The Diethylstilbestrol Legacy: A Powerful Case Against Intervention in Uncomplicated Pregnancy

Rebecca Troisi, ScD,[a] Elizabeth E. Hatch, PhD,[b] Linda Titus, PhD[c]

Although the basic tenet of medicine is "First, do no harm," history is filled with good intentions that were at best unhelpful and at worst harmful. Because medicine seeks to cure afflictions, there is an overwhelming desire on the part of health providers and patients to administer treatment. In certain settings, treatment can be reasonable despite a risk of adverse consequences: for example, if the disease is cured or its morbidity abated and the treatment consequences are less disabling than the disease itself.

In the absence of overt disease, the question of whether to apply an intervention is far more challenging. The safety of interventions must be weighed against the population's level of risk, the morbidity and/or mortality associated with the disease, and the intervention's efficacy (eg, *BRCA1* mutation, mastectomy, reduced breast cancer risk). Interventions must meet an especially high standard of safety and efficacy when administered in low-risk populations or in settings in which the morbidity associated with the disease is minor. In the worst-case scenario, an intervention may be both ineffective for its primary purpose and cause iatrogenic illness.

Interventions in pregnancy are especially problematic because of the complex physiology of the condition and the possibility of causing short- and long-term adverse consequences in both the mother and her offspring. The continuing story of diethylstilbestrol (DES), a synthetic estrogen, shows the importance of caution when evaluating the merits of interventions involving pregnant women. With regard to DES, investigators believed that pregnancy loss was caused in part by a decrease in estrogen and that administering DES to pregnant women would help maintain a healthy pregnancy. Moreover, because endogenous estrogen concentrations increase dramatically during a healthy pregnancy, supplementation with DES was deemed harmless. During its early years of use, DES was administered to women with threatened pregnancy loss or a history of pregnancy loss. Eventually, DES was advertised to the medical community for "routine

[a]*Epidemiology and Biostatistics Program, Division of Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland;* [b]*Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts; and* [c]*Geisel School of Medicine at Dartmouth and the Hood Center for Children and Families, Lebanon, New Hampshire*

Drs Troisi and Titus conceptualized the ideas expressed in the manuscript and drafted the initial manuscript; Dr Hatch conceptualized the ideas expressed in the manuscript and reviewed and revised the initial manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2015-4268G

Accepted for publication Feb 16, 2016

Address correspondence to Rebecca Troisi, ScD, Epidemiology and Biostatistics Program, Office of the Director, Division of Epidemiology and Genetics, National Cancer Institute, 9609/7E578, 9609 Medical Center Dr, Rockville, MD 20850. E-mail: troisir@mail.nih.gov

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr. Troisi is an intramural investigator at the National Institutes of Health. The research upon which this editorial is based was performed using intramural research funds. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

FIGURE 1
Advertisement for DES. (Reprint courtesy of DES Action advocacy group.)

prophylaxis in ALL pregnancies" and administered to women with otherwise healthy pregnancies (Fig 1).

By the time DES was formally evaluated, it was standard of care in high-risk obstetrics practices. The first clinical trial to determine the efficacy of DES, reported in 1953,[1] showed that DES did not improve pregnancy outcome. (Indeed, a subsequent reanalysis of the data revealed that DES increased the risk of spontaneous abortion, preterm birth, and neonatal death.[2]) Despite lack of evidence supporting a benefit, DES continued to be prescribed during pregnancy until 1971, when a small study showed a stunning 40-fold increase in the risk of clear cell adenocarcinoma (CCA) of the vagina and cervix in girls and young women who were prenatally exposed to DES.[3] Several months later, the Food and Drug Administration issued a bulletin indicating that the use of DES was contraindicated in pregnancy. By then, however, millions of women, along with their sons and daughters, had been needlessly exposed.

In addition to the increased risk of CCA of the vagina and cervix, daughters exposed in utero to DES also suffered from an increased occurrence of reproductive tract abnormalities, infertility, and pregnancy complications[4]; earlier menopause; twice the incidence of cervical dysplasia[4]; and a possible elevated risk of breast cancer and continued increased risk of CCA in middle age.[5] Recent preliminary data indicate the possibility of an increased risk of cardiovascular disease and diabetes in the prenatally exposed women.[6] Mothers administered DES during pregnancy have an increased risk of breast cancer incidence[7] and mortality.[8] Sons who were exposed in utero have an increased risk of genitourinary defects[9] and a possible increase in testicular cancer.[10] The possibility of epigenetic transmission with consequent adverse outcomes in the offspring of prenatally exposed women is under investigation. Preliminary findings showed increased menstrual irregularity[11] and a possible excess of ovarian cancer in very young women.[12]

The link between prenatal DES exposure and subsequent adverse health outcomes, most of which are fairly common, may easily have escaped detection. The investigation of DES outcomes was initiated solely because a rare tumor occurred in a cluster of cases at an unusually young age, decades before the usual age of presentation. This historical example underscores the necessity of carefully weighing the risks and benefits of interventions in pregnancy and long-term monitoring of the health outcomes in mothers and offspring.

Whether and/or when to use pharmaceutical intervention in pregnancy continues to pose special challenges. At the present time, progesterone used to prevent pregnancy loss appears to be effective, although more data are needed. Thus far, there is little evidence of short-term adverse consequences for the offspring, but continued monitoring of mothers and offspring is warranted to identify any short- or long-term adverse effects. The use of progestins for luteal phase and early pregnancy support after in vitro fertilization is routine, and there are even fewer data on potential short- and long-term risks of this therapy. The tragic legacy of DES supports a cautious approach to the use of pregnancy interventions and assiduous appraisal of their effects.

ACKNOWLEDGMENTS

We thank Dr Robert Hoover for his review of the manuscript and Dr Stacy Missmer for her consultation on in vitro fertilization.

ABBREVIATIONS

CCA: clear cell adenocarcinoma
DES: diethylstilbestrol

REFERENCES

1. Dieckmann WJ, Davis ME, Rynkiewicz LM, Pottinger RE. Does the administration of diethylstilbestrol during pregnancy have therapeutic value? *Am J Obstet Gynecol*. 1953;66(5):1062–1081
2. Brackbill Y, Berendes HW. Dangers of diethylstilboestrol: review of a 1953 paper. *Lancet*. 1978;2(8088):520
3. Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence. A report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). *Cancer*. 1970;25(4):745–757
4. Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*. 2011;365(14):1304–1314
5. Smith EK, White MC, Weir HK, Peipins LA, Thompson TD. Higher incidence of clear cell adenocarcinoma of the cervix and vagina among women born between 1947 and 1971 in the United States. *Cancer Causes Control*. 2012;23(1):207–211
6. Troisi R, Hyer M, Hatch EE, et al. Medical conditions among adult offspring prenatally exposed to

diethylstilbestrol. *Epidemiology*. 2013;24(3):430–438

7. Titus-Ernstoff L, Hatch EE, Hoover RN, et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *Br J Cancer*. 2001;84(1):126–133
8. Titus-Ernstoff L, Troisi R, Hatch EE, et al. Mortality in women given diethylstilbestrol during pregnancy. *Br J Cancer*. 2006;95(1):107–111
9. Palmer JR, Herbst AL, Noller KL, et al. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009;8:37
10. Strohsnitter WC, Noller KL, Hoover RN, et al. Cancer risk in men exposed in utero to diethylstilbestrol. *J Natl Cancer Inst*. 2001;93(7):545–551
11. Titus-Ernstoff L, Troisi R, Hatch EE, et al. Offspring of women exposed in utero to diethylstilbestrol (DES): a preliminary report of benign and malignant pathology in the third generation. *Epidemiology*. 2008;19(2):251–257
12. Titus-Ernstoff L, Troisi R, Hatch EE, et al. Menstrual and reproductive characteristics of women whose mothers were exposed in utero to diethylstilbestrol (DES). *Int J Epidemiol*. 2006;35(4):862–868

The Diethylstilbestrol Legacy: A Powerful Case Against Intervention in Uncomplicated Pregnancy

Rebecca Troisi, Elizabeth E. Hatch and Linda Titus

Pediatrics 2016;138;S42
DOI: 10.1542/peds.2015-4268G

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Diethylstilbestrol Legacy: A Powerful Case Against Intervention in Uncomplicated Pregnancy

Rebecca Troisi, Elizabeth E. Hatch and Linda Titus

Pediatrics 2016;138;S42
DOI: 10.1542/peds.2015-4268G