The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Excellence in Women's Health

Progesterone: Use in the second and third trimester of pregnancy for the prevention of preterm birth

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.

First endorsed by RANZCOG: March 2010
Current: July 2017
Review due: July 2020

Objectives: To provide advice on the use of progesterone to prevent preterm birth.

Outcomes: Reduced risk of preterm birth for all women who are found to have a short cervix at the time of the routine morphology scan.

Target audience: All health practitioners providing maternity care and patients.

Evidence: Medline was searched for randomised trials and cohort studies.

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 March 2010 and reviewed in July 2017.

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

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1. Patient 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 birth 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. The purpose of this document is to provide information to practitioners on the evolving place of progesterone in reducing the risk of spontaneous preterm birth to assist them in making clinical decisions regarding patient care.

2. Summary 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	
Progesterone therapy should be considered for women with a singleton pregnancy with a history of previous spontaneous preterm singleton birth.	Consensus-based recommendation

3. 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-analysis 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.

4. Discussion and recommendations

4.1 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.

4.2 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).

4.3 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. In one meta-analysis, progesterone administration in twins with a short cervix has been reported to be associated with a significant reduction in preterm birth <33 weeks' gestation (RR 0.69: 0.51-0.93) and in composite neonatal morbidity/ mortality (RR 0.61; 0.34-0.98). [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,]

4.4 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, stating as early as 16 weeks of gestation in women with a previous history of spontaneous preterm delivery 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 delivery.[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]

5. Conclusion

Vaginal progesterone therapy is recommended for women who are found to have a short cervix at the time of the routine midtrimester 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.

6. References

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7. Other suggested reading

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4. Perinatal Trials: PROGRESS Available at: http://wombatcollaboration.net/modules.php?name=Content&pa=showpage&pid=25

8. Links to other College statements

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

Measurement of Cervical Length in Pregnancy (C-Obs 27)

9. 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

Name	Position on Committee
Professor Yee Leung	Chair
Dr Joseph Sgroi	Deputy Chair, Gynaecology
Associate Professor Janet Vaughan	Deputy Chair, Obstetrics
Associate Professor Ian Pettigrew	EAC Representative
Dr Tal Jacobson	Member
Dr Ian Page	Member
Dr John Regan	Member
Dr Craig Skidmore	Member
Associate Professor Lisa Hui	Member
Dr Bernadette White	Member
Dr Scott White	Member
Associate Professor Kirsten Black	Member
Dr Greg Fox	College Medical Officer
Dr Marilyn Clarke	Chair of the ATSI WHC
Dr Martin Byrne	GPOAC Representative
Ms Catherine Whitby	Community Representative
Ms Sherryn Elworthy	Midwifery Representative
Dr Amelia Ryan	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 March 2010 and was most recently reviewed in July 2017. 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 2017 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.[4] 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 B 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.