



Perspective

The Long-Term Effects of In Utero Exposures — The DES Story

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It has been 40 years since the *Journal* published a seminal article by Herbst et al. (1971;284:878-81) noting the association of in utero exposure to a synthetic nonsteroidal estrogen, diethylstilbestrol

(DES), and the development of a rare clear-cell adenocarcinoma (CCA) of the vagina in young women 15 to 22 years later. The identification of an in utero exposure that caused alterations to the anatomical and histologic structure of the female genital tract, infertility, and malignant transformation has changed medical thinking about both the embryologic development of the genital tract and the mechanism of carcinogenesis.

DES was developed in 1938 and used widely, including as a supplement to cattle feed in the 1960s and in humans for symptom relief from estrogen-deficiency states, postpartum lactation suppression, and treatment of prostate and breast cancer.

Despite some evidence to the contrary, a 1948 study suggested that DES taken in early pregnancy prevented miscarriage.¹ Over the subsequent two decades, and despite mounting evidence of lack of efficacy, DES was commonly prescribed for that purpose. Ultimately, however, it was acknowledged to be ineffective in the prevention of miscarriage. The exact number of offspring exposed to DES in utero is unknown but is thought to be several million.

The Registry for Research on Hormonal Transplacental Carcinogenesis had collected information on 431 cases of vaginal CCA by 1994. A 2007 analysis of lifetime risks of CCA reported a total of 143 cases per 97,831

person-years among women exposed to DES in utero.² Estimates of CCA incidence among DES-exposed women range from 1 in 1000 to 1 in 10,000. Unlike the previously rare CCA that was found in postmenopausal women, CCA in DES-exposed women occurred at a median age of 19 years (range, 15 to 29 years). The registries also identified another cohort of young women — accounting for 20% of the total registry population — who were given that diagnosis during the same era but had no known history of DES exposure. This finding has led to conjectures that some of the mothers of women with CCA might have been exposed to DES through dietary sources.

The mechanism of carcinogenesis has been linked to aberrant embryologic development of the Müllerian ducts after exposure to DES. Chemicals that affect human fetal development are now called endocrine-disrupting

chemicals, and an understanding of the changes caused by DES, the prototypical endocrine disruptor, has led to the identification of genetic pathways that govern the development of the reproductive tract. At a crucial developmental window in utero, DES exposure disorganizes uterine muscle layers; prevents vaginal epithelial stratification and the resorption of vaginal glands, causing vaginal adenosis; and leads to loss of the uterotubal junction. The anomalies of the reproductive tract are thought to be attributable in part to estrogen's ability to alter stromal epithelial interactions. In the past decade, DES-induced alterations of the expression of the Hox and Wnt gene families, which are involved in the patterning of the reproductive tract, have been identified.^{3,4} The fact that the incidence of CCA peaked during the teen years suggests that the hormonal changes of menarche triggered malignant transformation in vaginal adenosis.

For the women who were exposed to DES in utero, it meant being subjected to the trauma of multiple pelvic examinations with colposcopy and repeated biopsies, as well as living with the fear of developing cancer. Small, T-shaped uteri and other uterotubal anomalies that made it impossible to accommodate a growing fetus caused many of these women to have miscarriages — which occurred at

twice the rate found among their non-DES-exposed contemporaries. Some sons of women who were given DES have also been reported to have epididymal cysts, microphallus, cryptorchidism, or testicular hypoplasia. The enormous health care costs for this cohort and the disruptions of their lives cannot be fully measured; in some cases, these effects have been devastating.

The lessons learned from the DES story are powerful. Endocrine disruptors may cause alterations in the reproductive tract that have severe consequences and form the basis of disease in adults decades later. Endocrine disruptors may come not only from ingested medicines, but potentially also from the environment through food. It is very difficult to recognize a teratogenic consequence of a prenatal exposure when the malformation does not manifest until 20 years later.

There continue to be unanswered questions about the cohort of DES-exposed offspring. Will they encounter other unique health problems as they age? A slight increase in the rate of breast cancer among DES-exposed women over 40 years of age has been reported, but there has been no increase in other gynecologic cancers. Are the children of DES-exposed people at higher risk for genetic changes and disease? Epigenetic changes have been seen

in studies in animals. However, a 2008 study of the third generation — the grandchildren of women who were given DES during pregnancy — did not uncover an increased risk of disease in humans.⁵

Ultimately, the DES story humbles us. It serves as a reminder that though the narrow lens of today might reassure us that an intervention is safe, it is only with the wisdom of time that the full consequences of our actions are revealed.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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