Gynecologic problems of androgen excess

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■ The patient with androgen excess may present with amenorrhea, oligomenorrhea, painless metromenorrhagia, or infertility. Adrenal and ovarian tumors, though uncommon, must be excluded in the workup. The long-term sequelae of untreated anovulation includes adenomatous hyperplasia and cancer of the endometrium. Treatment can range from uncomplicated follow-up with cosmetic advice to the use of potent drugs that induce ovulation.

□ INDEX TERMS: ANDROGEN EXCESS; CHRONIC ANOVULATION □ CLEVE CLIN J MED 1990;57:288–291

WHEN the patient presents with symptoms of anovulation such as amenorrhea, oligomenorrhea, painless metromenorrhagia, or infertility, androgen excess must be considered as a cause and treated effectively. Prolonged anovulation poses a threat to the endometrium and to the breasts; without treatment, these patients may present in later years with precancerous conditions such as cystic or adenomatous hyperplasia of the endometrium.

ENDOCRINE REVIEW

The complex of amenorrhea, oligomenorrhea, hirsutism, obesity, and enlarged, polycystic ovaries has traditionally been called Stein-Leventhal syndrome, first described in 1935. It is now more properly referred to as "persistent anovulation," with a broad spectrum of etiologic factors and clinical manifestations; for example, the patient may or may not be obese and the ovary may not necessarily be enlarged.

Morphologically, the classic Stein-Leventhal ovary was enlarged, smooth, and pearly white (*Figure 1*). This characteristic picture is caused by the dyssynchronous fluctuations in gonadotropins and by the high levels of luteinizing hormone (LH) associated with persistent anovulation. Cut section reveals a thickened tunica, numerous follicles in different stages of development, atresia, a stromal component that is often hyperplastic, and luteinized thecal cells (*Figure 2*).

Patients with persistent anovulation have increased production of estrogen and androgen dependent upon LH stimulation. The high-estrogen environment is linked with anterior pituitary secretion of LH and suppression of follicle-stimulating hormone (FSH).[1] These patients may have elevated basal levels of testosterone, androstenedione, 17-hydroxyprogesterone, dehydroepiandrosterone (DHA), estrone, and dehydroepiandrosterone sulfate (DHEAS). The testosterone, androstenedione, and DHA are secreted directly by the ovary while the DHEAS is an adrenal contribution. The ovary does not secrete increased amounts of estrogen and the estradiol levels are equivalent to early follicular-phase concentration. The increased estrogen results from the peripheral conversion of the increased androstenedione to estrone.[2,3]

The level of sex hormone-binding globulin (SHBG) is controlled by hormonal influences on its synthesis in the liver. Testosterone is inhibitory; estrogen and thy-

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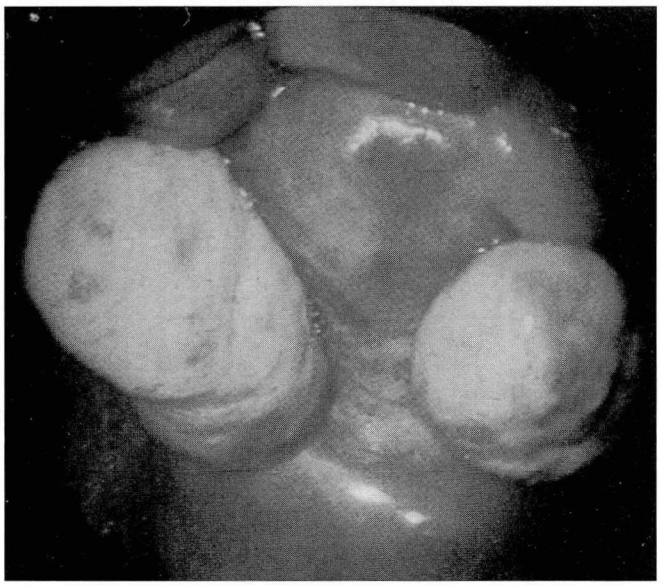

FIGURE 1. Uterus and polycystic ovary seen at laparoscopy.

roxine are stimulatory.[4] The increased testosterone levels in anovulatory patients cause an approximately 50% reduction in SHBG.

PRIMARY OR SECONDARY AMENORRHEA

Primary or secondary amenorrhea is seen in patients with persistent anovulation. A retrospective study of 252 patients with delayed menarche showed that 17 (6.7%) patients had androgen excess and amenorrhea.[5] Of these, 14 had hirsutism, 1 had a receding hairline, 1 had clitorimegaly, and 1 had acanthosis nigricans. All of these symptoms and signs may be seen in a patient with amenorrhea and androgen excess. In this study, the average age of presentation to the physician was 18 years, 10 months, which is relatively late.

The typical clinical picture in a young woman with primary or secondary amenorrhea is that of normal thelarche with no menarche. The patient is well developed with normal secondary sexual characteristics, some signs of androgen excess, and a normal uterus and vagina. Usually, there is abundant estrogenic cervical mucus at the external os. Some of these young girls present with an increased growth spurt prior to puberty. The workup must include a baseline measurement of testosterone as well as DHEAS to rule out tumors of the ovary or adrenal gland. Medroxyprogesterone acetate (Provera), administered by injection or orally, will produce a menstrual period in these patients.

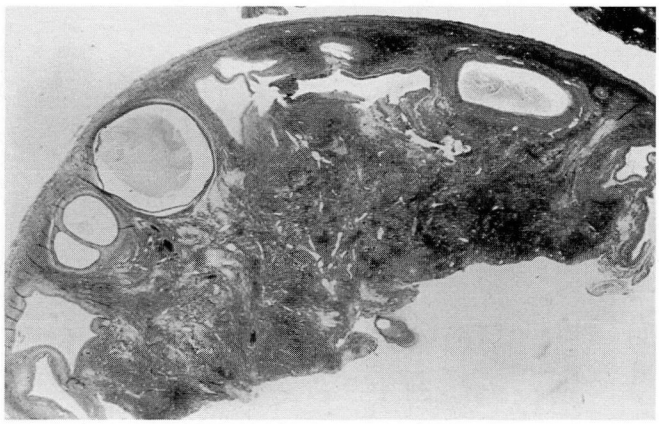

FIGURE 2. Cut section of polycystic ovary.

The differential diagnosis of polycystic ovarian condition or symptoms of androgen excess and abnormal menstruation includes Cushing's syndrome, adrenal enzymatic deficiency (late-onset 21-hydroxylase deficiency, 3-β-hydroxysteroid dehydrogenase-8-4-5 isomerase deficiency), functioning tumors of the ovary and adrenal glands, hyperthecosis, hyperprolactinemia, thyroid deficiency, and simple hirsutism.[6]

Irregular or dysfunctional bleeding may be the patient's chief complaint. This patternless, painless symptom often begins in the teenage years. Venturoli and associates evaluated the postmenarchal endocrine pattern in 95 such adolescents[7] and found that, despite persistent irregular cycles, in some adolescents all endocrine and ovarian parameters normalize as they reach maturity. Patients with persistent irregular, anovulatory cycles maintained marked hyperandrogenism, increasingly high LH values, and enlarged, polycystic ovaries. These patients require close follow-up and monitoring for the sequelae of chronic anovulation.

TUMOR *V* POLYCYSTIC DISEASE

Rarely, the symptoms of adrenal and ovarian tumors can mimic those of polycystic ovary, as shown in the two following cases.

Case 1

A girl, age 15 years 11 months, presented with a 1-year history of secondary amenorrhea. In the preceding 3 months, she had noted increasing hirsutism, acne, voice changes, and increasing abdominal girth. Serum testosterone was 214 ng/dL. A 24-hour urine sample showed 17-ketosteroids at 1,013 mg and 17-hydroxycor-

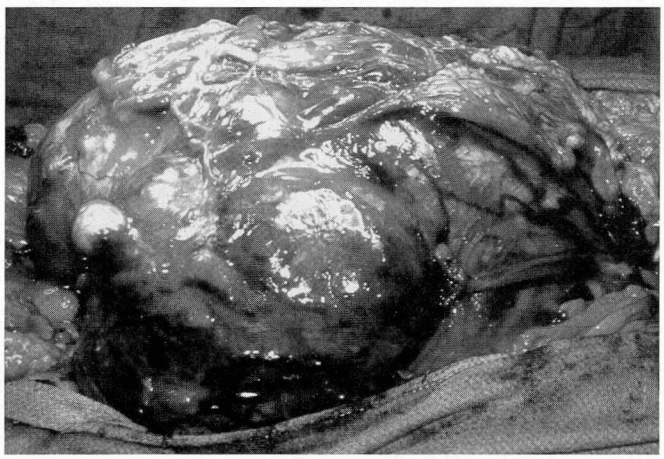

FIGURE 3. Gross pathologic specimen of adrenal carcinoma tumor.

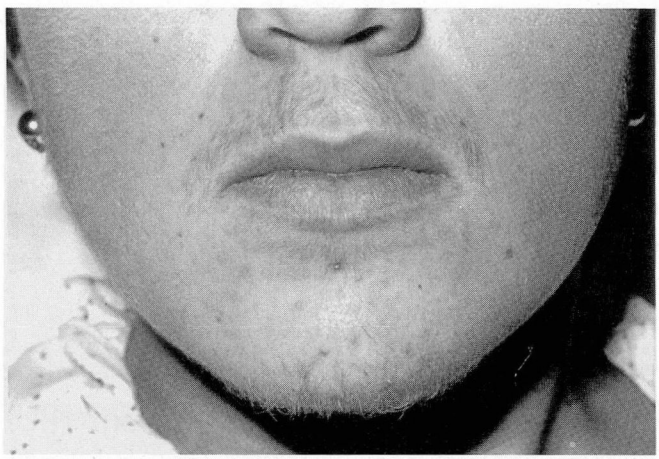

FIGURE 4. Acne and hirsutism in a patient with Sertoli- and Leydig-cell tumor.

ticosteroids at 52.6 mg. Serum amylase, β-human chorionic gonadotropin, and serum α_1-fetoprotein were all normal.

The patient had a left radical adrenalectomy with nephrectomy and a large adrenal carcinoma (*Figure 3*) was removed. Three months later she had a resection of the right lobe of the liver for metastatic disease, and died of intracerebral hemorrhage 7 months after the first operation.

Case 2

A girl, age 17 years 10 months, presented with a 1-year history of secondary amenorrhea and hirsutism that had increased during the preceding 6 to 8 months (*Figure 4*). The patient had been treated by a local physician with oral cortisone, but she reported minimal voice changes and a weight loss of 20 pounds. Examination revealed a pelvic mass 7 cm x 8 cm. Serum testosterone was 284 ng/dL, and a 24-hour urine collection showed normal levels of 17-ketosteroids and 17-hydroxycorticosteroids. A right salpingo-oophorectomy was done at laparotomy and a Leydig's cell tumor was seen in the right ovary (*Figures 5 and 6*). The patient is now 5 years post-surgery and has had regular periods with no new symptoms of androgen excess.

A blood DHEAS level greater than 700 μg is the cutoff for ruling out adrenal disease and has replaced the cumbersome 17-hour urinary measurements done in the past. When the DHEAS is elevated, a baseline 17-hydroxyprogesterone is needed to rule out 21-hydroxylase deficiency; a level greater than 300 ng/cc is usually considered diagnostic. Such a patient may present at puberty for the first time with symptoms and signs of androgen excess. A computed tomogram of the adrenal can rule out adrenal gland hyperplasia and tumors. Similarly, a pelvic examination and ultrasound will rule out most of the ovarian tumors that would produce significant amounts of androgen.

TREATMENT OF GYNECOLOGIC SYMPTOMS

Chronic anovulation that is not treated can cause endometrial hyperplasia and cancer. Furthermore, unopposed high estrogen and androgen levels may play a role in both fibrocystic disease and cancer of the breast. A retrospective study of 1,135 patients diagnosed as having polycystic ovarian disease showed that in these women, the relative risk of breast cancer developing after age 55 was 3.6.[8,9,10]

Treatment of gynecologic symptoms depends on the patient's needs. For example, the adolescent will want effective treatment for hirsutism, which can be achieved with a birth control pill in combination with spironolactone. Occasionally, in the patient who has an increased adrenal component, a small bedtime dose of dexamethasone may be beneficial. Since dexamethasone will increase fertility, a sexually active patient should be advised to use an effective method of contraception if a birth control pill is not already part of the treatment regimen.

The patient who is in her thirties may be less troubled by the cosmetic symptoms of androgen excess and menstrual irregularity. Nevertheless, she should be warned about the unopposed action of estrogen on the uterus

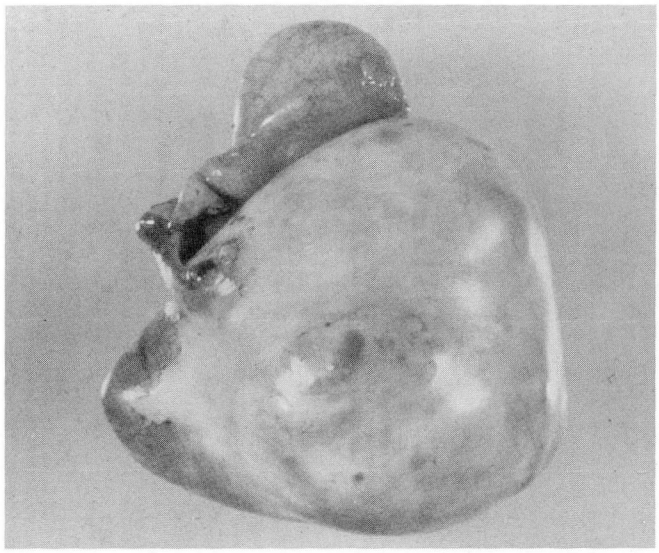

FIGURE 5. Surgical section of Sertoli- and Leydig-cell tumor.

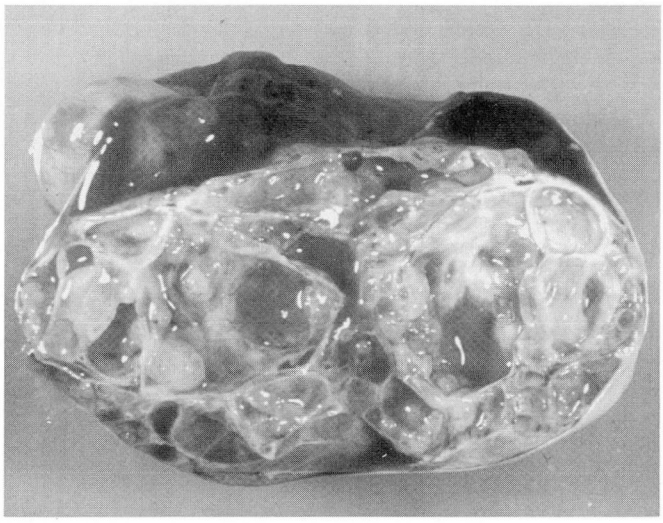

FIGURE 6. Cut section of Sertoli- and Leydig-cell tumor removed at surgery.

and breasts and started on a regimen of medroxyprogesterone to cause withdrawal bleeding and to protect the breasts from unopposed estrogen. If endometrial hyperplasia is suspected, then endometrial biopsy can be performed as an office procedure.

INFERTILITY

Infertility is a common presenting symptom of androgen excess. Ovulation usually can be verified clinically with a history of cyclical molimina and measurements of biphasic basal body temperature and midluteal phase progesterone. Endometrial biopsy, which is invasive and painful, is rarely needed. If necessary, kits that measure the LH level in urine can be used in office practice to establish ovulation.

Some 80% of patients can be made ovulatory with medical therapy; wedge resection and other surgical approaches for treatment of chronic anovulation are almost obsolete. Widely accepted modalities include drugs such as clomiphene citrate, human menopausal gonadotropins, pure FSH, and, more recently, the GnRH agonist leuprolide acetate (Lupron) followed by menotropins (Pergonal). In some in vitro fertilization programs, follicles are aspirated via ultrasound or laparoscopy.

Before exposing the patient to fertility drugs, her husband should be evaluated to rule out male factors contributing to infertility. Most fertility drugs have side effects, including the production of ovarian cysts and multiple pregnancies, that need to be discussed with the patient.

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