# Health Risks and Effects of Prenatal Exposure to Diethylstilbestrol

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The problems related to prenatal exposure to diethylstilbestrol (DES) have in recent years been the subject of concern, the source of much anxiety, and to many, a medicolegeal albatross. Both the lay and medical literature is filled with false assumptions and opinions that have created a considerable aura of confusion. Several new legitimate observations have been reported in recent literature that substantiate the health risk of the progeny of women exposed to DES.

Diethylstilbestrol (DES) is a synthetic nonsteroid estrogen first reported to be synthesized by Dodds et al in 1938.[1] DES and other similar nonsteroid estrogen substances currently are used to great advantage in the treatment of vasomotor symptoms, atrophic vaginitis, selective patients with primary ovarian failure, and hypogonadism. Patients with advanced prostate cancer with bone metastases appreciate quite rapid relief of pain with diethylstilbestrol use. The use of diethylstilbestrol in the treatment of metastatic breast carcinoma has declined as a result of other effective therapy options. As early as 1940, shortly after the initial synthesis of DES, the drug was promoted as useful in high-risk pregnancies in the treatment of threatened and habitual aborters. During the years of 1948 through 1955, DES enjoyed its greatest worldwide popularity with prescribing physicians. In 1971 the United States Food and Drug Administration issued a warning against the use of DES in pregnancy because of the association of clear cell vaginal adenocarcinomas in a small number of prenatally exposed patients.[2] In the 11 years since the clear cell vaginal cancer report by Herbst et al,[2] a host of genital anomalies and other health risks have been identified in the prenatally exposed patients.

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The embryonic development of the female genital tract is a delicate and complex sequence of events in which structural organization begins as early as the 4th to 5th gestational week and is virtually completed around the 18th week of gestation. The exact mechanism of the effect of prenatal exposure to DES and other synthetic estrogens is not fully understood; however, patients exposed to high doses of diethylstilbestrol early in the period of genital tract development (4th to 8th week) are those who generally show the most profound epithelial and anatomic changes of the vagina, cervix, and uterus.

## Neoplastic Risk

Clear cell vaginal adenocarcinoma is a very rarely diagnosed malignancy. The vast majority of cancers of the vagina are seen in women of perimenopausal and postmenopausal age. It was quite unexpected that eight young patients with clear cell cancer of the vagina would be treated within a relatively short period of time at the Massachusetts General Hospital. Seven of these initially reported patients had positive histories of prenatal exposure to diethylstilbestrol.[2] In the 11 years since this initial association, over 425 cases of clear cell genital cancer have been collected by the Registry for Research on Transplacental Carcinogens located at the University of Chicago. By far, the majority of these patients are reported from the United States; however, a host of other coun-

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**Table 1. Staging for Cancer of Vagina and Cervix**

| Stage | Vagina | Cervix |
|---|---|---|
| I | Limited to vaginal wall | Strictly confined to cervix |
| II | Involving subvaginal tissue but not extending to pelvic wall | Extending beyond the cervix but not to the pelvic wall |
| III | Extending to pelvic wall | Extending to the pelvic wall, lower one third of the vagina |
| IV | Extending beyond true pelvis or involving bladder or rectal mucosa | Extending beyond the true pelvis or involving bladder or rectal mucosa |

Note: Bullous edema does not permit allotment of a case to Stage IV
(Courtesy of the International Federation of Gynecology and Obstetrics)

tries have contributed reports, including Canada, Mexico, Israel, and European, Asian, and African countries.[3]

When it is considered that the population of progeny of women treated with DES may be as large as 2 to 3 million, the estimated risk of an exposed patient having clear cell vaginal cancer may be as low as 0.1 to 0.01/1000 DES exposed.[4] Although the median age of the reported cases in the registry is 18.9 years, patients have been reported as young as seven years of age. Clear cell cancers can pose diagnostic problems for the clinician. Generally patients present with a history of a bloody vaginal discharge after menarche. The lesions are usually polypoid and involve the upper anterior vagina. Occasionally patients have had submucosal lesions that are visually and cytologically negative and are diagnosed only by the palpation of a vaginal nodule and vaginal biopsy. Patient survival is primarily influenced by the stage of the disease (Table 1). Fortunately, most patients reported to the registry had early-staged tumors and usually were successfully treated by radical surgery or radiation therapy. The registry data note better survival for patients treated surgically vs those treated by radiation therapy. Patients who have cancer diagnosed at the age of 15 years and younger tend to have a worse prognosis than those patients over 18 years of age when cancer is diagnosed. Of the three major histologic varieties, the most favorable clinical outcome is noted in those with the well-differentiated tubulocystic variety vs the solid clear cell, and the mixed histologic varieties.

In 1972 Noller[5] first reported that the clear cell adenocarcinoma of the cervix was associated with prenatal DES exposure. The registry reports a lower incidence of prenatal DES exposure in these patients, but generally shows epidemiologic profiles similar to those of the vaginal cancer patients.[4] The question of whether squamous cancer of the cervix is more prevalent in DES-exposed patients is at present most controversial. Several centers have appreciated an increased prevalence rate of intraepithelial squamous neoplasm in DES-exposed patients.[6,7] The National Diethylstilbestrol Adenosis Study Group found a lower percentage of dysplasia in their study population, which represents the investigation of over 4,000 registrants from four different sectors of the United States.[8] Currently, there is a wait-and-see attitude regarding the prevalence of dysplasia and invasive squamous cancers in DES-exposed patients. Since many DES-exposed patients have large atypical transformation zones, the treatment of intraepithelial neoplasm may pose a problem. The colposcope usually affords quick and easy identification of abnormal vascular and epithelial patterns in patients not exposed to DES. In DES-exposed patients, the colposcopic findings are quite bizarre and require an experienced examiner for a useful interpretation.[9]

The most commonly appreciated vaginal epithelial anomaly related to prenatal exposure to DES is adenosis. Adenosis is defined as the presence of secretory epithelium located in the vagina. Normally, glandular epithelium is absent from the vagina, but progeny of women exposed to DES have vaginal adenosis or cervical erosion, present in virtually all patients exposed to DES in early gestation.[6] Although adenosis is commonly found in association with clear cell carcinoma, it is neither a malignant nor a premalignant lesion and generally requires no specific treatment. Most patients experience a slow resolution of these epithelial findings by a metaplastic transformation. It has been postulated that DES may inhibit the normal regression of müllerian epithelium, resulting in glandular epithelium being trapped in the vagina. Clinically some patients with pronounced adenosis may be symptomatic, with a pronounced vaginal discharge. Grossly the involved areas of the vagina may have a mottled, reddened appearance, and a Pap smear may be expected to show an abundance of columnar epithelium cells.

The ovary is now the newest subject of concern. The vast majority of ovarian cancers arise from the surface epithelium. Epithelial ovarian cancer is primarily a disease of the postmenopausal patient; however, three interesting cases of cystadenofibroma (one with borderline cancer components) were reported in three young DES-exposed patients from the University of North Carolina. Other benign ovarian cysts have also been reported in DES-exposed patients. The significance of these observations will likely be substantiated with time; nevertheless, they do alert the physician of possible ovarian pathology that must be considered in DES-exposed patients.[10]

## Reproductive Risks

Anatomic distortion and irregularities of the vagina and cervix are clinically evident in many DES-exposed patients. Sandberg[11] has described in detail numerous major and minor vaginal and cervical anatomic distortions relating to DES exposure. The cockscomb deformity,[11] pseudopolyp cervix, and the cervical hood are among the more commonly seen anomalies. It is important to realize that these more pronounced cervical anomalies result in altered cervical function and are associated with an increased incidence of prematurity, infertility, and spontaneous abortion.[12,13]

Kaufman et al[14] reported on upper genital tract anomalies related to prenatal exposure to DES. In his initial report, 69 percent of DES-exposed patients evaluated by hysterosalpingography had abnormal findings. The T-shaped uterus abnormality was most commonly seen in combination with various uterine defects (small uterine cavities, uterine construction, and other filling defects) on hysterosalpingogram. These uterine anomalies are also felt to severely compromise the fertility of these DES-exposed patients.

Like the upper vagina, cervix, and uterus, the fallopian tube is also of müllerian origin. The fallopian tubes are not spared the effects of DES. Cornual distortions have been described in patients with other DES-related uterine anomalies.[14] DeCherney et al[15] in a recent report noted shortened fallopian tubes with pinpoint ostia as a DES sequela in 16 DES-exposed women with histories of infertility. Thus, the entire müllerian system has now been shown to exhibit developmental changes related to prenatal exposure to diethylstilbestrol. With these profound anatomic deviations, it is assumed that there is also a functional tubal problem. Ectopic pregnancy has been reported to be diagnosed 3.5 to 5.5 times above normal in DES-exposed patients.[12-14]

The clinical evaluation of the DES-exposed patient is primarily aimed at screening for neoplastic lesions. The Pap smear, Lugol staining of the vagina, and adequate visualizing and palpation of the entire vagina are considered important steps in the screening process. Any vaginal nodularity or other visible lesion should be biopsied. Generally, patients with prominent adenosis are screened every six months or annually if there are minimal DES epithelial changes. Hysterosalpingograms may provide valuable information in the evaluation of infertility, especially since recently reported uterine and tubal anomalies may be the primary cause of reproductive difficulties.

Ovarian neoplasms are particularly difficult to screen. A carefully performed pelvic examination affords the clinician the best opportunity to make a diagnosis of ovarian pathology. The three cystadenofibromas reported by Schmidt and Fowler[10] were greater than 6 cm and clinically asymptomatic, but they were easily appreciated on pelvic examination.

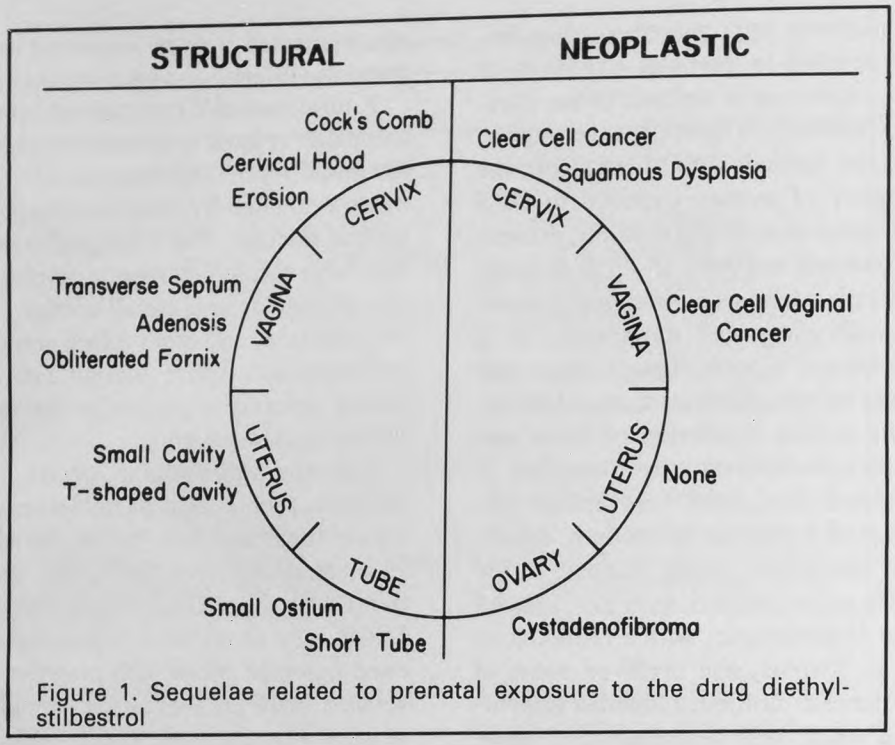


Figure 1. Sequelae related to prenatal exposure to the drug diethylstilbestrol


## Summary

Patients exposed prenatally to diethylstilbestrol have been shown to have a number of significant health risks that may be considered in the evaluation of this population. Neoplastic lesions of the cervix and vagina have been observed in a few patients. Increased prevalence of squamous intraepithelial neoplasms has been reported by several large clinical centers, and a recent observation of ovarian neoplasms has been reported. The significance of these observations remains to be substantiated. Anatomic deformities of the cervix, vagina, uterus, and fallopian tubes have been associated with increased pregnancy loss or infertility. The epithelial abnormalities of adenosis and cervical erosion essentially hallmark prenatal exposure to diethylstilbestrol. These changes are in themselves not malignant or premalignant and rarely warrant therapy (Figure 1).


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