Stilbestrol and Vaginal Cancer in Young Women

Arthur L. Herbst, M.D., Assistant Clinical Professor of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, is interviewed by Sidney L. Arje, M.D., Vice President for Professional Education, American Cancer Society, Inc., New York, N.Y.
Dr. Arje

During the late 1940's and early 1950's many physicians administered stilbestrol to high-risk pregnant patients. Now, the medical profession is confronted with an association between maternal ingestion of this medication and the appearance of vaginal adenocarcinoma in their female offspring years later. How do you suggest we handle this situation?

Dr. Herbst

Physicians are advised to examine patients whose mothers received stilbestrol during pregnancy. Periodic vaginal examinations are necessary once these girls reach the menarche. In addition, cancer must always be ruled out in any young woman who complains of abnormal vaginal bleeding or staining.

Dr. Arje

Abnormal vaginal bleeding is generally regarded as a symptom of anovulation in this early age group. Are you now suggesting that we consider a diagnosis of cancer as well?

Dr. Herbst

Yes. As a matter of fact, six of the original seven patients with vaginal adenocarcinoma that Dr. Robert E. Scully and I reported in 1970 presented with prolonged vaginal bleeding that was mistaken for anovulation. This, of course, delayed the correct diagnosis.

Dr. Arje

How was the diagnosis of vaginal adenocarcinoma made?

Dr. Herbst

By vaginal inspection. Although a complete gynecologic examination requires careful preparation of the patient and gentleness in performance, there is no substitute for it.

Dr. Arje

Was cytologic examination helpful in the diagnosis?

Dr. Herbst

Cytology is occasionally unreliable in the diagnosis of this cancer. Routine vaginal cytology, which was done in six of the seven above mentioned patients, revealed suspicious or malignant cells in only three. Heavy polymorphonuclear infiltration made identification of other cells difficult. These cancers do not appear to exfoliate readily and the malignant cells that are shed are sometimes well differentiated.

Dr. Arje

What did microscopic examination of these cancers reveal?

Dr. Herbst

In six of our original seven patients and in a subsequent one reported at another Boston hospital a microscopic diagnosis of clear-cell adenocarcinoma was made. These cancers were characterized by tubules and glands lined by "hobnail" cells or clear cells containing glycogen. There was also a high incidence of benign adenosis of the vagina. The remaining patient was histologically diagnosed as having an endometrioid carcinoma. There were no clear or hobnail cells and the stains for glycogen were negative.

Dr. Arje

What was the tissue of origin in these cancers?

Dr. Herbst

Although tumors containing clear cells and hobnail cells have been classified as "mesonephroma" in the past, my colleagues and I believe that they are Müllerian in origin. The confinement of three of the eight tumors to the anterior vaginal wall and the very superficial nature of three cancers suggested that they did not arise from mesonephric remnants. Six of the eight cancers were associated with vaginal adenosis. It is generally believed that vaginal adenosis is Müllerian in origin.

Dr. Arje

It appears then that these cancers originate from adenomatous vaginal lesions that become malignant.

Dr. Herbst

That is our hypothesis. The high inci-
dence of benign vaginal adenosis in these patients suggests that an anomaly of vaginal epithelial development may be a predisposing condition. Previous reports have described an association between adenosis and this cancer when it occurs in older women. It is possible that stilbestrol alters vaginal cells in utero and that the changes do not appear as cancer until years later.

**Dr. Arje**

*What prompted you to study these eight patients?*

**Dr. Herbst**

As you know, cancer of the vagina is rare even in women over the age of 50. The seven patients with adenocarcinoma (clear-cell and endometrioid type) at the Vincent Memorial Hospital in Boston and the subsequent patient, from another Boston hospital, represented a larger number of these rare cancers in young women than the total previously reported in the world literature. All of these cancers appeared within a four-year span. Even more striking was the fact that all of these patients were between 15 and 22 years of age. One mother had mentioned to Dr. Howard Ulfelder that she had received stilbestrol during pregnancy. Therefore, a retrospective study was done with Drs. Ulfelder and David C. Poskanzer comparing the eight patients and their families with matched controls in order to discover all factors that might be associated with this rare cancer.

**Dr. Arje**

*What specific data were you gathering?*

**Dr. Herbst**

Information was sought from the mothers of the patients and controls regarding their age at the birth of the child, smoking (at least 10 cigarettes per day prior to delivery), bleeding during pregnancy, prior pregnancy loss, medications taken during pregnancy, breast feeding, intrauterine X-ray exposure and other items.

**Dr. Arje**

*And your results?*

**Dr. Herbst**

Seven of the eight mothers whose daughters had vaginal cancer had been treated with stilbestrol during the first trimester of pregnancy. Other, less significant differences between the mothers of the patients and controls were maternal bleeding and prior pregnancy loss which led to the administration of stilbestrol. No significant differences were found for maternal age, smoking, uterine X-ray exposure or breast feeding.

**Dr. Arje**

*You mention that seven mothers of these patients received stilbestrol during pregnancy. What about the mother of the eighth patient?*

**Dr. Herbst**

There was no evidence that stilbestrol or any similar medication was administered during this woman’s pregnancy nor had she experienced prior pregnancy loss or bleeding.

**Dr. Arje**

*In other words, there may be factors other than maternal ingestion of stilbestrol?*

**Dr. Herbst**

Yes. However, stilbestrol appears to be a most important factor. Also, we know that stilbestrol can cause several types of cancer in experimental animals and is therefore a possible factor in man as well.

**Dr. Arje**

*Since your report of these eight patients in 1970, is there more evidence of an association between maternal stilbestrol administration and vaginal cancer in the offspring?*

**Dr. Herbst**

Yes. More than 80 cases of vaginal and cervical adenocarcinoma in young women have been brought to our attention. In most cases, the maternal medi-
cal history revealed intrauterine exposure to stilbestrol, dienestrol or hexestrol. The latter two agents are nonsteroidal estrogens, similar in biochemical structure to stilbestrol.

**Dr. Arje**

Have steroidal estrogens also been implicated?

**Dr. Herbst**

So far there have been no cancers associated with steroidal estrogens. Remember, however, that the nonsteroidal compounds were most frequently used to support pregnancies in the past.

**Dr. Arje**

The number of young patients with vaginal cancer reported to date seems relatively low compared to the number of mothers who received stilbestrol.

**Dr. Herbst**

That's true. Relatively few cases of vaginal cancer in young girls have been discovered so far compared to the thousands, perhaps even millions, of mothers throughout the world who were treated with stilbestrol or similar medications. Yet, it is possible that more cases will still be discovered and that vaginal adenocarcinomas will appear in older women as the “at-risk” population matures. So, although the risk at present appears low, I believe there is enough epidemiologic evidence to support an association between stilbestrol and vaginal cancer in young women.

**Dr. Arje**

I certainly agree that epidemiologic evidence to support this association is significant but certainly more information is needed.

**Dr. Herbst**

Of course. Since the experience of any one clinic will be small, a Registry for Clear-cell Adenocarcinoma (Mesonephroma) of the Genital Tract in Young Women has been established to centralize and evaluate data, study pathogenesis, maternal histories and therapy in the U.S. and abroad. We hope physicians will provide us with information on all cases of vaginal adenocarcinoma occurring in women under 25 years of age whether or not there is a history of maternal hormone ingestion.

**Dr. Arje**

Where should this information be sent?

**Dr. Herbst**

Communications should be directed to:

Registry for Clear-cell Adenocarcinoma (Mesonephroma) of the Genital Tract in Young Women

Warren 275
275 Charles Street
Boston, Massachusetts 02114

Arthur L. Herbst, M.D., Director
Robert E. Scully, M.D., Pathologist

**Dr. Arje**

While you collect and study the facts, isn't some preventive action warranted?

**Dr. Herbst**

Action has already been taken. The Food and Drug Administration has warned all physicians that stilbestrol is contraindicated in pregnant women. Also, a regulation prohibiting the use of stilbestrol in animal feed for seven days prior to slaughter has been issued by the U.S. Department of Agriculture.

**Dr. Arje**

What advice do you have for physicians who are contacted by worried mothers or anxious young women?

**Dr. Herbst**

These women can be assured that, as yet, the risk appears to be low. However, the public should be made aware that adolescent girls and young women who had fetal exposure to stilbestrol need regular vaginal examinations.

**Dr. Arje**

Thank you, Dr. Herbst.

---

Funds to support the original retrospective study and initiate the Registry for Clear-cell Adenocarcinoma (Mesonephroma) of the Genital Tract in Young Women were provided by the American Cancer Society, Massachusetts Division, Inc. Funds to support continuing investigation and operation of the Registry have been provided by grants from the National Cancer Institute and American Cancer Society, Inc.