Induction of Urogenital Neoplasia and Abnormalities from Prenatal Exposure to Diethylstilbestrol

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ABSTRACT

The occurrence of vaginal clear cell adenocarcinoma in young women following exposure in utero to diethylstilbestrol (DES) is now well documented. In addition to this carcinogenic potential, DES has been shown to be teratogenic. In females, the DES-related malformations include vaginal adenosis, transverse ridges of the vagina or cervix and uterine abnormalities. Although no neoplasms have been observed in DES-exposed males, malformations of the epididymis, testes and phallus are relatively common and may result in infertility.

The carcinogenic mechanism of DES may be either a direct induction of malignant potential in vaginal cells or a teratogenic effect causing ectopic Müllerian epithelium which could be exposed later to mutagenic agents in the vagina. The absence of malignancy in DES-exposed males may favor the latter hypothesis since male Müllerian remnants are internal structures and thus would not be exposed to surface carcinogens.

In the early 1970’s, reports of vaginal tumors in young women exposed in utero to diethylstilbestrol (DES) documented the carcinogenic potential of this compound.11,16 Subsequent studies in both males and females have shown non-neoplastic changes,2,6,7,12 some of which are congenital, suggesting that DES is also teratogenic. This paper will review both effects of DES on exposed offspring.

DES, a nonsteroidal estrogenic substance, was synthesized in 1938 and gained rapid acceptance because of its novel characteristics. It was effective when given orally and its synthesis was both simple and inexpensive.16 Following a study by Smith et al,20 it was widely prescribed to prevent threatened abortion and other complications of pregnancy during the 1940’s and 1950’s. During this time, DES was used in approximately 7 percent of all pregnancies at the Mayo Clinic, and general estimates of the number of women who received DES sometime during their gestation range from 500,000 to perhaps as many as two million.16 Subsequent studies questioned the therapeutic value of the drug in pre-
venting threatened abortion, and its popularity for this use decreased quickly after 1960.\textsuperscript{8} In 1971, following the reports of Herbst et al\textsuperscript{11} describing clear cell adenocarcinoma in association with \textit{in utero} exposure to DES, the Food and Drug Administration banned its use during pregnancy.

**Results of Exposure to DES \textit{In Utero} in Female Offspring**

**CLEAR CELL ADENOCARCINOMA**

Clear cell adenocarcinoma (CCA) had been reported almost exclusively in older women\textsuperscript{18} until 1966, when Fawcett et al\textsuperscript{4} showed that this was the most common tumor of the cervix in the pediatric age range. In 1971, Herbst et al\textsuperscript{11} reported the occurrence of CCA in seven young females at Massachusetts General Hospital between 1966 and 1969. A search for a common denominator in their medical histories showed a high incidence of \textit{in utero} exposure to DES. These observations led to the establishment in 1971 of the Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females. Over 300 cases were thus ascertained and showed: (1) an average age of 17 years at the time of diagnosis, with an overall range of 7 to 28 years,\textsuperscript{18} and a peak incidence at age 19 years which thereafter dropped precipitously;\textsuperscript{10} (2) that the diagnosis of most cases was made in a narrow age range of 10 years (14–23 years) which makes DES-related adenocarcinoma unusual;\textsuperscript{10} (3) a marked increase in the frequency of these cancers after age 14 years, suggesting a relationship to the events of puberty;\textsuperscript{18} (4) a documented exposure to DES always prior to the 18th week of gestation in approximately two-thirds of the patients in whom maternal histories were available;\textsuperscript{18} (5) that as little as 1.5 mg of DES administered throughout pregnancy was associated with the development of cancer in female offspring;\textsuperscript{1} (6) that women born in 1951 to 1953 had higher incidence rates than those born in the previous or subsequent three-year periods, possibly indicating an increased exposure during the early 1950's;\textsuperscript{10} and (7) that the estimated risk of developing adenocarcinoma of the vagina through age 24 following DES exposure \textit{in utero} was 0.14 to 1.4 per thousand.\textsuperscript{10}

In two-thirds of cases the tumors have been confined to the vagina while most of the remainder involve the vaginal portion of the cervix.\textsuperscript{18} Those which can be accurately localized almost always arise from the anterior wall, suggesting a Müllerian (paramesonephric) rather than a mesonephric origin, since the Wolffian remnants commonly are lateral in position.\textsuperscript{3} The tumors, usually polypoid and nodular, range in size from 3 mm to more than 10 cm and exfoliate cells which allow for cytologic detection. Cervical-vaginal smears, however, are negative in about one-fourth of patients, usually because of technical reasons and only rarely due to confinement of the tumor to the lamina propria with complete covering by the normal squamous epithelium.\textsuperscript{18} The tumors are radiosensitive, and radiation therapy or radical surgery have been used effectively to treat them; limited follow-up has prevented a decision concerning the superiority of either therapeutic modality. Almost all patients with small, asymptomatic CCA are curable. Larger tumors, associated with lymph nodes metastases and recurrences in approximately one-fourth of patients, are usually lethal.\textsuperscript{18}

**SQUAMOUS CELL DYSPLASIA AND CARCINOMA**

Other related conditions which may rarely occur in DES-exposed women are squamous cell dysplasia and carcinoma \textit{in situ}.\textsuperscript{14, 15, 23} The incidence of vaginal rather than cervical dysplasia appears slightly increased,\textsuperscript{17} but almost all biopsy specimens show squamous metaplasia, which occasionally may be misinterpreted as
dysplasia. A few reports of invasive squamous cell carcinoma have appeared in the literature, but the possible progression from dysplasia to invasive carcinoma and increased risk of the latter following DES exposure remain unproved.

**NON-NEOPLASTIC ABNORMALITIES**

Vaginal adenosis may be an antecedent condition in the development of CCA. It has been reported to occur in over 90 percent of women exposed to DES in utero and consists of heterotopic glandular epithelium without the normal squamous cell covering. Ultrastructural studies by Fenoglio et al have identified endometrial-type cells which may be the cell of origin for CCA. The relative rarity of these endometrial-type cells may be an important explanation for the infrequency of these cancers.

Glandular epithelium located in the vaginal portion of the cervix, or cervical ectropion, is found in nearly all DES-exposed females and is usually extensive. This abnormality may be distinct from vaginal adenosis, as indicated by subtle histologic differences, but cytologic smears in both conditions are similar.

Transverse ridges, called hoods, cockscomb cervix, rims, collars or pseudo-polyps, are other anomalies found in the upper vagina or cervix in about 25 percent of DES-exposed females. Hypoplasia of the cervix also occurs and can result in functional changes, such as cervical incompetency.

In addition to the abnormalities of the lower structures, changes of the upper genital tract associated with exposure in utero to DES have been reported recently. Kaufman et al using hysterosalpingograms, found that 40 of 60 DES-exposed women had abnormal uteri while none of 23 controls showed comparable changes. These abnormalities included a widening of the interstitial and isthmic portions of the oviducts, giving the uterus a T-shaped appearance, constriction bands, narrowing or widening of the lower two-thirds of the uterus and shortening of the uterine cavity. Ninety percent of patients with changes noted in the uterus had gross anatomic changes of the cervix. The functional significance of these uterine abnormalities for reproduction has not yet been established, but infertility, menstrual irregularities and premature deliveries may result.

**Results of Exposure to DES In Utero in Males**

The development of cancer in human males has not been reported following prenatal exposure to DES. However, several abnormalities have been described despite the small number of men examined. Bibbo et al reported a significantly higher incidence of epididymal cysts, hypotrophic testes and capsular induration in 163 DES-exposed males compared to 168 unexposed controls. They also found that 64 percent of the DES-exposed group had a pathologic semen with a reduced ejaculate volume and lower numbers and mobility of sperm. Two-thirds of these subjects had abnormal genital findings, including four with microphallus. As a consequence of these abnormalities, 30 percent of the DES-exposed group were estimated to be subfertile. Henderson et al, reporting the results of a questionnaire survey, found an increased incidence of difficulties in micturition and urethral stenosis or hypospadius among DES-exposed males. These observations await clinical confirmation.

**Teratogenesis and Pathogenesis**

Several observations support the suggestion by numerous authors that DES has teratogenic effect. In the first place, the gross and microscopic anomalies are detected only when exposure occurs during the first 18 weeks of pregnancy, which includes the period of
organogenesis for the vagina, cervix and other urogenital structures. Furthermore, the chance of teratogenic effects progressively decreases as embryogenesis and differentiation advance to completion. Normally, during the period of approximately the 4th to 18th week of development, the Müllarian ducts of the embryo extend caudally and fuse to form a solid structure. Squamous cells arising in the epithelium of the urogenital sinus invade from below and replace completely the Müllarian mucosa up to the level of the external cervical os. That DES can have a teratogenic effect on this orderly process is indicated by the finding of congenital vaginal adenosis in human fetuses and newborns. Whether DES stimulates the persistence of Müllarian epithelium or inhibits its replacement by squamous epithelium in the vagina is uncertain at this time, but the latter seems embryologically more likely. Other malformations associated with adenosis, such as ridges, strictures and pseudopolyps, are true morphologic aberrations which probably result from an effect of DES on the mesodermal stroma from which derive the fibrous and muscular coats of the vagina, cervix and uterus.

The preceding observations substantiate the teratogenicity of DES, but the question of whether it is also a carcinogen in humans remains unanswered. The findings of DES-related malignancy satisfy the premise that exposure to a cancer-causing agent may have ceased long before disease occurs. It is possible that DES, in addition to being a teratogen, is an extremely weak carcinogen, inducing latent neoplastic changes in utero which are delayed in their manifestation or require stimulation by other agents at the time of puberty for their expression. This would suggest that cancer may develop from adenosis and, in fact, almost every cancer is found in the presence of benign adenosis. However, no instance also showing a transitional lesion has ever been reported.

An alternative explanation is that DES is only a teratogen, which does not itself produce a precancerous condition. In this hypothesis, DES would only cause ectopy of normal Müllarian epithelium, which could be exposed at a later age to mutagenic stimuli in the vagina. Evidence indicates that this may be the mechanism for induction of squamous cell carcinoma in situ following transplacental DES exposure. The risk for this carcinoma in situ is increased in those women with an extensive transformation zone (glandular epithelium undergoing squamous metaplasia), such as is frequently caused by DES. These observations suggest the presence of vaginal carcinogens, the effect of which would be significantly greater when the transformation zone is extensive. This postulate could also be true for DES-related adenocarcinoma, but data on this point are lacking.

The low carcinogenicity of DES and the small number of DES-exposed males who have been studied may explain the failure to demonstrate urogenital tumors in men. Another explanation may be the different hormonal responses of males and females at puberty. Alternatively, these tumors may not occur because, unlike the vaginal adenosis in females, the Müllarian remnants in the male (prostatic utricle and appendices of the testes) are strictly internal structures and would not be exposed to surface carcinogens. Cysts occur in the efferent ductules and superior epididymis in DES-exposed males and may represent teratogenic abnormalities of Müllarian duct remnants.

From this review, it is obvious that DES, a nonsteroidal estrogen, can cause abnormal Müllarian development. These effects correlate with exposure not only to DES and chemically related estrogenic compounds but may also be related to the use of steroidal estrogens. Changes similar to those caused by DES, including cancer, have been reported following exposure to natural estrogens and proges-
terone and to progesterone alone. These types of hormones are widely used by women as contraceptives, sometimes even during early, unrecognized pregnancies. Such observations indicate the need to examine closely these offspring for disorders similar to those caused by prenatal exposure to DES.

References


