



Diethylstilboestrol (DES) exposure in utero

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.

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.

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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 November 2006 and reviewed in March 2018.

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1. Patient summary

Diethylstilboestrol (DES) is a synthetic oestrogen prescribed from the 1940's to the 1980's to reduce the risk of a pregnancy complication. However DES was subsequently shown to be ineffective in preventing miscarriage, premature labour or other pregnancy complications. DES has since been shown to interfere with the reproductive and endocrine system.

Women who were prescribed DES (DES mothers) are at an increased risk of developing breast cancer.

Women who were exposed to DES in utero (DES daughters) because their mother took DES during that pregnancy are at an increased risk of breast cancer, rare vaginal and cervical clear cell adenocarcinoma (CCA), precancerous changes to the cells in the vagina and cervix, fertility problems and pregnancy problems. These women also have higher rates of structural abnormalities of the uterus; these are associated with increased perinatal risks of preterm birth and reproductive loss.

Men who were exposed to DES in utero (DES sons) because their mother took DES during that pregnancy are at an increased risk of testicular abnormalities but not testicular cancers or fertility problems.

More research is required to determine the health risks of the grandchildren (DES third generation) of DES mothers.

2. Summary of recommendations

Good Practice Point 1	Reference
The DES mother has a 30% increased risk of developing breast cancer and breast cancer related death. DES mothers should have regular health checks, in particular breast screening.	4
Good Practice Point 2	Reference
DES mothers should be encouraged to inform their children who had in utero exposure to DES	4
Good Practice Point 3	Reference
DES daughters should have a lifetime annual gynaecological examination consisting of a general examination, colposcopic inspection of the lower genital tract, cervical co-test (HPV and LBC test) and bimanual examination to detect any vaginal induration. Documentation of reproductive tract structural abnormalities should be noted.	NCSP 2016 Guidelines
Good Practice Point 4	Reference
DES daughters should have regular breast examination and screening as is recommended for all women.	Consensus-based recommendations

Good Practice Point 5	Reference
DES sons should have documentation of any testicular abnormalities	Consensus-based recommendations
Good Practice Point 6	Reference
DES third generation do not require any additional specific follow up. However long term follow-up should be considered in the absence of any specific data for this cohort These women should be screened with a Cervical Screening Test (CST) every 5 years. However, if these women have concerns, testing similar to that recommended for their DES-exposed mothers could be considered on an individual basis.	NCSP 2016 Guidelines
Good Practice Point 7	Reference
Women exposed to DES in utero, who have a screen detected abnormality, should be managed by an experienced colposcopist.	NCSP 2016 Guidelines

3. Introduction

Diethylstilboestrol (DES) is a synthetic oestrogen prescribed from the 1940's to the 1980's to reduce the risk of a miscarriage, premature labour and other pregnancy complications. Although the efficacy of DES was questioned in a 1953 report, the drug continued to be prescribed until the 1980's.¹

In 1971 it was reported that in utero exposure to DES was strongly associated with the development of vaginal (and cervical to a lesser extent) clear cell adenocarcinoma (CCA) in young women.² This study helped researchers subsequently identify the drug as a teratogen. Other lifetime health risks have since been identified for the DES mother, DES daughter and son. There is no evidence of increased health risk for the DES third generation but research is continuing in this area.

Over 10 million people were exposed to DES worldwide. Of these, over 4 million women were exposed in utero. Approximately 10,000 of these women were in Australia.

4. Evidence Summary and Basis for Recommendations

4.1 Health risks for DES mothers

DES mothers have been found to have an increased risk of developing breast cancer (1.27 x the risk of the general population)³ and breast cancer related death⁴ There has been no increase in incidence of any other cancers.⁵

4.2 Health risks for DES daughters

4.2.1 Vaginal and cervical cancer and DES daughters

As of April 2015, there have been 775 reported cases of vaginal and cervical clear cell adenocarcinoma (CCA) worldwide. 2/3 of these cases are in women with in utero exposure to DES (<http://www.cdc.gov/des/hcp/nurses/history.html>). The majority of cancers in DES patients are diagnosed as Stage I or II disease with reported survival rates of 80-90%

The risk of DES daughters developing CCA is estimated to be 1.5/1000. Expressed differently, this is about 40 times increase in risk when compared with the unexposed population. The peak incidence of these tumours in exposed women is age 15-25 with a range reported from age 7-62. As the youngest DES affected women will only be menopausal in 2030-2040, it is unknown whether these women will be at an additionally increased risk of CCA compared with the general population that also experiences a peak in incidence at this age. The increased risk may be lifelong.⁶

4.2.2 Vaginal and cervical pre-invasive changes

DES daughters are frequently observed to have a large cervical ectropion resulting in relatively greater areas of immature metaplasia on the cervix and vagina compared with an unexposed population.⁷ DES daughters have a 2.28 fold increase risk of high grade cervical and vaginal intraepithelial neoplasia.⁸ However, with close monitoring and early treatment, this has not resulted in an increased incidence of squamous cell cancer either of the cervix or vagina.⁹

Vaginal adenosis has been reported in 33 – 50% of DES daughters.¹⁰ The significance of the presence of adenosis in the development of CCA of the vagina is not established and the tumour does not necessarily develop in an area of adenosis. With time, adenosis usually undergoes metaplastic change and is replaced by normal squamous epithelium.⁷

4.2.3 Clear cell carcinoma and Oncogenic HPV

In a recent systematic review, "19 studies were identified that tested for the presence of HPV DNA in samples of clear cell carcinoma of the cervix or vagina. Overall, oncogenic HPV was detected in about one third of the 158 samples of clear cell carcinoma of the cervix.¹¹ For this reason it would be prudent to continue to include cytology of the cervix in annual 'screening' in addition to testing for oncogenic HPV: ie Cervical co-test.

4.2.3 Breast cancer

Combined results of cohort studies in the US suggest DES daughters have a 1.82 fold increased risk of developing breast cancer after age 40.^{8 12} This increased risk was not confirmed in a 2010 European study.⁶

4.2.4 Reproductive tract structural abnormalities

Uterine malformations have been reported in up to 69% of DES exposed women and include a T-shaped uterine cavity, hypoplastic uterus and endometrial adhesions.¹³ Cervical malformations have been found in 25-33% of exposed women and include hypoplasia, cervical hood, collar and polyps.¹⁴ Some of these changes may result in pregnancy related complications.

4.2.5 Pregnancy complications

Women exposed to DES in utero appear to have high rates of subfertility, miscarriage, preterm birth and ectopic pregnancy. These may be explained by the structural abnormalities described above. Higher rates of pre-eclampsia and still birth have also been reported. The hazard ratios are summarised in the Table 1.⁸

Adverse Outcome	Exposed Women	Unexposed Women	Hazard Ratio (95% CI) †
	<i>no./total no.</i>		
Infertility	1144/3769	252/1654	2.37 (2.05 to 2.75)
Spontaneous abortion‡	916/2690	328/1291	1.64 (1.42 to 1.88)
Ectopic pregnancy‡	255/2692	36/1293	3.72 (2.58 to 5.38)
Loss of second-trimester pregnancy‡	201/2692	35/1293	3.77 (2.56 to 5.54)
Preterm delivery§	624/2385	100/1238	4.68 (3.74 to 5.86)
Preeclampsia§	216/2412	80/1159	1.42 (1.07 to 1.89)
Stillbirth§	54/2385	16/1239	2.45 (1.33 to 4.54)
Neonatal death§	57/2383	7/1238	8.12 (3.53 to 18.65)
Early menopause	181/3993	49/1682	2.35 (1.67 to 3.31)
Cervical intraepithelial neoplasia, grade ≥2	208/4120	40/1785	2.28 (1.59 to 3.27)
Breast cancer at ≥40 yr	61/3693	21/1647	1.82 (1.04 to 3.18)
Clear-cell adenocarcinoma	4/4652	0/1926	∞ (0.37 to ∞)

* Total numbers of women vary among outcomes, primarily reflecting whether all, gravid, or parous women were included in the analyses, but also owing to some missing responses to the questionnaires ascertaining the outcome and to missing covariates. CI denotes confidence interval.

† Hazard ratios were calculated with age as the time metric and adjustment for date of birth and cohort.

‡ The analysis was restricted to gravid women and adjusted for number of pregnancies.

§ The analysis was restricted to parous women and adjusted for number of births.

4.2.6 Other health risks

The results of these indicate that exposed women may experience menopause slightly earlier.^{8, 15}

Studies regarding a link to autoimmune diseases¹⁶, psychiatric diseases¹⁷ and obesity¹⁸ have not been able to establish an association. As the youngest cohort of DES daughters are expected to become menopausal in 2020-2030, longer term studies are required to determine the health outcomes of these women.

4.3 Health risks for DES sons

Male offspring are affected with an increase in the development of epididymal cysts, hypogonadism and undescended testes (approximately 2% of exposed men). No specific cancer risk has been established apart from the inherent risk of testicular cancer associated with undescended testes. DES sons do not appear to have an increased risk of infertility.¹⁹

4.4 Health risks for 3rd generation

It has been hypothesized that the next generation of children may be at increased risk of adverse health outcomes. This is based on animal studies suggesting DES may cause methylation changes to the DNA and these changes may be inherited. However a recent study showed adult women exposed to DES *in utero* had no evidence of large persistent changes in blood DNA methylation.²⁰

The number of events of cancer risk, reproductive tract structural abnormalities and infertility in DES third generation are currently too few in number to determine the health risk for this group. Longer term studies are required to determine the health effects.

5. Follow-up recommendations

- J DES mothers should have regular breast examination and screening as is recommended for all women.
- J DES mothers should be encouraged to inform their children who had in utero exposure to DES
- J DES daughters should have a lifetime annual gynaecological examination consisting of a general examination, colposcopic inspection of the lower genital tract, cervical co-test (HPV and LBC test) and bimanual examination to detect any vaginal induration. Documentation of reproductive tract structural abnormalities should be noted.
- J DES daughters should have regular breast examination and screening as is recommended for all women.
- J DES sons should have documentation of any testicular abnormalities
- J DES third generation do not require any additional specific follow up. However long term follow-up should be considered in the absence of any specific data for this cohort. These women should be screened with a Cervical Screening Test (CST) every 5 years. However, if these women have concerns, testing similar to that recommended for their DES-exposed mothers could be considered on an individual basis¹¹.

6. References

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7. Links to other College statements

Cytological follow up after hysterectomy (C-Gyn 08)

[https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Cytological-follow-up-after-hysterectomy-\(C-Gyn-8\)-Review-November-2015.pdf?ext=.pdf](https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Cytological-follow-up-after-hysterectomy-(C-Gyn-8)-Review-November-2015.pdf?ext=.pdf)

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

[https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20General/Evidence-based-medicine,-Obstetrics-and-Gynaecology-\(C-Gen-15\)-Review-March-2016.pdf?ext=.pdf](https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20General/Evidence-based-medicine,-Obstetrics-and-Gynaecology-(C-Gen-15)-Review-March-2016.pdf?ext=.pdf)

8. Useful Resources

[The National Cervical Screening Program: Guidelines for the management of screen- detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding.](#)

9. RANZCOG 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 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 Contributing Authors

The Women's Health Committee acknowledges the contribution of Prof Ian Hammond (FRANZCOG) to this statement.

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 2006 and was most recently reviewed in March 2018. 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 June 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 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 July 2018. 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.