CATEGORY: BEST PRACTICE STATEMENT

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

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.

First endorsed by RANZCOG: November 2006
Current: March 2021
Review due: March 2024

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. It was reviewed again in November 2020 in response to align the frequency of screening with national screening program.

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

Table of contents

1. Plain language 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 (known as 'stilboestrol' in New Zealand) 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, and this does not increase with age.

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

Recommendation 1	Level
DES mothers should have regular health checks, in particular breast screening.	Good Practice Point
Recommendation 2	**Level**
DES mothers should be encouraged to inform their children who had in utero exposure to DES.	Good Practice Point
Recommendation 3	**Level**
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.	Good Practice Point (Source: NCSP 2016 Guidelines, updated 2018)
Recommendation 4	**Level**
DES daughters should have regular breast examination and screening as is recommended for all women.	Good Practice Point
Recommendation 5	**Level**
DES sons should have documentation of any testicular abnormalities	Good Practice Point
Recommendation 6	**Level**

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) in accordance with national screening programs. However, if these women have concerns, testing similar to that recommended for their DES-exposed mothers could be considered on an individual basis.	Good Practice Point (Source: NCSP 2016 Guidelines, updated 2018)
Recommendation 7	**Level**
Women exposed to DES in utero, who have a screen detected abnormality, should be managed by an experienced colposcopist.	Good Practice Point (Source: NCSP 2016 Guidelines, updated 2018)

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. The drug (known as stilboestrol in New Zealand) was prescribed to about 1,000 New Zealand women. While the number of women in Australia who took DES is not known, it is estimated that approximately 15,000 women used the drug during pregnancy.[3] DES was prescribed to about 1,000 pregnant women in New Zealand.

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)[4] and breast cancer related death.[5] There has been no increase in incidence of any other cancers.[6]

4.2 Health risks for DES daughters

4.2.1 Vaginal and cervical cancer and DES daughters

As at April 2015, there were 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 at a younger age (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.[7]

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.[8] DES daughters have a 2.28 fold increase risk of high grade cervical and vaginal intraepithelial neoplasia.[9] 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.[10]

Vaginal adenosis has been reported in 33%-50% of DES daughters.[11] 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.[8]

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.[12] 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.

4.2.4 Breast cancer

On average, 1 in 7 Australian women, and 1 in 8 New Zealand women, will develop breast cancer in their lifetime. The DES mother has an approximate 30% increased risk of developing breast cancer and breast cancer related death (after covariate adjustment and based on higher dosages) than the risk for non-exposed women. [5]

Combined results of cohort studies in the US suggest DES daughters have a 1.82 fold increased risk of developing breast cancer after 40 years of age.[9, 13] This increased risk was not confirmed in a 2010 European study.[7]

4.2.5 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.[14] Cervical malformations have been found in 25-33% of exposed women and include hypoplasia, cervical hood, collar and polyps.[15] Some of these changes may result in pregnancy related complications.

4.2.6 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 below. Higher rates of pre-eclampsia and still birth have also been reported. The hazard ratios are summarised in Table 2.[9]

Table 2. Hazard Ratios for Adverse Health Outcomes in Women with and Those without Diethylstilbestrol (DES) Exposure.*

Adverse Outcome	Exposed Women	Unexposed Women	Hazard Ratio (95% CI)†
	no./total no.		
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.

4.2.7 Other health risks

The results of Table 2 indicate that exposed women may experience menopause slightly earlier. [9,16]

Studies regarding a link to autoimmune diseases [17], psychiatric diseases [18] and obesity [19] have not been able to establish an association. As the youngest cohort of DES daughters are expected to become menopausal in 2030-2040, 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. [20]

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. [21]

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

- DES mothers should participate in the national BreastScreen mammographic screening program.
    - BreastScreen Australia actively invites women aged 50-74 years to undergo free mammographic screening every two years.
    - BreastScreen Aotearoa provide eligible women aged between 45 and 69 years with free mammographic screening every two years.
- DES mothers should be encouraged to inform their children who had in utero exposure to DES.
- 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. Self-collection for HPV testing (5-yearly HPV testing) is not recommended.
- DES daughters should participate in national BreastScreen mammographic screening programs.
    - BreastScreen Australia actively invites women aged 40-49 years to undergo free mammographic screening every two years.
    - BreastScreen Aotearoa provide eligible women aged between 45 and 69 years with free mammographic screening every two years.
- DES sons should have documentation of any testicular abnormalities
- 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) in accordance with national screening programs (currently every 3 years in New Zealand; and every 5 years in Australia). However, if these women have concerns, testing similar to that recommended for their DES-exposed mothers could be considered on an individual basis. [12]

6. 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

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

7. Useful Resources

Australian Government Department of Health. BreastScreen Australia.
http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/breast-screening-1.

New Zealand Time to Screen. https://www.timetoscreen.nz/breast-screening/

The National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding. https://wiki.cancer.org.au/australia/Clinical_question:Oncogenic_HPV_types_not_16/18

8. 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

9. References

1 Dieckmann WJ, Davis ME, Rynkiewicz LM, Pottinger RE. Does the administration of diethylstilbestrol during pregnancy have therapeutic value? American journal of obstetrics and gynecology. 1953;66(5):1062-81.

2 Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the Vagina. New England Journalof Medicine. 1971;284(16):878-81

3 Cancer Council Australia Cervical Cancer Screening Guidelines Working Party. National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities,screening in specific populations and investigation of abnormal vaginal bleeding, Chapter 17. Screening in DES-exposed women. Cancer Council Australia. 2018. [Available at: https://wiki.cancer.org.au/australia/Clinical_question:DES-exposed_women#Systematic_review_evidence]

4 Titus-Ernstoff L, Hatch EE, Hoover RN, Palmer J, Greenberg ER, Ricker W, et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. Br J Cancer. 2001;84(1):126-33

5 Titus-Ernstoff L, Troisi R, Hatch EE, Palmer JR, Wise LA, Ricker W, et al. Mortality in women given diethylstilbestrol during pregnancy. Br J Cancer. 2006;95(1):107-11

6 Giusti RM, Iwamoto K, Hatch EE. Diethylstilbestrol revisited: a review of the long-term health effects. Ann Intern Med. 1995;122(10):778-88.

7 Verloop J, van Leeuwen FE, Helmerhorst TJ, van Boven HH, Rookus MA. Cancer risk in DES daughters. Cancer Causes Control. 2010;21(7):999-1007

8 Kaufman RH, Adam E. Findings in female offspring of women exposed in utero to diethylstilbestrol. Obstetrics and gynecology. 2002;99(2):197-200

9 Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, et al. Adverse health outcomesin women exposed in utero to diethylstilbestrol. The New England journal of medicine.
2011;365(14):1304-14

10 Hatch EE, Herbst AL. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States). Cancer Causes and Control 2002;12:837-45

11 O'Brien PC, Noller KL, Robboy SJ, Barnes AB, Kaufman RH, Tilley BC, et al. Vaginal epithelial changes in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) project. Obstetrics and gynecology. 1979;53(3):300-8

12 Hammond I, Saville M. The National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding 2017

13 Palmer JR, Wise LA, Hatch EE, Troisi R, Titus-Ernstoff L, Strohsnitter W, et al. Prenatal diethylstilbestrol exposure and risk of breast cancer. Cancer Epidemiol Biomarkers Prev.2006;15(8):1509-14

14 Kaufman RH, Adam E, Noller K, Irwin JF, Gray M. Upper genital tract changes and infertility in diethylstilbestrol-exposed women. American journal of obstetrics and gynecology. 1986;154(6):1312-8

15 Kaufman RH. Structural changes of the genital tract associated with in utero exposure to diethylstilbestrol. Obstet Gynecol Annu. 1982;11:187-202

16 Hatch EE, Troisi R, Wise LA, Hyer M, Palmer JR, Titus-Ernstoff L, et al. Age at natural menopause in women exposed to diethylstilbestrol in utero. Am J Epidemiol. 2006;164(7):682-8

17 Strohsnitter WC, Noller KL, Troisi R, Robboy SJ, Hatch EE, Titus-Ernstoff L, et al. Autoimmune disease incidence among women prenatally exposed to diethylstilbestrol. J Rheumatol. 2010;37(10):2167-73

18 Kebir O, Krebs MO. Diethylstilbestrol and risk of psychiatric disorders: a critical review and new insights. World J Biol Psychiatry. 2012;13(2):84-95

19 Hatch EE, Troisi R, Palmer JR, Wise LA, Titus L, Strohsnitter WC, et al. Prenatal diethylstilbestrol exposure and risk of obesity in adult women. J Dev Orig Health Dis. 2015;6(3):201-7

20 Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, et al. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. Environ Health. 2009;8:37

21 Harlid S, Xu Z, Panduri V, D'Aloisio AA, DeRoo LA, Sandler DP, et al. In utero exposure to diethylstilbestrol and blood DNA methylation in women ages 40-59 years from the sister study. PloS one. 2015;10(3):e0118757.

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 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 Ashleigh Seiler	Trainee Representative
Prof Caroline De Costa	Co-opted member (ANZJOG member)
Dr Christine Sammartino	Observer

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 reviewed routinely to March 2018. It was reviewed again in November 2020 in response to feedback of changes in the recommended screening frequency, aligned to national screening programs. It was most recent reviewed and updated in March 2021. 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)
- At the March 2021 Women's Health Committee (via Zoom), the existing good practice points were reviewed and updated (where appropriate) based on the available body of evidence and clinical expertise. These 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 andare 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 entirecommittee.

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

Purpose

This Guideline has been developed to provide general advice to practitioners about women's health issues concerning Diethylstilboestrol (DES) exposure in utero 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 person with DES exposure or a related condition. 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 person with DES exposure or a related condition and the particular circumstances of each case.

Quality of information

The information available in the Diethylstilboestrol (DES) exposure in utero is intended as a guide and provided for information purposes only. The information is based on the Australian and New Zealand context using the best available evidence and information at the time of preparation. While the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) had endeavoured 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. The use of this information is entirely at your own risk and responsibility.

For the avoidance of doubt, the materials were not developed for use by patients, and patients must seek medical advice in relation to any treatment. The material includes the views or recommendations of third parties and does not necessarily reflect the views of RANZCOG or indicate a commitment to a particular course of action.

Third-party sites

Any information linked in this guideline is provided for the user's convenience and does not constitute an endorsement or a recommendation or indicate a commitment to a particular course of action of this information, material, or content unless specifically stated otherwise.

RANZCOG disclaims, to the maximum extent permitted by law any responsibility and all liability (including without limitation, liability in negligence) to you or any third party for inaccurate, out of context, incomplete or unavailable information contained on the third-party website, or for whether the information contained on those websites is suitable for your needs or the needs of any third party for all expenses, losses, damages and costs incurred.

Exclusion of liability

The College disclaims, to the maximum extent permitted by law, all responsibility and all liability (including without limitation, liability in negligence) to you or any third party for any loss or damage which may result from your or any third party's use of or reliance of this guideline, including the materials within or referred to throughout this document being in any way inaccurate, out of context, incomplete or unavailable for all expenses, losses, damages, and costs incurred.

Exclusion of warranties

To the maximum extent permitted by law, RANZCOG makes no representation, endorsement or warranty of any kind, expressed or implied in relation to the materials within or referred to throughout this guideline being in any way inaccurate, out of context, incomplete or unavailable for all expenses, losses, damages and costs incurred.

These terms and conditions will be constructed according to and are governed by the laws of Victoria, Australia.