GYNECOLOGY

Prenatal diethylstilbestrol exposure and high-grade squamous cell neoplasia of the lower genital tract

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BACKGROUND: Prenatal diethylstilbestrol (DES) exposure is associated with an excess risk of clear-cell adenocarcinoma of the vagina and cervix, and of high-grade squamous neoplasia.

OBJECTIVE: We explored whether neoplasia risk remains elevated among DES-exposed women as they age.

STUDY DESIGN: In all, 4062 DES-exposed and 1837 unexposed daughters were followed for approximately 30 years (1982 through 2013) for pathology-confirmed diagnoses of cervical intraepithelial neoplasia grade ≥2 (CIN2+) of the lower genital tract (n = 178). Hazard ratios (HR) and 95% confidence intervals (CI) were estimated adjusting for birth year and individual study cohort.

RESULTS: The cumulative incidence of CIN2+ in the DES-exposed group was 5.3% (95% CI, 4.1—6.5%) and in the unexposed group was 2.6% (95% CI, 1.5—3.7%). The HR for DES and CIN2+ was 1.98 (95% CI, 1.33—2.94), and was similar with further adjustment for frequency of cervical cancer screening (HR, 1.97; 95% CI, 1.33—2.93). The HR was 2.10 (95% CI, 1.41—3.13) with additional adjustment for other potential confounders. The HR for DES exposure was elevated through age 44 years (age <45 years HR, 2.47; 95% CI, 1.55—3.94), but not in women age ≥45 years (HR, 0.91; 95% CI, 0.39—2.10). In exposed women, HRs for DES were 1.74 (95% CI, 1.09—2.79) among those who had earlier evidence of vaginal epithelial changes (VEC), presumably reflecting glandular epithelium undergoing transformation to normal, adult-type squamous epithelium, and 1.24 (95% CI, 0.75—2.06) among those without VEC, compared with unexposed women. The HRs for DES and CIN2+ were higher among women with earlier intrauterine exposure (HR, 2.64; 95% CI, 1.64—4.25 for <8 weeks' gestation and HR, 1.41; 0.88-2.25 for ≥8 weeks' gestation), and lowest when exposure began >15th week (HR, 1.14; 95% CI, 0.59—2.20).

CONCLUSION: CIN2+ incidence was higher among the DES exposed, particularly those with early gestational exposure and VEC. The HR for DES and CIN2+ remained positive and significant until the mid-40s, confirming that the recommendation of annual cytological screening among these women is appropriate. Whether those ≥45 years of age continue to require increased screening is unclear, and would require a careful weighing of possible risks and benefits.

Key words: cervical dysplasia, cervix, diethylstilbestrol, Pap smear screening, squamous neoplasia, vagina

Introduction

The association between prenatal exposure to diethylstilbestrol (DES), a nonsteroidal synthetic estrogen given in pregnancy, and vaginal and cervical clear-cell adenocarcinoma in young women was first described nearly 45 years ago.[1] Subsequently, benign pathological findings of the genital tract were associated with DES, including an increased prevalence of vaginal adenosis, ectropion, and a wider cervical transformation zone.[2,3]

The National Cooperative Diethylstilbestrol and Adenosis (DESAD) study sought to determine the prevalence and incidence of cervical and vaginal neoplasia in a large cohort of DES-exposed and unexposed women. Baseline screening examination data from this study did not provide evidence of an increased prevalence of squamous neoplasia[4]; however, a later follow-up study of incident cases showed a nearly 2-fold increased risk.[5] In the National Cancer Institute (NCI) Combined DES Cohorts Follow-Up Study, Hatch et al[6] also reported a doubling of risk of high-grade dysplasia in primarily younger women, with adjustment for history of routine cervical cancer screening.

The recognition of the causal association of human papillomavirus (HPV) with cervical neoplasia and the increasingly widespread use of the HPV vaccine has prompted a reevaluation of the guidelines for screening Pap smears. The American Congress of Obstetricians and Gynecologists (ACOG) issued a revised practice bulletin in November 2012[7] that reduced screening cytology frequency to every 3 years among women aged 21-65 years without risk factors or previous cervical disease. Women with prenatal DES exposure were disqualified from reduced screening frequency because of their increased risk of cervical neoplasia.

The objective of the current study was to determine whether the elevated risk of high-grade squamous neoplasia associated with in utero DES exposure has continued with age.

Materials and Methods

Cohorts

The NCI Combined DES Cohorts Follow-Up Study consists of the following: (1) women who participated in the DESAD cohort[8]; (2) women whose mothers participated in a clinical trial of DES in 1951 through 1952 (Dieckmann[9] cohort); (3) women whose mothers were treated in a large private infertility practice in Massachusetts (Horne Cohort); and (4) women from Massachusetts, New Hampshire, Maine, and the Mayo Clinic whose mothers participated in the Women's Health

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Study (WHS) cohort, a study of the subsequent health effects of DES in women who were administered DES during their pregnancy.[10]

Mailed questionnaires and physical examinations

The follow-up of the 4 combined cohorts by NCI began in 1994 with a mailed questionnaire, with subsequent questionnaires mailed in 1997, 2001, 2006, and 2011. Prior to the combined follow-up questionnaire study (1984 through 1989), DESAD[8] cohort members were mailed annual questionnaires, and medical records and pathology reports were collected for cancers and gynecologic neoplasia. In 1982 through 1983, many members of the DESAD[8] cohort still participated in annual screening examinations as part of the study protocol. The last routine follow-up of the Dieckmann[9] cohort consisted of a mailed questionnaire in 1990. The Horne cohort was reassembled for follow-up along with unexposed siblings in the mid-1970s, and mailed annual questionnaires through the 1980s. Daughters from the WHS[10] cohort had not been followed up before the combined follow-up in 1994.

The Dieckmann[9] and DESAD[8] studies incorporated a comprehensive gynecologic examination around the time of recruitment in the mid-1970s into their original cohorts that systematically identified vaginal epithelial change (VEC) by means of colposcopy or iodine staining. Identical screening protocols were used for the exposed and unexposed women. VEC is glycogen-poor squamous epithelium found in the vagina or exocervix that presumably reflects glandular epithelium undergoing transformation over time to glycogenated, normal adult-type squamous epithelium. These changes were more frequent in women prenatally exposed to DES early in pregnancy who also had large cumulative doses of DES by the end of pregnancy.[11] No attempt was made to systematically physically examine members of the Horne or WHS[10] cohorts.

Institutional review board approvals were obtained at the field centers and the NCI. Participants indicated their informed consent by completion of a questionnaire or telephone interview, and/or with written consent for pathology and slide reports.

DES exposure and covariate ascertainment

For all combined cohort participants, prenatal exposure to DES, or the lack thereof, was documented by the medical record or a physician's note. Gestational week of first DES use was available for 75% of all exposed women, and for 80.2% of the DESAD[8] and Dieckmann[9] exposed groups. Because data for total cumulative DES dose were available for only 38% of the women, we classified the individual cohorts as high- or low-dose based on differences in prescribing practices by US region (unknown for a subgroup of the WHS[10]). Agreement between the dose categories and individual doses was excellent among those with complete data.[12] Information on highest level of education, smoking status, and frequency of routine medical examinations, including Pap smears, in the last 5 years was collected on the 1994 questionnaire. Smoking status was updated on the 2006 questionnaire, and menopausal status and frequency of Pap smears were ascertained on all 5 questionnaires and treated as time-dependent.

Cervical intraepithelial neoplasia grade ≥2 confirmation

Reports of cervical intraepithelial neoplasia (CIN) grade ≥2 (CIN2+) were available from 2 sources: records from the original cohorts (1982 through 1988) and the NCI combined cohort study questionnaires (1989 through 2011); the methods for confirmation of cases were similar. The combined cohort study questionnaires ascertained new diagnoses of neoplasia, and biopsies of the cervix, vagina, or vulva that indicated a precancerous condition (dysplasia or carcinoma in situ, but not abnormal Pap smears only). Pathology records were obtained for reported biopsy-confirmed, genital-tract neoplasia of any grade (including HPV infection). Slides also were requested for pathology-confirmed diagnoses of CIN2+, and were reviewed by 1 pathologist (S.J.R.), blinded to DES-exposure status.

Among participants included in the analysis, 5237 (89% of exposed and 88% of unexposed) completed a questionnaire during the 1994 follow-up or after, and 1247 women (23.8%) reported having had a biopsy of the lower genital tract. Pathology reports were obtained for 986 (79%) of those reporting a biopsy, and of these, 206 (21%) indicated CIN2+. Pathology reports for the remaining self-reports indicated CIN1 (n = 280) or other benign diagnoses (n = 500, eg, squamous metaplasia, inflammation, HPV only). Representative slides were reviewed for 169 (82%) CIN2+ cases confirmed by pathology reports, and 30 cases were downgraded to CIN<2. Eight of the CIN2 cases were glandular cell type, and not included in the main analysis. All 8 glandular lesions were cervical; 7 were DES-exposed (2 were invasive, 1 was adenocarcinoma in situ, 3 were CIN3, and 1 was CIN2), and 1 was unexposed (CIN3). An additional 10 cases were not reported as biopsies, but identified from pathology reports obtained for other reasons. Of the 178 pathology-confirmed diagnoses of squamous CIN2+ included in the analysis, 163 were cervix (including n = 11 cases of invasive carcinoma of the cervix), 9 were vagina, and 6 were vulva (n = 2 were invasive). The National Death Index was routinely searched and 1 additional invasive case was identified, resulting in a total of 3 deaths in the exposed group from invasive lower genital tract cancer among CIN2+ cases.

Exclusions and follow-up information

Information from patient history and medical record review was used to ascertain history of diagnoses and treatments. Table 1 shows exclusions and follow-up information. Of 7232 women in the study, 460 who were lost to follow-up or died before 1982 were excluded. To limit the analysis to incident disease, 200 cases were excluded due to pathology-confirmed high-grade neoplasia diagnosed before the start of follow-up and an additional 107

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