity between study findings. For example, among women with a past history of preterm birth, cervical surveillance may identify those with cervical shortening (see below) who may benefit most from progesterone administration. In addition, the majority of these studies have used intramuscular rather than transvaginal progesterone, and further studies are needed to better define the role of vaginal progesterone in women with a past history of preterm birth. Further studies will also address the optimal dose, timing and administration of progesterone, and provide useful data on how these short term benefits may translate into longer term health outcomes in infancy and childhood.

6.2. What are the management considerations for asymptomatic women with a short cervix at 18-24 weeks?

A short cervix detected with transvaginal ultrasound in the mid trimester is a powerful predictor of spontaneous preterm birth. Several large randomised controlled trials have confirmed a significant reduction in the risk of spontaneous preterm birth among asymptomatic women administered progesterone following the diagnosis of a short cervix on transvaginal ultrasound. [8, 10, 11] A recent updated meta-analysis demonstrated that vaginal progesterone reduces the risk of preterm birth prior to 34 weeks' from 27.5% to 18.1% (RR 0.66; 0.52-0.83) among women with a short cervix (25mm or less). [2] The largest trial included women with a transvaginal sonographic cervical length between 10 and 20mm. [11] Treatment with progesterone was also shown to reduce the risk of preterm birth at <28 to <36 weeks' gestation (RR 0.51 to 0.79); , as well as showing significant reductions in respiratory distress (RR 0.47; 0.27-0.81), composite neonatal morbidity and mortality (RR 0.59; 0.38-0.91), birth weight <1500g (RR 0.52; 0.33-0.81) and admission to NICU (RR 0.67; 0.50-0.91), although the risk reduction for perinatal mortality was not significant (RR 0.63; 0.34-1.18).

6.3. What other indications should be considered when using Progesterone to prevent preterm birth?

Despite their increased risk of preterm birth, routine administration of progesterone from 24 weeks has not been shown to reduce the risk of preterm birth in multiple pregnancies. [12, 13] In multiple pregnancies where a short cervix has been noted, progesterone has also not been shown to significantly reduce the risk of preterm birth,[14] but it should be noted that the numbers in some of these trials are small. One meta-analysis (2017) had reported progesterone administration in twin pregnancies with a short cervix to be associated with a significant reduction in preterm birth <33 weeks' gestation, however this analysis was compromised by the subsequent retraction of a key study. In correspondence from the authors, an updated meta-analysis of individual patient data on the efficacy of vaginal progesterone for the prevention of preterm birth and neonatal morbidity and mortality in asymptomatic women with a twin gestation and a sonographic cervical length (CL) ≤25 mm, found that vaginal progesterone reduced significantly the risk of preterm birth <33 weeks' gestation (38.5% vs 55.8%; RR, 0.60 (95% CI, 0.38–0.95) and in composite neonatal morbidity/ mortality (RR, 0.59 (95% CI, 0.33–0.98)). [15] More research is needed to determine if there is a subset of multiple pregnancies that may benefit from progesterone.

Several studies have evaluated the role of progesterone in populations with varied risk factors, including a history of uterine malformation or of 'cervical incompetence'. The heterogeneity of the studies, and the numbers involved do not give sufficient power to determine whether treatment for these indications is effective. [1] There are limited data supporting its use as a long term tocolytic for women who present with threatened preterm labour at <34 weeks gestation and further research is needed to examine the role of progesterone in this context. [16]

6.4. What is the ideal route of administration and the correct dosage?

A variety of progestins have been used in the preterm birth prevention trials. The US datasets predominantly use 17-alpha-hydroxyprogesterone caproate, given as a weekly intramuscular injection, but this preparation is not currently available in Australia.

Vaginal pessaries of progesterone are available and have the potential advantage of high uterine bioavailability and few systemic side effects, although vaginal irritation can be problematic. This route of administration has been studied using doses of 90mg - 400mg and the optimal dosage is not clearly

established, although the recent meta-analysis of Romero et al. showed no difference in effect between 90-100mg and 200 mg progesterone pessaries for women with a short cervix. [2]

Timing of therapy has also varied between studies, starting as early as 16 weeks of gestation in women with a previous history of spontaneous preterm birth and continuing to 37 weeks is some trials. Early cessation of 17 alpha-hydroxyprogesterone caproate has been associated with an increased risk for recurrent preterm birth.[17]

Commencing progesterone therapy in the second trimester (i.e., 16-24 weeks) of pregnancy appears to be safe for both the mother and the fetus and no teratogenic effects have been observed. Infants recruited to the NICHD trial whose mothers received 17 alpha-hydroxyprogesterone caproate were followed to four years of age and no detrimental effects were observed. [8]

7. Conclusion

Vaginal progesterone therapy is recommended for women who are found to have a short cervix at the time of the routine mid-trimester scan. Current evidence suggests that progesterone reduces the risk of preterm birth in these women, with evidence of improved perinatal outcomes. It remains to be determined how these benefits will translate into long term health benefits, and further research is also needed to determine both the optimal timing, dose and administration of progesterone. Participation in relevant clinical trials should be encouraged.

8. References

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9. Links to College statements

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

10. Consumer resources

RANZCOG patient information pamphlets can be viewed at: www.ranzcog.edu.au/pip

11. Links to relevant ATMs and learning modules

FRANZCOG Training Program Handbook. Basic Obstetric Skills Workshop (mandatory workshop). Available at: https://ranzcog.edu.au/wp-content/uploads/2022/05/FRANZCOG-Training-Program-Handbook_After-1st-December-2013.pdf

12. Legal and ethical implications

13. Recommendations for future research

With the retraction of a study of individual patient data from one meta-analysis on vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix, the authors deduce that further research on this topic would benefit future guidance.

14. Other suggested reading

1. ACOG Practice Bulletin> Prediction and prevention of preterm birth. Number 130, October 2012.
2. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol. 2012 May;206(5):376-86. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. https://doi.org/10.1016/j.ajog.2012.03.010
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5. Perinatal Trials: PROGRESS Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01412761/full
6. The PROSPECT study (NCT02518594) a randomised controlled trial to evaluate the use of vaginal progesterone to prevent early preterm birth in women carrying twins and with a CL<30mm between 16 and 23weeks of gestation. The study began in November 2015 and the estimated completion date is February 2025. https://www.med.unc.edu/mfmu/current-studies/prospect/ Accessed 17 November 2023.

Appendices

Appendix A: Women's Health Committee Membership

Name	Position on Committee
Dr Scott White	Chair
Dr Anna Clare	Deputy Chair, Gynaecology
Associate Professor Amanda Henry	Deputy Chair, Obstetrics
Dr Nisha Khot	Member and Councillor
A/Professor Jared Watts	Member and Councillor
Dr Marilla Druitt	Member and Councillor
Dr Samantha Scherman	Member and Councillor
Dr Kasia Siwicki	Member and Councillor
Dr Angela Beard	Māori Representative
Dr Marilyn Clarke	Aboriginal and Torres Strait Islander Representative
Professor Kirsten Black	SRHSIC Chair
Dr Pallavi Desai	SIMG Representative
Dr Martina Mende	Diplomate Representative
Dr James Brown	State representative - NSW
Dr Kathy Saba	State representative - Queensland
Dr Frank Clarke	State representative - Tasmania
Dr Victoria Carson	State representative - Victoria
Dr Elizabeth Gallagher	Territory representative - ACT
	Midwifery Representative, Australia
Ms Adrienne Priday	Midwifery Representative, Aotearoa New Zealand
Emma Preece Boyd	Community Representative
Ms Leigh Toomey	Community Representative
Dr Sara Ooi	Trainee Representative
Dr Steve Resnick	Co-opted member

Appendix B: Acknowledgment

RANZCOG wishes to acknowledge the significant contribution of Dr Scott White MFM in conducting the interim update of this statement to provide guidance to registered health practitioners on the evolving function of progesterone in reducing the risk of spontaneous preterm birth.

Appendix C: Overview of the development and review process for this statement

i. 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 RANZCOG Women's Health Committee or working groups.

A declaration of interest form specific to guidelines and statements (approved by the RANZCOG Board in September 2012). All members of the Statement Development Panels and Women's Health Committee 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.

ii. Steps in developing and updating this statement

This statement was first published in March 2010 and reviewed in July 2017. In July 2020 a review of the statement was proposed but held over pending outcomes of the Australian Preterm Birth Prevention Alliance (Commonwealth funded). The most recent interim update of this statement was in November 2023, in response to an updated meta-analysis on vaginal progesterone reducing the chances of preterm birth <33 weeks' gestation among women a twin pregnancy and short cervix. 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.
- An interim review of review of meta-analyses and systematic reviews was undertaken in lieu of a full review of all published evidence. The statement update included a more recent meta-analysis on vaginal progesterone reducing the chances of preterm birth <33 weeks' gestation among women a twin pregnancy and short cervix, replacing outdated data (meta-analysis comprising a retracted study).

RANZCOG statements are developed according to the standards of the Australian 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.

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 D: Full Disclaimer

Purpose

This Statement has been developed to provide general advice to registered health practitioners regarding the use of progesterone in the second and third trimesters 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 person. 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 person and the particular circumstances of each case.

Quality of information

The information available in this statement is intended as a guide and provided for information purposes only. The information is based on the Australian/Aotearoa New Zealand context using the best available evidence and information at the time of preparation. While the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) has endeavoured 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. The use of this information is entirely at your own risk and responsibility.

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These terms and conditions will be constructed according to and are governed by the laws of Victoria, Australia.

Version	Date of Version	Pages revised / Brief Explanation of Revision
v1.0	March / 2010	The statement was first published by RANZCOG Maternal Fetal Medicine Committee, approved by Board.
V2.0	July / 2017	Update to statement authors by Dr A Fung. Approved by RANZCOG Women's Health Committee/Board.
V3.0	July / 2020	Routine update of the statement by Dr A Fung deferred.
V3.1	November / 2023	Interim update in response to updated metanalysis. Approved by RANZCOG Women's Health Committee/Council.

Policy Version:	Version 3.1
Policy Owner:	Women's Health Committee
Policy Approved by:	RANZCOG Council/Board
Review of Policy:	November / 2024