ADENOCARCINOMA OF THE VAGINA*

Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women

ARTHUR L. HERBST, M.D., HOWARD ULFELDER, M.D., AND DAVID C. POSKANZER, M.D.

Abstract Adenocarcinoma of the vagina in young women had been recorded rarely before the report of several cases treated at the Vincent Memorial Hospital between 1966 and 1969. The unusual occurrence of this tumor in eight patients born in New England hospitals between 1946 and 1951 led us to conduct a retrospective investigation in search of factors that might be associated with tumor appearance. Four matched controls were established for each patient; data were obtained by personal interview. Results show maternal bleeding during the current pregnancy and previous pregnancy loss were more common in the study group. Most significantly, seven of the eight mothers of patients with carcinoma had been treated with diethylstilbestrol started during the first trimester. None in the control group were so treated (p less than 0.00001). Maternal ingestion of stilbestrol during early pregnancy appears to have enhanced the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

CANCER of the vagina is rare, occurring usually as epidermoid carcinoma in women over the age of 50 years.[1] Between 1966 and 1969, however, seven girls 15 to 22 years of age with adenocarcinoma of the vagina (clear-cell or endometrial type) were seen at the Vincent Memorial Hospital.[2] Although isolated case reports of histologically similar adenocarcinomas of the vagina had previously been published,[3-8] these carcinomas, too, were usually in older patients. No such case in the younger age group had been seen at this institution before 1966.

The tumor typically caused prolonged vaginal bleeding that, occurring in young women, was mistaken for anovulatory bleeding and delayed the correct diagnosis. Routine vaginal cytology was often negative, and the tumor was not palpated on rectal examination. The correct diagnosis was arrived at only after vaginal examination had been performed.

Histologically, one of the tumors resembled endometrial carcinoma, but the remainder were characterized by tubules and glands lined by clear cells containing glycogen or "hobnail" cells. The clear cells also appeared in solid nests. There was a high prevalence of benign adenosis of the vagina in this group of patients. Although these tumors with clear cells and hobnail cells have been termed "mesonephroma," there is evidence that they are of Müllerian origin.[2]

Because of the apparent clustering of these cases, which appeared within four years, attention was focused on possible other similarities among them. However, they did not uniformly use any intravaginal irritant, douches or tampon. Only one patient had had sexual exposure. Before the onset of the present illness, none had been given birth-control pills. We then decided to conduct a case-control, retrospective study that would compare in detail these patients and their families with an appropriate control group to uncover factors that might be associated with the sudden appearance of these tumors.

METHODS

Four matched controls for each patient with vaginal carcinoma were selected by examination of the birth records of the hospital in which each patient was born. Females born within five days and on the same type of service (ward or private) as the eight propositae were identified. Women who gave birth to daughters closest in time to each patient with carcinoma were first considered. Interviewing of all mothers was done from a standard questionnaire by personal interview carried out by a trained interviewer.

In addition to the seven cases cited above, an eighth identical case of clear-cell adenocarcinoma of the vagina occurred in 1969 in a 20-year-old patient, who was treated at another Boston hospital. † Because she and her family with their matched controls were as available as our own cases, this patient has been included with the original group, and these eight cases form the basis of this study.

Comparison of the data obtained from patients and controls was carried out with the use of the paired t-test for parametric data and the matched control method suggested by Pike and Morrow[9] for nonparametric data. Unpaired t-tests and chi-square tests with Yates correction were also carried out but were not significantly different from the results obtained with the paired methodologies.

RESULTS

Table 1 summarizes chronologic details of each patient with her therapy and results. The table demonstrates the clustering of patients for time of birth and occurrence of tumor. In Table 2 the data for seven pertinent areas of inquiry for each patient

*From the Vincent Memorial Hospital (Gynecological Service of the Massachusetts General Hospital) (address reprint requests to Dr. Herbst at the Vincent Memorial Hospital, Fruit St., Boston, Mass. 02114).

Supported by a grant (1393-C-1) from the American Cancer Society (Massachusetts Division), Inc.

†We are indebted to Dr. Donald P. Goldstein, of Boston, for permission to include his case in this study.

Table 1. Summary of Cases with Carcinoma.

Case No.	Age at 1st Symptoms (Yr)	Yr of Birth	Yr of Treatment	Therapy	Status 1971
1	20	1949	1969	Posterior exenteration & vaginectomy	Living & well
2	15	1951	1967	Radical hysterectomy & vaginectomy, with vaginal replacement	Living & well
3	14	1950	1968	Exploratory laparotomy	Died (1968)
4	15	1950	1966	Wide local excision	Living & well
5	19	1949	1969	Radical hysterectomy & vaginectomy, with vaginal replacement	Living & well
6	16	1951	1967	Radical hysterectomy & vaginectomy, with vaginal replacement	Living & well
7	18	1949	1968	Anterior exenteration, with bowel substitution of vagina	Living & well
8	22	1946	1968	Anterior exenteration, with bowel substitution of vagina	Living & well

and her matched controls are displayed, including maternal age at the birth of the child, maternal smoking (at least 10 cigarettes per day before the birth of the child), bleeding during study pregnancy, any prior pregnancy loss, maternal estrogen therapy during study pregnancy, breast feeding of infant and intrauterine x-ray exposure.

There is a highly significant association between the treatment of the mothers with estrogen diethylstilbestrol during pregnancy and the subsequent development of adenocarcinoma of the vagina in their daughters (p less than 0.00001). Other factors found to be different between propositae and controls but at lower levels of significance are maternal bleeding in the study pregnancy (p less than 0.05) and any prior pregnancy loss (p less than 0.01). No significant differences between the populations were found for maternal age at time of birth of patient, smoking in parents, intrauterine x-ray exposure and breast feeding. Other topics covered in the questionnaire that also were not statistically significant are listed in Table 3.

All the mothers who took stilbestrol began therapy in the first trimester of pregnancy. They received either a constant dose administered throughout the pregnancy, or a continually increasing dose given almost to term. Six of the seven mothers volunteered the information that stilbestrol had been prescribed for them. The seventh was uncertain, but her obstetrician identified the drug as diethystilbestrol. Bleeding during this pregnancy or previous pregnancy loss (or both) led to the administration of stilbestrol in all seven cases. The programs of management for these pregnancies occasionally included vitamins, iron or calcium.

Discussion

By the choice of a control group consisting of females born within five days of the birth of the propositae in the same hospital and on the same type of service, socioeconomic differences are reduced. Of the candidates for the control group found on hospital birth lists 25 per cent could not be located. A selection bias is therefore possible because only the families

Table 2. Summary of Data Comparing Patients with Matched Controls.

Case No.	Maternal Age (Yr)		Maternal Smoking		Bleeding in This Pregnancy		Any Prior Pregnancy Loss		Estrogen Given in This Pregnancy		Breast Feeding		Intra-uterine X-Ray Exposure	
	Case	Mean of 4 Controls	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
1	25	32	Yes	2/4	No	0/4	Yes	1/4	Yes	0/4	No	0/4	No	1/4
2	30	30	Yes	3/4	No	0/4	Yes	1/4	Yes	0/4	No	1/4	No	0/4
3	22	31	Yes	1/4	Yes	0/4	No	1/4	Yes	0/4	Yes	0/4	No	0/4
4	33	30	Yes	3/4	Yes	0/4	Yes	0/4	Yes	0/4	Yes	2/4	No	0/4
5	22	27	Yes	3/4	No	1/4	No	1/4	No	0/4	No	0/4	No	0/4
6	21	29	Yes	3/4	Yes	0/4	Yes	0/4	Yes	0/4	No	0/4	No	1/4
7	30	27	No	3/4	No	0/4	Yes	1/4	Yes	0/4	Yes	0/4	No	1/4
8	26	28	Yes	3/4	No	0/4	Yes	0/4	Yes	0/4	No	0/4	Yes	1/4
Total			7/8	21/32	3/8	1/32	6/8	5/32	7/8	0/32	3/8	3/32	1/8	4/32
Mean	26.1	29.3												
Chi square (1 df)*			0.53		4.52		7.16		23.22		2.35		0	
p value			0.50		<0.05		<0.01		<0.00001		0.20			
	(N.S.)†		(N.S.)								(N.S.)		(N.S.)	

*Matched control chi-square test used as described by Pike & Morrow.[9]

†Standard error of difference 1.7 yr (paired t-test); N.S. = not statistically significant.

Table 3. Additional Factors Compared in Patients and Controls Not Found to Be Significantly Different.*

Birth weight
Age at onset of menses
Complications & outcome of study pregnancy
Ingestion of other medications during pregnancy
Childhood diseases of mothers & patients
History of tonsillectomy
Childhood ingestions
Household pets
Noteworthy illnesses of patients & parents
Cosmetic use in patients & mothers
Cigarette smoking in patients
Alcohol consumption in parents
Occupation & yr of education of parents

*Events compared before date of onset of present illness for each study patient & her matched controls.

remaining in the same area could be reached for comparison. However, all eight of the families of our patients are still living in or near the community where the patients were born. Control subjects still living in the community may be a more suitably matched study population. One potential control family was excluded because the birth record indicated that the offspring had Down's syndrome. It was necessary to locate only 34 women to obtain 32 control families who would collaborate with this study.

It should be emphasized that among the eight study mothers there was a total of 10 prior pregnancy losses and only six among the 32 controls. As can be seen from Table 2, bleeding during pregnancy was also more frequent in the study group. The fact that these were truly high-risk pregnancies was the indication for stilbestrol administration. The associations observed with bleeding in the study pregnancy and with previous pregnancy loss may reflect the characteristics of the population that was selected for estrogen treatment. In one of the eight mothers whose daughter had clear-cell adenocarcinoma, there was no evidence that estrogens were administered during pregnancy, nor had she experienced prior pregnancy loss or bleeding during the study pregnancy. Furthermore, these tumors were known to occur, though rarely, in women born before the availability of oral estrogens. Thus, factors other than maternal stilbestrol ingestion appear to be operative in their development. Moreover, the stilbestrol pills prescribed for these mothers were those available between 1946 and 1951. The ingredients of these tablets, the estrogenic potency of stilbestrol and its other chemical properties must all be recognized as possible elements in the association observed. Finally, among four of the eight families there are five female siblings, ranging in age from 18 to 22 years, who are also products of pregnancies during which their mothers took diethylstilbestrol. Up to the present, a vaginal tumor has not developed in any of these girls.

To try to estimate the frequency of stilbestrol administration and the risk of development of these tumors in female offspring whose mothers took stilbestrol during pregnancy, we have examined the files of one of the hospitals in this study for the years 1946 through 1951. During this interval there was a special high-risk pregnancy clinic at the Boston Lying-in Hospital in which stilbestrol was prescribed to 675 ward patients. There were approximately 14,500 ward deliveries, indicating that at that time roughly one in 21 ward patients at the Boston Lying-in Hospital were treated during pregnancy with stilbestrol. Thus, it appears to be well within the range of statistical expectation to have a control group in which the frequency of stilbestrol use was 0 in 32. In the interval 1946 to 1951 the private service at the Boston Lying-in Hospital had more deliveries than the ward service. We have knowledge of only one case of clear-cell adenocarcinoma developing in a patient born at the Boston Lying-in Hospital, and she was delivered on the private service. Whatever the risk of tumor development in the exposed offspring, it appears to be small.

The high concurrence of benign vaginal adenosis with these adenocarcinomas suggests that an anomaly of vaginal epithelial development may be a predisposing condition. Previous reports have described an association between adenosis and this tumor in older women,[3,8] and their concurrence in younger patients was initially noted in the present cases.[2] It may be that an increase in adenosis occurs at menarche in these patients and results in greater quantities of benign tissue at risk for malignant change. It is also possible that stilbestrol alters fetal vaginal cells in utero, with changes that do not become manifest in a malignant form until years later. Animal experiments as well as further follow-up data on patients who were exposed to estrogens in utero may provide some answers. Regardless of the ultimate explanation, histologic observations of associated adenosis combined with the known estrogenic effect of stilbestrol further support a Müllerian and not a mesonephric origin for these adenocarcinomas.

The time of birth of these patients (1946 to 1951) coincides with the beginning of the widespread use of estrogens in support of high-risk pregnancy.[10] It is likely that more patients with this tumor will appear as girls who were exposed in utero come to maturity. Furthermore, although our oldest patient was discovered at the age of 22 years, it is possible that these tumors will appear in even older women as the "at-risk" population matures. Although the chance of development of these tumors appears to be very small, the results of this study suggest that it is unwise to administer stilbestrol to women early in pregnancy. Furthermore, abnormal bleeding in adolescent girls can no longer be assumed to be due to anovulation, and the possibility of vaginal tumor should be excluded by a physician's examination.

We are indebted to Miss Jean Sheridan, who carried out the interviews and helped with analyses and preparation of the manuscript, to Dr. Theodore Colton, of the Department of Preventive Medicine, Harvard Medical School, for helpful suggestions with statistical analysis, to Dr. Robert E. Scully, of the Department of Pathology, Massachusetts General Hospital and Harvard Medical School, for assistance, and to the directors and record librarians of the participating hospitals for co-operation.

REFERENCES

1. Herbst AL, Green TH Jr, Ulfelder H: Primary carcinoma of the vagina: an analysis of 68 cases. Am J Obstet Gynecol 106:210-218, 1970
2. Herbst AL, Scully RE: Adenocarcinoma of the vagina in adolescence: a report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). Cancer 25:745-757, 1970
3. Plaut A, Dreyfuss ML: Adenosis of vagina and its relation to primary adenocarcinoma of vagina. Surg Gynecol Obstet 71:756-765, 1940
4. Novak E, Woodruff JD, Novak ER: Probable mesonephric origin of certain female genital tumors. Am J Obstet Gynecol 68:1222-1242, 1954
5. Studdiford WE: Vaginal lesions of adenomatous origin. Am J Obstet Gynecol 73:641-656, 1957
6. Nix HG, Wright HL: Mesonephric adenocarcinoma of the vagina. Am J Obstet Gynecol 99:893-899, 1967
7. Droegemueller W, Makowski EL, Taylor ES: Vaginal mesonephric adenocarcinoma in two prepubertal children. Am J Dis Child 119:168-170, 1970
8. Sandberg EC, Danielson RW, Cauwet RW, et al: Adenosis vaginae. Am J Obstet Gynecol 93:209-222, 1965
9. Pike MC, Morrow RH: Statistical analysis of patient-control studies in epidemiology: factor under investigation an all-or-none variable. Br J Prev Soc Med 24:42-44, 1970
10. Smith OW: Diethylstilbestrol in the prevention and treatment of complications of pregnancy. Am J Obstet Gynecol 56:821-834, 1948

SPECIAL ARTICLE

NATIONAL HEALTH INSURANCE: WHAT KIND AND HOW MUCH (First of Two Parts)*

ROBERT D. EILERS, PH.D.

Abstract The major forces behind the movement for national health insurance — health care costs, suboptimal mortality and morbidity levels, dissatisfaction with health care delivery and limitations of private insurance — must be considered in the development of criteria for evaluating national health insurance proposals. Although financial accessibility to health care for all citizens is a necessary criterion, the acceptability of health delivery arrangements to individual consumers is of equal importance. A reorientation of health delivery, emphasizing efficiency by imposing upon physicians both financial accountability and opportunities to share in cost savings, is a vital ingredient for any proposal. Also, to be acceptable, a proposal must articulate a comprehensive plan for phasing in the program over a period of possibly a decade. Other objectives are minimization of governmental regulation, consumer participation in cost, and maintenance of quality of care.

THE accelerated pace in the social acceptance of a national health insurance scheme is now readily apparent. The notion that national health insurance is inevitable is held even among some of the more conservative elements in the health care professions and health care financing organizations. A surprisingly large number of physicians and insurance-company executives, for example, appear to consider some form of national health insurance program entirely appropriate for our nation. They thus join the many labor leaders and hospital-association officials who have long espoused the desirability of national health insurance.

The diminution of opposition to national health insurance is amply reflected in the attitude of the Congress, which, since the consideration of the Wagner-Murray-Dingell bills of the 1940's, has given little serious attention to national health insurance proposals. Currently, however, extensive official and unofficial congressional discussions are being held on specific proposals.

*Presented at the annual meeting of the American Sociological Association, Washington, D.C., September 3, 1970 (address reprint requests to Dr. Eilers at the Leonard Davis Institute of Health Economics, W-136 Dietrich Hall, University of Pennsylvania, Philadelphia, Pa. 19104).

THE CURRENT HEALTH SYSTEM

A valid and complete set of criteria for a workable national health insurance program must be sensitive to certain defects in the current arrangements for financing and delivering health care.

Cost Problems

The most obvious problem in health care, and perhaps the most compelling force in the movement toward national health insurance, is that of costs — both the absolute level of health care costs and the cost escalation from year to year. Considerable attention is focused in this regard on the unit costs of care ("factor prices"), including daily hospital rates and physicians' fees. The opportunities are severely limited for any health care scheme to make important inroads toward reducing unit costs, except for the following: through a reduction in aggregate demand for certain types of health care that — with no reduction in the short-run availability of the service — could reduce the factor price; through the substitution of lower cost elements in performing a service (e.g., the substitution of allied health personnel); or through better management technics. In spite of these efforts, the average unit cost for most