

Amenorrhea (Excluding Hyperprolactinemia)

Edward L. Marut, MD, and M. Yusoff Dawood, MD

*University of Illinois College of Medicine
Chicago, Illinois*

While primary and secondary amenorrhea associated with hyperprolactinemia are discussed elsewhere in this volume, this section will deal with normoprolactinemic secondary amenorrhea: that is, cessation of menses for at least 3 months, subsequent to previous normal menstrual function. There is some overlap between causes of primary and secondary amenorrhea, and this relationship will be noted where pertinent. Our discussion will consider the differential diagnosis of amenorrhea, with a description of the probable pathophysiologic mechanisms, the clinical and laboratory evaluation, the diagnosis, and the specific treatment of each entity.

Differential Diagnosis

Once hyperprolactinemia is ruled out, the differential diagnosis of amenorrhea falls into five main categories, including the four compartments of the hypothalamic-pituitary-ovarian-endometrial axis requiring coordinated performance to effect regular menstruation, and the fifth category of other endocrinopathies that may affect this reproductive axis.

Hypothalamic Causes

Until recently, hypothalamic amenorrhea was diagnosed by excluding identifiable factors, but advances in neuroendocrinology have enabled a more precise clinical diagnosis. In hypothalamic dysfunction, there is failure of adequate gonadotropin-releasing hormone (GnRH) release necessary to stimulate appropriate pulsatile gonadotropin secretion. Pulsatile release of GnRH is responsible for the typical circhoral pattern of luteinizing hormone (LH) secretion associated with normal ovulatory cycles.¹⁻³ Aberrations in the frequency or amplitude of GnRH "pulses" result in nonpulsatile LH and follicle-stimulating hormone (FSH) secretion or abnormal ratios of these two gonadotropins. Inappropriate pulsatile release of GnRH may cause ovulatory dysfunction ranging from a normoestrogenic state to a hypogonadal state. Hypothalamic amenorrhea may coexist with a normal estrogen milieu due to an exaggerated negative feedback⁴ or absent positive feedback⁵ of estradiol on LH secretion. Breakthrough bleeding is not unusual. Hypothalamic amenorrhea is distinguished from polycystic ovarian syndrome, where the normal feed-

back response is intact, but there is inappropriate steroid effect on the hypothalamus due to excess ovarian or adrenal androgen and peripheral aromatization to estrogens.⁶

More severe hypothalamic dysfunction is characterized by low estrogen levels that are insufficient for adequate endometrial proliferation necessary for spontaneous or progestin-induced withdrawal bleeding. Failure of both the negative and positive feedback responses is frequent. LH pulsatility is usually abolished as reflected by the minimal ovarian estrogen production.^{3,7}

In hypothalamic hypogonadotropic amenorrhea, the endogenous opioid-dopaminergic system appears to inhibit GnRH release.⁸ Both naloxone, an opioid antagonist, and metoclopramide, a dopamine antagonist, increased LH secretion in some patients with hypothalamic amenorrhea. Others do not respond, suggesting a more profound inhibition of GnRH or an entirely different mechanism. Modulation of GnRH inhibition by endogenous opioids acting on dopaminergic neurons has also been shown to exist in the postpartum state⁹ and the luteal phase.^{10,11}

The clinical correlates of hypothalamic amenorrhea are extremely varied and are associated with neuropharmacologic agents, weight loss, and stress states, either psychological or physical.

Neuropharmacologic agents such as psychotropic and antihypertensive drugs that interfere with neurotransmission may produce amenorrhea through a mechanism separate from their effect on prolactin secretion.¹² While interference with dopamine or augmentation of serotonin in the hypothalamus almost always elevates prolactin levels, disruption of noradrenergic effects can suppress GnRH secretion. Currently it is unclear whether prolonged neuropharmacologic hypothalamic suppression or an underlying disease process accounts for the persistent amenorrhea. Therefore, the use of neuropharmacologic agents still requires exclusion of other underlying pathology.

With postpill and postpartum amenor-

rhea, it is debatable whether oral steroid contraceptives (or gestation) "cause" subsequent amenorrhea or they mask an underlying pathologic process that is uncovered when the patient stops taking the pill.^{13,14} Amenorrhea while taking the pill is due to the progestational effect on the endometrium and is not related to later menstrual disturbances. Ovulatory dysfunction can be explained in almost all cases by prior abnormality of menses or intercurrent changes such as stress or weight loss.¹⁵

Weight loss is a well-established factor in amenorrhea.¹⁵⁻¹⁸ The "critical weight for height" hypothesis is useful in explaining many cases of amenorrhea.¹⁹ Although at first a critical weight alone appeared essential for initiation of menarche, it is now clear that body fat as a percentage of total weight is the more important determinant. A fat content of 17% of the total body weight is necessary for initiating menarche, but 22% is the critical percentage required to maintain regular menstruation after the age of 16 years. According to this hypothesis, the cessation or return of menses revolves around this critical body fat index of 22%. Simple weight loss of 10-15% of total body weight will often result in amenorrhea because the loss is mainly fat. Anorexia nervosa is the prime example of extreme weight loss with amenorrhea.^{20,21} Nevertheless, the amenorrhea often precedes the weight loss, suggesting a preexisting abnormality in the hypothalamus or higher centers.²²

Significant menstrual dysfunction may be associated with jogging, running, aerobic dancing, and other exercises.²³ The pathophysiology of such exercise-related amenorrhea is debatable, because not all women engaging in strenuous exercise become amenorrheic. Puberty and menarche can be delayed in girls who are involved in physical training, although they may have reached their critical weight for height.^{24,25} In addition, interruption of the physical training results in progression of sexual development and initiation of menses without weight change. Similarly, ballerinas who are amen-

orrheic will resume cyclic menses when injury forces them to stop dancing although no change in weight occurs.²⁶

Clearly, risk factors for exercise-related amenorrhea exist for the individual woman.²³ The most susceptible are the young nullipara who have a history of delayed menarche or irregular menses and have a lower body fat content before or due to exercise. Other factors include psychological stress, intensity of training, or nutritional aberrations. Amenorrheic athletes tend to have lower estradiol and progesterone and higher testosterone and dehydroepiandrosterone sulfate levels than menstruating athletes. They also lose the stimulatory effect of acute exercise on peptide and steroid hormones.²⁷ All things considered, the concept of an "energy drain" is valid in explaining amenorrhea associated with physical training.

Psychologic stress may be due to changes in employment, school, personal relationships, moving, or other emotional disturbances. The interrelationships among higher neural centers and the hypothalamus make the association between psychologic phenomena and reproductive dysfunction understandable, although specific psychoneuroendocrine events are not completely worked out.²⁸ The endogenous opioid and dopaminergic systems are probably involved in stress-induced amenorrhea, because women with hypothalamic hypogonadotropic amenorrhea often demonstrate some degree of psychologic abnormality.^{8,29} While resolution of the emotional events usually heralds the return of normal cyclic menstrual function, this is not necessarily the case, and amenorrhea may be related to a more chronic process.

Anorexia nervosa is also the best example of psychogenic amenorrhea accompanied by weight loss.^{16,20,21} The syndrome, which consists of distorted body image, abnormal investment of emotional content in food and eating, obsessive-compulsive behavior, nutritional deficit, life-threatening weight loss, and other psychosexual components,

results in multiple hypothalamic derangements. As mentioned, the amenorrhea may precede the weight loss, suggesting a primary psychiatric disease. There is loss of pulsatility of gonadotropin release,^{22,30} together with regression to a prepubertal response of LH and FSH to exogenous GnRH stimulation.³¹ This is further supported by the finding that recovery from the disease results in progression of gonadotropin secretion from nocturnal pulsatility to circadian pulsatility of LH as observed in the normal progression of puberty. Exogenous GnRH administration will eventually duplicate the normal adult pattern.³¹ Because recovery from anorexia nervosa involves both improvement of psychiatric aspects as well as weight gain, these cannot be easily separated. The similarity between anorexia nervosa and exercise-related amenorrhea lies in the frequent accompaniment of intense physical activity with anorexia nervosa in a deliberate attempt by the patient to induce a negative caloric balance. Also, women demonstrating exercise-associated amenorrhea are at significantly greater risk for development of overt anorexia in the future.

In contrast, psychogenic amenorrhea manifesting as pseudocyesis presents itself as a eugonadal state similar in some ways to polycystic ovarian syndrome, with an elevated LH to FSH ratio, pulsatility of LH, and an elevated prolactin level.³² The diagnosis is made by absence of a clinically or sonographically detectable pregnancy. Psychiatric treatment obviously is mandatory.

Polycystic ovarian syndrome will be discussed under ovarian causes for amenorrhea; however, there is good argument for a hypothalamic involvement. Yen points out that the hypothalamus is actually responding to an inappropriate steroid feedback signal in an appropriate fashion,⁶ although some evidence for disruption of dopaminergic neurotransmission exists, such as associated hyperprolactinemia or the ability of dopamine and its agonists to suppress the elevated LH levels.^{33,34}

Finally, hypothalamic tumors that re-

place or disrupt neural pathways important in modulation of gonadotropin release will result in amenorrhea. The most common is a craniopharyngioma,³⁵ presenting usually in the adolescent, but other tumors such as germinomas, teratomas, and gliomas may be responsible.³⁶ These tumors may present with multiple endocrinopathies, as well as other neurologic symptoms of a space-occupying lesion. Granulomatous disease such as Hand-Schüller-Christian disease (multiple eosinophilic granulomata), tuberculosis, and sarcoidosis, as well as trauma or irradiation, may also affect the hypothalamus. For any of these lesions, the symptom is rarely amenorrhea alone. Isolated gonadotropin deficiency (Kallmann's syndrome) due to failure of GnRH secretion presents as primary amenorrhea and pubertal failure. Anosmia and midline facial defects may be part of the familial syndrome that has variable penetrance and expressivity.³⁷

Pituitary Causes

Pituitary causes of amenorrhea fall into two categories: those with hyperprolactinemia and those with normal or low prolactin levels. Only the latter will be discussed.

The pituitary causes of secondary amenorrhea are neoplastic or traumatic. Other forms of partial or complete hypopituitarism with failure of gonadotropin secretion will present as primary amenorrhea and likely abnormal pubertal development. These include panhypopituitarism, true gonadotropic dysfunction (not related to GnRH deficiency), and selective gonadotropin deficiency.

Acquired pituitary defects due to neoplasms often have an indolent course when there is normoprolactinemia. Traumatic causes of pituitary defects causing amenorrhea are often related to treatment of a pituitary or hypothalamic tumor (or other head or neck neoplasm), where radiation or surgery has destroyed some or all of the gonadotrophs. The hypothalamus is more sensitive than the pituitary to irradiation and may be the source of the deficit.³⁸ Head trauma, such as in a motor vehicle accident, that results in

pituitary stalk damage will usually be accompanied by hyperprolactinemia due to interruption of dopaminergic fibers, which are responsible for tonic inhibition of the lactotrophs. However, a partial stalk injury could theoretically avoid decreasing prolactin inhibition while disrupting GnRH neural fibers.

Although a patient with the empty sella syndrome may have hyperprolactinemia, she may be euprolactinemic.^{39,40} This condition is thought to be due to infarction of a previously undetected (or sometimes diagnosed and even treated) pituitary tumor. If the tumor is not a prolactinoma, or the lactotrophs are largely destroyed, gonadotroph destruction associated with ischemic necrosis of normal pituicytes may result in amenorrhea. Radiologic methods of detecting the empty sella have evolved from pneumoencephalography to computerized axial tomography (CAT) scan with intrathecal contrast material demonstrating communication of the sella turcica with the subarachnoid space due to a defect in the diaphragma sellae. Visual field defects are notably absent, while headaches are common.

Postpartum pituitary ischemic necrosis (Sheehan's syndrome) is an acute infarction of the hypertrophied and hyperplastic gestational pituitary gland due to hemorrhage and shock in the peripartum interval.⁴¹ Clinically, it is rapidly evident by loss of multiple, if not all, trophic hormones. The degree of hypopituitarism is variable, with severe cases involving the posterior pituitary and resulting in diabetes insipidus. Similarly, recovery of pituitary function is also highly variable.⁴² Vascular necrosis due to other causes, such as atherosclerosis, vasculitis, or thrombosis, is less common than Sheehan's syndrome. The former will not result in prolactin deficiency, as does the latter. Again, it is unusual for gonadotrophs alone to be impaired.

Pituitary neoplasms, either functioning or nonfunctioning, can result in gonadotropin abnormalities and amenorrhea.⁴³ Hypothalamic tumors that extend to the pituitary have been mentioned earlier. Primary

pituitary tumors may secrete prolactin, adrenocorticotrophic hormone (ACTH), growth hormone, and even the glycoproteins (thyroid-stimulating hormone [TSH], FSH and LH) or their subunits. Therefore, they may present as Cushing's syndrome, acromegaly, hyperthyroidism, or galactorrhea-amenorrhea. Chromophobe adenomas may not secrete detectable hormones and will appear by destruction of normal pituitary tissue later in the course of development. With pituitary causes of amenorrhea, there is hypoenestrogenism because of altered capacity of the gonadotrophs to respond to GnRH pulses.

Ovarian Causes

Ovarian causes of secondary amenorrhea produce clinical manifestations ranging from hypoenestrogenism to hyperestrogenism. The extent of the pathophysiologic derangement determines whether there is oligomenorrhea, intermittent dysfunctional uterine bleeding, or frank amenorrhea. In polycystic ovarian syndrome^{44,45} and other ovarian hyperandrogenic states,^{46,47} the excess androgen can either enhance or suppress gonadotropin release via the estrogens produced through peripheral aromatization. LH pulsatility may be constantly enhanced by increasing the sensitivity of the pituitary to GnRH, resulting in an increased steady state release of LH.^{48,49} Because the positive feedback on LH is accompanied by a negative feedback on FSH, the LH-FSH ratio is increased, but negative feedback on both FSH and LH may occur with extremely high androgen levels. Increased androgen levels tend to lower testosterone-estradiol binding globulin (TeBG), resulting in increases in free testosterone, estradiol, and estrone levels, with accompanying increased biologic effects.^{50,51} With pathologic states more severe than polycystic ovarian disease, the androgen levels can suppress gonadotropins and cause hypoenestrogenism. Clinically, hirsutism is seen with modest elevation of testosterone, and virilization with marked elevation.

The adrenal may become the primary

source of androgen in the peripheral pool.^{52,53} In adrenal hyperplasia due to an attenuated or peripubertal expression of a steroid enzyme deficiency, the pattern of gonadotropin and steroid hormone levels may resemble that of the polycystic ovarian syndrome due to a similar pathophysiologic mechanism on the hypothalamus and pituitary.^{54,55}

In polycystic ovarian syndrome, an ovarian enzymatic defect in the aromatization of testosterone and androstenedione to estradiol and estrone, respectively, has been suggested as the primary abnormality.⁵⁶ Therefore abnormal intraovarian androgen metabolism results in atretic follicles⁵⁷ and perpetuates the vicious cycle leading to relative suppression of FSH and enhancement of LH release through peripheral aromatization of androgens to estrogens. FSH may also be suppressed by the greater amount of inhibin produced from the multiple ovarian follicles.⁵⁸

Dopaminergic sensitivity may be altered in polycystic ovarian syndrome, as mentioned previously, with an effect on gonadotropin secretion^{33,34} or with hyperprolactinemia, which may stimulate adrenal androgen secretion.⁴⁴

In contrast, in primary ovarian failure there is an absence or loss of viable ovarian follicles with accompanying failure of ovarian estradiol production. In contrast to normal menopause, premature ovarian failure occurs at 35 years of age or earlier. It is unclear if it is always pathologic, or merely an extreme variation of the normal distribution of age of menopause. While obvious ovarian trauma, such as neoplastic or inflammatory replacement, radiation, cytotoxic drugs, vascular insult or surgery, is easily recognizable, idiopathic ovarian failure may be less obvious clinically. Gonadal dysgenesis usually appears as primary amenorrhea and pubertal failure. There is a sex chromosome aberration or early loss of ovarian follicles. Occasionally, cyclic ovarian function and pregnancies have occurred in such patients followed by premature ovarian failure when the follicles are ex-

hausted, as seen in Turner's syndrome with mosaicism.^{59,60} Therefore, with premature ovarian failure, chromosome karyotyping is indicated for diagnostic and prognostic purposes. With a normal karyotype, apparent ovarian failure may only be transient with return of spontaneous menses or demonstration of viable unstimulated ovarian follicles.⁶¹ The "resistant ovary syndrome," which is due to insensitivity of the ovarian follicles to FSH, secondary to ovarian gonadotropin receptor abnormalities, presents with amenorrhea with normal to elevated gonadotropin levels.⁶² While exogenous menopausal gonadotropins have been given to induce ovulation, replacement with estrogen and progestin appears more rational because spontaneous remission may occur because of estrogen induction of FSH receptors after stopping steroid replacement.

Uterine Causes

Asherman's syndrome, or amenorrhea traumatica, is characterized by intrauterine synechiae or fibrosis resulting in endometrium insufficient for response to ovarian steroids.⁶³ This condition usually arises from overenthusiastic uterine curettage both in pregnant and nonpregnant states, with or without infection. While elective first-trimester abortion is currently the leading cause, cesarean section and metroplasty are less frequent causes. Endometrial agenesis and endometrial fibrosis secondary to granulomatous disease are unusual causes of amenorrhea.

Thus, the existence of Asherman's syndrome can almost always be traced to a definite endometrial insult predating the amenorrhea. The diagnosis can be confirmed radiologically (Fig. 1.) and hysteroscopically.⁶⁴ With less extensive intrauterine synechiae, regular or scanty periods may coexist and can confound early diagnosis.

Adrenal and Thyroid Causes

In polycystic ovarian syndrome, there may be an adrenal contribution to the cause. Determination of androgen levels in patients



FIG. 1. *Hysterosalpingogram of a woman with secondary amenorrhea due to intrauterine synechiae (Asherman's syndrome).*

with hyperandrogenism may indicate the source. Elevated testosterone and androstenedione suggest the ovary, while elevated dehydroepiandrosterone sulfate (DHEAS) implicates the adrenal as the source.⁶⁵ Elevated adrenal androgens have been attributed to an effect secondary to elevated ovarian androgens⁶⁶ or to an attenuated form of adrenal enzyme deficiency in some patients.^{34,55,67} Sometimes, combined ovarian and adrenal suppression have been used to normalize androgen levels.⁶⁸ Nevertheless, except to rule out an adrenal adenoma, extensive diagnostic steps may not be necessary.

In contrast, Cushing's syndrome presents with elevated androgens, but the hallmark is hypercortisolism and a typical clinical picture.⁶⁹ Reversal of diurnal cortisol levels,

elevated urinary-free cortisol, and suppression of cortisol by high dose but not low-dose dexamethasone aid in the diagnosis of pituitary Cushing's disease, where ACTH oversecretion causes the adrenal hyperplasia. Failure of adrenal suppression and low ACTH levels suggest autonomous adrenal overactivity, while nonsuppressible cortisol with high ACTH may be due to ectopic ACTH. Pseudo-Cushing's disease may mimic pituitary Cushing's but it is due to depression or alcoholism and is difficult to separate from organic pathologic conditions. Cushing's syndrome is associated with amenorrhea mainly due to the hyperandrogenism.

Adrenal insufficiency secondary to adrenal replacement by tumor, granulomatous disease, or hemorrhage may cause amenorrhea because of hypothalamic effects secondary to the accompanying systemic illness and weight loss.⁷⁰ Adrenal insufficiency may also be part of a polyendocrine autoimmune syndrome where antiadrenal antibodies cause Addison's disease and antiovarian antibodies produce ovarian failure.^{71,72} Corticosteroid and mineralocorticoid replacement therapy should correct the amenorrhea, possibly even if ovarian autoimmunity is present.

Thyroid disease produces amenorrhea through different mechanisms. In primary hypothyroidism, low thyroxine levels may result in elevated TSH and TRF, the latter causing hyperprolactinemia and thus amenorrhea. Subnormal thyroid function also reduces testosterone-estradiol-binding globulin (TeBG) levels, which increase the metabolic clearance rate (MCR) of testosterone while that of androstenedione is unchanged, leading to an increased androstenedione to testosterone and estradiol metabolic pathway.⁷³ Further disruption occurs as estradiol is increasingly metabolized to estriol, which is a weaker estrogen; the hypothalamic feedback is inappropriate and, therefore, anovulation occurs.⁷⁴

In contrast, hyperthyroidism increases TeBG and reduces MCR of testosterone,⁷³ causing a shift to androstenedione and ultimately estrone,⁷⁵ thus creating a situation similar to polycystic ovarian syndrome.

Pathways leading to the catecholestrogens rather than estriol are enhanced by the excessive thyroid hormone as well.⁷⁶

Evaluation of Secondary Amenorrhea

The history and physical examination will often direct the clinician to the cause of the amenorrhea; onset of the amenorrhea, related physical and psychologic events, and obvious medical or surgical manipulation can isolate the cause early in the investigation. The presence of hirsutism, virilism, galactorrhea, emaciation, obesity, and so on will aid in pinpointing the true cause. The estrogenic state as assessed by genital tissue maintenance, cervical mucus properties, and possible menopauselike symptoms will also be important in considering the nature of the endocrinopathy.

Every woman with secondary amenorrhea must be considered pregnant until proven otherwise, and gestation should be ruled out before undertaking extensive evaluation. After this, it is crucial to uncover conditions that are life threatening or have high morbidity. Assessment of the estrogenic milieu is critical, because hypoestrogenemia has serious ramifications if untreated. After the history and physical examination, *all* patients should have a fasting serum prolactin, repeated if necessary to confirm any initial elevation. If there is hirsutism or virilism, serum testosterone and dehydroepiandrosterone sulfate (DHEAS) are done. A serum testosterone greater than 200 ng/dl (2.0 ng/ml) is suggestive but not diagnostic of testosterone-producing ovarian neoplasm. DHEAS is a useful index of adrenal androgen, and a level greater than 700 µg/dl (7.0 µg/ml) suggests an adrenal tumor.⁷⁷ ACTH stimulation may discriminate attenuated adrenal enzyme abnormalities, but is not an established clinical tool.^{54,55,67,78}

Early measurement of gonadotropins can avoid spurious levels later, after possible hormone treatment has been attempted but

failed. Elevated FSH (> 40 mIU/ml) and LH levels are indicative of at least functional ovarian failure. An elevated LH to FSH ratio ($> 2:1$) confirms polycystic ovarian syndrome. Low FSH and LH levels, especially the latter, can indicate severe hypothalamic disease, as well as pituitary failure. However, normal gonadotropins are also consistent with hypothalamic amenorrhea, because decreased pulsatility can only be diagnosed by serial sampling.

We do an initial TSH level to screen for asymptomatic hypothyroidism because essential treatment makes the relatively low detection rate worthwhile. Clinically apparent thyroid disease should be evaluated more extensively with full thyroid function studies.

After the necessary tests are drawn, progesterone (100–200 mg progesterone in oil, intramuscularly) is administered to assess endogenous estrogen status. A withdrawal bleed should occur in 2–7 days. Occasionally progesterone may induce ovulation in the estrogen-primed patient, and bleeding may be postponed for about 14 days, or, rarely, pregnancy could ensue. Parenteral progesterone avoids compliance, absorption, and bioavailability problems, as well as potential concern about teratogenesis if any early pregnancy was undetected. An alternate progestin for the progesterone challenge test is medroxyprogesterone acetate (Provera, Upjohn, Kalamazoo, Mich) 10 mg a day for 5–10 days.

If withdrawal bleeding occurs, it suggests an estradiol level of at least 40 pg/ml and confirms an intact normal endometrium. If no withdrawal bleeding occurs within 14 days and the patient is not pregnant, either she is hypoestrogenic or has Asherman's syndrome. If the history initially suggests the latter, documentation of intrauterine adhesions can be made with hysterosalpingography and further endocrine testing obviated. To rule out Asherman's syndrome, the patient is given sequential estrogen and progestin, such as conjugated estrogens 2.5 mg/day for 25 days with medroxyprogesterone acetate 10 mg/day the last 10 days. A

withdrawal bleed confirms severe hypothalamic or pituitary disease, while failure to bleed suggests Asherman's syndrome. If the patient without ovarian failure fails to withdraw to progesterone but does from estrogen-progestin, a skull series or computerized tomography (CT) scan should be done to rule out a nonprolactin-secreting pituitary or hypothalamic tumor. If she does not withdraw to the sequential or combination steroids, hysterosalpingography and/or hysteroscopy are required to confirm intrauterine synechiae. If the patient has ovarian failure, a chromosome karyotype should be performed to ascertain the cytogenetic abnormality and prognosis.

Treatment

Much of the treatment depends on the patient's needs and desires, especially regarding fertility. Hypothyroidism is easily and readily treated with thyroid hormone replacement. Hyperthyroidism requires complete evaluation and medical or surgical treatment and likewise with Cushing's syndrome or Addison's disease.

Premature ovarian failure requires replacement with estrogen and progestin because of the risk of osteoporosis, genital atrophy, and vasomotor symptoms.⁷⁹ If fertility is desired, a trial of estrogen-progestin might be considered so that it may be determined if ovulation occurs. Otherwise, monthly estrogen-progestin replacement is indicated. We use conjugated estrogens 1.25 mg/day for the first 25 days and medroxyprogesterone acetate 10 mg/day from days 16–25, every month. Cyclic withdrawal bleeding may occur.

The anovulatory (polycystic ovarian) hyperandrogenic woman seeking treatment of hirsutism but not desiring fertility is placed on a low-dose combination oral contraceptive.^{80–82} If there is contraindication to estrogens, continuous progestin may be used.^{83,84} If there is prolonged amenorrhea with heavy irregular vaginal bleeding, endometrial sampling is required to rule out neoplasia prior to therapy.⁸⁵ If hirsutism is absent,

fertility not desired, and contraception not required, medroxyprogesterone acetate 10 mg daily for 5–10 days every 6–8 weeks will induce withdrawal bleeding, prevent endometrial hyperplasia, and possibly allow resumption of spontaneous menses. If pregnancy is desired, ovulation induction with clomiphene citrate⁸⁶ or bromocriptine³⁴ is undertaken. Supplementary corticosteroid therapy may be necessary in those with a significant androgen contribution by the adrenals for either hirsutism or ovulation-induction therapy.⁸⁷ Bromocriptine may reduce both LH and its resultant excessive ovarian androgen production, as well as reduce prolactin, and the associated adrenal stimulation. Rarely, polycystic ovarian syndrome with high androgens and no response to suppressive therapy or ovulation induction may require microsurgical ovarian wedge resection for both therapy and diagnosis.⁸⁸ Currently, clomiphene failures without elevated androgens receive human menopausal gonadotropin (hMG), (Pergonal, Serono, Braintree, Mass), and human chorionic gonadotropin (hCG) as the next mode of therapy,⁸⁹ although exogenous pulsatile GnRH administration has been successful.^{90,91}

Psychotherapy, weight gain, or reduction in energy drain are indicated in some patients. Amenorrheic runners may be at risk for bone depletion and thus may require estrogen replacement if there is no change in their levels of exercise.⁹²

Treatment of Asherman's syndrome includes hysteroscopic lysis of intrauterine adhesions, insertion of an intrauterine device (IUD), Foley catheter balloon or silastic bag, and regeneration of endometrial tissue with high-dose estrogen–progesterin such as 5.0–10.0 mg conjugated estrogens daily for 3 cycles, followed by medroxyprogesterone acetate 10 mg for 10 days before the IUD is removed.^{93,94}

Conclusion

The causes of secondary amenorrhea have become better understood and defined be-

cause of progress in neuroendocrinology, receptor biochemistry, and steroid metabolism. New modes of therapy including use of dopamine agonists, exogenous GnRH and its agonists, and endoscopy have increased the possibility of successfully treating the variety of pathophysiologic conditions more efficiently and safely.

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