Medical Progress

Polycystic Ovarian Disease

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Polycystic ovarian disease represents a poorly defined spectrum of clinical disorders having oligo-ovulation or anovulation as a common feature. There is no single, universally accepted biochemical or clinical definition. Clinical findings usually include anovulation resulting in irregular uterine bleeding and infertility, androgen excess resulting in hirsutism and acne, and obesity. The pathophysiology involves altered functions of the hypothalamus, pituitary, ovary and adrenal glands, resulting in failure of folliculogenesis to regularly proceed to ovulation. The cause of the initiating event in this disease process remains enigmatic. Therapy for the various abnormalities in polycystic ovarian disease is tailored to a patient's needs and may include preventing endometrial hyperplasia, controlling irregular uterine bleeding, controlling hirsutism and inducing ovulation.

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There is as yet no precise biochemical or clinical definition of polycystic ovarian disease; the disease is not a single entity but a spectrum of disorders unified by the central problem of ovarian dysfunction. The diagnosis usually is made on clinical grounds, but a consensus concerning the criteria required for the diagnosis is lacking. In this discussion, the clinical spectrum of polycystic ovarian disease will be considered first; then the nature of the various hormonal and biochemical changes associated with the disorder will be analyzed. Possible etiologic factors will be reviewed and, finally, a discussion of current therapeutic modalities and their rationale will be presented.

The incidence of polycystic ovarian disease is difficult to determine. Estimates range from 1% to 4% of all women,[1] with some evidence of a familial tendency. Patients assigned this diagnosis usually present with evidence of anovulation or oligo-ovulation. They may have menstrual irregularity or infertility. The diagnosis of polycystic ovarian disease is inappropriate for patients with regular ovulatory cycles. A second major clinical characteristic is usually some degree of androgen excess, manifest as hirsutism or acne, or both. The third clinical correlation is with weight gain, obesity or difficulty in losing or maintaining weight. The extremes of these symptoms account for the classic triad of the Stein-Leventhal syndrome: amenorrhea, hirsutism and obesity.[2] Milder degrees of dysfunction in each of these categories allow for the variability in presentation mentioned above (Table 1).

There is no biochemical characteristic that is found in all women who have polycystic ovarian disease that either confirms or excludes the diagnosis. One major characteristic of this disease spectrum is an association with acyclic ovarian activity, not ovarian quiescence. It can be distinguished easily from lack of ovarian stimulation, as seen in hypothalamic amenorrhea or hypogonadotropic hypogonadism, because of the characteristic production of ovarian steroids, particularly androgens, in cases of polycystic ovarian disease. The production of estrogens (principally estrone) may cause endometrial proliferation leading to spontaneous irregular bleeding or to a positive progestin withdrawal challenge. Typically, estradiol production tends to be in the range of that seen in the early follicular phase of the normal cycle, without the increases noted at midcycle. Estrone, derived primarily from peripheral (extragonadal) conversion of androgen precursors, usually is in the high-normal range.[3] Androgens are produced in increased amounts by the ovary, often reflected in elevated circulating androstenedione and testosterone concentrations. These androgens, coupled with the small follicles and the relatively low follicle-stimulating hormone (FSH) levels, to be described later, contribute to the inhibition of the aromatase reaction in the ovary, thereby enhancing follicular atresia and inhibiting follicular maturation. The pituitary hormones are variably affected by these steroid profiles, but the pattern usually seen in patients (more than 80%) with a clinical diagnosis of polycystic ovarian disease is an increase in luteinizing hormone (LH) concentrations and an elevated LH-to-FSH ratio, usually greater than 3 to 1.[4] Proper interpretation of LH and FSH measurements requires consideration of the pronounced pulsatile release of LH that can significantly

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
SHBG = sex hormone-binding globulin

alter the LH-FSH ratio within minutes. This can limit the clinical usefulness of a single measurement of LH and FSH levels.

Changes also may be seen in the adrenal production of androgens. Dehydroepiandrosterone and dehydroepiandrosterone sulfate are increased in many cases, as are all Δ^5-3β-hydroxysteroids; these levels are typically suppressed by the administration of dexamethasone, suggesting their adrenal origin.[5]

Some women with polycystic ovarian disease also have hyperprolactinemia,[6] which usually is associated with altered gonadotropin secretion. The hyperprolactinemia could result from the abnormal serum estrogen concentrations found in some cases of this disease, but may be a reflection of a common central abnormality, such as altered dopaminergic activity, affecting prolactin and gonadotropin secretion. Exposure of the ovary to these abnormal concentrations of pituitary hormones—that is, increased LH, decreased FSH and possibly increased prolactin—can greatly alter ovarian function. Polycystic ovarian disease also may be associated with acanthosis nigricans.

Although the histopathologic features of the ovary are variable, all ovaries in polycystic ovarian disease show signs of chronic stimulation, with many follicles in various stages of early maturation and atresia. In some cases, the ovary may be substantially enlarged with numerous microfollicular cysts and a thickened sclerotic capsule, or the ovary may be of normal size with increased stromal tissue, varying in amount from minimally increased to true hyperthecosis. Similar ovarian pathology is found in patients with other diseases resulting in anovulation, including hypothyroidism and hyperthyroidism, Cushing's disease, congenital adrenal hyperplasia and androgen-producing tumors.

TABLE 1.—*Symptoms of Polycystic Ovarian Disease*

Ovulatory Dysfunction
Amenorrhea or oligomenorrhea
Infertility
Dysfunctional uterine bleeding
Hyperandrogenism
Hirsutism
Acne
Excess sebaceous gland secretions
Anabolic State
Obesity
Difficulty losing weight

The pathophysiology of the disruption of normal cyclic ovarian responsiveness has not been established definitively. However, it is possible to explain the observed biochemical abnormalities in accordance with the known physiology of the reproductive axis. The salient features of the disease that need to be explained are the increased androgen production, the increased secretion of LH compared with FSH and the failure of folliculogenesis to proceed to ovulation.

Each of these three abnormalities in endocrine physiology can be linked together in a chain of events that perpetuates the syndrome (Figure 1). The factor responsible for the initiation of this chain of events remains unclear. The major endocrine systems involved in polycystic ovarian disease are the hypothalamic-pituitary axis, the ovary, the adrenal gland and peripheral tissues.

Altered hypothalamic-pituitary function is reflected in altered gonadotropin secretion. Several factors exist to explain the increased LH-FSH ratio. Although there is great variation in the pulsatile secretion of gonadotropins in polycystic ovarian disease, the most frequently found abnormality is increased frequency and amplitude of LH pulses. Stimulation of the pituitary with gonadotropin-releasing hormone (GnRH) results in an exaggerated LH response and minimal increases in FSH in women with this disease compared with normal women.[7] Estrogen is known to augment the LH response to GnRH. The mild tonic elevations of estrogen, predominantly estrone, in cases of polycystic ovarian disease may contribute to this altered gonadotropin release. An inhibinlike substance, which selectively inhibits FSH secretion, also may contribute to altered gonadotropin secretion. Increased inhibinlike activity has been found in follicular fluid of ovaries from women with polycystic ovarian disease when

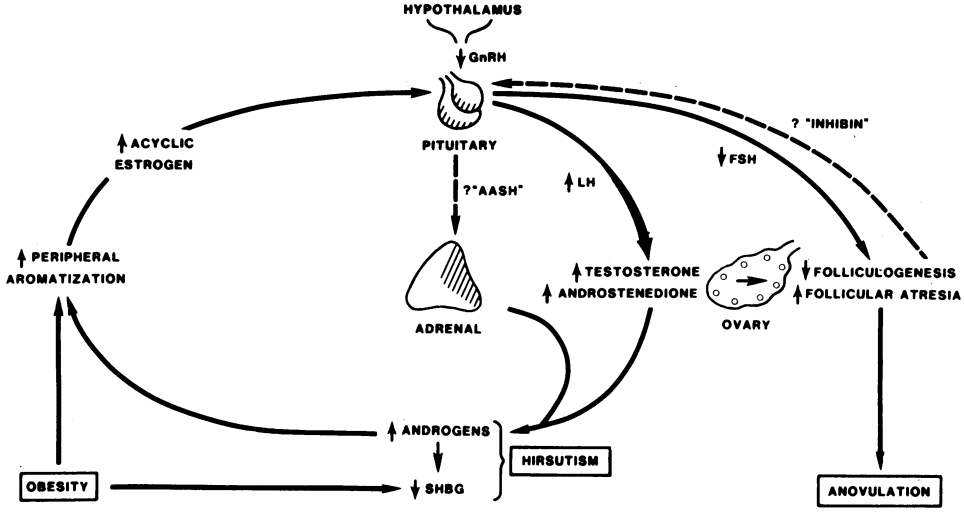

Figure 1.—This schematic shows the abnormalities in endocrine physiology that lead to the obesity, hirsutism and anovulation of polycystic ovarian disease. GnRH = gonadotropin-releasing hormone, "AASH" = adrenal androgen-stimulating hormone, LH = luteinizing hormone, FSH = follicle-stimulating hormone, SHBG = sex hormone-binding globulin.

compared with follicular fluid from similar-sized follicles in normal ovaries.[8]

Prolonged exposure to elevated LH levels may lead to hyperplasia of theca cells and increased production of the ovarian androgens, androstenedione and testosterone. Increased intraovarian androgen levels increase the rate of follicular atresia and contribute to decreased folliculogenesis by inhibiting the conversion of androgen to estrogen by enzymatic (aromatase) activity.[9] In spite of an abundant supply of androgenic substrate, polycystic ovaries have a decreased ability to aromatize androgens to estrogens. The relative deficiency in FSH and the absence of large follicles[9] are key factors in the loss of aromatase activity. Although specific enzyme defects have been reported in women with polycystic ovarian disease, the underlying cause of the morphologic and endocrinologic ovarian abnormalities appears to be inappropriate gonadotropin stimulation.

Alterations in adrenal function and steroid concentrations are found in women with polycystic ovarian disease, but their relative importance in the pathogenesis of this syndrome is uncertain. The contribution of the adrenal gland to total circulating androgen varies among different subgroups of patients with this syndrome. Elevated dehydroepiandrosterone sulfate concentrations suggest increased adrenal androgen secretion.

In the final link in the chain of events, elevated circulating androgens, principally androstenedione, are converted by aromatase in peripheral tissues such as adipose tissue to estrogens, predominantly estrone. This endogenous source of estrogen may contribute to the altered secretion of LH and FSH.

Although the total concentration of androgen and estrogen is often in the upper limits of the normal range, the peripheral effects of these steroids may be exaggerated because a larger portion of the total steroid concentration is in the free or unbound form. The reason for this increased free steroid in cases of polycystic ovarian disease is the decreased concentration of sex hormone-binding globulin (SHBG), which binds both estrogens and androgens. Both increased androgens and obesity lower SHBG concentrations.

Serum insulin levels also are increased in women with polycystic ovarian disease. Insulin resistance is known to be associated with obesity, but recent studies in nonobese women with polycystic ovaries indicate that insulin resistance in such cases may be related to hyperandrogenism.[10]

Factors, still to be defined, for initiating this chain of events may be linked to abnormal endocrine development at puberty. Careful questioning of women with this disease can often date the onset of the symptoms—that is, obesity, hirsutism or menstrual irregularity—to puberty. Theories to explain the initiation of polycystic ovarian disease include (1) an exaggerated adrenarche leading to elevated androgen levels of adrenal origin at puberty, (2) obesity resulting in decreased SHBG levels and increased peripheral aromatization resulting in an altered steroidal milieu, (3) altered central nervous system control of gonadotropin secretion and (4) enzymatic defects in either ovarian or adrenal gland (or both) steroidogenesis.

The evaluation for possible polycystic ovarian disease should include assessment of thyroid and adrenal function, measurement of circulating prolactin levels and administration of a progestin such as medroxyprogesterone acetate, 10 mg taken by mouth for 5 days, to ascertain whether bleeding occurs following progestin withdrawal. This withdrawal bleeding reflects the presence of significant circulating estrogen. Significant abnormal uterine bleeding in women older than 35 years warrants assessment of endometrial histologic appearance with an endometrial biopsy. There is an increased incidence of endometrial carcinoma in women with untreated polycystic ovarian disease.[1]

If hirsutism is a complaint, the following tests are indicated: measurement of serum androgen concentrations, of androstenedione and testosterone to detect an ovarian source and of dehydroepiandrosterone sulfate to detect an adrenal source. The presence of greatly elevated values for any of these steroids warrants further workup to rule out the presence of an androgen-producing tumor or Cushing's disease. Often serum androgen measurements are normal in spite of considerable hirsutism. Recent studies indicate that androstanediol glucuronide, an androgen metabolite, is a uniquely sensitive indicator of increased peripheral androgen action[11] and often may be elevated even with normal circulating androgens.

There are many treatment options (Table 2). The choice of treatment depends partly on the individual symptom complex, the severity of each aspect of the presenting symptoms and the therapeutic goals desired—that is, whether the primary problem is infertility or hirsutism.

When ovulation is desired for fertility, it can be induced with the use of clomiphene citrate in 80% of patients and pregnancy achieved in 40%. Those patients who do not respond to clomiphene use may be candidates for incremental doses of clomiphene, clomiphene plus human chorionic gonadotropin or clomiphene plus dexamethasone if adrenal androgen levels are elevated. The susceptibility of the ovary to cyst formation is variable and must be kept in mind during any of these regimens. Pergonal (human menopausal gonadotropins [menotropins]) or "pure" FSH can induce ovulation in clomiphene-resistant patients. Unfortunately, these patients are unpredictably sensitive to gonadotropin therapy and have a high incidence of ovarian hyperstimulation and multiple births.[12] A new alternative to gonadotropins for inducing ovulation is the manipulation of the hypothalamic-pituitary axis with the use of GnRH-pump therapy, providing pulsatile administration of GnRH on a fixed schedule. Higher doses of

TABLE 2.—*Treatment of Polycystic Ovarian Disease*

Ovulation Induction
Clomiphene citrate
+ Human chorionic gonadotropin
+ Dexamethasone
Gonadotropins
Follicle-stimulating hormone only
+ Dexamethasone
Gonadotropin-releasing hormone
Wedge resection
Abnormal Uterine Bleeding/Prevention of Endometrial Hyperplasia
Oral contraceptives
Medroxyprogesterone acetate
Hirsutism/Acne
Oral contraceptives
Spironolactone
Gonadotropin-releasing hormone analog

GnRH per pulse appear to be needed in patients with polycystic ovarian disease compared with patients with hypothalamic amenorrhea. In spite of this increased dose, there is a low incidence of ovarian hyperstimulation (E. Schriock, M. Martin and R.B. Jaffe, unpublished observations, 1984).[13] Surgical therapy (ovarian wedge resection) is occasionally appropriate for patients who have failed to respond to any of these medical forms of management, since conception rates after wedge resection are about 50%. The effects of wedge resection are frequently temporary and patients often are left with pelvic adhesions. The use of modern microsurgical techniques may decrease the incidence of this complication. However, none of these treatment modalities appears to offer a permanent reversal of the underlying disorder, and many of these patients will have only a temporary remission of the ovarian dysfunction.

The treatment of the associated obesity in the hope of restoring normal levels of SHBG and decreasing peripheral androgen production is generally characterized by frustration on the part of patient and practitioner. When ovulation is not an immediate goal and the irregularity or infrequency of bleeding is the major symptom and concern, oral contraceptives or progestin administered at periodic intervals may be used. If protection against pregnancy is not an associated objective, then many of these obese women will do well with progestin taken every second month. This prevents endometrial hyperplasia and menometrorrhagia and allows a predictable frequency of withdrawal bleeding. It also allows an opportunity for a normal cycle to intervene. Should contraception be a desired feature of therapy, then the oral contraceptives will regulate bleeding, increase SHBG production and often reduce hirsutism.

The treatment of hirsutism itself often can be accomplished with the use of spironolactone.[14] This potassium-sparing diuretic appears to act directly at the androgen receptor in addition to decreasing ovarian androgen production.

Thus, all of the above forms of treatment attempt to interrupt the pathologic chain of events of polycystic ovarian disease. Clomiphene, an antiestrogen, interrupts the tonic estrogen exposure at the hypothalamic-pituitary level. Gonadotropin therapy replaces the deficit of FSH. Giving GnRH attempts to correct the altered pulsatile gonadotropin secretion pattern. The therapeutic effect of wedge resection, though not completely understood, is probably related to a decrease in the ovarian androgen or inhibin production, or both. Oral contraceptives increase SHBG and decrease LH secretion. Spironolactone both decreases ovarian androgen production and inhibits peripheral androgen action by competing for the androgen receptor. Unfortunately, all of these modes of therapy usually have only temporary benefit.

In summary, polycystic ovarian disease is a spectrum of clinical disorders having oligo-ovulation or anovulation as a common feature. The pathophysiology is best described by a chain of events that involves the pituitary, ovary, adrenal glands and peripheral tissues as summarized in Figure 1. The initiating events are unknown, but the consequences of anovulation lead to a broad spectrum of associated symptoms and problems. Treatment should be tailored to an individual patient and is based on the symptom complex of major concern to that patient. Treatment cannot yet be directed toward permanent correction of the underlying primary disturbance.

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