



C-Obs 8

Diethylstilboestrol (DES) Exposure in Utero

Diethylstilbestrol, a nonsteroidal oestrogen, was used from 1940 onwards to prevent miscarriage and avoid pregnancy complications. Discovered in 1938, it was predominantly used in Australia from 1946 onwards until 1971 when it was discovered that in utero exposure to DES was strongly associated with the development of vaginal (and cervical to a lesser extent) clear cell adenocarcinoma in young women. This rare tumour had previously only been seen in elderly women and the appearance of this tumour in a group of young women whose mothers had been given this drug during their pregnancies raised the alarm. To date, there have been almost 700 cases of clear cell adenocarcinoma (CCA) world wide and the risk of developing this complication in DES exposed women is estimated to be between 1/1000 and 1/15,000. The vast majority of these tumors occurred in the late teens and early 20's although there have been sporadic reports of cases occurring at virtually all ages (1). The unknown issue is whether there will be a second peak incidence of CCA when this group of women enter the age group at which CCA "naturally occurs", i.e., from the age of 60 years onwards. It is only now that the follow up group of DES exposed women are entering the age group of a possible second peak occurrence of this cancer.

It is estimated that up to 4 million women worldwide were exposed in utero to DES, 10,000 of which were in Australia. Although clinical trials conducted in the 1950's showed DES was not effective in preventing miscarriage, its use continued to a lesser extent up until 1971. From 1960 onwards, it was predominantly replaced by the use of Progestogens, but not completely.

Known Risks

Apart from the risks of developing this rare form of cancer, these women exposed in utero to DES were found to have significantly higher rates of miscarriage, cervical incompetence and ectopic pregnancy. This is due to structural abnormalities of the cervix and corpus uteri. Vaginal adenosis (the presence of glandular epithelium within the vagina) was seen in 50% of these women and the vast majority of them also had a large cervical ectropion resulting in vast areas of immature metaplasia on the cervix and vagina (2). This resulted in a slight increase in incidence of cervical and vaginal intraepithelial neoplasia but with close monitoring and early treatment, this has not resulted in an increased incidence of squamous cell cancer either of the cervix or vagina (3). 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 (2).

Male offspring were affected as well with the development of epididymal cysts, hypogonadism and undescended testes in a small number of offspring (2%). No specific cancer risk has been established apart from the inherent risk of testicular cancer associated with undescended testes (2).

The women who actually took the drug during their pregnancies (DES Mothers) have been found to have an increased risk of developing breast cancer (1.27 x the risk of the general population), predominantly from the age of 70 onwards (4). There has been no increase in incidence of any other cancers.

New Problems

The risk of a second peak of lower genital tract CCA is as yet unknown but as there is a theoretical possibility, close surveillance is mandatory to detect any early occurrence.

A prospective study by Prof. Julie Palmer from Boston (5), looking at the risk of breast cancer in women exposed in utero to DES has found a significant increased risk. It has been reported that a statistically significant 1.9 fold increased risk was observed among women aged 40 years and above compared to unexposed women of the same ages. For women 50 years and over, the risk was even higher but the relatively small number of cases as yet in this group makes the age gradient imprecise.

DES granddaughters i.e., daughters of the in utero DES exposed women, have not been found to have any increase in incidence of DES related problems. Animal models using nude mice have suggested a possible increase in risk of reproductive tract cancers (6) although this cannot be extrapolated to humans as the relative doses used were incomparable.

Screening Recommendations

- Women who have been exposed in utero to DES should have An annual gynaecological examination consisting of a general examination, separate cervical and vaginal Pap smears and a bimanual examination of the pelvis to detect any pelvic tumours or vaginal induration. Four quadrant Pap smears of the vagina are unnecessary and uncomfortable. A single sweep of the spatula or brush over the whole of the upper vagina is sufficient. Separate 4 quadrant vaginal smears would not be accurate enough to localize an abnormality and colposcopy would be required anyway if any abnormal cells were detected.
- The use of colposcopy to accurately assess the cervix and vagina should be offered to the woman although it is not strictly necessary in all women particularly if the transformation zone has receded into the endocervical canal. However, in view of the possible risk of a second peak in the development of vaginal CCA and the difficulty of obtaining thorough vaginal sampling via cytology alone would make it highly desirable that a careful colposcopic evaluation of the cervix and vagina be included in the annual examination.
- A breast examination should be performed at each annual check-up. Annual mammography is recommended for women aged 40 years and over in view of the recent reports of increased breast cancer risks in these age groups. Although radiation levels in mammography are low, women are encouraged to seek information from the Radiologist about risks of radiation exposure during mammography.
- DES Granddaughters (and grandsons) do not require any specific follow up but any abnormal bleeding should be carefully investigated along the usual lines.

The NHMRC (2005) advise the following guidelines for women exposed to DES in utero: (7, 8, 9)

DES-exposed women should be offered annual cytological screening and colposcopic examination of both the cervix and vagina.	Level IV (Hacker 2000, RCOG 2002)
Screening should begin any time at the women's request and continue indefinitely. A balanced perspective should be maintained.	Level IV (Hacker 2000, RCOG 2002)
DES-exposed women who have a screen-detected abnormality should be managed in a specialist centre by an experienced colposcopist.	Level IV (Hacker 2000, RCOG 2002)

References

1. Herbst AL. Diethylstilbestrol and adenocarcinoma of the vagina. *Am J Obstet Gynecol* 1999;181 (6):1576-8.
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3. Hatch EE, Herbst AL, et al. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States). *Cancer Causes and Control* 2002; 12: 837-845.
4. Titus-Ernstoff L, Hatch EE et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer* 2001; 84:125-33.
5. Palmer JR, Wise LA, et al. Prenatal Diethylstilbestrol Exposure and Risk of Breast Cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15 (8) 1509-14.
6. Newbold RR, Hanson RB, et al. Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. *Carcinogenesis* 1998; 19:1655-63.
7. NHMRC *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities*. NHMRC, Canberra, 2005. http://www.nhmrc.gov.au/publications/_files/wh39.pdf
8. Hacker NF. Vaginal carcinoma. In: *Practical Gynaecologic Oncology*, 3rd edition, Berek JS and Hacker NF (eds), Lippincott Williams and Wilkins, Philadelphia, 2000;605.
9. RCOG (Royal College of Obstetricians and Gynaecologists) (2002). Statement No. 2, April 2002. DES exposed in utero females.

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