



RANZCOG position Assisted reproductive treatment for women of advanced maternal age

This RANZCOG position has been developed and reviewed by the Women's Health Committee, and has also been reviewed by RANZCOG CREI subspecialists. This position has been 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 Women's Health 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: November 2013

Current: November 2017

Review due: November 2020

Objectives: To provide a RANZCOG position on the provision of Assisted Reproductive Treatment for women of advanced maternal age.

Target audience: All health practitioners providing Assisted Reproductive Treatment, and patients.

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 of this position was funded by RANZCOG.

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1. Patient Summary

It becomes increasingly difficult for women to become pregnant once they reach, and advance past, the mid- to late-forties. In many cases, women in this age group who wish for pregnancy will consider the use of eggs, or less commonly embryos, donated from a younger woman. Women considering this decision, regardless of whether they are attempting IVF with their own gametes, or plan to use donated eggs/embryos, need to be aware that they face an increase in the risk of complications in pregnancy, including diabetes, high blood pressure, serious bleeding during pregnancy, thrombosis as well as risks to the neonate.

It is important to note that women with pre-existing co-morbidities may be at higher risk and this should be considered when making an assessment on age. There is an increased risk of pre-existing co-morbidities with increasing maternal age.

Before fertility treatment, women aged 45 years and older should be informed about the increased risks of complications of pregnancy, with the discussion specifically taking into account the woman's personal health and circumstances. In some cases, it will be safer not to become pregnant.¹

2. Definition of advanced maternal age

The writing group recognises that it is difficult to specifically define advanced maternal age. Different studies have used different definitions of advanced maternal age. A suggested approach is to define advanced maternal age as over 45 years of age at time of treatment.

3. Introduction

The use of donated oocytes/embryos in assisted reproductive treatment (ART) is common in Australia and New Zealand. Data published by ANZARD in 2016 showed that there was a total of 2684 recipient cycles, and 1058 egg donation cycles. Of the 2684 recipient cycles, 37.8% were to women aged 40-44, and 24.8% to women 45 years or older.²

The number of women who undergo treatment with donated oocytes in countries other than Australia and New Zealand is unknown, but estimates have been published suggesting that approximately 500 babies are delivered each year following conception with donated oocytes from overseas.

Most studies of the obstetric outcomes of pregnancy at advanced maternal age have included both women who conceived naturally, and those with ART. Several studies have been published regarding outcomes of donor oocyte pregnancies, but the sample sizes are relatively small (numbering in the low hundreds) and likely result from very rigorous maternal pre-pregnancy screening, so it is not possible to comment on their generalisability.³⁻⁵ Since severe adverse outcomes of pregnancy, including maternal death, stroke and myocardial infarction are rare, it is difficult to ascertain true relative risks from such case series without population data.

However, increasing maternal age is closely associated with increasing risk of most adverse outcomes of pregnancy, including gestational diabetes, hypertensive disorders, antepartum haemorrhage, pulmonary embolism, stillbirth and maternal death.⁶⁻¹¹

It is well recognised that the prevalence of established cardiovascular disease increases with increasing age in women. Reduced cardiac reserve, and associated established cardiovascular disease, exposes older pregnant women to greater risk when they are pregnant, especially given the large increase in cardiac

output during pregnancy. They may be further seriously challenged by life threatening obstetric complications such as major haemorrhage or severe pre-eclampsia.

The study by Fitzpatrick et al¹² compared older women age 48 or more to a younger comparison group. The women of advanced maternal age were more likely than comparison women to be overweight (33% versus 23%, P = 0.0011) or obese (23% versus 19%, P = 0.0318), nulliparous (53% versus 44%, P = 0.0299), have pre-existing medical conditions (44% versus 28%, P < 0.0001), a multiple pregnancy (18% versus 2%, P < 0.0001), and conceived following assisted conception (78% versus 4%, P < 0.0001). Older women appeared more likely than gestational comparison women to have pregnancy complications including gestational hypertensive disorders, diabetes, postpartum haemorrhage, caesarean delivery, iatrogenic and spontaneous preterm delivery on univariable analysis and after adjustment for demographic and medical factors.

Women of advanced maternal age are more likely to have co-morbidities and, as group, are at a greater risk of most adverse outcomes of pregnancy. What is yet to be clearly established, however, is the level of risk for women who are in good health with no risk factors. In the Fitzpatrick study, adjustment for multiple pregnancy or use of assisted conception attenuated most effects, with significant associations remaining only with gestational diabetes (adjusted odds ratio [aOR] 4.81, 95% CI 1.93–12.00), caesarean delivery (aOR 2.78, 95% CI 1.44–5.37) and admission to an intensive care unit (aOR 33.53, 95% CI 2.73–412.24).

Women of advanced maternal age receiving ART should avoid multiple pregnancy, and should only receive single embryo transfer. This is a particular issue and concern for women receiving ART overseas, sometimes in centres where less importance is placed on the importance of single embryo transfer. Women need to be counselled that their chance of becoming pregnant, given a suitable donor, is comparable to that of younger women.

4. Evidence summary and basis for recommendations

Although data regarding pregnancy outcomes are limited by the numbers of patients and pregnancies studied, there are significant risks for older women and in particular, women with any pre-existing cardiovascular disorder or with risk factors for cardiovascular disease. For this reason, extreme caution should be exercised during pre-treatment assessment of women, counselling and informed consent, and during treatment.

It is vital that the recipients of ART at an advanced maternal age undergo additional testing over and above that of routine fertility investigation. Full cardiovascular evaluation is recommended, and this evaluation is undertaken before any ART is commenced. This includes assessment of non-modifiable risk – family history of heart disease – as well as modifiable risk: smoking, either active or passive; increased cholesterol and abnormal lipid profile; hypertension; pre-existing diabetes; physical inactivity; overweight or obesity; depression, social isolation, and lack of quality support.

Recommendation 1	Grade and reference
Older women should be assessed for cardiovascular risk and other serious co-morbidities. If indicated, referral to a medical practitioner with the necessary expertise to assess these risks.	Consensus-based recommendation

Recommendation 2	Grade and reference
Where the clinician feels the risks preclude treatment a second opinion should be sought.	Consensus-based recommendation
Recommendation 3	Grade and reference
Before undergoing ART, older women should give informed consent that includes: <ul style="list-style-type: none"> a. detailed written information with respect to the risks to both themselves and any offspring; and b. an appreciation of the risk of mortality, permanent disability or other serious morbidities that may result from ART procedures, and from medical complications in any resulting pregnancy 	Consensus-based recommendation
Recommendation 4	Grade and reference
Creating multiple pregnancies should be avoided.	Consensus-based recommendation
Recommendation 5	Grade and reference
A Fellow should consider whether it is unethical to assist a patient to obtain ART overseas in circumstances where their cardiovascular risk is such that the ART being obtained overseas would not be considered reasonable and ethical practice in Australia or New Zealand.	Consensus-based recommendation

5. References

1. Shufaro YS, JG. The risks and outcome of pregnancy in an advanced maternal age in oocyte donation cycles. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* 2014;27(16):1703-9.
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3. Antinori S, Gholami GH, Versaci C, Cerusico F, Dani L, Antinori M, et al. Obstetric and prenatal outcome in menopausal women: a 12-year clinical study. *Reproductive biomedicine online.* 2003;6(2):257-61.
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6. AIHW. Cardiovascular disease: Australian facts 2011. . Canberra: AIHW: 2011.
7. Luke B, Brown MB. Elevated risks of pregnancy complications and adverse outcomes with increasing maternal age. *Human reproduction.* 2007;22(5):1264-72.
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10. Callaway LK LK, McIntyre HD. . Pregnancy outcomes in women of very advanced maternal age. The Australian & New Zealand journal of obstetrics & gynaecology. 2005;45:12-6.
11. Ludford I SW, Tucker G, Grivell R. Pregnancy outcomes for nulliparous women of advanced maternal age in South Australia, 1998-2008. The Australian & New Zealand journal of obstetrics & gynaecology. 2012;52(3):235-41.
12. Fitzpatrick KT, D. Kurinczuk, JJ. Knight, M. Pregnancy at very advanced maternal age: a UK population-based cohort study. BJOG : an international journal of obstetrics and gynaecology. 2017;124(7):1097-106.

6. Links to other College statements

[Cross border reproductive care \(C-Gyn 36\)](#)

[Evidence-based Medicine, Obstetrics and Gynaecology \(C-Gen 15\)](#)

[Pre-pregnancy Counselling \(C-Obs 03a\)](#)

7. Appendices

A Appendix A Women's Health Committee Membership

Name	Position on Committee
Professor Yee Leung	Chair
Dr Joseph Sgroi	Deputy Chair, Gynaecology
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
Associate Professor Janet Vaughan	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 RANZCOG position

i. Steps in developing this RANZCOG position

This RANZCOG position was developed in 2013. The Women's Health Committee carried out the following steps in developing this position:

- Declarations of interest were sought from all members prior to developing this position. No conflicts of interest were present.
- Structured clinical questions were developed.
- A literature search was undertaken to answer the clinical questions.
- A draft was prepared and recommendations were graded as set out below in Appendix B part iii).
- The draft was circulated to RANZCOG CREI sub-specialists for comment.
- At the July 2017 face-to-face committee meeting, Women's Health Committee reviewed this position and suggested edits.
- At the November 2017 face-to-face committee meeting, Women's Health Committee reviewed this position and approved the statement.

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 position 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.⁸ 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 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.

Categorically denying older women a biologically available option to reproduce contradicts their rights and personal freedom.

On the other hand, it is our duty to protect these women from harm via sound and transparent guidelines which will assure that pregnancy will be achieved safely and result in a good outcome.

Even when all screening tests turn out to be negative, we believe that an absolute line should eventually be drawn. The precise position of this line should be in accordance to specific social and medical factors such as culture, religion, life expectancy, quality of medical care and antenatal management.

Such an age limitation should be periodically revised and updated in accordance to life expectancy, the level of the available medical support and social trends. Just as the currently feasible pregnancy at age 50 would have been considered extremely risky 20 years ago, we foresee that if (and where) the life expectancy and life quality parameters continue to rise, the currently accepted age limit will become obsolete and a new one will be established in accordance to timely circumstances.