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Excessive estradiol secretion in polycystic ovarian disease

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Polycystic ovarian disease is both a hyperestrogenic and a hyperandrogenic syndrome, and all studies have shown that hyperestrogenemia is the result of an elevation of estrone with plasma estradiol levels in the normal follicular range. Because a literature search failed to reveal any report of polycystic ovarian disease with significantly elevated estradiol levels, we report a case in which the plasma estradiol was so massively elevated as to mimic an estrogen-producing neoplasm. This case also suggests that although polycystic ovarian disease is a very rare cause of such excessive estradiol production, it should be included in the differential diagnosis of estrogen-producing neoplasms. (Am J Obstet Gynecol 1993;169:1223-6.)

Key words: Polycystic ovarian disease, estradiol, hyperestrogenemia

It is widely accepted that polycystic ovarian disease is both a hyperestrogenic and a hyperandrogenic syndrome associated with anovulation. However, all studies have shown that the hyperestrogenic state is the result of an elevation of estrone with plasma estradiol levels in the normal follicular range, although the free (unbound) estradiol is increased because of the androgen-induced decrease in sex hormone–binding globulin.[1] We present a case in which other sources of excessive estradiol production were excluded; the case met criteria warranting the diagnosis of polycystic ovarian disease, and yet the estradiol levels were markedly elevated. A literature search failed to reveal any report of polycystic ovarian disease with significantly increased estradiol levels, especially in the high range found in our case.

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Case report

A 39-year-old black woman, para 4-0-4-4, was admitted to the Queens Hospital South Jamaica Clinic on April 24, 1991, because she had had 21 months of secondary amenorrhea. A week before she came to the clinic she had had a 4-day flow from March 1 through March 4, 1991, without menstrual molimina. She denied any medical illnesses or surgery apart from three suction curettages for pregnancy terminations, and she was not taking any estrogen or other medications. She also denied any acne, hirsutism, or galactorrhea, but she had gained 30 pounds in the previous 2 to 3 years. Results of a physical examination revealed an obese but otherwise normal-appearing patient who weighed 228 pounds and was 68 inches tall. The blood pressure was 110/70 mm Hg and the results of the breast and abdominal examinations were normal except for obesity. Pelvic examination results were unremarkable; the adnexa were not palpable or tender, but detailed palpation was difficult because of the obesity.

Table I. Endocrine data

	Follicle-stimulating hormone (IU/L)	*Luteinizing hormone (IU/L)*	*Estradiol (pg/ml)*	*Estrone (pg/ml)*	*Thyroid-stimulating hormone (mIU/ml)*	*Prolactin (ng/ml)*	*Testosterone (ng/ml)*	*Dehydroepiandrosterone (μg/dl)*	*Progesterone (ng/ml)*	*17α-Hydroxyprogesterone (ng/dl)*
Preoperative levels										
April 24, 1991	<2	<2	987		1.89	51.2				
June 3, 1991	2.7	7.4	626			33.9				
Oct. 9, 1991	9.4	14.9	425				116	403	1.1	56.3
Postoperative levels										
Jan. 2, 1992	16.4	10.4	118	79		6.4	78	325		
June 10, 1992	2.6	2.3	442	371			78	533		

Normal ranges are as follows: estradiol, normal follicular phase 20 to 140 pg/ml, luteal phase 50 to 275 pg/ml; estrone, normal follicular phase 50 to 100 pg/ml; thyroid-stimulating hormone, 0.46 to 3.59 mIU/ml; prolactin, <20 ng/ml; testosterone, 30 to 90 ng/ml; dehydroepiandrosterone, 100 to 350 μg/dl; progesterone, normal follicular phase 0.1 to 1.5 ng/ml, luteal phase 2.5 to 28.1 ng/ml; 17α-hydroxyprogesterone, normal follicular phase 10 to 88 ng/dl.

The results of endocrine testing carried out on three successive occasions are shown in Table I, and endometrial biopsy specimens revealed an anovulatory proliferative pattern on two occasions. A pelvic sonogram showed bilateral cystic ovaries, and a computed tomography scan revealed a normal anterior pituitary gland and normal adrenal glands; liver and kidney function test results were within normal limits.

Because of the persistence of the markedly elevated estrogen levels, with secondary suppression of follicle-stimulating hormone and luteinizing hormone and probable secondary stimulation of prolactin, it was considered necessary to determine whether there was an estrogen-producing ovarian tumor, such as a granulosa-theca cell tumor or an estrogen-producing adrenal tumor. Accordingly, on Jan. 2, 1992, an exploratory laparotomy was performed. The uterus, tubes, and left ovary were normal on gross examination, but the right ovary was twice the normal size and had multiple cysts; the adrenal glands were normal to palpation. Peritoneal washings were taken for cytologic analysis. A right salpingo-oophorectomy was performed, as were a wedge resection of the left ovary and an omental biopsy. The pathology report on the right ovary indicated numerous follicle cysts with luteinization of the theca interna (Figs. 1 and 2); the left ovary showed several follicle cysts, and there was no granulosa-theca cell tumor in either ovary. The omentum was normal, and the peritoneal cytologic analysis was negative for malignant cells.

One month after the operation, as shown in Table I, the estradiol and prolactin levels had dropped, the follicle-stimulating hormone and luteinizing hormone levels had risen, and the testosterone and dehydroepiandrosterone levels had remained elevated. On June 10, 1992, 5 months postoperatively, the laboratory findings reverted to levels similar to the preoperative ones (Table I). Gonadotropin-releasing hormone analog administration was planned to determine further whether the hyperestrogenemia was gonadotropin dependent, but the patient was lost to follow-up.

Comment

Persistently elevated estradiol levels that are above the peak physiologic range seen at the midcycle surge are usually a result of estrogen-producing tumors. Most of these tumors are granulosa-theca cell tumors of the ovary, but germ cell tumors of the ovary that produce human chorionic gonadotropin, such as embryonal carcinomas or choriocarcinomas, or tumors elsewhere in the body that produce human chorionic gonadotropin, such as hepatoblastomas of the liver, can result in excess ovarian estrogen production by stimulating the theca interna of the follicle to produce androstenedione, the immediate precursor of estrogens. Autonomous ovarian estrogen production is also recognized and is found to occur in the McCune-Albright syndrome, as well as in the occasional case of isosexual precocious pseudopuberty caused by gonadotropin-independent gonadal secretion of estrogen by autonomous benign ovarian follicle or luteal cysts. However, such autonomous estrogen production is usually at most in the normal physiologic range and has not been reported to reach such supraphysiologic levels as occurred in the case reported here. A tumor of the ovaries or adrenals as the source of the excess estrogen production was excluded in this case not only by imaging techniques (ultrasonogram and computed tomography scans) but also by laparotomy. Excess estrogen production caused by a human chorionic gonadotropin–producing tumor was ruled out by the repeated finding of normal serum human chorionic gonadotropin levels and by the absence of radiologic and laparotomy evidence of such a tumor.

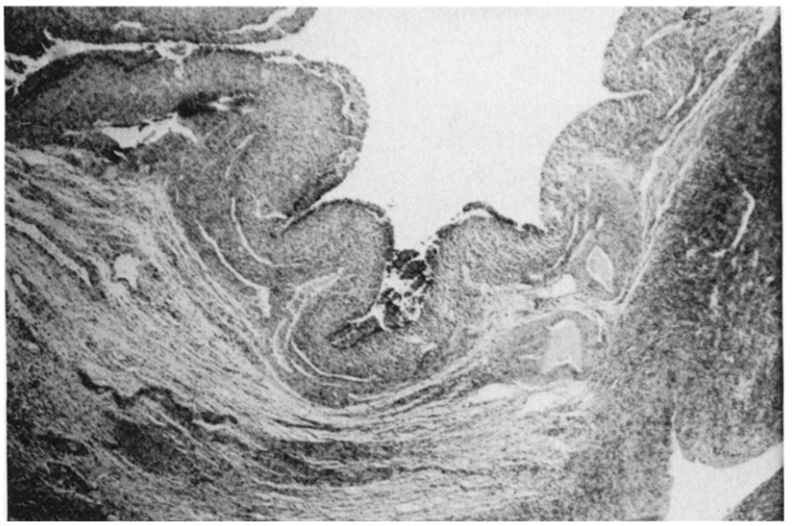

Fig. 1. Photomicrograph of portion of cyst of right ovary with convoluted lining. (Hematoxylin and eosin. Original magnification ×100.)

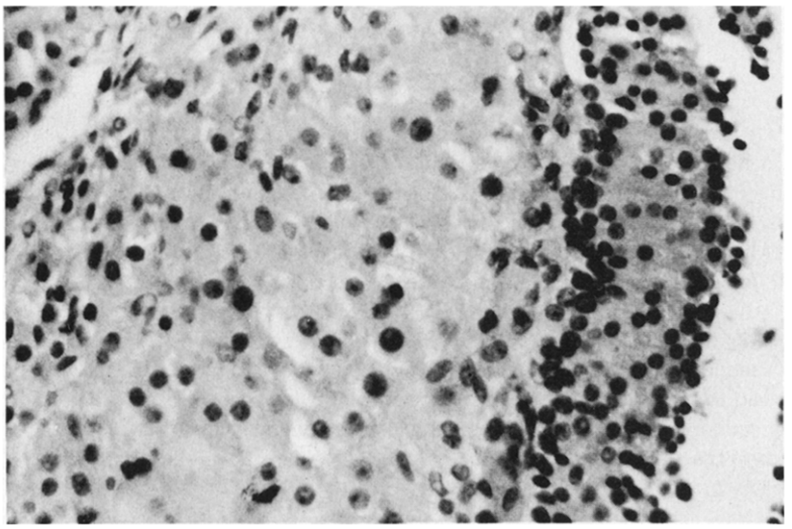

Fig. 2. Detail of specimen shown in Fig. 1. Photomicrograph of portion of ovarian cyst lining with granulosa cells forming inner layer and luteinized theca cells forming outer layer. (Hematoxylin and eosin. Original magnification ×250.)

On the other hand, there were many features to suggest a diagnosis of polycystic ovary syndrome in this case. The patient had bilateral polycystic ovaries and the histologic features were those of polycystic ovarian disease, namely, follicles lined with granulosa cells and thickened luteinized theca interna cells. Once the oophorectomy and wedge resection had been completed, the estrogen levels fell temporarily and the follicle-stimulating hormone and luteinizing hormone levels rose; such a temporary remission followed by recurrence, as occurred in this case, is a very common sequel to wedge resection in polycystic ovarian disease. The inverse follicle-stimulating hormone/luteinizing hormone ratio found on two occasions in this case is characteristic of the inappropriate gonadotropin secretion reported to be a basic feature of polycystic ovarian disease. The moderately elevated levels of dehydroepiandrosterone and testosterone seen in this case are also common findings in polycystic ovarian disease, the former being present in 50% of the cases and the latter being a common finding.[2]

This case is unique in two respects. First, all studies have shown that the hyperestrogenic state of polycystic ovarian disease is a result of an elevation of the estrone level, while the estradiol level remains in the normal follicular range; in this case the hyperestrogenemia was

primarily a result of marked hypersecretion of estradiol. Second, a literature search failed to reveal any report of polycystic ovarian disease that resulted in such a massive secretion of estradiol as to mimic an estrogen-producing tumor. The occurrence of this case also suggests that polycystic ovarian disease should be included in the differential diagnosis of estrogen-producing neoplasms, in spite of its being a very rare cause of such excessive estradiol production.

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Blood flow variations in internal carotid and middle cerebral arteries induced by postmenopausal hormone replacement therapy

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OBJECTIVE: Our purpose was to clarify the mechanisms by which postmenopausal estrogen replacement therapy exerts its protective effect on cardiovascular risk.
STUDY DESIGN: By means of a bidirectional Doppler ultrasonographic system we measured pulsatility index variations the internal carotid artery and middle cerebral artery in 25 early postmenopausal women during a 6-month period of hormone replacement therapy. Transdermal estradiol (50 μg/day) was continuously administered. A 12-day course of medroxyprogesterone acetate (10 mg/day) was added every second month.
RESULTS: The pulsatility index showed a significant ($p = 0.0001$) reduction in both arteries after 6 weeks. At 22 weeks a 25% reduction was measured. No variation of the estrogen-induced pulsatility index reduction was observed at the end of every cyclic progestogen supplementation.
CONCLUSIONS: In early postmenopausal women hormone replacement therapy causes a rapid reduction of pulsatility index in brain arteries. Cyclical progestational supplementation does not modify this positive effect on reactivity of the blood vessels. (Am J Obstet Gynecol 1993;169:1226-32.)

Key words: Hormone replacement therapy and cardiovascular protection, hormone replacement therapy and blood flow, pulsatility index in brain arteries

Hormone replacement therapy is known to reduce the risk of ischemic heart disease in postmenopausal women,[1-4] although the mechanism by which it exerts this effect is not completely understood. Favorable plasma lipid variations induced by hormone replacement therapy (high-density lipoprotein increase and low-density lipoprotein decrease)[4-6] seem to account for about half the effect on cardiovascular mortality risk.[4] In fact, experimental studies performed on monkeys with food-induced hypercholesterolemia, in which a surgical menopause was obtained, showed that hormone replacement therapy highly reduces both atherosclerotic plaque size[7] and coronary artery low-density lipoprotein uptake,[8] but that these effects seem to be only partially related to plasma lipoprotein variation. Besides these favorable actions on both lipid profile and atherosclerotic process, evidence exists about the presence and functionality of estrogen receptors on female baboon myocardium and aorta[9] so that a direct, receptor-mediated effect of estrogens on the cardiovascular

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