



Setting standards to improve women's health

FETAL AND MATERNAL RISKS OF DIETHYLSTILBOESTROL EXPOSURE IN PREGNANCY

1. Introduction

Diethylstilboestrol (DES) was given to pregnant women in the belief that it would provide luteal support in situations such as threatened miscarriage or poor reproductive performance, in particular that associated with maternal diabetes.¹ It was widely used in the USA but less frequently in the UK and Europe from about 1940 onwards.

Two randomised controlled trials (RCTs) were conducted in the 1950s, one in the USA involving 2000 non-diabetic pregnant women² and one in the UK between 1950–3.³ In the latter, 80 women with diabetes received DES and ethisterone and were compared with 76 non-hormone-treated controls. Neither trial showed any benefit for the treated group. Nevertheless, the use of DES was still being described in a 1971 reprint of the third edition of TNA Jeffcoate's textbook, *Principles of Gynaecology*.

In 1970, Herbst and Skully reported seven cases of clear-cell adenocarcinoma (CCA) of the vagina⁴ and in 1971 Herbst identified an association with exposure to DES *in utero*.⁵ In May 1973, a letter from the Committee on Safety of Medicines alerted UK doctors to Herbst's reports but stated that, at that time, no similar cases had been found in the UK.⁶

2. Cancer risks to the female children

The only consistent risk appears to be that of vaginal CCA with an incidence of one in 1000 between birth and age 34 years in exposed individuals.⁷ The critical period of exposure appears to be before 18 weeks of gestation, as after the vagina is fully formed DES susceptibility is lost.

There appears to be a steep rise after age 14 years, suggesting an influence of puberty. If all CCA are considered, even excluding those associated with DES exposure, there are twin peaks of incidence at ages 26 and 71 years, suggesting possible pubertal and menopausal effects.⁸

No malignant tumours were reported in long-term follow-up of the children of the women in the UK RCT.⁹ Further UK data reveal reports of one case of vaginal cancer¹⁰ and one case of carcinoma *in situ* of the cervix.¹¹ In the West Midlands between 1974 and 1998 only eight primary vaginal cancers were recorded, of which only four were CCA in type. Only one of these cases had been exposed *in utero* to DES. A further six anecdotal cases were reported but, even allowing for under reporting, the scale of the problem in the UK appears to be small in relation to an estimate of approximately 10 000 mothers exposed.^{12,13}

This is reinforced by a review of Cancer Registry Data (Trent Region 1990–99), which shows no evidence of any increasing incidence of CCA in the relevant age cohort.¹⁴

However, in spite of the increased surveillance to which women known to have been DES-exposed *in utero* are subjected, studies suggest that the risk of invasive cervical cancer is increased two- to three-fold.^{15,16} No substantial excess of any other type of cancer has been observed.

One study has produced limited support for an increased risk of breast cancer in young women, but only vaginal CCA is consistently increased.¹⁷

3. Cancer risks to male children

Although one study showed a slight increase in testicular cancers, the numbers were small and the effect did not reach statistical significance.¹⁸ No cancers were found in the male children of women treated with DES in the UK RCT.⁹

4. Cancer risks to the mother

Long-term follow-up of the 80 mothers given DES in the UK RCT revealed four cases of breast cancer and none among the controls, suggesting a possible latent period of 15 years or longer before the tumour becomes apparent.¹⁹ Although these numbers were small, they point in the same direction as the larger studies conducted on women exposed in the USA, which indicate that there may be a modest increase in relative risk of breast cancer of 1.27 (0.95% CI 1.07–1.52).²⁰

5. Female fertility and pregnancy

The incidence of benign structural abnormalities of the reproductive tract following *in utero* exposure to DES is high. In one paper, 69% had uterine abnormalities, classically a hypoplastic, T-shaped uterus, while 44% had cervical abnormalities including collars, hoods, cockscombs etc.²¹

It has also been reported that the fallopian tubes are more likely to be ‘withered’ in appearance and to have paratubal cysts. There is no associated increase in renal abnormalities.^{22,23}

Pregnancy rates are not decreased, although the time to achieve pregnancy has not been evaluated. However, the risk of ectopic pregnancy would appear to be increased ten-fold while the risk of spontaneous miscarriage is doubled, as is the incidence of preterm labour. In this meta-analysis, 59% of women exposed to DES delivered at term, with a 76% livebirth rate, compared with 83% and 92%, respectively, in non-DES-exposed controls.²⁴

6. Male fertility

There appears to be some evidence from one study in the USA of a possible reduction of male fertility.²⁵ The long-term UK study⁹ showed a correlation between single status and higher dose exposure earlier in pregnancy implying a possible interference with sexual function.

7. Conclusions

It would be prudent for those women who believe they may have been exposed to DES *in utero* and who are anxious about the risks of vaginal and cervical cancer to be offered careful monitoring by annual colposcopic examinations in specialist centres.* These examinations should be commenced at the woman’s request at any point in her reproductive life or post-menopause, once she finds out she has been exposed to DES and is concerned. They should be repeated indefinitely for the reasons outlined below.

There is a need to be aware of the biphasic peaks of incidence of vaginal CCA, especially as exposed women will now be approaching their fifth decade.

Evidence for an increased risk of other cancers to both themselves and their mothers is less convincing but they would be sensible to participate in the National Breast Screening Programme.

Pregnant women who know that they were exposed *in utero* to DES should inform their obstetrician and be aware of the increased risks of ectopic pregnancy and preterm labour. Notwithstanding these risk factors, only a small minority of DES-exposed individuals will experience serious problems and proper perspective should be maintained.

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