CLINICAL VIGNETTE

Screening of Diethylstilbestrol (DES) Exposed Patients

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Case Report

The patient is a 59-year-old female who presents to establish care. She was diagnosed with invasive ductal carcinoma of the breast at age 46 and also has a remote history of abnormal Pap smears status post loop electrosurgical excision procedure (LEEP). She reports that she was exposed to diethylstilbestrol (DES) in-utero when her mother was prescribed the drug to prevent miscarriage. She has a 22-year-old daughter who is in good health. Her physical exam was unremarkable except for healed surgical scar on her left breast. She has questions and concerns regarding screening for complications related to her in-utero DES exposure and whether there are risks to her daughter's future health.

DES was a synthesized nonsteroidal estrogen that was developed for the management of post-menopausal symptoms and endometriosis, and was used as an emergency contraceptive. It more commonly was used for the prevention of miscarriage, preterm birth, and other pregnancy issues. In 1971, United States Food and Drug Administration advised against its use when in-utero exposure to DES became linked to vaginal clear cell adenocarcinoma (CCA). It is estimated that 5-10 million women were exposed to the drug before 1971[1]. It is difficult to determine the scope of DES exposure as there were also some prenatal vitamins at that time that contained DES.

DES Mothers

Women who received DES during pregnancy, or "DES mothers", have a small increased risk of breast cancer. Their lifetime risk of breast cancer is increased from 1 in 8 to 1 in 6[2]. DES mothers are not at increased risk for ovarian or endometrial cancer[3]. DES mothers are recommended to follow current guidelines for breast cancer screening and other prevention appropriate for their age group.

DES Daughters

Women exposed to DES in-utero, or "DES daughters", have an increased risk of cervicovaginal clear cell adenocarcinoma (CCA), congenital anomalies of the reproductive tract, subfertility and adverse pregnancy outcomes, an earlier age of menopause, breast cancer, and cervical intraepithelial neoplasia[4].

DES daughters have a fortyfold increase risk of clear cell adenocarcinoma of the vagina and cervix compared to the general population (lifetime incidence of this rare cancer in DES daughters is estimated to be 1/1000-1/10,000)[1,5]. This is a lifelong concern for although most cases are diagnosed in patients in their teens or early twenties; cases have been reported in DES daughters older than 50 years old. Screening for CCA should continue in postmenopausal women. DES daughters should be examined yearly with cytologic examination of the cervix and vagina, as well as, careful palpation of the cervix and entire vaginal wall. Colposcopy should be performed for any cytologic abnormality found and biopsy should performed for any palpable ridges, nodules or colposcopy abnormalities as there is a twofold increase risk (6.9% versus 3.4%) for high-grade squamous intraepithelial lesions in DES daughters[4].

Based on the available data, there is no evidence for increased risk of breast cancer before age 40; however, there is an increased risk for breast cancer in DES daughters over 40 (3.9% versus 2.2%)[4]. Due to relatively small numbers of DES daughters in existing cohort studies, there is little evidence for increased risk of other malignancies (other than breast cancer or clear cell adenocarcinoma) among DES exposed daughters[4,5].

Because DES crosses the placenta, exposure to DES during a critical period of organogenesis can lead to reproductive tract abnormalities. Congenital reproductive tract anomalies associated with DES daughters include: T-shaped uterine cavity, hypoplastic uterus, endometrial cavity constrictions or adhesions, vaginal adenosis, vaginal ridges, transverse vaginal septa, cervical hypoplasia, cervical collars, cervical hoods and cervical polyps[1].

It is felt that these reproductive tract abnormalities lead to increased risks for subfertility, ectopic pregnancies, and cervical intraepithelial neoplasia (due to increased length of the transformational zone,

there is an increased risk of susceptibility to human papilloma virus).

There is a higher risk of subfertility as DES daughters were twice as likely to experience infertility (33.3% versus 15.5%)[4,6]. DES daughters also have an increased risk of an ectopic pregnancy (14.6% versus 2.9%)[4]. Thus, DES daughters should be evaluated for ectopic pregnancy early in the first trimester. DES daughters have higher rates of miscarriage (50.3% versus 38.6%) and premature birth (53.3% versus 17.8%) which also may be related to the structural abnormalities of the cervix/uterus[4]. DES daughters also appear to have an increased risk of preeclampsia (26.4% versus 13.7%) as well as an increased risk in stillbirth (8.9% versus 2.6%)[4].

DES daughters are more likely to experience early natural menopause compared to unexposed women (5.1% versus 1.7%)[4,7].

DES Sons

Men exposed to DES in-utero, or "DES sons", had an increased risk of cryptorchidism and testicular inflammation or infection. Most studies report no infertility in DES sons. There is controversy as to whether DES sons may have an increased risk for testicular cancer due to the small number of cases[8].

Third-Generation Effects

At this time there is no clear increased risk of cancer in the third-generation males and females. Based on 3 cases in one study, there was a suggestion of an increased incidence of ovarian cancer in daughters of DES daughters[9]. However, this third-generation cohort is still young at this time and further follow up studies are needed.

DES is a well-known transplacental carcinogen in humans and given the long-term health risks, we need to continue to monitor and study the exposed mothers and their offspring.

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