Diethylstilbestrol Exposure

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Diethylstilbestrol is a synthetic nonsteroidal estrogen that was used to prevent miscarriage and other pregnancy complications between 1938 and 1971 in the United States. In 1971, the U.S. Food and Drug Administration issued a warning about the use of diethylstilbestrol during pregnancy after a relationship between exposure to this synthetic estrogen and the development of clear cell adenocarcinoma of the vagina and cervix was found in young women whose mothers had taken diethylstilbestrol while they were pregnant. Although diethylstilbestrol has not been given to pregnant women in the United States for more than 30 years, its effects continue to be seen. Women who took diethylstilbestrol during pregnancy have a slightly higher risk of breast cancer than the general population and therefore should be encouraged to have regular mammography. Women who were exposed to diethylstilbestrol in utero may have structural reproductive tract anomalies, an increased infertility rate, and poor pregnancy outcomes. However, the majority of these women have been able to deliver successfully. Recommendations for gynecologic examinations include vaginal and cervical digital palpation, which may provide the only evidence of clear cell adenocarcinoma. Initial colposcopic examination should be considered; if the findings are abnormal, colposcopy should be repeated annually. If the initial colposcopic examination is normal, annual cervical and vaginal cytology is recommended. Because of the higher risk of spontaneous abortion, ectopic pregnancy, and preterm delivery, obstetric consultation may be required for pregnant women who had in utero diethylstilbestrol exposure. The male offspring of women who took diethylstilbestrol during pregnancy have an increased incidence of genital abnormalities and a possibly increased risk of prostate and testicular cancer. Routine prostate cancer screening and testicular self-examination should be encouraged. (Am Fam Physician 2004:69:2395-400,2401-2.

A patient information handout on diethylstilbestrol, written by the authors of this article, is provided on page 2401.

See page 2291 for definitions of strength-of-recommendation labels.

Between 1938 and 1971, as many as 4 million women in the United States took diethylstilbestrol (DES), an oral synthetic nonsteroidal estrogen, for the purpose of improving pregnancy outcomes.[1,2] In 1953, it was demonstrated that DES did not prevent miscarriage and other pregnancy complications. However, physicians continued to prescribe DES to pregnant women until at least 1971, when a connection was established between in utero DES exposure and the development of clear cell adenocarcinoma of the vagina and cervix in the daughters of women who had taken DES during pregnancy.[3] In 1971, the U.S. Food and Drug Administration issued a warning against the use of DES in pregnant women.[4] DES continued to be used in various European countries until the early 1980s.

In 1971, the U.S. Food and Drug Administration warned against the use of diethylstilbestrol in pregnant women because of an increased risk of clear cell adenocarcinoma in female offspring.

The association between in utero DES exposure and vaginal clear cell adenocarcinoma has been well documented. Other adverse associations have been identified in DES-exposed women and their offspring, and animal studies have shown effects in the next generation (grandchildren).[5,6] The Centers for Disease Control and Prevention has instituted a campaign to educate health care professionals and patients about the risks associated with exposure to this synthetic estrogen.

It is difficult to determine the number of persons with DES exposure. However, physicians should be alert for patients who may have been exposed to this agent and should be aware of the possible consequences of such exposure.

Dosages of DES varied greatly, as did the time during pregnancy that DES was taken. These factors may contribute to the wide range of adverse effects in the offspring of women who took DES while they were pregnant.

Illustrative Case

A 37-year-old woman who had been trying to conceive for two years came to her physician's office to discuss fertility issues. Her basal body temperature charts illustrated presumed ovulatory cycles, and her husband had a normal semen analysis. She had an abnormal Papanicolaou (Pap) smear 15 years previously, but all subsequent Pap smears had been normal. However, her previous physician had noted that her cervix "looked funny." The patient was the oldest of four siblings; her mother had two miscarriages before the patient was born.

The patient's general physical examination was normal. On pelvic examination, her vagina was normal, but her cervix had a pseudopolyp. Because of the patient's history of infertility and the consideration that she might have been exposed to DES in utero, hysterosalpingography was ordered, and the patient was asked to discuss the possibility of DES exposure with her mother.

The patient's mother accompanied her to the follow-up visit. The hysterosalpingogram showed that the patient had a T-shaped uterus. Her mother vaguely remembered taking medication to prevent another miscarriage when she was pregnant with her daughter.

Subsequent to a follow-up visit, the patient's mother contacted her physician for a copy of her obstetric records. The patient was referred to a reproductive endocrinologist for evaluation of infertility.

TABLE 1
Identifying DES-Exposed Patients

Patient	*Approach to identifying DES exposure, and subsequent actions*
Woman who may have taken DES during pregnancy*	Questions: Have you ever had a miscarriage? More than one miscarriage? Did you take any prescription medicines while you were pregnant? If so, what medicine and for what reason? Actions: If the patient is not sure about the medications that she took, try to obtain her obstetric records. If DES exposure is documented or surmised from the history, counsel all of the patient's offspring.
Daughter or son who may have been exposed to DES in utero†	Questions: Did your mother have one or more miscarriages? Did your mother take any prescription medicines while she was pregnant with you? Actions: If the patient has reproductive tract anomalies consistent with those seen in DES-exposed offspring, attempt to obtain the mother's obstetric records. If the records cannot be obtained, consider the patient to have been exposed to DES.

DES = diethylstilbestrol.

**—Although DES was not used in pregnant women in the United States after 1971, it continued to be used in other countries until the early 1980s.*

†*—Born in the United States from 1938 through 1971, or born outside the United States from 1938 through the early 1980s.*

Information from Centers for Disease Control and Prevention. DES update. Accessed online February 19, 2004, at: http://www.cdc.gov/DES.

Identifying DES Exposure

It is important to include questions about DES in the routine medical history of women who gave birth between 1938 and 1971, and of patients who were born during those years[3,7] *(Table 1)*.[2] In persons born outside the United States, there is a chance of DES exposure if they gave birth or were born as late as the 1980s. Many women may not be aware that they received DES during pregnancy, in part because the synthetic estrogen was marketed under many different names.[2,8]

One recent study[9] found that an office system intervention was successful in increasing awareness of DES exposure among clinical staff. The intervention entailed the addition of questions about DES exposure to the routine health history form.

Women Who Took DES During Pregnancy

Women who took DES while they were pregnant have a slightly higher incidence of

TABLE 2
Structural Abnormalities in Women with in Utero DES Exposure

Cervix	**Vagina**
Hypoplastic cervix	Clear cell adenocarcinoma
Cockscomb cervix	Adenosis
Cervical collar	**Uterus**
Pseudopolyp	T-shaped uterus

DES = diethylstilbestrol

Women who took diethylstilbestrol during pregnancy have a slightly increased risk of breast cancer.

breast cancer compared with the general population. The relative risk ranges from 1.27 to 1.35 in several studies.[10] In comparison, the relative risk of breast cancer is 1.3 in women who have taken hormone therapy for more than five years,[11] and 2.1 in women with a family history of breast cancer.[12] Women who were prescribed DES during pregnancy should have annual mammography and clinical breast examinations after the age of 50.[12] [Strength of recommendation (SOR) A, evidence-based guideline]

No increased risk of other hormone-dependent cancers has been found in women with DES exposure during pregnancy. Therefore, other preventive and screening measures should be based on standard guidelines.

Daughters with in Utero DES Exposure

In the daughters of women who took DES during pregnancy, the incidence of clear cell adenocarcinoma of the vagina and cervix ranges from 1.4 cases per 1,000 exposed persons to one case per 10,000 exposed persons.[13] Clear cell adenocarcinoma is most likely to develop when women with in utero DES exposure are between 17 and 22 years of age. However, cases have been diagnosed in women in their 30s and 40s, and there is concern about a possible second age-incidence peak of clear cell adenocarcinoma as women with in utero DES exposure grow older.[14] Clear cell adenocarcinoma of the vagina and cervix is rare in women without in utero DES exposure; in such cases, the cancer usually develops in the postmenopausal period.[15]

Many women who were exposed to DES in utero are just beginning to reach menopause. Because of the concern about a second peak in the incidence of clear cell adenocarcinoma, continued surveillance for this cancer is warranted in these women.[16]

Women with in utero DES exposure do not have a higher documented incidence of any other cancer. Data from several studies[17,18] suggest that these women may have a higher incidence of high-grade cervical intraepithelial neoplasia, but not invasive cervical carcinoma. However, the findings of these studies have been questioned, in that women with in utero DES exposure may receive increased cytologic screening. A link with breast cancer is under investigation.[2]

Many women who were exposed to DES in utero have a range of structural reproductive tract abnormalities[19,20] *(Table 2)*. The National Collaborative Diethylstilbestrol Adenosis project[19] followed approximately 4,500 DES-exposed women for almost 20 years and found an 18 percent incidence of structural uterine, cervical, or vaginal abnormalities. The incidence of these abnormalities may be as high as 33 percent in women with in utero DES exposure.[2]

DES can cause changes in the vaginal epithelium, including adenosis (columnar epithelium located in the upper one third of the vagina). Although vaginal adenosis is benign, it sometimes causes abnormal bleeding. The degree of adenosis depends on the DES dosage and the stage during the pregnancy that the agent was taken. The most severe changes occur in the daughters of

TABLE 3
Clinical Recommendation for Women with in Utero DES Exposure

Perform colposcopy as part of the first pelvic examination. If the colposcopic examination is normal, no further screening is needed. If the examination is abnormal, repeat colposcopy annually along with cervical and vaginal (four-quadrant) cytology.
Perform annual cervical cytology, four-quadrant vaginal cytology, and careful digital palpation for adenosis and vaginal clear cell adenocarcinoma.
Provide counseling about increased risk of infertility and poor pregnancy outcome.
Refer pregnant patients for high-risk obstetric management.

women who took DES during the first trimester.[20] Although vaginal clear cell adenocarcinoma generally develops in areas of adenosis, whether individual areas of adenosis progress to this cancer remains unknown.

Performance of colposcopy (to assess for abnormal epithelium) frequently is recommended during the first pelvic examination in all women with in utero DES exposure *(Table 3)*.[21] If the initial colposcopic examination is normal, annual pelvic examinations and annual cervical Pap smears and four-quadrant vaginal Pap smears are adequate, and colposcopy does not need to be repeated.[21,22] [Reference 22: SOR C, consensus practice guideline based on expert opinion] If the initial colposcopic examination demonstrates any abnormalities, annual colposcopy with cytology is indicated.

For the four-quadrant Pap smear, cells are obtained from all four walls of the upper vagina. Cells first are obtained from the two lateral walls; then the speculum is rotated 90 degrees, and specimens are obtained from the anterior and posterior walls. The four-quadrant Pap smear should be performed annually to screen for adenosis and clear cell adenocarcinoma in women with in utero DES exposure.

Routine cervical cytology also should be performed annually in women who were exposed to DES in utero. In addition, the cervix and upper vaginal walls should be palpated carefully during the bimanual examination to feel for thickening that might indicate adenosis or clear cell adenocarcinoma.[22]

Women with in utero DES exposure should be counseled about their slightly increased risk of infertility and a possibly increased risk of adverse pregnancy outcome. Infertility is most common in women with underlying structural abnormalities and usually is caused by uterine or tubal factors.[23] Women who were exposed to DES in utero should be monitored closely during pregnancy.[24-26]

Although most women with in utero DES exposure have normal pregnancies, there is evidence for an increased risk of first- and second-trimester spontaneous abortion, ectopic pregnancy, and preterm delivery.[26] The most comprehensive study[26] to date found that 64.5 percent of women with in utero DES exposure had full-term infants, compared with 84.5 percent of matched women who had not been exposed to DES. In addition, the DES-exposed women had higher rates of preterm delivery (19.4 percent versus 7.5 percent), ectopic pregnancy (4.2 percent versus 0.77 percent), and second-trimester spontaneous abortion (6.3 percent versus 1.6 percent). Consequently, high-risk obstetric care

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may be indicated for pregnant women who were exposed to DES in utero.

Contraceptive management may be complicated in women with in utero DES exposure. Use of intrauterine devices is controversial because of the high incidence of structural uterine abnormalities, as well as possible changes in the elasticity of endometrial tissue. Because of cervical abnormalities, diaphragms and cervical caps may be difficult to fit.[27] No evidence indicates that oral contraceptive pills are not safe for use in women with in utero DES exposure, although some experts are reluctant to prescribe hormonal contraception of any type to these women.[3]

Sons with in Utero DES Exposure

The sons of women who took DES during pregnancy are three times more likely to have genital structural abnormalities than men without such exposure.[28] The most common abnormalities are epididymal cysts, undescended testes, and small testes. Epididymal cysts have no clinical implications, but undescended testes and small testes are associated with an increased risk of testicular cancer.[29] Men with in utero DES exposure also have sperm and semen abnormalities but do not have an increased risk of infertility or sexual dysfunction.[30]

There is some concern about the effects of DES on the prostate.[31] One study[32] that examined the prostatic utricle of male stillborns who were exposed to DES in utero showed a significantly higher incidence of squamous metaplasia in this müllerian-derived tissue.

A recent study[33] showed a possibly increased incidence of testicular cancer in men with in utero DES exposure. Although this finding was not statistically significant, the investigators concluded that the connection between DES and testicular cancer "remains uncertain," and suggested that ongoing clinical surveillance would be prudent. Therefore, the sons of women who took DES during pregnancy should be encouraged to practice routine testicular self-examination.

The sons of women who took diethylstilbestrol during pregnancy have an increased incidence of genital structural abnormalities, testicular cancer, and sperm and semen abnormalities.

Future Considerations

An increased susceptibility to reproductive tract tumors has been demonstrated in mice that are descended from parents with prenatal DES exposure (i.e., multigenerational effect),[6] but this relationship has yet to be observed in humans. To date, no studies have shown an increased risk of cancer in the offspring of men and women who were exposed to DES in utero. Two studies[34,35] of "DES granddaughters" (third-generation females) have found no health effects related to DES exposure. However, one small study[36] of "DES grandsons" showed an increased risk of hypospadias.

DES currently is being studied as an experimental hormonal treatment (i.e., a type of estrogen therapy) in men with refractory prostate cancer.[37]

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