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

Tamoxifen and the endometrium

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.

The committee will acknowledge contributing authors in Appendix B.

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: May 1996
Current: July 2019
Review due: July 2022

Target audience: Health professionals providing gynaecological 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 May 1996 and most recently reviewed in July 2019.

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

Table of contents

1. Plain language summary

Tamoxifen is commonly used as endocrine therapy for oestrogen-receptor positive breast cancer and is a safe and effective medication. Because of the potential for hormone-like effects, tamoxifen can cause benign changes in the lining of the uterus. In post-menopausal women there is a very small chance of cancer of the lining of the uterus with longer-term use. This risk is low and should not stop women from using tamoxifen to reduce their risk of recurrence of breast cancer. However, it is important that postmenopausal women who are taking tamoxifen have a plan for careful follow-up and investigation of any vaginal bleeding.

2. Discussion and summary of recommendations

Tamoxifen is the endocrine treatment of choice for selected patients with breast cancer. In women with oestrogen-receptor positive breast cancer, tamoxifen reduces the risk of breast cancer recurrence, new breast cancers and mortality from breast cancer. In premenopausal women at high inherited risk of breast cancer, tamoxifen reduces breast cancer risk. Tamoxifen is a Selective oEstrogen Receptor Modulator (SERM) with anti-oestrogen effects in the breast but oestrogenic effects in other tissues including blood (increased VTE risk), bone and endometrium.

2.1 Gynaecological effects of tamoxifen

- Oestrogen-like changes in the vaginal epithelium of some patients.
- Stimulation of endometriosis, with worsening of symptoms in some patients. Stimulation of the growth of benign fibroids.
- In premenopausal women prescribed Tamoxifen for risk reduction, its effect on ovarian function, and consequently bleeding pattern, is not known.

2.2 Endometrial effects

- Benign cystic hyperplasia – cystic dilated endometrial glands with condensed peri-glandular stroma and atrophic overlying epithelium giving an ultrasound appearance falsely suggestive of cystic endometrial hyperplasia.[3]
- An increased incidence of benign endometrial polyps (some with the same histopathological appearance as above), endometrial proliferation and hyperplasia.
- Women with endometrial pathology prior to starting tamoxifen have a statistically significant higher risk of developing lesions at two years compared to patients that did not have a pre-existing endometrial lesion.[1]
- An increased risk of endometrial adenocarcinoma in postmenopausal (but not premenopausal) tamoxifen (RR = 4.01).[4] The cumulative risk of endometrial cancer with Tamoxifen use is 1.6% at five years and 3.1% if used for 5-14 yrs.[2] .
- Population based data suggest a small increase in the risk of uterine sarcoma with Tamoxifen.[5]

2.3 Other effects

Tamoxifen can induce ovulation and may be teratogenic.

2.4 Screening for endometrial changes

Routine screening of asymptomatic women taking Tamoxifen, using either ultrasound or endometrial biopsy, is not recommended. The incidence of endometrial carcinoma is very low (2-3/1000 women per year) during or after Tamoxifen therapy; asymptomatic tamoxifen users do not need to be investigated for endometrial pathology.

Management of asymptomatic postmenopausal women with an incidental finding of a thickened endometrium on ultrasound scan is controversial. The presence of typical Tamoxifen-related changes detected on ultrasound alone without vaginal bleeding may not require further endometrial assessment. Decisions about endometrial sampling in asymptomatic women should be individualised depending on the presence of other endometrial cancer risk factors such as obesity, hypertension, family history[10] and duration of use, particularly after 2 years. In a longitudinal cohort study that included 151 breast cancer survivors on Tamoxifen undergoing hysteroscopic endometrial surveillance, no cases of atypia were observed in women with endometrial thickening in the absence of abnormal uterine bleeding[11]. An incidental finding of an endometrial polyp should be managed as if the patient was symptomatic.

The LNG-IUS should not be used to prevent endometrial cancer in women on Tamoxifen. A Cochrane Review did not find clear evidence that the LNG-IUS prevents endometrial cancer in women with breast cancer on Tamoxifen[6]. There was also no conclusive data on whether the risk of breast cancer recurrence or breast cancer-related deaths increased with use of the LNG-IUS.

2.5 Managing pregnancy risk

Pre-menopausal women with oestrogen-sensitive breast cancers on Tamoxifen, and those at high risk for breast cancer that are taking Tamoxifen to reduce their breast cancer risk, should be advised to use non-hormonal methods of contraception

Case reports have suggested that tamoxifen use in pregnancy may increase risk of congenital abnormalities. A month wash out period is recommended between ceasing the medication and attempting conception.

Recommendation 1	Grade
All women taking Tamoxifen should be informed of its potential side effects, including specifically an increased risk of endometrial cancer in postmenopausal women (RR = 4.01).[4]	Consensus-based recommendation
Recommendation 2	**Grade**
In the presence of abnormal gynaecological symptoms e.g. bleeding, appropriate investigation should be undertaken, with low threshold for biopsy due to the difficulties with imaging.	C
Recommendation 3	**Grade**
Routine screening of asymptomatic women taking Tamoxifen, using either ultrasound or endometrial biopsy, is not recommended.	C
Recommendation 4	**Grade**
If ultrasound assessment is indicated, a vaginal ultrasound is preferred and should be performed by a clinician skilled in the interpretation of gynaecological ultrasound.	Consensus-based recommendation
Recommendation 5	**Grade**
The incidental finding of a thickened endometrium on ultrasound, typical of Tamoxifen effect, in the absence of vaginal bleeding or additional risk factors, may not require further investigation.	C
Recommendation 6	**Grade**
There is insufficient data to support the safety or efficacy of LNG IUS in the prevention of Tamoxifen-associated endometrial cancer.[6, 7, 8]	Consensus-based recommendation
Recommendation 7	**Grade**
Premenopausal women on Tamoxifen should be offered non-hormonal forms of contraception. Tamoxifen can induce ovulation and may be teratogenic.	Consensus-based recommendation

3. References

1. Berliere M, Radikov G, Galant C, Piette P, Marbaix E, Donnez J. Identification of women at high risk of developing endometrial cancer on tamoxifen, Eur J Cancer. 2000;36 Suppl 4:S35-6.

2. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial, Lancet. 2013;381(9869):805-16.

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Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuv ant tamoxifen: A cochrane review summary. Maturitas 2016 Jul;89:1-2. doi: 10.1016/j.maturitas.2016.03.009. Epub 2016 Mar 15.

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10. Wolfman W. No. 249-Asymptomatic Endometrial Thickening. J Obstet Gynaecol Can. 2018 May;40(5):e367-e377. doi: 10.1016/j.jogc.2018.03.005.

11. Saccardi C, Gizzo S, Patrelli TS, Ancona E, Anis O, Di Gangi S, Vacilotto A, D'Antona D, Nardelli GB. Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation: observational longitudinal cohort study. Endocr Relat Cancer. 2013 Jun 24;20(4):455-62. doi: 10.1530/ERC-13-0020. Print 2013 Aug.

4. Other suggested reading

Gynaecologic Surveillance of Women on Tamoxifen: First Do No Harm, Editorial, Runowicz, Carolyn D. MD, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY. Journal of Clinical Oncology (C) 2000 American Society of Clinical Oncology; Volume 18 (20): 3457-3458.

Barakat RR, Gilewski TA, Almadrones L, Saigo PE, Venkatraman E, Hudis C, Hoskins WJ. Effect of Adjuvant Tamoxifen on the Endometrium in Women with Breast Cancer: A Prospective Study Using Office Endometrial Biopsy. Journal of Clinical Oncology (C) 2000 American Society of Clinical Oncology; Volume 18 (20): 3459-3463.

Gerber B, Krause A, Muller H, Reimer T, Kulz T, Makovitzky J, Kundt G, Friese K. Effects of Adjuvant Tamoxifen on the Endometrium in Postmenopausal Women with Breast Cancer: A Prospective Long-Term Study Using Transvaginal Ultrasound. Journal of Clinical Oncology (C) 2000 American Society of Clinical Oncology; Volume 18 (20): 3464-3470.

Fung MF, Reid A, Faught W, Le T, Chenier C, Verma S, Brydon E, Fung KF. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol 2003 Oct; 91 (1): 154-9.

Fleischer AC, Wheeler JE, Lindsay I, Hendrix SL, Grabill S, Kravitz B, MacDonald B. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. Am J Obstet Gynecol 2001 Jan; 184 (2): 70-5.

Geller BA, Vogel VG. Chemoprevention of breast cancer in postmenopausal women. Breast Dis 2005-2006; 24: 79-92.

eviQ Cancer Institute New South Wales. Breast Adjuvant Tamoxifen: https://www.eviq.org.au/medical-oncology/breast/adjuvant/32-breast-adjuvant-tamoxifen#11981

5. Links to other related College statements

Consent and the Provision of Information to Patients in Australia regarding Proposed Treatment (C-Gen 02a) https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20General/Consent-and-provision-of-information-to-patients-in-Australia-(C-Gen-2a)-Review-July-2016.pdf?ext=.pdf

Consent and the Provision of Information to Patients in New Zealand regarding Proposed Treatment (C-Gen 02b) https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20General/Consent-and-provision-of-information-NZ-(C-Gen-2b)-Review-March-2016.pdf?ext=.pdf

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

6. 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 and Board Member
Dr Gillian Gibson	Deputy Chair, Gynaecology
Dr Scott White	Deputy Chair, Obstetrics and Subspecialties Representative
Associate Professor Ian Pettigrew	Member and EAC Representative
Dr Kristy Milward	Member and Councillor
Dr Will Milford	Member and Councillor
Dr Frank O'Keeffe	Member and Councillor
Professor Sue Walker	Member
Dr Roy Watson	Member and Councillor
Dr Susan Fleming	Member and Councillor
Dr Sue Belgrave	Member and Councillor
Dr Marilyn Clarke	ATSI Representative
Associate Professor Kirsten Black	Member
Dr Thangeswaran Rudra	Member
Dr Nisha Khot	Member and SIMG Representative
Dr Judith Gardiner	Diplomate Representative
Dr Angela Brown	Midwifery Representative
Ms Ann Jorgensen	Community Representative
Dr Rebecca Mackenzie-Proctor	Trainee Representative
Prof Caroline De Costa	Co-opted member (ANZJOG member)

Appendix B Contributing Authors

The Women's Health Committee acknowledges the contribution of Professor Martha Hickey and Dr Paul Cohen to this document.

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 May 1996 and was most recently reviewed in July 2019. 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 May 2019 teleconference, 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 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.