Turner's syndrome

Results of estrogen therapy

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Endometrial adenocarcinoma with Turner's syndrome has been reported in young women on a regimen of exogenous estrogen since 1963.[1-5] The Department of Gynecology became interested when one of us (JCS) saw a 23-year-old woman with a well-differentiated adenocarcinoma in 1977. This patient had been receiving estrogen for replacement therapy since age 16 when gonadal agenesis had been diagnosed.

The practical question emanating from this case was should these patients, without any symptoms of abnormal bleeding, be subjected to a yearly endometrial biopsy? This procedure has been advocated by various authors.[5] A study was undertaken to answer this query.

Patients and methods

We reviewed the charts of patients with the diagnosis of Turner's syndrome treated at the Cleveland Clinic from 1951 to 1975. The patients included in this study met the following criteria: (1) diagnosis of gonadal dysgenesis made by karyotype or Barr body analysis with physical stigmata of Turner's syndrome and (2) use of estrogen (type of estrogen and dose varied) for at least 2 years after the diagnosis of Turner's syndrome.

Usually, estrogen therapy had been prescribed

for patients only after they were 13 years old, but was not usually prescribed if the diagnosis of gonadal agenesis was made after age 40.

Forty-three women fulfilled these criteria, and letters were sent to them requesting that they return for follow-up. Those who returned had pelvic examination, Pap smear with a sample obtained from the endocervix, and endometrial biopsy by Vabra aspiration in the office when technically possible.

Thirty-four women returned for follow-up. One patient had died of rhabdomyosarcoma of the lung at age 25, approximately 8 years after she had begun estrogen-progesterone therapy. No abnormality of the endometrium was seen during the postmortem examination.

Of 43 patients receiving substitution therapy, 13 were receiving estrogen alone; therapy for 24 had been changed to estrogen-progesterone in the late 1960s when cases of adenocarcinoma of the uterus were reported, and 6 had discontinued taking estrogen (*Table 1*). One of the six had spontaneous periods and the other five felt they were doing well without it and would not take the medication.

Thirty-five of the group of 43 had karyotype done (*Table 2*). Turner's syndrome was diagnosed in the remaining eight patients by deciphering the Barr body or gonadotrophin assay and by typical clinical pictures.

The number of patients and number of years they received medication are listed in *Table 3*. Six patients were not taking estrogen. No follow-up was available on nine patients who had been contacted for the original study, and one died 8 years later. The remaining 27 patients had been taking medication from 2 to 20 years. No abnormality of the endometrial lining was noted. They gave no history of intermenstrual spotting or bleeding. It was not possible to do endometrial sampling on two of the women in this group of 27 due to a small introitus or a stenotic os. Five patients had congenital heart disease or coarctation of the aorta or other cardiac anomalies that necessitated the use of penicillin prophylactically to prevent subacute bacterial endocarditis at the time of endometrial biopsy.

Table 1. Hormones used for substitution therapy

Substitution therapy	No. of patients
Estrogen	13
Estrogen and progesterone	24
No estrogen	6
Total	43

Discussion

Abnormal bleeding in the form of menorrhagia or menometrorrhagia has been the presenting symptom in all cases of adenocarcinoma of the endometrium

Table 2. Chromosomal karyotype of 43 patients

Karyotype	No. of patients
45 XO	17
45 X, 46 XX	10
46 XX	4
46 XX, 45 XO	4
Chromosome unavailable	8
Total	43

Table 3. Use of estrogen

	No. of patients
No estrogen	6
No follow-up	9
Died 8 years later	1
Estrogen use	
2–5 yr	11
6–10 yr	8
11–15 yr	6
16–20 yr	2

that have been reported. In short, there was a change from previous menstrual patterns. Patients with gonadal dysgenesis receiving estrogen replacement are at high risk for development of endometrial carcinoma at an early age. Endometrial sampling is not mandatory each year, in view of the low yield obtained in our study. This procedure is technically difficult because of the hypoplastic organ and the presence of concomitant cardiac abnormalities.

We recommend a yearly examination and a Pap smear with an endocervical specimen obtained as recommended by the American College of Obstetricians and Gynecologists Technical Bulletin.[6] If there is any sign of menstrual aberration, an endometrial biopsy obtained in the office, or dilatation and curettage should be performed. It is important to impress upon the patient the importance of careful follow-up that is necessary with the intake of estrogen in Turner's syndrome. Patients should not be given more than one year's supply of replacement therapy.

Dewhurst et al,[7] in their study of 21 patients with gonadal dysgenesis treated with estrogen alone and with a combination of estrogen-progesterone or curettage showed that the addition of progesterone produced a normal, secretory endometrium. The addition of progesterone, however, did not prevent the formation of polyp or even carcinoma, as reported by McCarroll et al.[5] The large number of benign endometrial samplings obtained in our series may be the result of administration of estrogen with progesterone in most of our cases. It is incumbent to perform a thorough curettage should the patient have any irregular bleeding, even though she is receiving estrogen and progesterone.

The dose of estrogen that produces abnormal changes in all of these studies, including ours, has varied, but the larger the dose of estrogen, the higher the risk of abnormal endometrium developing.[8]

A large dose of estrogen is recommended initially in the early teenage years when the breasts are developing. For substitution therapy after development, a low-dose oral contraceptive, 20 mg estrogen (Loestrin-21), would suffice according to McDonough et al,[9] and would offer low cost and a package that is easy to remember to use. Alternatives are sodium estrone sulfate (Premarin), 0.3 to 0.6 mg for 3 weeks, with medroxyprogesterone acetate (Provera), 10 mg for 5 days each menstrual cycle. These small doses may not induce cyclical bleeding. However, is this necessary?

Yearly surveillance examination of these patients should include pelvis, cytological sampling of the endocervix and portio, blood pressure monitoring, breast examination, and determination of triglycerides and blood glucose if indicated.

Summary

From the findings of this small study, we believe yearly endometrial sampling is unnecessary for this group of patients at high risk as long as a progestogen is added monthly. A thorough curettage, however, is necessary if menstrual aberrations are noted.

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