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

Progesterone support of the luteal phase and in the first trimester

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.

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 2009
Current: March 2018
Review due: March 2021

Objectives: To provide advice on the use of progesterone or progestogen support in the luteal phase and early pregnancy.

Options: Hormonal treatment versus no treatment.

Outcomes: To improve outcomes of those women undergoing hormonal treatment.

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

Evidence: Medline was searched for systematic reviews, meta-analyses, randomised trials and cohort studies relating to progesterone support in the luteal phase.

Values: The evidence was reviewed by the Women's Health Committee (RANZCOG) and local generalisability and applicability factors relating to Australia and New Zealand were taken into account.

Background: This statement was first developed by RANZCOG in November 2009 and was revised in March 2018.

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

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1. Patient summary

Progesterone is a hormone secreted by the ovary and plays an important role in normal pregnancy. A number of studies have been undertaken to determine whether the use of progesterone supplements have a benefit in the luteal phase of the menstrual cycle and in early pregnancy. There is no evidence to suggest that giving progesterone supplements to otherwise healthy women in the first trimester of pregnancy reduces the risk of spontaneous miscarriage. However, for some women who experience bleeding in early pregnancy, the use of progesterone supplements may reduce the risk of miscarriage. For women who become pregnant with in-vitro fertilisation (IVF), the use of progesterone supplements is beneficial and improves pregnancy outcomes.

2. Summary of recommendations

Recommendation 1	**Grade and reference**
First trimester progestogen supplementation in an unselected population of women does not reduce the incidence of miscarriage and should not be used.	Consensus-based recommendation [1, 2]
Recommendation 2	**Grade and reference**
Progestogen supplementation until the second trimester in women presenting with a clinical diagnosis of threatened miscarriage may reduce the rate of spontaneous miscarriage and may be considered.	Consensus-based recommendation [3, 4]
Recommendation 3	**Grade and reference**
The routine use of progestogens for patients presenting with recurrent spontaneous miscarriage does not improve pregnancy outcomes and is not recommended.	Consensus-based recommendation [5, 6]
Recommendation 4	**Grade and reference**
Luteal phase support with synthetic progestogens should be provided in in vitro fertilisation (IVF) as it is associated with an improved live birth rate.	Consensus-based recommendation [7]

3. Introduction

Supplementation of progesterone in the luteal phase and continuance of progesterone therapy during the first trimester has been found in several studies to have benefits in promoting fertility, preventing miscarriages and even preventing preterm labour.

A literature search for systematic reviews of randomised controlled trials was undertaken to answer the following clinical questions:

What is the role of progesterone or progestogen support in various contexts including:

- Unselected populations of women in the first trimester of pregnancy?
- Women presenting with a clinical diagnosis of threatened miscarriage?
- Women with a history of recurrent miscarriage?
- Luteal support in assisted reproductive technologies (ART)?

Any hormonal treatment in the luteal phase and in early pregnancy must always be used with caution owing to the theoretical possibility of teratogenesis. Outside the context of an appropriate clinical trial, unproven treatments should be avoided. The evidence supporting progestogen use in recurrent miscarriage and threatened miscarriage[3, 4] must be viewed cautiously owing to the heterogeneity in treatment regimens that were pooled for meta-analysis. Further methodologically robust research is required to provide stronger evidence to guide clinical practice.

4. Recommendations

4.1 What is the role of progestogen supplementation in unselected populations of women in the first trimester of pregnancy?

For an **unselected population of women in the first trimester of pregnancy**, there is no evidence of benefit of progestogen therapy, either natural or synthetic, to in the prevention of miscarriage.

Recommendation 1	Grade and reference
First trimester progestogen supplementation in an unselected population of women does not reduce the incidence of miscarriage and should not be used.	Consensus-based recommendation [1, 2]

4.2 What is the role of progestogen supplementation in women presenting with a clinical diagnosis of threatened miscarriage?

For women presenting with a clinical diagnosis of **threatened miscarriage**, there is preliminary evidence of a reduction in the rate of spontaneous miscarriage with the use of progestins. This conclusion is based on data from a meta-analysis of four RCTs including 411 women.

Miscarriage was significantly less likely to occur in women receiving progestogens than those receiving placebo or no treatment (RR 0.53; 95% CI 0.35 to 0.79). There was no evidence of increase in the rate of antepartum haemorrhage, hypertensive disorders of pregnancy, or fetal anomalies.[3] There is significant methodological heterogeneity in these trials, with two assessing oral dydrogesterone and two assessing vaginal progesterone. A further systematic review of the use of oral dydrogesterone demonstrated a significant reduction in the rate of miscarriage for women presenting with a threatened miscarriage from 24% to 11% (OR 0.47; 95% CI 0.31 to 0.70) with a favourable safety profile.[4]

The current evidence for the use of progestogen support in threatened miscarriage is limited by methodological inconsistencies. Whilst the current evidence shows potential benefit, further well-designed clinical trials would add strength to the current evidence base.

Recommendation 2	Grade and reference
Progestogen supplementation until the second trimester in women presenting with a clinical diagnosis of threatened miscarriage may reduce the rate of spontaneous miscarriage and may be considered.	Consensus-based recommendation 3, 4

4.3 What is the role of progestogen supplementation in women with a history of recurrent miscarriage?

In women with a history of unexplained recurrent miscarriage the PROMISE trial[5] showed no difference in the rate of miscarriage in women using vaginal micronized progesterone compared to placebo. This trial included 836 women who conceived spontaneously who were randomly assigned to receive either twice-daily progesterone from 6-12 weeks' gestation (404 women) or placebo (432 women). The live birth rate by intention to treat analysis was 66% in the trial group and 63% controls (RR 1.04; 95% CI 0.94 to 1.15. There were no significant differences in adverse events.

By contrast, a recent meta-analysis[6] of ten trials including 1,586 women with recurrent miscarriage showed that women with a history of unexplained recurrent miscarriage who were randomised to receive progestogens in the first trimester had a lower risk of miscarriage (RR 0.72; 95% CI 0.53 to 0.97). However, the addition of the negative result of the PROMISE trial to this meta-analysis would likely eliminate any significant benefit of progestogens in this context.

It should be noted that there is significant heterogeneity in the clinical trials of progestogens and the possibility of a benefit from some forms of progestogen supplementation in women with recurrent miscarriage cannot be excluded. Further well-designed studies are required to address this question, but at this stage there is insufficient evidence to support this practice and it is not recommended outside of the setting of appropriately designed clinical trials.

Recommendation 3	Grade and reference
The routine use of progestogens for patients presenting with recurrent spontaneous miscarriage does not improve pregnancy outcomes and is not recommended.	Consensus-based recommendation [5, 6]

4.4 What is the role of luteal phase progestogen support in assisted reproductive technologies?

For luteal **support in in vitro fertilisation (IVF)**, exogenous progesterone is associated with a significantly higher pregnancy rate than placebo or no treatment, with better results obtained with synthetic progestogens than micronized progesterone.[9,7] Furthermore, there is no evidence to favour a specific route or duration of administration of progestogens. Currently, synthetic progesterone is the best option for luteal phase support in women undergoing ART treatment.

A recent non-inferiority randomised controlled trial demonstrated equal efficacy and tolerability of oral dydrogesterone and vaginal micronized progesterone. It is important to note that in this study luteal support was continued to 12 weeks' gestation which is not routine practice.

Recommendation 4	Grade and reference
Luteal phase support with synthetic progestogens should be provided in in vitro fertilisation (IVF) as it is associated with an improved live birth rate.	Consensus-based recommendation [7]

5. References

1. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev. 2013(10):CD003511.
2. Practice Committee of the American Society for Reproductive M. The clinical relevance of luteal phase deficiency: a committee opinion. Fertil Steril. 2012;98(5):1112-7.
3. Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. The Cochrane database of systematic reviews. 2011(12):CD005943.
4. Carp H. A systematic review of dydrogesterone for the treatment of threatened miscarriage. Gynecol Endocrinol. 2012;28(12):983-90.
5. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al. A Randomized Trial of Progesterone in Women with Recurrent Miscarriages. The New England journal of medicine. 2015;373(22):2141-8.
6. Saccone G, Schoen C, Franasiak JM, Scott RT, Jr., Berghella V. Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. Fertil Steril. 2017;107(2):430-8 e3.
7. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015(7):CD009154.
8. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. The Cochrane database of systematic reviews. 2008(2):CD003511.
9. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. The Cochrane database of systematic reviews. 2011(10):CD009154.
10. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Hum Reprod. 2017;32(5):1019-27.

6. Links to other College statements

1. Evidence-based Medicine, Obstetrics and Gynaecology (C-Gen 15)
http://www.ranzcog.edu.au/component/docman/doc_download/894-c-gen-15-evidence-based-medicine-obstetrics-and-gynaecology.html?Itemid=341

7. 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

8. 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, Obstetric
Associate Professor Lisa Hui	Member
Associate Professor Ian Pettigrew	EAC Representative
Dr Tal Jacobson	Member
Dr Ian Page	Member
Dr John Regan	Member
Dr Craig Skidmore	Member
Professor Susan Walker	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 Contributing Authors

The Women's Health Committee acknowledges the contribution from Prof Roger Hart.

Appendix C 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 2009 and was most recently reviewed in March 2018. The Women's Health Committee carried out the following steps in reviewing this statement:

- Structured clinical questions were developed and agreed upon.
- An updated literature search to answer the clinical questions was undertaken.
- At the March 2018 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 ii).

ii. 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 D 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.