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In the early 1990s, Dr. Hoover and his colleagues combined three cohort studies of DES-exposed women that had begun in the mid-1970s, so that the pooled subjects could be followed periodically with self-report questionnaires. Their Combined Cohort Study of DES Exposure involved 4,001 DES-exposed women and 1,683 nonexposed control subjects from the original cohorts, who were born between the late 1940s and the early 1960s and whose average age at last follow-up was 48 years. Twelve adverse health outcomes were significantly associated with DES in previous studies were assessed in the combined cohort, and all 12 were found to be significantly associated with DES in this combined analysis. The hazard ratios (HRs) associated with DES exposure, compared with nonexposure, ranged from a low of 1.42 for preeclampsia to a high of 8.12 for neonatal death (usually related to preterm delivery). In ascending order, the HRs were 1.64 for spontaneous abortion; 1.82 for breast cancer diagnosed at age 40 or older; 2.28 for cervical intraepithelial neoplasia of grade 2 or higher; 2.35 for early menopause; 2.37 for infertility; 2.45 for stillbirth; 3.72 for ectopic pregnancy; 3.77 for loss of second-trimester pregnancy; and 4.68 for preterm delivery, the investigators wrote (N. Engl. J. Med. 2011;365:1304-14).

DES-exposed women who had clinical evidence of vaginal epithelial changes at a young age—a marker of high DES dose and exposure early in gestation—were found to have significantly higher risks for adverse outcomes than did exposed women who showed no vaginal epithelial changes. This finding provides additional support for the argument that DES exposure caused, and was not just linked to, the adverse outcomes, they said. The researchers also calculated the excess risk of adverse outcomes that could be attributed directly to DES exposure. This excess risk was 1.7% for breast cancer, 3.4% for early menopause, 3.5% for GIN, 6.3% for stillbirth, 7.2% for neonatal death, 11.7% for both spontaneous abortion and ectopic pregnancy, 12.7% for preeclampsia, 14.7% for loss of second-trimester pregnancy, 17.8% for infertility, and 33.4% for preterm delivery.

The Combined Cohort Study of DES Exposure was supported by the National Cancer Institute. Dr. Robbey reports receiving consulting fees from UCB, Belgium. Dr. Karlan reports holding stock in and receiving board membership fees from IRIS International. Dr. Hatch receives royalties as a reviewer of the DES card on the UpToDate medical information site.