

ACTIVITY: Naval Regional Medical Center, Portsmouth, Virginia

TITLE: Urinary Tract Evaluation of DES Exposed Progeny

INVESTIGATORS:

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Percent of time required for study: 5%
Projected rotation date: Indefinite

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A. OBJECTIVES:

1. To investigate any structural or functional changes of the urinary system which may be present in patients exposed in-utero to diethylstilbestrol.
2. To relate any urinary tract changes to previously documented cervical and vaginal effects of diethylstilbestrol exposure.

B. BACKGROUND:

Since Herbst and Scully first reported 7 cases of adenocarcinoma of the vagina in adolescent girls exposed to diethylstilbestrol (DES) in-utero, an association of clear cell carcinoma of the vagina with DES exposure during the first 20 weeks of gestation has been made by many. There are now over 341 cases of clear cell adenocarcinoma reported in the registry on clear cell adenocarcinoma of the vagina, and approximately two-thirds of these cases have been related to intrauterine exposure to nonsteroidal synthetic estrogens. In addition to clear cell carcinoma of the vagina, adenosis (columnar epithelium in the vagina) has been noted in from 35% to 91% of DES exposed progeny. (A report from this center combined with a group of patients from University of Michigan noted that adenosis occurred in 59% of 208 patients.) Over two-thirds of the examined DES exposed progeny have been noted to have various benign abnormalities of the cervix such as ectropian, cocks comb, hood changes, transverse septa, and narrowing of the vaginal apex. Notably, recent studies have shown that males exposed to DES in-utero may have abnormalities of the genital tract such as epididymal cysts, hypotrophic testes, hypoplastic penis plus relatively low sperm counts.

~~That 07% of 00 DES exposure...~~
uterine cavity demonstrated by hysterosalpingogram. In this report, they suggested that changes in the urinary system as measured by intravenous pyelogram (IVP) might be present. Since development of the urinary and genital systems is closely related, especially during the early stages, drugs that affect the genital tract when given during the first 20 weeks of development could conceivably affect the urinary system. In early development the mesonephros is the midkidney. At about the fifth week the metanephros, which becomes the permanent kidney, develops and eventually gives rise to the renal pelvis and ureter. At 9 weeks the paramesonephric ducts (from which the uterine tubes, uterus, and a portion of the vagina develop) are in close approximation to the metanephros. The bladder and at least some portion of the vagina later develop from the urogenital sinus.

Upper urinary tract developmental anomalies have been previously described in association with Mullerian (paramesonephric) duct developmental anomalies. Furthermore, mice exposed in-utero to DES have developed a persistent urogenital sinus. Finally, in one of the early registry reports, Herbst et al noted congenital anomalies, such as double ureter and absent kidneys, in 6% of patients with clear cell adenocarcinoma. If only patients with a history of DES exposure were considered, 5.4% had abnormal IVP studies. Our intention is to study patients with a history of DES exposure in-utero or patients with findings compatible with this exposure by the use of IVP in order to detect urinary tract anomalies.

APPROACH:

1. Patient selection

a. Criteria for admission to the study

- (1) History of exposure to diethylstilbestrol in-utero confirmed either by review of prenatal records or by contact with the patient's mother if records are not available (or findings compatible with DES exposure)
- (2) Colposcopic examination of the cervix and vagina searching for evidence of vaginal adenosis or other DES related abnormalities
- (3) Willingness to obtain an intravenous pyelogram

b. Criteria for exclusion

- (1) History of an allergic reaction to iodinated dyes or iodine containing substances, especially Hypaque(R)
- (2) Pregnancy
- (3) Pheochromocytoma
- (4) Multiple myeloma
- (5) Homozygous sickle cell disease

(6) A previous intravenous pyelogram will not be repeated.

(7) Unwillingness to obtain an intravenous pyelogram.

2. Methods

- a. Each patient will be interviewed and a detailed history obtained of her exposure to DES as well as any prior history of a urologic disorder.
- b. Each patient's Colposcopy Clinic record will be reviewed, and if biopsy evidence of vaginal adenosis has not been obtained, further colposcopic evaluation will be done.
- c. An intravenous pyelogram will be obtained in routine fashion. The X-rays will be reviewed by the investigators.
- d. Significant urinary abnormalities which are detected will be further investigated as deemed appropriate, employing creatinine clearance and cystoscopy, if needed.
- e. If urologic abnormalities are detected, an attempt will be made to correlate these with the amount of the patient's exposure to DES as well as with the other stigmata of DES exposure.

3. Patient population

It is hoped that a total of approximately 60 patients will be included in this study.

4. Patient dropout

Patients who decide subsequent to their interview not to have an intravenous pyelogram, or for other reasons wish not to be included, will be dropped from the study.

D. INVESTIGATIONAL NEW DRUG OR HUMAN VOLUNTEER PLANS: Before initiation of this study, the proposal will be reviewed and approved by the Clinical Investigation Advisory Committee and the Committee for the Protection of Human Subjects of this Command. Patients informed consent (written) will be obtained from all subjects involved in this study.

E. INVESTMENT EQUIPMENT: None

F. OTHER SPECIAL CONSIDERATIONS, NEEDS, AND SUPPORTING DATA: None

1. An intravenous pyelogram (dye injected in the arm to evaluate the kidneys) will be done on all female patients exposed to diethylstilbesterol (DES) while in the uterus (wombs) of their mothers. There are a small number of young women who will develop cancer when exposed to DES during the first 20 weeks of gestation (first $\frac{1}{2}$ of pregnancy). Previous reports from other institutions, and our own work from NRMC Portsmouth, indicate that vaginal and cervical changes can be found in over 50% of exposed females when a colposcope is used. These changes suggest that some women exposed to DES may later develop cancer and should be followed closely. We have such a group of women, age 16-32, who have been previously identified and are followed in our colposcopy clinic. It has been recently reported that 67% of DES exposed women have changes in the intrauterine cavity when the cavity is examined by dye techniques. Since the embryological development of the urinary and genital systems are similar, we propose a study to detect abnormalities of the upper urinary tract, the kidneys and ureter. Approximately 60 patients with DES exposure will be examined using standard IVP technique under the direction of one of the investigators, Dr. Altaffer.

2. The major benefits to the patient from this study are knowledge of possible abnormalities of her urinary system. Additionally, if a patient has any abnormalities, she would be more likely to have abnormalities of the uterine cavity. She could be counseled for consideration for a dye test of her uterus if she desired, and the situation warranted such a test. The benefits to society are primarily for other women exposed to DES in utero. If a significant number of patients in our study have abnormalities, this procedure may become part of the routine, indicated work-up for all DES exposed patients.

3. The risk to the patients involved include possible swelling from the IV site, possible infection at the site and a rare allergic reaction such as hives. Precautions include those already carried out for IVP procedures; aseptic techniques, availability of anti-histamine drugs (work against allergic reactions), and the presence of a physician. Dr. Altaffer will be responsible for medical supervision of the patients during injection of the dye.

4. The protocol will be explained by one of the investigators and a consent form will be read and explained to each subject.

5. The patient's name (or initials) will not be attached to any data tabulation. Written permission will be obtained for use of x-ray studies.

6. The patient may refuse the IVP examination.

7. There will be no changes in experimental design.

8. This is not a continuation of a project previously reviewed by the committee.