Menstrual Disorders and Hyperandrogenism in Adolescence

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Abstract

The evaluation of menstrual disorders in adolescents requires special consideration. Adolescents are in the midst of developing physically and physiologically to achieve adult reproductive function. Thus, the normal variation in the age of onset of puberty and subsequent menarche should be taken into account when evaluating adolescent girls. Menarche will be delayed if puberty is delayed in onset.

Keywords

Delayed puberty • Amenorrhea • Anovulation • Hyperandrogenism • Polycystic ovary syndrome

The evaluation of menstrual disorders in adolescents requires special consideration. Adolescents are in the midst of developing physically and physiologically to achieve adult reproductive function. Thus, the normal variation in the age of onset of puberty and subsequent menarche should be taken into account when evaluating adolescent girls. Menarche will be delayed if puberty is delayed in onset. The average age of menarche is 12.6 years in the normal-weight general American population, with the normal range being 11.0-14.1 years [1]. It occurs approximately 0.5 year earlier in overweight girls and in non-Hispanic Black girls, with Mexican-American girls being intermediate. In addition, because of immaturity of the hypothalamic–pituitary–ovarian axis, about half of menstrual cycles are anovulatory or have attenuated ovulation during the first 2 years after menarche [2–4]. This "physiologic adolescent anovulation" accounts for the greater menstrual irregularity and longer average intermenstrual length in the early post-menarcheal

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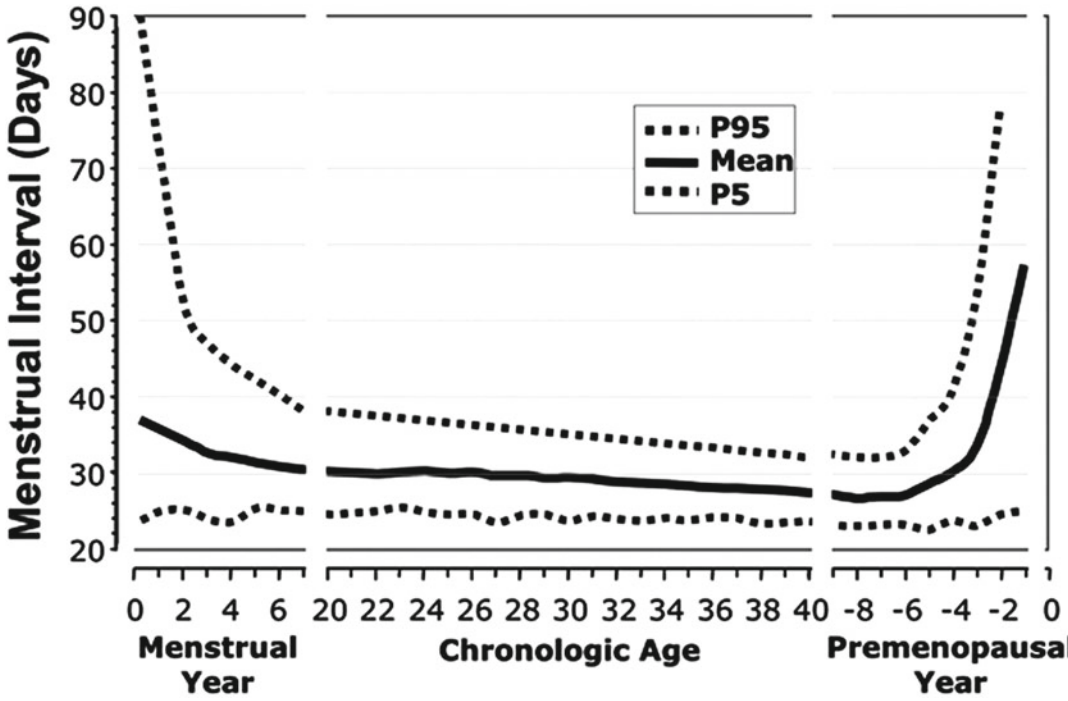

Fig. 25.1 Menstrual cycle lengths throughout reproductive life from menarche to menopause. Tenth, fiftieth, and ninetieth percentiles are shown (Reproduced with permission from Treloar et al. [5])

years than in adults (Fig. 25.1) [5]. However, about half of these seemingly "anovulatory" menstrual cycles are of normal length by adult standards, so menstrual regularity is greater than ovulatory frequency would suggest. In contrast, menstrual irregularity always indicates ovulatory irregularity.

The menstrual disorders that should concern endocrinologists are *primary amenorrhea* (failure of menses to begin at a normal age), *secondary amenorrhea* (cessation of menstrual periods for 90 days or more after initially menstruating), o*ligomenorrhea* (less than eight menstrual periods a year, an average of >45 days between menses), and *dysfunctional uterine bleeding* (anovulatory bleeding that occurs more often than at 21-day intervals or is excessive, as indicated by bleeding for more than 7 days or requiring pad or tampon changes more than every 1–2 h) [4]. Because these menstrual patterns are statistically abnormal within the first year after menarche (occurring in less than 5% of adolescents), they are more appropriately considered to represent "symptomatic" rather than "physiologic" adolescent anovulation, and evaluation may be required. A two-thirds risk of persistent menstrual irregularity exists if symptoms persist 2 years beyond menarche; thus, evaluation is recommended if symptoms persist for 2 years after menarche [6].

Etiology

Two general types of disorders cause menstrual abnormalities: those that are associated with genital tract disorders and, more often, those that result from anovulation. The etiology of menstrual disorders is given in Table 25.1 [6].

Table 25.1 Causes of adolescent menstrual disorders[a]

Abnormal genital structure
Aplasia[b]
Hymenal
Vaginal
Müllerian
Intersex
Endometrial adhesions
Ambiguous genitalia
Intersex
Pseudointersex
Anovulatory disorders
Hypoestrogenism: FSH elevated
Primary ovarian insufficiency
Congenital
Chromosomal disorders
Genetic disorders
Resistant ovaries
Bioinactive gonadotropin
Steroidogenic block
Acquired
Oophorectomy
Radiotherapy or chemotherapy
Oophoritis
Idiopathic
Hypoestrogenism: FSH not elevated
Gonadotropin deficiency
Congenital
Acquired
Organic
Functional (nonorganic)
Delayed puberty
Constitutional delay[b]
Growth-retarding disease
Primary ovarian insufficiency
Complete, if BA < 11 year[b]
Incomplete, if BA > 11 year
Virilization
Estrogenized: FSH not elevated
Pregnancy
Functional hypothalamic anovulation
Athletic amenorrhea
Psychogenic amenorrhea
Idiopathic functional hypothalamic amenorrhea
Post-pill amenorrhea
Secondary hypothalamic anovulation
Chronic disease
Undernutrition or obesity
Cushing's syndrome
Hypothyroidism
Hyperprolactinemia
Hyperandrogenism

[a]Adapted from Rosenfield et al. [6] with permission from Elsevier
[b]Cause only primary amenorrhea

Genital Tract Disorders

Primary amenorrhea can result from structural abnormalities of the genital tract that occur independently or are secondary to a disorder of sexual differentiation (DSD). Varying degrees of vaginal and uterine aplasia are found in the Rokitansky–Kustner–Hauser syndrome [7]. This syndrome occurs as a single-gene defect or as an acquired teratogenic event which sometimes affects differentiation of the urinary tract. A subtype due to *Wnt4* gene defects is associated with hyperandrogenism [8]. Obstruction of the genital outflow tract—most commonly due to imperforate hymen—causes hydrocolpos, which results in a protruding vaginal mass, or hydrometrocolpos when the uterus is involved, which may present as an abdominal mass. Uterine aplasia may also result from DSD syndromes in which anti-Müllerian hormone secretion by testicular tissue has occurred. For this reason, primary amenorrhea may be the presenting symptom of phenotypic girls with complete androgen resistance (testicular feminization syndrome), congenital deficiency in one of the enzymes necessary for testicular testosterone secretion, or in patients with ambiguous genitalia due to partial versions of these disorders or due to 5α-reductase deficiency.

Intrauterine adhesions (Asherman's syndrome) may result from trauma, such as postcurettage or as a complication of radiation therapy of pelvic disease or chronic inflammatory disease [9].

Abnormal bleeding, on the other hand, can result from genital tract trauma or infection. The most common examples of these are sexual abuse and foreign body. Bleeding may also result from genital tract tumors.

Anovulatory Disorders

Anovulatory disorders, the most common cause of menstrual disorders, can be categorized into

those disorders associated with hypoestrogenemia due to varying degrees of hypogonadism or those disorders associated with normal serum estrogen. If hypogonadism is complete and is present prior to the onset of neuroendocrine puberty, it causes sexual infantilism. If hypogonadism is slightly less severe or is manifested in the early teenage years, it may permit some feminization, but too little to permit the onset of menses. In either case, primary amenorrhea is a result. Milder, partial, or incomplete forms of hypogonadism may cause either secondary amenorrhea or oligomenorrhea. At its mildest, hypogonadism may present with the anovulatory symptoms of dysfunctional uterine bleeding or with excessively frequent periods due to short luteal phase.

Hypogonadism can be categorized according to whether or not gonadotropins, particularly serum follicle-stimulating hormone (FSH) levels, are elevated (Table 25.1). Hypoestrogenism with elevated FSH indicates primary ovarian failure (hypergonadotropic hypogonadism). The causes include both hereditary and acquired disorders. Gonadal dysgenesis due to deficiency of genes on the X chromosome causing Turner syndrome is the most common cause of primary ovarian failure, with an incidence of about 1 in 2,500 live-born girls. About 5% of Turner syndrome patients present with secondary amenorrhea, even though they have congenitally dysgenetic ovaries [10]. Fragile X-chromosome permutation is associated with some cases of X-linked premature ovarian failure [11, 12]. Premature ovarian failure may result from hereditary gonadotropin resistance: LH receptor and FSH receptor mutations cause autosomal-recessive gonadotropin resistance [13]. These have been associated with a spectrum of defects ranging from primary amenorrhea to oligomenorrhea. Partial gonadotropin resistance is common in the Albright osteodystrophy form of pseudohypoparathyroidism because of the generalized defect in G-protein signal transduction [14]. Bioinactive gonadotropins on rare occasions may simulate primary gonadal failure [15, 16]. Steroidogenic blocks in estradiol biosynthesis can also cause secondary amenorrhea [17]. Acquired ovarian failure commonly results from irradiation, chemotherapy, trauma to the ovary, galactosemia, or autoimmune disease. Unexplained acquired ovarian failure has an autoimmune basis less than one-third of cases [12].

Hypoestrogenism without elevated FSH levels usually indicates secondary ovarian failure (gonadotropin deficiency, hypogonadotropic hypogonadism) because a normal gonadotropin level is inappropriate in the setting of hypoestrogenism. Gonadotropin deficiency can be congenital or acquired. Congenital gonadotropin deficiency can occur in association with cerebral, hypothalamic, or pituitary dysfunction or as an isolated defect. Congenital hypopituitarism may be due to a chromosomal disorder (such as in Prader–Willi syndrome), single-gene mutations in the gonadotropin-releasing hormone (GnRH) signaling [18], or pituitary development cascades [19] or be associated with congenital brain defects of unknown origin. Congenital isolated gonadotropin deficiency may result from autosomal-recessive disorders, of which GnRH receptor deficiency is more common in women than the anosmia-associated Kallmann's syndrome [20].

Acquired gonadotropin deficiency may be organic or functional (nonorganic). Organic acquired gonadotropin deficiency can be a consequence of tumors, trauma, autoimmune hypophysitis [21], degenerative disorders involving the hypothalamus and pituitary [22], irradiation [23], or chronic illness of virtually any organ system [24]. Functional hypogonadotropism is commonly caused by eating disorders [25]. Anorexia nervosa is the prototypic form, but bulimia nervosa, the binge eating/purging variant, is easily overlooked because the weight is often normal and vomiting surreptitious. Hyperprolactinemia can also cause functional gonadotropin deficiency, as discussed below.

Gonadotropin deficiency can be mimicked by primary ovarian failure in two circumstances. The most common is in children who are too young to have undergone neuroendocrine puberty, as indicated by a bone age less than about 11 years. Gonadotropin levels may also not be elevated in incomplete or early premature ovarian insufficiency because gonadotropin levels may be normal as the ovary begins to fail during

the menopausal transition [12, 26]. Suppression of gonadotropins and estrogens occurs in frankly virilizing disorders.

Menstrual disturbance in the presence of adequate estrogenization is probably the single most common problem that is encountered. Pregnancy, hypothalamic anovulation, with its diverse causes including hyperprolactinemia, and hyperandrogenism are the considerations.

Hypothalamic anovulation occurs in patients who secrete sufficient gonadotropin tonically to estrogenize normally but have disorders which interfere with the ability to produce a midcycle surge of luteinizing hormone. In this group of disorders, there are disturbances of cyclic or pulsatile GnRH release that interfere with the positive feedback mechanism. Functional hypothalamic amenorrhea is often seen in the setting of weight loss, hyperathleticism, or psychogenic stress. Even when these factors are not obvious, similar mechanisms seem to underlie idiopathic functional hypothalamic amenorrhea [27]. Post-pill amenorrhea may be suspected after the long-term use of hormonal contraceptives. However, this entity usually results from an undetected antecedent anovulatory disturbance or an intercurrent illness, so a workup is required.

Chronic disease of virtually any organ system can mimic gonadotropin deficiency or hypothalamic anovulation. Obesity may cause amenorrhea via the overproduction of estrogen from plasma precursors in adipose tissue [28] or via a direct effect [29]. Glucocorticoid excess causes amenorrhea by multiple mechanisms, prime among which is interference with gonadotropin responsiveness to GnRH [30, 31]. Thyroid disorders are well-known causes of menstrual irregularity [32].

Hyperprolactinemia requires special consideration since it varies greatly in its presentation. This is because it engenders variable degrees of gonadotropin deficiency. Prime among the multiple mechanisms is disruption of GnRH pulsatility [33, 34]. Galactorrhea is present in about half of the patients, particularly those with residual estrogen production. The causes of hyperprolactinoma are diverse and include hypothalamic or pituitary disorders, drugs, hypothyroidism, renal or liver failure, peripheral neuropathy, stress, and idiopathy [35]. It is not only in the differential diagnosis of hypogonadotropic hypogonadism and hypothalamic amenorrhea; it may cause short or inadequate luteal phase (characterized by menstrual cycles less than 22 days), dysfunctional uterine bleeding, or a hyperandrogenic picture.

Hyperandrogenism is the most frequent cause of anovulation, after pregnancy, so it is considered in more detail next.

Hyperandrogenism

Hyperandrogenemia is of ovarian origin in the vast majority of cases. It occasionally is of adrenal origin; in a few cases, it appears to be caused by abnormalities in the peripheral formation of androgen, and it is rarely caused by tumors or by self-administration. The causes of hyperandrogenism are listed in Table 25.2 [36].

Polycystic Ovary Syndrome

PCOS accounts for 85% or more of androgen excess presenting at or after the onset of puberty. The classic syndrome originally described by Stein and Leventhal is characterized by various combinations of amenorrhea, hirsutism (defined as excessive male-pattern hair growth), obesity, and polycystic ovaries. PCOS is now defined as otherwise unexplained hyperandrogenic oligoanovulation ("National Institutes of Health criteria") [37]. If anovulatory symptoms are lacking, it is now widely accepted that a polycystic ovary is an alternative criterion for the diagnosis ("Rotterdam criteria") [38, 39]. However, a polycystic ovary in isolation is a normal variant, found in about 20% of healthy women [40, 41]. Consequently, there is not uniformity of agreement about the alternative Rotterdam criterion of anovulatory symptoms and a polycystic ovary in the absence of hyperandrogenism [38].

About two-thirds of patients with classic PCOS have hirsutism (or the hirsutism equivalents, acne vulgaris, or pattern alopecia), two-thirds have anovulatory symptoms (which vary from amenorrhea to dysfunctional uterine bleeding to unexplained infertility), and half are obese. Thus, only about a third of otherwise classic

Table 25.2 Causes of hyperandrogenism[a]

Functional gonadal hyperandrogenism
Primary (dysregulational) functional ovarian hyperandrogenism[b]
Secondary polycystic ovary syndrome
• Poorly controlled classic congenital adrenal hyperplasia
• Syndromes of severe insulin resistance
• Ovarian steroidogenic blocks
Adrenal rests
Disorder of Sexual Differentiation
Chorionic gonadotropin related
Functional adrenal hyperandrogenism
Primary (dysregulational) functional adrenal hyperandrogenism[c]
Congenital adrenal hyperplasia
Prolactin or growth hormone excess
Dexamethasone-resistant functional adrenal hyperandrogenism
• Cushing's syndrome
• Cortisol resistance
• Apparent cortisone reductase deficiency
Peripheral androgen overproduction
Obesity
Idiopathic hyperandrogenism
Tumoral hyperandrogenism
Androgenic drugs

[a]Adapted from Rosenfield 1997 [36], with permission from Elsevier
[b]Common form of PCOS
[c]Uncommon form of PCOS

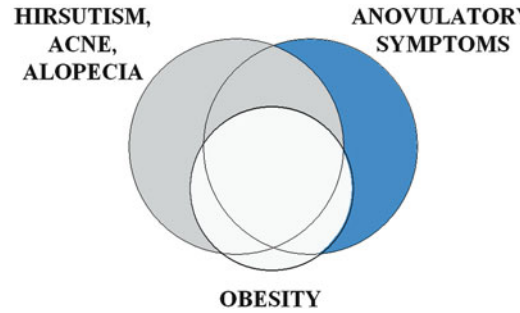

Fig. 25.2 Manifestations of polycystic ovary syndrome in approximate proportion to their relative incidence and coincidence. Cutaneous symptoms include hirsutism, acne, or acanthosis nigricans. Anovulatory symptoms include amenorrhea, oligomenorrhea, dysfunctional uterine bleeding, and infertility (Reproduced from Rosenfield [36] with permission from Elsevier)

cases have the full-blown clinical picture (Fig. 25.2). While obesity and insulin resistance are not necessary or diagnostic features of PCOS, they are common and appear to play a role in pathogenesis of many cases. Acanthosis nigricans, a sign of insulin resistance, may be prominent.

PCOS in adolescents has clinical and endocrine features similar to that of adults [41]. There may be an antecedent history of congenital virilization, premature pubarche, or syndromic obesity (pseudo-Cushing's syndrome or pseudo-acromegaly) [42]. Ovarian dysfunction is often found in the perimenarcheal phase of development, but it may not be demonstrable until 3 years after menarche [43].

Pathophysiology. There has been considerable debate over whether PCOS is fundamentally a neuroendocrine disorder (in which hyperpulsatility of GnRH is the origin of the problem), an ovarian disorder (in which intrinsic ovarian dysfunction is the origin), or a metabolic disorder (in which insulin resistance is a key element). Our research has led us to favor the concept that the essence of PCOS is intrinsic functional ovarian hyperandrogenism (FOH) that is closely linked to the metabolic disorder [44, 45].

The theory that PCOS is a fundamentally neuroendocrine disorder is rooted in the observation that baseline LH levels and responses to GnRH are elevated in about half of PCOS patients. Compared to control women, women with PCOS have increased LH pulse frequency and amplitude. Since LH stimulates theca cell development, expression of steroidogenic enzymes, and steroidogenesis, the increased LH of PCOS was initially considered the cause of the androgen excess. However, this theory does not account for the large subset of women with PCOS who do not have elevated LH levels. In addition, the normal response to excessive LH stimulation is homologous desensitization of theca cells. Desensitization involves downregulation of LH receptor expression and androgen secretion in response to further LH stimulation. Downregulation of androgen secretion is primarily exerted at the rate-limiting step in androgen formation, the 17,20-lyase activity of cytochrome P450c17, which has both 17-hydroxylase and 17,20-lyase activities: as a consequence, 17-hydroxyprogesterone levels rise

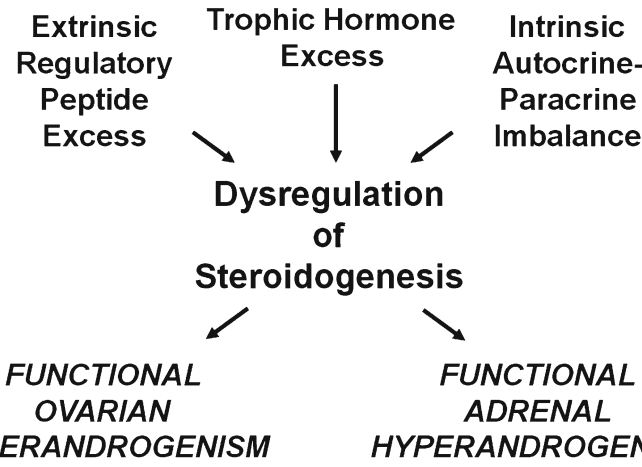

Fig. 25.3 Model of factors causing the common types of functional ovarian and adrenal hyperandrogenism. A mild degree of androgen excess can arise from excess trophic hormone (LH or ACTH) stimulation. Disturbances either extrinsic or intrinsic to these endocrine glands can amplify the effect of normal levels of trophic hormones. Extrinsic regulatory peptide excess is exemplified by hyperinsulinemia. Intrinsic peptides capable of inappropriately upregulating steroidogenesis include IGFs (Reproduced from Rosenfield [45] with permission from Elsevier)

in response to increased LH levels, but the downstream androgenic response to LH is limited [41, 46, 47]. Therefore, LH excess does not seem to be a fundamental cause of the hyperandrogenism although the disorder is gonadotropin dependent, i.e., suppression of gonadotropin levels corrects hyperandrogenemia.

The excessive LH levels in women with PCOS may be explained by abnormal sex steroid feedback [29]. The LH pulse frequency of women with PCOS is less sensitive than that of controls to sex steroid suppression. Antiandrogen therapy can restore the inhibitory effect of progesterone on LH pulse frequency.

We favor the concept that the hyperandrogenism of PCOS is caused by intrinsic defects in steroidogenesis. The FOH is characterized by an elevated free testosterone after suppression of adrenocortical function with dexamethasone. Two-thirds of these women also exhibit hypersensitivity to LH stimulation, as demonstrated by hyperresponsiveness to LH of 17-hydroxyprogesterone relative to other ovarian steroids. Put another way, these women have "escaped" from normal desensitization to LH. Overexpression of the steroidogenic enzyme cytochrome P450c17 seems to be particularly important. In vitro studies indicate that the abnormal steroidogenesis is due to an intrinsic defect in the theca cells of PCOS patients [48, 49].

A related steroidogenic defect sometimes seems to involve the adrenal gland. About a quarter of women with FOH have a related steroidogenic defect in adrenal formation of the 17-ketosteroid dehydroepiandrosterone (DHEA) and its precursor, 17-hydroxypregnenolone, without evidence of a steroidogenic block in response to ACTH stimulation, as would occur in congenital adrenal hyperplasia. This pattern is termed functional adrenal hyperandrogenism (FAH). FAH had earlier been mistaken for nonclassic 3ß-hydroxysteroid dehydrogenase deficiency, which is now known to be a rare disorder, and was considered to be "exaggerated adrenarche."

These steroidogenic defects have been postulated to result from dysregulation of steroidogenesis. This dysregulation is, in turn, postulated to result from imbalance among various intrinsic and extrinsic factors involved in the modulation of trophic hormone action (Fig. 25.3). Defects within ovarian theca cells causing overexpression of steroidogenic enzymes lead to hyperrespon-

siveness to normal or excessive LH stimulation and resultant excessive androgen production.

Obesity and insulin-resistant hyperinsulinemia are common features of PCOS, [50, 51]. The degree of obesity is inversely correlated with LH levels [29]. Insulin resistance is out of proportion to the degree of obesity, and compensatory hyperinsulinemia appears to be an important factor in the pathophysiology of PCOS. Women with PCOS have a high incidence of metabolic syndrome and are predisposed to type 2 diabetes mellitus [52]. Treatments which lower insulin levels reduce the androgen excess. Insulin counters homologous desensitization and steroidogenic downregulation in response to LH excess. Insulin also stimulates formation of testosterone by 17ß-hydroxysteroid dehydrogenase. It does so by stimulating expression of KLF15, a Kruppel-like transcription factor that is part of the gene's proximal promoter co-activator complex [53]. In adipocytes, KLF15 also stimulates lipogenesis. Thus, the hyperinsulinemia that is compensatory for the insulin resistance of PCOS seems to contribute to both androgen and fat excess in a state of resistance to the glucose-metabolic effects of insulin.

Follicular maturation and development of the dominant follicle is impaired in women with PCOS, leading to polycystic ovaries and anovulation. This dysregulation of folliculogenesis seems at least in part caused by intraovarian androgen excess, but an independent defect cannot be ruled out [47, 54].

Pathogenesis. The cause of PCOS is unknown. Like type 2 diabetes mellitus, PCOS likely arises because of interaction between genetic predisposing factors with environmental factors [42]. There is a strong heritable component to hyperandrogenemia and polycystic ovaries; each appears to be inherited as an independent autosomal dominant trait. Seventy-five percent of our adolescents with PCOS have a parent with metabolic syndrome, indicating a close relationship to obesity, insulin resistance, and diabetes [52]. Environmental influences that promote obesity and associated hyperinsulinemia are aggravating and possibly precipitating pathogenetic factors. Any treatment, including weight loss, that lowers insulin levels improves ovarian dysfunction and ovulation [55–59].

Prenatal androgen excess is a distinct predisposing factor [42]. All congenital virilizing syndromes are complicated by a high risk for PCOS. This is a common cause of persistent anovulation in well-controlled virilizing congenital adrenal hyperplasia. Experimental evidence suggests that the mechanism may involve reduction of hypothalamic progesterone receptor expression, with consequent hypersecretion of LH, by prenatal androgen excess [60]. Other proposed precipitating factors include intrauterine growth retardation, premature adrenarche, and heterozygosity for congenital adrenal hyperplasia [61].

Other Causes of Functional Ovarian Hyperandrogenism

Other functional causes of FOH can mimic PCOS (Table 25.2). Extraovarian androgen excess (as in poorly controlled congenital adrenal hyperplasia) and ovarian steroidogenic blocks (such as 3ß-hydroxysteroid dehydrogenase, 17ß-hydroxysteroid dehydrogenase, or aromatase deficiency) are causes. Excessive stimulation via the LH receptor is a rare cause of hilus cell hyperplasia or chorionic gonadotropin-related hyperandrogenism during pregnancy [62, 63]. All known forms of extreme insulin resistance, including the hereditary cases which are due to insulin receptor mutations, as well as acromegaly [64], are accompanied by PCOS, apparently by excessively stimulating the IGF-I signal transduction pathway to cause escape from desensitization to LH. Functional ovarian hyperandrogenism may also result from adrenal rests of the ovaries in congenital adrenal hyperplasia or from true hermaphroditism. PCOS has also been reported as a complication of the impaired steroid metabolism which occurs as a complication of portasystemic shunting [65]. The antiepileptic drug valproic acid causes hyperandrogenism [66, 67].

Other Causes of Functional Adrenal Hyperandrogenism

Less than 10% of adrenal hyperandrogenism can be attributed to the well-understood disorders listed in Table 25.2. Congenital adrenal hyper-

plasia arises from an autosomal-recessive deficiency in the activity of any one of the adrenocortical enzyme steps necessary for the biosynthesis of corticosteroid hormones. Mild enzyme deficiency causes nonclassic ("late-onset") presentations, which lack the genital ambiguity of classic congenital adrenal hyperplasia and cause adolescent or adult onset of anovulatory symptoms and/or hirsutism. Women with the nonclassic disorder may have polycystic ovaries and high serum luteinizing hormone levels, but FOH seems to be unusual except in the presence of adrenal rests of the ovaries [68]. Nonclassic 21-hydroxylase deficiency is the most common form of congenital adrenal hyperplasia and accounts for about 5% of hyperandrogenic adolescents in the general population. Deficiencies of 3ß-hydroxysteroid dehydrogenase (3ß-HSD) or 11ß-hydroxylase are forms of congenital adrenal hyperplasia which have on rare occasions presented in adolescence. Apparent cortisone reductase deficiency is a rare autosomal-recessive form of functional adrenal hyperandrogenism [69].

Dexamethasone-resistant forms of hyperandrogenism such as Cushing's syndrome and cortisol resistance are even more unusual than nonclassic congenital adrenal hyperplasia. Prolactin excess causes adrenal hyperandrogenism [70]. Cushing's and hyperprolactinemia sometimes occur in association with polycystic ovaries [71, 72].

Other Causes of Hyperandrogenism

In approximately ten percent of hyperandrogenic patients, a gonadal or adrenal source of androgen cannot be ascertained after thorough testing. Many of these cases meet PCOS criteria and seem to be due to obesity. In the absence of menstrual dysfunction, this is termed idiopathic hyperandrogenemia. Obesity may explain some of these cases because adipose tissue has the capacity to form testosterone from androstenedione. Other idiopathic cases may be due to hereditary quirks in peripheral metabolism of steroids. Tumor and exogenous ingestion of anabolic steroids are more rare causes of virilization.

Differential Diagnosis

Workup for primary amenorrhea should be undertaken if spontaneous menses have not occurred by 15.0 years of age or earlier if menses have not occurred 3 years after breast budding. A diagnostic approach to primary amenorrhea is shown in Fig. 25.4 [6]. The history should include a search for clues to chronic disease or eating disorders. The key features on physical examination are determinations of whether puberty is delayed (or indeed whether it has even begun), whether the child is underweight [73, 74], and whether the external genitalia are normal. All should have a panel of screening tests for chronic disease. Other key initial laboratory tests in the sexually *immature* patient are bone age radiograph and gonadotropin levels. Other key initial laboratory tests in the sexually *mature* patient are pregnancy test, plasma testosterone, and pelvic ultrasound examination.

In patients with secondary amenorrhea or oligomenorrhea, the occurrence of menarche indicates that a substantial degree of development of the reproductive system will have occurred. A pregnancy test and serum gonadotropin levels are the key tests with which to initiate the workup, as shown in Fig. 25.5 [6]. However, because breast development persists even if hypoestrogenism ensues, the presence of a mature breast stage does not preclude the possibility of hypoestrogenism. A simple first step to assess the adequacy of estrogenization is to determine whether withdrawal bleeding occurs in response to a progestin challenge; a positive response indicates an estradiol level that averages ≥40 pg/mL [75].

If the above evaluation of a sexually mature girl does not yield a definitive diagnosis, further investigation for an anovulatory disorder should be undertaken (Fig. 25.6) [6]. Dysfunctional uterine bleeding is an alternate presentation of anovulatory cycles. If present, other causes of dysfunctional uterine bleeding, such as sexual abuse, bleeding disorder, genital tract tumor, or feminizing cyst, should also be considered. The history of a woman with anovulatory symptoms should be carefully reviewed for evidence of the

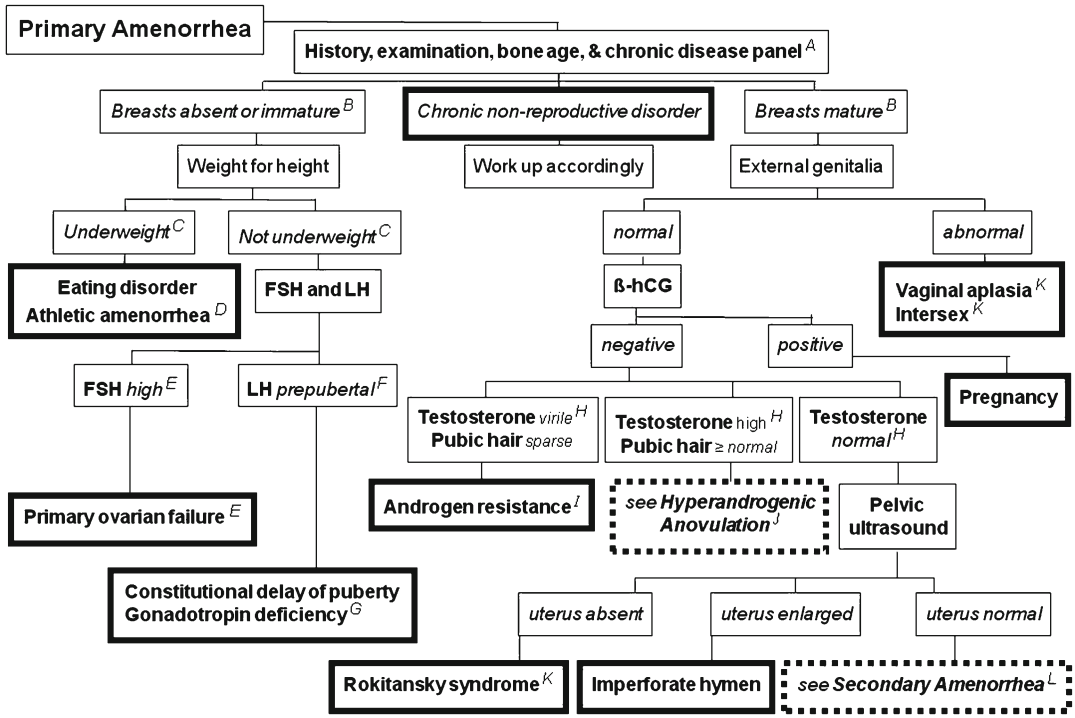

Fig. 25.4 Differential diagnosis of primary amenorrhea (Modified with permission from Rosenfield, RL. Primary amenorrhea and abnormal genital anatomy. In: Hochberg Z, editor. Practical algorithms in pediatric endocrinology. 2nd ed. Basel. S. Karger AG; 2007) [A]Prime among the causes of primary amenorrhea are growth-retarding or growth-attenuating disorders. In the absence of specific symptoms or signs to direct the workup, laboratory assessment for chronic disease typically includes bone age radiograph if the adolescent is not sexually mature and a chronic disease panel (complete blood count and differential, sedimentation rate, comprehensive metabolic panel, celiac panel, thyroid panel, cortisol and insulin-like growth factor I levels, and urinalysis). [B]Breast development ordinarily signifies the onset of pubertal feminization. However, mature breast development does not ensure ongoing pubertal estrogen secretion (see Figs. 25.5 and 25.6). [C]BMI < 10th percentile generally corresponds to body composition <20% body fat, which is the critical factor. [D]BMI may not accurately reflect body fat in serious athletes (who have a disproportionately greater muscle mass) or bulimia nervosa. [E]FSH is preferentially elevated over LH in primary ovarian failure. The most common cause of primary amenorrhea due to primary ovarian failure is gonadal dysgenesis due to Turner syndrome, but acquired causes must be considered (such as cytotoxic therapy). The workup of primary ovarian failure is considered in detail in the next algorithm (Fig. 25.5, secondary amenorrhea and oligomenorrhea). Lack of FSH elevation virtually rules out primary ovarian failure only when the bone age is appropriate for puberty (11 years or more). [F]"Pediatric" gonadotropin assays sensitive to ≤0.15 U/L are critical to the accurate diagnosis of gonadotropin deficiency and delayed puberty. A low LH level is more characteristic of these disorders than a low FSH level. Congenital gonadotropin deficiency is closely mimicked by the more common extreme variation of normal, constitutional delay of puberty. [G]History and examination may yield clues to the cause of hypogonadotropic hypogonadism, such as evidence of hypopituitarism (midline facial defect, extreme short stature, visual field defect) or anosmia (Kallmann's syndrome) or functional hypothalamic disturbance (bulimia, excessive exercise). Random LH levels in hypogonadotropic patients are usually below 0.15 IU/L, but often overlap those of normal pre- and midpubertal children. The GnRH test, measuring the gonadotropin response to a 50- to 100-μg bolus, in the premenarcheal teenager strongly suggests gonadotropin deficiency if the LH peak is less than 4.2 IU/L by monoclonal assay. However, the GnRH test has limitations because of overlap between hypogonadotropic and normal teenager responses. GnRH agonist testing (e.g., leuprolide acetate injection 10 μg/kg SC) may discriminate better. It may not be possible to definitively establish the diagnosis of gonadotropin deficiency until puberty fails to begin by 16 years of age or progress at a normal tempo. [H]Plasma total testosterone is normally 20–60 ng/dL (0.7–2.1 nM) in women and 300-1,200 ng/dL in men but varies somewhat among laboratories. Plasma free (or bioavailable) testosterone is about 50% more sensitive than total testosterone in detecting hyperandrogenemia. However, there are many pitfalls in testosterone assays at the low levels of women, reliable testosterone assays are not available to many physicians, and assaying the free testosterone introduces other potential sources of error. Therefore, it is reasonable to begin the evaluation with a total

nutritional disorders and the physical or emotional stress that are common causes of the menstrual symptoms. The examination should particularly focus on the possibility of intracranial disorders, galactorrhea, and evidence of hirsutism or its cutaneous equivalents, treatment-resistant acne vulgaris, or male-pattern balding. The workup is then directed differently according to the patient's estrogen and prolactin status (Fig. 25.6). GnRH testing is indicated in confirmed hypoestrogenic cases. GnRH agonist testing yields similar results and in addition allows assessment of gonadotropin reserve in gonadotropin deficiency and also permits assessment of ovarian responsiveness to gonadotropins [76–78]. Imaging of either the ovaries or the brain is usually indicated.

Hyperandrogenism is the final consideration in the differential diagnosis of menstrual disorders (Fig. 25.7) [79]. The diagnosis may be difficult to establish [80, 81]. Classically, when hirsutism or cutaneous hirsutism equivalents are present, this is considered as clinical evidence of hyperandrogenism. However, mild hirsutism and its cutaneous equivalents are common normal variants that are not associated with hyperandrogenemia. In addition, cutaneous manifestations are absent in approximately one-third of hyperandrogenism because there is considerable individual variability in pilosebaceous unit sensitivity to androgens. Therefore, hyperandrogenism is most firmly established if hyperandrogenemia can be reliably documented by biochemical testing.

Unfortunately, dependable testosterone assays are not available to many practitioners. Validated testosterone assays are also not widely available. The automated assays of total testosterone, available as part of multichannel immunometric panels, are very inaccurate at the relatively low testosterone levels of women and children; thus, they give misleading information about androgen status in women. Determination of free or "bioavailable" testosterone is 50% more sensitive than total testosterone for the detection of hyperandrogenemia, as sex hormone-binding globulin (SHBG), the main determinant of the bioactive portion of serum testosterone, is often low in hyperandrogenic women. Direct assays of free testosterone are inaccurate. The most reliable method for total testosterone uses a chromatographic purification step before quantification by radioimmunoassay or mass spectrometry and measures women's testosterone levels with a precision and accuracy of about 12-30% [82]. The serum free testosterone is then calculated as the product of the total testosterone and the function of testosterone binding to SHBG (i.e., free testosterone concentration = total testosterone concentration × percent free testosterone).

It is reasonable to begin the evaluation with a total testosterone determination by a reliable method, as suggested above and in Figs. 25.4 and 25.6. Most patients with PCOS have serum total testosterone concentrations between 40 and 150 ng/dL. A total testosterone over 200 ng/dL increases the likelihood of a virilizing neoplasm. The routine assay of other androgens is probably of little utility for the detection of hyperandrogenemia in most populations. DHEA sulfate (DHEAS) may be useful if cystic acne is a major symptom or there is a high suspicion for a virilizing tumor. DHEAS levels are often markedly elevated (over 700 μg/dL) if a tumor of adrenal origin is present. Patients who have clinical features consistent with PCOS or otherwise unexplained anovulatory symptoms but an initial normal total testosterone should have an early

Fig. 25.4 (continued) testosterone determination if a free testosterone test in a reliable specialty laboratory is not available to the practitioner. [I]Androgen resistance is characterized by a frankly male plasma testosterone level when sexual maturation is complete, male karyotype (46, XY), and absent uterus. External genitalia may be ambiguous (partial form) or normal female (complete form). [J]The differential diagnosis of hyperandrogenism is shown in a later algorithm (Fig. 25.7). [K]Vaginal aplasia in a girl with normal ovaries may be associated with uterine aplasia (Rokitansky–Kustner–Hauser syndrome). When the vagina is blind and the uterus aplastic, this disorder must be distinguished from androgen resistance. If the external genitalia are ambiguous, it must be distinguished from other disorders of sex development (intersex). [L]Secondary amenorrhea differential diagnosis is presented in Fig. 25.5

morning plasma free testosterone level performed in a reliable specialty laboratory.

If hyperandrogenemia is documented, we advise further diagnostic evaluation, as detailed in Fig. 25.7. An ultrasonographic examination is important to exclude tumor although the prevalence is only 0.2% and to reassure patients who have polycystic ovaries that the "cysts" are benign. While the presence of polycystic ovaries is supportive of a diagnosis of PCOS, this finding is not specific for PCOS nor are polycystic ovaries necessary for the diagnosis of PCOS [68, 71, 72]. Hyperandrogenic anovulation, in the absence of other causes of anovulation (Figs. 25.4, 25.5, and 25.6) including hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, nonclassic congenital adrenal hyperplasia, and virilizing neoplasm, fulfills widely accepted criteria for the diagnosis of PCOS [38, 81].

PCOS may be mimicked by some rare disorders undetected by the above studies. Whether more extensive laboratory testing is performed varies upon the individual clinical features, circumstances, concerns, and preferences of each patient. For example, a history of rapid virilization, clitoromegaly, or rapid progression would be indications for a more extensive workup. It is our practice to initiate further workup for rare disorders according to the algorithm presented in Fig. 25.8 [79, 80]. An early morning blood sample for free testosterone and steroid intermediates and 24-h urine for 17alpha-hydroxysteroids are obtained [69], followed by a dexamethasone androgen-suppression test. We reserve ACTH testing, which is expensive if comprehensive, for the subset of patients with dexamethasone-suppressible androgen excess. There has been considerable confusion about the interpretation of moderately abnormal responses of steroid intermediates to this test. The experience to date indicates that mutations indicative of nonclassic congenital adrenal hyperplasia cannot be documented unless one of the steroid intermediates rises over 5 SD above average in response to ACTH [83–85]. If the source of androgen excess cannot be localized by these tests, one may be able to definitively demonstrate an ovarian source by a GnRH agonist challenge test [41]. If no source for the androgen excess can be found, one is dealing with idiopathic hyperandrogenemia.

Management

Appropriate therapy of menstrual disorders depends upon the diagnosis. Amenorrhea due to genital tract outflow obstruction often requires surgical treatment, as in the case of vaginal aplasia or imperforate hymen. Some cases of intrauterine adhesions respond to hysteroscopic lysis. If a DSD is diagnosed, utmost sensitivity must be used when discussing the diagnosis with the patient and family. The gender identity and wishes of the patient must be considered when recommending hormonal therapy. In many cases, surgical removal of dysgenic gonadal tissue may be necessary.

In some cases, treatment of hypogonadism is achieved without hormone replacement. The treatment of choice for prolactinoma is dopaminergic agents. Hyperprolactinemia will be maximally suppressed within one month and menstrual cycle normalized within 3 months by an effective regimen. Cabergoline 0.5-1.0 mg once or twice weekly will usually control galactorrhea and shrink prolactinomas [35]. To minimize nausea, it is best to start with a low dose at bedtime. Two years of treatment will minimize recurrence. Transsphenoidal resection of prolactinomas is considered if the patient's condition or eyesight is critical and for the rare treatment failures. A link between cabergoline treatment and mild–moderate tricuspid valve regurgitation has been suggested in elderly patients with Parkinson's disease who often take large doses of the drug. Whether this link also exists in patients with hyperprolactinemia, who are generally prescribed five- to tenfold smaller doses, is yet to be established [86].

Hypogonadism due to chronic diseases such as cystic fibrosis, heart failure, cirrhosis, chronic renal failure, regional enteritis, or systemic lupus erythematosus is best treated by controlling the underlying illness. Anorexia nervosa is best managed by an experienced multidisciplinary team. Refeeding is the first priority, accompanied by long-term management of the psychodynamic

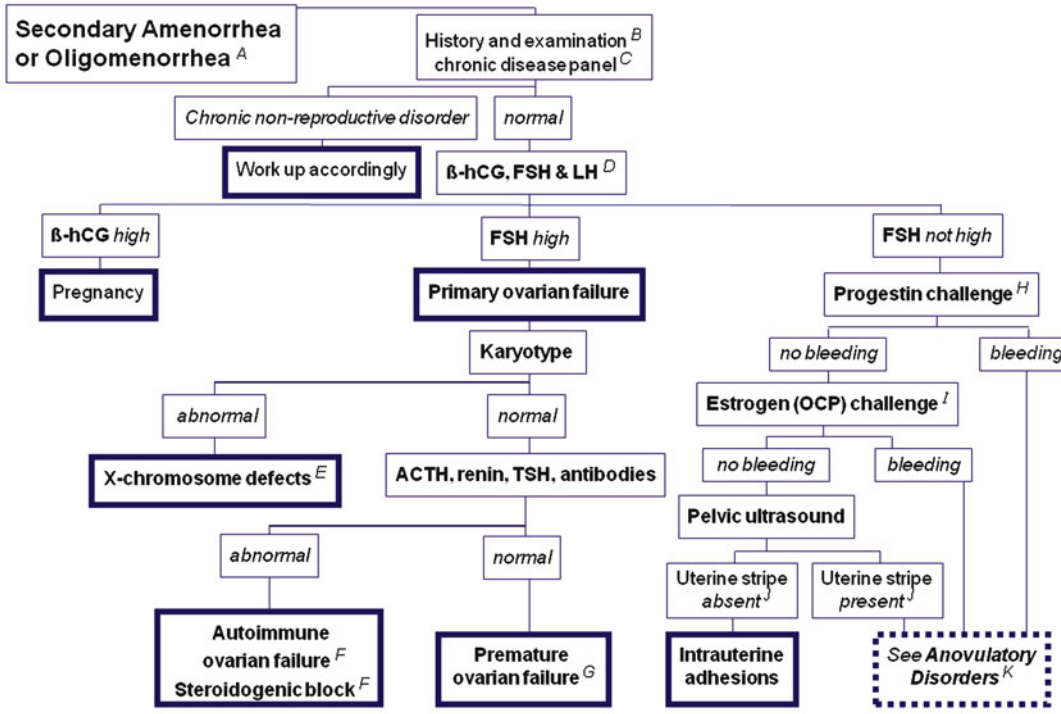

Fig. 25.5 Differential diagnosis of secondary amenorrhea or oligomenorrhea (Modified with permission from Rosenfield RL. Secondary amenorrhea or oligomenorrhea. In: Hochberg Z, editor. Practical algorithms in pediatric endocrinology. 2nd ed. Basel. S. Karger AG; 2007) [A]Mature secondary sex characteristics are characteristic because the occurrence of menarche indicates a substantial degree of development of the reproductive system. [B]Diverse disorders of many systems cause anovulation. The history may reveal excessive exercise, symptoms of depression, gastrointestinal symptoms, radiotherapy to the brain or pelvis, or rapid virilization. Physical findings may include hypertension (forms of congenital adrenal hyperplasia, chronic renal failure), short stature (hypopituitarism, Turner syndrome, pseudohypoparathyroidism), abnormal weight for height (anorexia nervosa, obesity), decreased sense of smell (Kallmann's syndrome), optic disc or visual field abnormality (pituitary tumor), cutaneous abnormalities (neurofibromatosis, lupus), goiter, galactorrhea, hirsutism, or abdominal mass. [C]In the absence of specific symptoms or signs to direct the workup, evaluation for chronic disease in a sexually mature adolescent typically includes complete blood count and differential, sedimentation rate, comprehensive metabolic panel, celiac panel, thyroid panel, cortisol and insulin-like growth factor I levels, and urinalysis. [D]"Pediatric" gonadotropin assays sensitive to ≤0.15 U/L are critical to the early diagnosis of many anovulatory disorders. [E]Patients missing only a small portion of an X chromosome may not have the Turner syndrome phenotype. Indeed, among 45,X patients the classic Turner syndrome phenotype is found in less than one-third (with the exception of short stature in 99%). Ovarian function is sufficient for about 10% to undergo some spontaneous pubertal development and for 5% to experience menarche. If chromosomal studies are normal and there is no obvious explanation for the hypogonadism, special studies for fragile X premutation and autoimmune oophoritis should be considered. [F]Autoimmune ovarian failure may be associated with tissue-specific antibodies and autoimmune endocrinopathies such as chronic autoimmune thyroiditis, diabetes, adrenal insufficiency, and hypoparathyroidism. Nonendocrine autoimmune disorders may occur, such as mucocutaneous candidiasis, celiac disease, and chronic hepatitis. Rare gene mutations causing ovarian insufficiency include steroidogenic defects that affect mineralocorticoid status (17-hydroxylase deficiency is associated with mineralocorticoid excess and lipoid adrenal hyperplasia with mineralocorticoid deficiency) and mutations of the gonadotropins or their receptors. Ovarian biopsy is of no prognostic or therapeutic significance. LH is disproportionately high in steroidogenic defects or autoimmune disease specifically affecting theca cells. [G]The history may provide a diagnosis (e.g., cancer chemotherapy or radiotherapy). Other acquired causes include surgery and autoimmunity. Chromosomal causes of premature ovarian failure include X-chromosome fragile site and point mutations. Other genetic causes include gonadotropin-resistance syndromes such as LH or FSH receptor mutation and pseudohypoparathyroidism. A pelvic ultrasound that shows preservation of ovarian follicles carries some hope for fertility. [H]Withdrawal bleeding in response to a 5- to 10-day course of progestin (e.g., medroxyprogesterone acetate 10 mg HS) suggests an overall estradiol level greater than 40 pg/mL. However, this is not entirely reliable, and thus, in the interest of making a timely diagnosis, it is often worthwhile to proceed to further studies. [I]A thin uterine stripe suggests hypoestrogenism. A thick one suggests endometrial hyperplasia, as may occur in polycystic ovary syndrome. [J]A single cycle of an OCP containing 30–35 μg ethinyl estradiol generally suffices to induce withdrawal bleeding if the endometrial lining is intact. [K]The differential diagnosis of other anovulatory disorders continues in Fig. 25.6

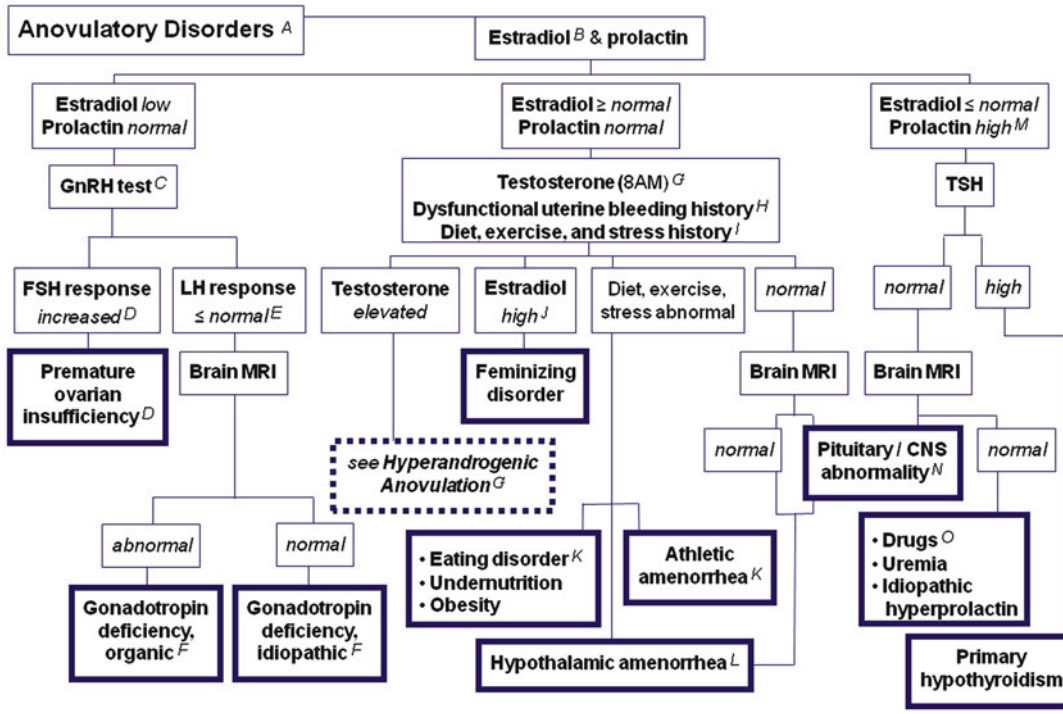

Fig. 25.6 Differential diagnosis of anovulatory disorders (Modified with permission from Rosenfield, RL; Bourguignon, J-P. Anovulatory disorders. In: Hochberg Z, editor. Practical algorithms in pediatric endocrinology. 2nd ed. Basel. S. Karger AG; 2007) [A]Anovulatory disorders should be considered in any girl with unexplained amenorrhea or oligomenorrhea, irregular menstrual bleeding, short cycles, or excessive menstrual bleeding. The workup in this algorithm progresses from negative studies in the Fig. 25.5 algorithm. [B]Once breast development has matured, the breast contour does not substantially regress when hypoestrogenism develops. Hypoestrogenism is suggested if plasma estradiol is persistently <40 pg/mL in a "pediatric" assay sensitive to <10 pg/mL. However, a single estradiol level may be misleading because of cyclic or episodic variations. [C]Gonadotropin-releasing hormone (GnRH) testing is usually performed by assaying LH and FSH before and 0.5 h after the administration of 1 mcg/kg GnRH intravenously. GnRH agonist testing may alternatively be performed by administering 10 mcg/kg leuprolide acetate subcutaneously and assaying LH and FSH at 3-4 h to assess gonadotropin reserve and at 18-24 h to assess the ovarian steroid response to endogenous gonadotropin release. [D]Baseline gonadotropin levels may be normal as the ovary begins to fail, as in early menopause, but an exaggerated FSH response to GnRH and subnormal E2 response to the gonadotropin elevation induced by acute GnRH agonist challenge are characteristic. The further workup is shown in Fig. 25.5. [E]LH responses to GnRH may vary from nil to normal in gonadotropin deficiency: normal LH and FSH responses in the presence of hypoestrogenism indicate inadequate compensatory hypothalamic GnRH secretion. [F]Gonadotropin deficiency may be congenital or acquired, organic, or functional. Congenital causes include midline brain malformations or specific genetic disorders such as Prader–Willi syndrome, Laurence–Moon–Biedl syndrome, or Kallmann's syndrome. Kallmann's syndrome, the association of anosmia with gonadotropin deficiency, occurs in both the X-linked and autosomal-recessive forms. Special MRI views often demonstrate absence of the olfactory tracts. Acquired gonadotropin deficiency may be secondary to a variety of organic CNS disorders, varying from hypothalamic–pituitary tumor to radiation damage to empty sella syndrome. Autoimmune hypophysitis is a rare disorder, sometimes accompanying a polyendocrine deficiency syndrome. The prototypic form of functional gonadotropin deficiency is anorexia nervosa. Idiopathic hypogonadotropic deficiency may sometimes occur in families with anosmia, suggesting a relationship to Kallmann's syndrome. [G]Plasma free (or bioavailable) testosterone is about 50% more sensitive than total testosterone in detecting hyperandrogenemia. However, there are many pitfalls in testosterone assays at the low levels of women, reliable testosterone assays are not available to many physicians, and assaying the free testosterone introduces other potential sources of error. Therefore, it is reasonable to begin the evaluation with a total testosterone determination if a free testosterone test in a reliable specialty laboratory is not available to the practitioner. Simultaneous assay of 17-hydroxyprogesterone is indicated in subjects at high risk for congenital adrenal hyperplasia, such as Ashkenazi Jews. Differential diagnosis of hyperandrogenic evaluation is outlined in Fig. 25.7. [H]Dysfunctional uterine bleeding or menorrhagia not controlled

issues [87]. Menses resume when psychotherapy is effective and body fat is restored to normal. Estrogen treatment of patients with eating disorder will mask the psychopathology which underlies the menstrual disturbance and does not yield the recovery of bone loss that occurs with weight gain [88].

Hormone replacement is the treatment of choice in hypergonadotropic hypogonadism and organic causes of hypogonadotropic hypogonadism, such as congenital or acquired hypopituitarism. Stature is an important consideration in sexually immature teenagers, especially those with Turner syndrome. The dose of estrogen in standard oral contraceptive pills (OCPs) will inhibit growth and lead to premature fusion of the epiphyses in sexually immature patients. If maximizing height potential is patient important, substantial benefit can only be expected if treatment is initiated long before the induction of puberty; this is seldom realistic if initiated after 14 years of age. Panhypopituitary patients require replacement of growth hormone and cortisol deficits to obtain a normal degree of breast development. Further discussion of growth hormone therapy is beyond the scope of this chapter.

Optimal estrogen replacement therapy in the sexually immature girl requires the induction of puberty in a physiologic manner with extremely low doses of estrogen to maximize growth. Gradual, physiologic replacement of estrogen can be started at a peer-appropriate age without compromising height potential. This technique has been validated using intramuscular depot estradiol [89]. However, as intramuscular estradiol at the low doses required to mimic physiology at puberty start is most accurately provided with the support of a compounding pharmacy, transdermal E2 6.25 μg daily is a reasonable alternative [10]. We deliver this dose by applying a 25-mcg patch continuously for 7 days monthly. Equivalent starting doses are 0.25 mg micronized E2 by mouth daily or 5 mcg ethinyl estradiol (one-fourth of the smallest available tablet) by mouth daily for three weeks out of four. The dose is increased every 6 months over a span of 2 years to adult replacement doses of transdermal estradiol 75-100 mcg daily, ethinyl estradiol 20 mcg, or conjugated estrogen 0.625 mg PO daily for 3 weeks out of four. Although conjugated equine estrogen has been effectively used to induce feminization, doses as low as 0.325 mg daily inhibit

Fig. 25.6 (continued) by progestin or OCP therapy additionally requires a pelvic ultrasound examination (for genital tract tumor or feminizing tumor), coagulation workup (which includes platelet count, prothrombin time, thromboplastin generation test, and bleeding time), and consideration of the possibility of sexual abuse. [I]The equivalent of 4 miles per day or more is generally required before body fat stores fall to the point where amenorrhea occurs. Physical or psychosocial stress may cause amenorrhea. [J]The normal range for estradiol over the menstrual cycle is wide: values >95 pg/mL usually indicate the preovulatory or luteal phase but are compatible with a feminizing disorder. [K]Mild forms of stress disorders associated with low body fat (anorexia nervosa, bulimia nervosa, and athletic amenorrhea) may cause acquired hypothalamic amenorrhea rather than frank gonadotropin deficiency. The low body fat content of athletic amenorrhea may not be reflected by weight for height because of high muscularity. Dual-photon absorptiometry scan may be useful in documenting body fat below 20%. Patients with anorexia nervosa may become amenorrheic before or when weight loss begins, indicating an important psychological component to the etiology. Obesity is also associated with anovulatory cycles and raises the possibility of Cushing's syndrome. [L]Hypothalamic amenorrhea is a diagnosis of exclusion. It is a form of partial gonadotropin deficiency in which baseline estrogen secretion is normal but a preovulatory LH surge cannot be generated. It may result from organic CNS disorders or be functional, due to stress, undernutrition or obesity, diverse types of endocrine dysfunction, chronic disease, or idiopathy. It may be difficult to distinguish from hyperandrogenemia. [M]Hyperprolactinemia is heterogeneous in its presentation. Some have normoestrogenic anovulation, which may be manifested as hypothalamic anovulation, hyperandrogenism, dysfunctional uterine bleeding, or short luteal phase. On the other hand, some are hypoestrogenic; these do not have galactorrhea. [N]Large hypothalamic–pituitary tumors or other types of CNS injury cause variable pituitary dysfunction, which may include complete or partial gonadotropin deficiency and various manifestations of hypopituitarism (including secondary hypothyroidism). If they interrupt the pituitary stalk, hyperprolactinemia ensues. Hyperprolactinemia may also be caused by prolactinomas. [O]Drugs, particularly neuroleptics of the phenothiazine or tricyclic type, may induce hyperprolactinemia

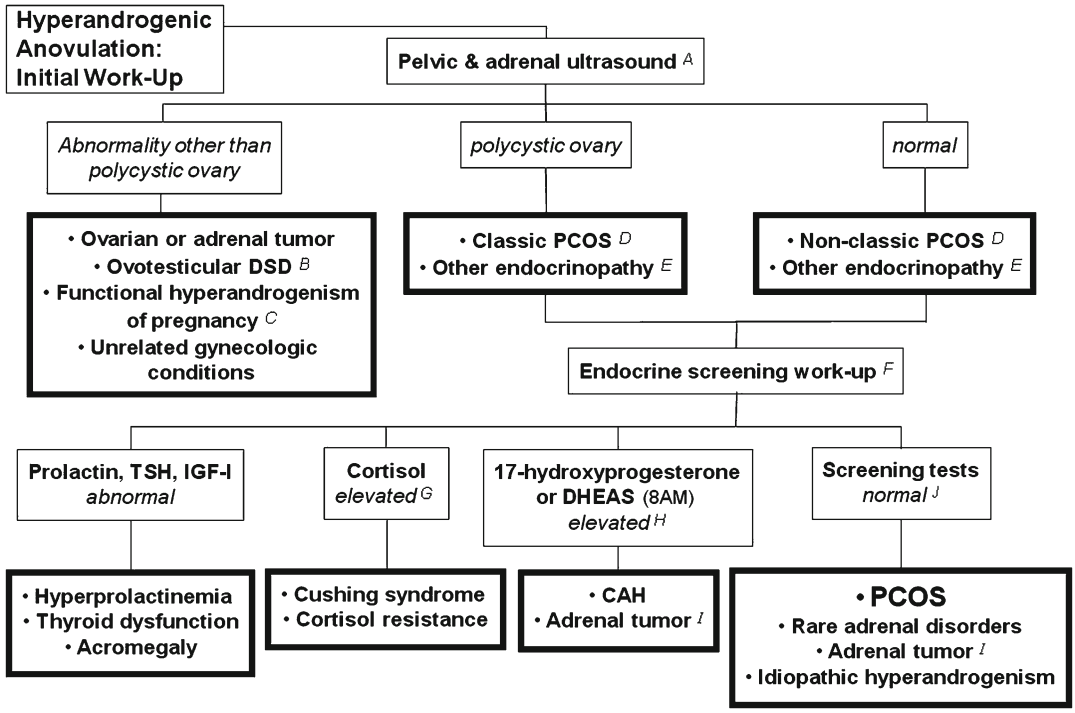

Fig. 25.7 Initial workup of hyperandrogenemic anovulation. Polycystic ovary syndrome (PCOS) accounts for the vast majority of cases; its most widely accepted definition is currently otherwise unexplained hyperandrogenic anovulation ("National Institutes of Health criteria") (Adapted with from Buggs and Rosenfield [79] with permission from Elsevier) [A]Ultrasonography is the initial study that detects polycystic ovaries and excludes ovarian pathology other than polycystic ovaries. The abdominal ultrasound that is indicated for pelvic ultrasonographic imaging in virginal adolescents can be used to screen for adrenal enlargement/mass. A polycystic ovary has been defined by international consensus as an ovary with a volume ≥10.5 cc (10.8 cc in adolescence) and/or containing ≥12 follicles (equivalent to ≥10 follicles in the maximum plane). [B]Ovotesticular DSD (disorder of sex development) was formerly termed true hermaphroditism. [C]Virilization during pregnancy may be due to androgen hypersecretion by a luteoma or hyperreactio luteinalis. [D]"Classic" PCOS is here used synonymously for those cases that have a polycystic ovary and supports the diagnosis, but a polycystic ovary is not necessary for diagnosis. [E]A polycystic ovary is not specific for PCOS; it has been reported in several specific endocrinopathies (e.g., hypothyroidism and Cushing's disease) and is also common in asymptomatic individuals. [F]Further evaluation should include levels of serum prolactin, thyroid-stimulating hormone (TSH), insulin-like growth factor I (IGF-I), cortisol, 17-hydroxyprogesterone, and dehydroepiandrosterone sulfate (DHEAS). An abnormality of any of these endocrine tests is suggestive of one of the hyperandrogenic disorders that most commonly mimics PCOS. [G]Plasma cortisol <10 mcg/dL essentially rules out endogenous Cushing's syndrome. [H]8 a.m. 17-hydroxyprogesterone >170 ng/dL is approximately 95% sensitive and 90% specific for detecting common-type (21-hydroxylase deficient) nonclassic congenital adrenal hyperplasia (CAH) in anovulatory or follicular phase women; it is often found in virilizing neoplasms. DHEAS >700 mcg/dL suggests adrenal virilizing tumor or a rare type of CAH (3ß-hydroxysteroid dehydrogenase deficiency). [I]Computed tomographic scanning of the adrenal gland is a more definitive study for identifying adrenal tumor than is ultrasound. [J]Exclusion of the preceding disorders in a hyperandrogenic patient with menstrual dysfunction meets National Institutes of Health criteria for PCOS with approximately 95% reliability. However, this workup does not identify rare adrenal disorders (e.g., some types of CAH, cortisone reductase deficiency), rare testosterone-secreting adrenal tumor, or, most commonly, idiopathic hyperandrogenism (here used to signify hyperandrogenism of unknown origin, which can arise from obesity or possibly metabolic abnormalities).

growth [90]. Progestin should be added to estrogenic regimens after 2 years of estrogen replacement treatment or after bleeding occurs: we start physiologic replacement with micronized progesterone (Prometrium®) 100 mg daily for 7 days monthly and advance to a full maintenance dose of 200 mg daily for 10 days monthly. In the setting of estrogen replacement at adult doses, the

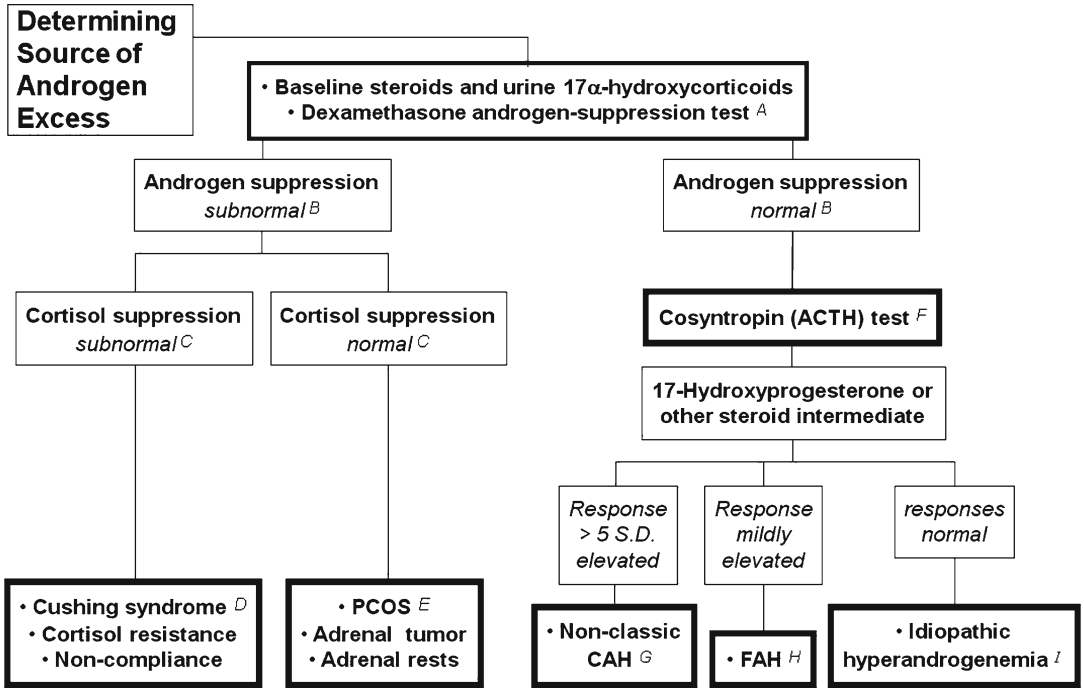

Fig. 25.8 Differential diagnosis of hyperandrogenism and hirsutism (Adapted from Buggs and Rosenfield [79] with permission from Elsevier). [A]After obtaining an early morning blood sample for baseline steroid intermediates (e.g., 17-hydroxypregnenolone, 17-hydroxyprogesterone (17OHP), androstenedione, dehydroepiandrosterone) and a 24-h urine for 17 alpha-hydroxycorticoids, a dexamethasone androgen-suppression test is performed. This consists of a 4-day course (7 days if body weight ≥100 kg) of dexamethasone 0.5 mg four times daily. A normal result is defined as suppression of adrenal androgens below the normal range and by at least 75%. [B]Androgen suppression is normal if level of 17OHP < 50 ng/dL (1.5 nmol/L), total testosterone <28 ng/dL (1.0 nmol/L), and DHEAS < 80 mcg/dL (2.1 μmol/L) (>75% fall); free testosterone falls below 8 pg/mL (27.7 pmol/L) in our hands. [C]Normal corticoid suppression results in cortisol <2.0 mcg/dL (54 nmol/L). [D]If both androgen and cortisol are not normally suppressed, Cushing's syndrome and cortisol resistance should be considered. Poor suppression can result from noncompliance with the dexamethasone regimen. [E]A subnormal suppression of testosterone and 17OHP and a normal suppression of cortisol and DHEAS are characteristics of PCOS, but the rare virilizing adrenal tumor or adrenal rests should be considered on the basis of clinical factors. Computed tomography is the most definitive test for adrenal tumor. [F]A cosyntropin (ACTH) stimulation test is appropriate if androgen suppression by dexamethasone is normal. [G]The diagnosis of congenital adrenal hyperplasia (CAH) is suggested if the steroidogenic intermediate response to ACTH is >5 SD above the average norm: for 17OHP, this is >1,000 ng/dL (30 nmol/L) and for 17-hydroxypregnenolone >5,000 ng/dL (158 nmol/L). [H]Primary functional adrenal hyperandrogenism (FAH) (suggested by a modest rise in 17-hydroxypregnenolone or 17OHP that does not meet the criteria for the diagnosis of CAH) is sometimes the only demonstrable source of androgen excess in PCOS. [I]Idiopathic hyperandrogenemia (distinct from idiopathic hirsutism) is the diagnosis when the source of androgen excess remains unexplained after intensive investigation (approximately 10% of cases). It is most commonly associated with obesity. Cortisone reductase deficiency is a rare consideration, in which the elevated urinary corticoids consist primarily of cortisone metabolites

addition of progesterone is necessary to lower the risk of endometrial hyperplasia and endometrial carcinoma [91].

Hypoestrogenism in sexually mature girls may be managed by administration of an oral contraceptive (OCP). OCPs are the most convenient option. Although the current generation of OCPs carries very little risk of venous thromboembolic disease [92] and the progestational component protects against endometrial hyperplasia, emerging evidence in postmenopausal women suggests that transdermal estradiol is slightly safer [93]. The lowest estrogen dosage currently available in combination OCPs in the

United States is 20 mcg ethinyl estradiol (e.g., with 1.0 mg norethindrone acetate in Loestrin 20 1/21®, 3 mg drospirenone in Yaz ®, 0.15 mg desogestrel in Mircette®). Higher estrogen doses are available, such as 30 mcg ethinyl estradiol (e.g., with 3 mg drospirenone in Yasmin®). Obese patients tend to require higher doses of estrogen. However, patients sensitive to estrogen because of such conditions as hypertension, migraine, or lymphedema are best advised to use a more physiologic type of therapy, estradiol itself in a form delivered systemically, bypassing the liver. Preparations of estradiol that are not oral include depot estradiol given intramuscularly with medroxyprogesterone acetate (Lunelle®) or estradiol patches. When using estrogen alone, a progestin is administered for the last 7-10 days of each course of estrogen (e.g., micronized progesterone 100-200 mg daily); the more progestin administered, the less the risk of endometrial hyperplasia, but the greater the risk of premenstrual symptoms.

In sexually mature adolescents with menstrual irregularities who experience withdrawal bleeding in response to progesterone during the diagnostic workup (Fig. 25.4), oral progestin therapy may be repeated in 2-3-month cycles in order to detect the emergence of spontaneous menses that signals the resolution of the physiologic anovulation of adolescence. This treatment seldom causes side effects and has never been incriminated as a cause of post-pill amenorrhea; thus, it has the appeal of potentially disturbing the developing neuroendocrine system less than OCPs. However, patients must be made aware that this is not a contraceptive treatment.

An acute episode of dysfunctional uterine bleeding requires the administration of estrogen, given together with a progestin as a low-dose OCP, one tablet four times daily for 7 days. Treatment is then stopped for 5 days, and the patient is warned that heavy withdrawal bleeding with cramps may occur. Therapy with a low-dose OCP, given as for contraception, is then begun to prevent recurrence of dysfunctional bleeding and is continued for about three cycles. Cyclic progesterone is an alternative treatment to oral contraceptive pills.

A patient who is hypovolemic because of rapid, heavy dysfunctional bleeding should be hospitalized and treated with intravenous fluids and blood products as necessary. Premarin® in a dose of 25 mg intravenously every 3–4 h for 3–4 doses is customary. When medical management fails, a bleeding diathesis or uterine structural abnormality should be considered. If heavy bleeding persists, curettage should be performed by a gynecologist.

The management of hyperandrogenic states is individualized according to symptoms and patient goals—hirsutism, acne, and alopecia; menstrual irregularity; and obesity and insulin resistance—and the source of androgen excess. The hyperandrogenism associated with congenital adrenal hyperplasia, Cushing's syndrome, virilizing tumors, DSD, hyperprolactinemia, or acromegaly improves with appropriate treatment of the underlying cause. Undesirable side effects of glucocorticoid treatment of congenital adrenal hyperplasia can typically be minimized by using a modest bedtime dose (about 5–7.5 mg prednisone). Obtaining adrenal steroids while on treatment is necessary to monitor for adrenal suppression. Control of androgens in congenital adrenal hyperplasia may not suffice unless nocturnal progesterone excess is also controlled [94]. This treatment will typically normalize the menstrual pattern in nonclassic congenital adrenal hyperplasia, but the effect in classic congenital adrenal hyperplasia is more problematic, since PCOS complicates many of these cases, apparently as the result of congenital or perinatal masculinization [68].

The management of PCOS is directed toward treating symptoms and monitoring for associated disorders. The risk of metabolic syndrome and type 2 diabetes mellitus is increased in PCOS; thus, a fasting lipid panel and oral glucose tolerance test are recommended in patients with central obesity, hypertension, or family history of type 2 diabetes mellitus [95]. The 2-h blood sugar during an oral glucose tolerance test deteriorated at an average rate of 9 mg/dL/year over about a 3-year period in one study [51]. Primary relatives have been shown to have higher rates of diabetes mellitus and metabolic syndrome; thus, these tests are also recommended in obese or hypertensive primary relatives [52].

Treatment of menstrual irregularities in PCOS is recommended to prevent amenorrhea and the associated risk of endometrial hyperplasia and carcinoma. The combination OCP containing estrogen and progestin is the first-line treatment to induce regular menstrual cycles, especially in patients with hirsutism or its cutaneous equivalents. The estrogen component decreases bioactive testosterone by suppressing LH secretion, ovarian androgen production, and serum SHBG. The decrease in bioactive testosterone, assessed 3 months after start of therapy, is associated with an improvement in hyperandrogenic cutaneous symptoms. All estrogen–progestin combinations generally suffice for women with acne or mild hirsutism, in combination with cosmetic measures. OCPs containing non-androgenic progestins such as norgestimate (Ortho-Cyclen®) or ethynodiol diacetate (Demulen 1/50®) generally have favorable risk–benefit ratios and optimize lipid profiles. Those with antiandrogenic progestins in low dose may confer an additional benefit: drospirenone is available in the USA with 20 mcg (Yaz®) or 30 mcg (Yasmin®) ethinyl estradiol. Obese patients may require a higher dose of estradiol to provide menstrual regularity.

Progestin-only regimens can be used to induce menstrual regularity as detailed above, especially if hirsutism and its cutaneous equivalents are not a concern. Progestin-only regimens are also useful in patients in whom OCPs are contraindicated or in patients with objections to use of contraceptive therapy.

Hirsutism and its cutaneous equivalents are treated by topical dermatologic and cosmetic measures and/or endocrinologic treatment. The choice between the treatment options depends upon symptoms and patient preference. Mild hirsutism can be treated by hair removal techniques such as shaving, bleaching, or waxing. Eflornithine hydrochloride cream (Vaniqa®) is a topical agent that is FDA approved for the removal of unwanted facial hair. Six to eight weeks of use is required before effects are seen, and it must be used indefinitely to prevent regrowth. It is often not covered by third party payers. Laser therapy and electrolysis are techniques of permanent hair reduction. Because of expense, discomfort, and occasional scarring, these techniques are most appropriate for limited areas in patients who do not respond to other means of treating hirsutism.

As an adjunct to cosmetic treatments, OCPs, by decreasing bioavailable testosterone, can improve acne within 3 months and arrest progression of hirsutism within 9-12 months in most PCOS patients. Androgen-lowering treatment reduces the androgen-induced transformation of vellus to terminal hairs, and the effects of these agents are maximal at 9–12 months because of the long growth cycles of sexual hair follicles. Thus, a minimum of 6 months is required to determine improvement. OCPs are recommended as a first-line treatment of hirsutism [67]. Many OCPs contain progestins that may have a mild androgenic component. It is logical, therefore, to treat hirsute women with OCPs that contain non-androgenic or antiandrogenic progestins, as detailed above. If after 6 months of treatment no substantial improvement in hirsutism occurs, antiandrogen therapy is suggested [67]. Spironolactone has been shown to be effective to the extent of lowering hirsutism score by about one-third [96], with considerable individual variation, and is probably the most potent and safe antiandrogen available in the USA. We recommend starting with 100 mg twice daily, then reducing the dosage to 50 mg twice daily for maintenance therapy after the maximal effect has been achieved. This dosage is usually well tolerated; fatigue and hyperkalemia at higher doses may limit its usefulness, however. It is potentially teratogenic to fetal male genital development and may cause menstrual disturbance; therefore, it should be prescribed with an oral contraceptive. Flutamide is another antiandrogen of similar efficacy, but is not recommended because of potential hepatotoxicity and expense [67].

Weight loss improves ovulation, acanthosis nigricans, androgen excess, and cardiovascular risk in PCOS patients [58, 59, 97], while antiandrogens have only a modest effect on metabolic abnormalities [98]. This observation lends promise to the idea that insulin-lowering agents could be useful in the treatment of PCOS. The biguanide metformin is the most studied of the insu-

lin-lowering agents in the treatment of PCOS. Metformin suppresses appetite and enhances weight loss. Randomized trials in adolescents demonstrate that metformin increases the frequency of menses and ovulation, and modestly lowers testosterone levels [99, 100]. The decrease in testosterone is not sufficient to improve hirsutism. In addition, it is unclear whether the effect of metformin on menstrual frequency is primary or secondary to the induced weight loss [101]. It is recommended that metformin be considered as an adjunct to weight-control measures in women with impaired glucose tolerance, especially if weight-loss measures fail [102]. Thiazolidinediones also increase insulin sensitivity [57], but their use in adolescents is not recommended because of the associated weight gain, risk of hepatotoxicity, and possible long-term cardiovascular side effects.

Psychological support is an important aspect of the management of teenagers with menstrual disorders. Girls with delayed puberty, whether it has an organic or functional basis, can almost always be assured that they will feminize and, if a uterus is present, that they will experience menses. Girls can be reassured that menstrual abnormalities will be regulated. In addition, patients with Turner syndrome or similar primary hypogonadism disorders can hold hope for the ability to carry a pregnancy, and patients with hypogonadotropic hypogonadism and chronic anovulatory disorders can hold hope for the ability to conceive, though in both situations this will require special care by a reproductive endocrinologist.

References

1. Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics. 2009;123(1):84–8.
2. Apter D, Viinikka L, Vihko R. Hormonal pattern of adolescent menstrual cycles. J Clin Endocrinol Metab. 1978;47(5):944–54.
3. Zhang K, Pollack S, Ghods A, Dicken C, Isaac B, Adel G, et al. Onset of ovulation after menarche in girls: a longitudinal study. J Clin Endocrinol Metab. 2008;93(4):1186–94.
4. American Academy of Pediatrics Committee on Adolescence, American College of Obstetricians and Gynecologists Committee on Adolescent Health Care, Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Pediatrics. 2006;118(5):2245–50.
5. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil. 1967;12(1 Pt 2):77–126.
6. Rosenfield RL, Cooke DW, Radovick S. The ovary and female maturation. In: Sperling MA, editor. Pediatric endocrinology. 3rd ed. Philadelphia, PA: Elsevier; 2008. p. 530–609.
7. Golan A, Langer R, Bukovsky I, Caspi E. Congenital anomalies of the mullerian system. Fertil Steril. 1989;51(5):747–55.
8. Biason-Lauber A, De Filippo G, Konrad D, Scarano G, Nazzaro A, Schoenle EJ. WNT4 deficiency—a clinical phenotype distinct from the classic Mayer-Rokitansky-Kuster-Hauser syndrome: a case report. Hum Reprod. 2007;22(1):224–9.
9. March C. Acquired intrauterine adhesions. In: Adashi E, Rock J, Rosenwaks Z, editors. Reproductive endocrinology, surgery, and technology philadelphia. Philadelphia, PA: Lippincott-Raven; 1996. p. 1475–88.
10. Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007;92(1):10–25.
11. Goswami D, Conway GS. Premature ovarian failure. Hum Reprod Update. 2005;11(4):391–410.
12. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med. 2009;360(6):606–14.
13. Layman LC, McDonough PG. Mutations of follicle stimulating hormone-beta and its receptor in human and mouse: genotype/phenotype. Mol Cell Endocrinol. 2000;161(1–2):9–17.
14. Namnoum AB, Merriam GR, Moses AM, Levine MA. Reproductive dysfunction in women with Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 1998;83(3):824–9.
15. de Zegher F, Jaeken J. Endocrinology of the carbohydrate-deficient glycoprotein syndrome type 1 from birth through adolescence. Pediatr Res. 1995;37(4 Pt 1):395–401.
16. Layman LC. Genetics of human hypogonadotropic hypogonadism. Am J Med Genet. 1999;89(4):240–8.
17. Bose HS, Pescovitz OH, Miller WL. Spontaneous feminization in a 46,XX female patient with congenital lipoid adrenal hyperplasia due to a homozygous frameshift mutation in the steroidogenic acute regulatory protein. J Clin Endocrinol Metab. 1997;82(5):1511–5.
18. Root AW. Reversible isolated hypogonadotropic hypogonadism due to mutations in the neurokinin B regulation of gonadotropin-releasing hormone release. J Clin Endocrinol Metab. 2010;95(6):2625–9.
19. Pfaeffle RW, Savage JJ, Hunter CS, Palme C, Ahlmann M, Kumar P, et al. Four novel mutations of the LHX3 gene cause combined pituitary hormone deficiencies with or without limited neck rotation. J Clin Endocrinol Metab. 2007;92(5):1909–19.
20. Beranova M, Oliveira LMB, Bedecarrats GY, Schipani E, Vallejo M, Ammini AC, et al. Prevalence,

phenotypic spectrum, and modes of inheritance of gonadotropin-releasing hormone receptor mutations in idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2001;86(4):1580–8.
21. Komatsu M, Kondo T, Yamauchi K, Yokokawa N, Ichikawa K, Ishihara M, et al. Antipituitary antibodies in patients with the primary empty sella syndrome. J Clin Endocrinol Metab. 1988;67(4): 633–8.
22. Hendricks SA, Lippe BM, Kaplan SA, Bentson JR. Hypothalamic atrophy with progressive hypopituitarism in an adolescent girl. J Clin Endocrinol Metab. 1981;52(3):562–4.
23. Rappaport R, Brauner R, Czernichow P, Thibaud E, Renier D, Zucker JM, et al. Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors. J Clin Endocrinol Metab. 1982;54(6):1164–8.
24. Van den Berghe G, de Zegher F, Bouillon R. Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab. 1998;83(6):1827–34.
25. Becker AE, Grinspoon SK, Klibanski A, Herzog DB. Eating disorders. N Engl J Med. 1999;340(14): 1092–8.
26. Razdan AK, Rosenfield RL, Kim MH. Endocrinologic characteristics of partial ovarian failure. J Clin Endocrinol Metab. 1976;43(2):449–52.
27. Laughlin GA, Dominguez CE, Yen SSC. Nutritional and endocrine-metabolic aberrations in women with functional hypothalamic amenorrhea. J Clin Endocrinol Metab. 1998;83(1):25–32.
28. Edman CD, MacDonald PC. Effect of obesity on conversion of plasma androstenedione to estrone in ovulatory and anovulator young women. Am J Obstet Gynecol. 1978;130(4):456–61.
29. Rosenfield RL, Bordini B. Evidence that obesity and androgens have independent and opposing effects on gonadotropin production from puberty to maturity. Brain Res. 2010;1364:186–97.
30. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA. 1992;267(9):1244–52.
31. Lado-Abeal J, Rodriguez-Arnao J, Newell-Price JD, Grossman AB, Besser GM, et al. Menstrual abnormalities in women with Cushing's disease are correlated with hypercortisolemia rather than raised circulating androgen levels. J Clin Endocrinol Metab. 1998;83(9):3083–8.
32. Winters SJ, Berga SL. Gonadal dysfunction in patients with thyroid disorders. Endocrinologist. 1997;7:167–73.
33. Sauder SE, Frager M, Case GD, Kelch RP, Marshall JC. Abnormal patterns of pulsatile luteinizing hormone secretion in women with hyperprolactinemia and amenorrhea: responses to bromocriptine. J Clin Endocrinol Metab. 1984;59(5):941–8.
34. Colao A, Lombardi G. Growth-hormone and prolactin excess. Lancet. 1998;352(9138):1455–61.
35. Klibanski A. Clinical practice, prolactinomas. N Engl J Med. 2010;362(13):1219–26.
36. Rosenfield RL. Current concepts of polycystic ovary syndrome. Baillieres Clin Obstet Gynaecol. 1997; 11(2):307–33.
37. Zawadzki J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens J, Haseltine F, Merriam G, editors. Polycystic ovary syndrome. Cambridge, MA: Blackwell Scientific Publications; 1992. p. 377–84.
38. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456–88.
39. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.
40. Lowe P, Kovacs G, Howlett D. Incidence of polycystic ovaries and polycystic ovary syndrome amongst women in Melbourne, Australia. Aust N Z J Obstet Gynaecol. 2005;45(1):17–9.
41. Mortensen M, Ehrmann DA DA, Littlejohn E, Rosenfield RL. Asymptomatic volunteers with a polycystic ovary are a functionally distinct but heterogeneous population. J Clin Endocrinol Metab. 2009;94(5):1579–86.
42. Rosenfield RL. Clinical review: identifying children at risk for polycystic ovary syndrome. J Clin Endocrinol Metab. 2007;92(3):787–96.
43. Ibanez L, Potau N, Zampolli M, Street ME, Carrascosa A. Girls diagnosed with premature pubarche show an exaggerated ovarian androgen synthesis from the early stages of puberty: evidence from gonadotropin-releasing hormone agonist testing. Fertil Steril. 1997;67(5):849–55.
44. Ehrmann DA, Barnes RB, Rosenfield RL. Polycystic ovary syndrome as a form of functional ovarian hyperandrogenism due to dysregulation of androgen secretion. Endocr Rev. 1995;16(3):322–53.
45. Rosenfield RL. Ovarian and adrenal function in polycystic ovary syndrome. Endocrinol Metab Clin North Am. 1999;28(2):265–93.
46. McCartney CR, Bellows AB, Gingrich MB, Hu Y, Evans WS, Marshall JC, et al. Exaggerated 17-hydroxyprogesterone response to intravenous infusions of recombinant human LH in women with polycystic ovary syndrome. Am J Physiol Endocrinol Metab. 2004;286(6):E902–8.
47. Hirshfeld-Cytron J, Barnes RB, Ehrmann DA, Caruso A, Mortensen MM, Rosenfield RL. Characterization of functionally typical and atypical types of polycystic ovary syndrome. J Clin Endocrinol Metab. 2009;94(5):1587–94.
48. Nelson VL, Legro RS, Strauss III JF, McAllister JM. Augmented androgen production is a stable steroidogenic phenotype of propagated theca cells from polycystic ovaries. Mol Endocrinol. 1999;13(6):946–57.
49. Nelson VL, Qin KN, Rosenfield RL, Wood JR, Penning TM, Legro RS, et al. The biochemical basis for

increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001;86(12):5925–33.
50. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. 2005;352(12):1223–36.
51. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;22(1):141–6.
52. Leibel NI, Baumann EE, Kocherginsky M, Rosenfield RL. Relationship of adolescent polycystic ovary syndrome to parental metabolic syndrome. J Clin Endocrinol Metab. 2006;91(4):1275–83.
53. Du X, Rosenfield RL, Qin K. KLF15 Is a transcriptional regulator of the human 17beta-hydroxysteroid dehydrogenase type 5 gene. A potential link between regulation of testosterone production and fat stores in women. J Clin Endocrinol Metab. 2009;94(7):2594–601.
54. Dewailly D, Pigny P, Soudan B, Catteau-Jonard S, Decanter C, Poncelet E, et al. Reconciling the definitions of polycystic ovary syndrome: the ovarian follicle number and serum anti-Mullerian hormone concentrations aggregate with the markers of hyperandrogenism. J Clin Endocrinol Metab. 2010;95(9):4399–405.
55. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev. 2003;(3): CD003053.
56. Ehrmann DA, Cavaghan MK, Imperial J, Sturis J, Rosenfield RL, Polonsky KS. Effects of metformin on insulin secretion, insulin action, and ovarian steroidogenesis in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1997;82(2):524–30.
57. Ehrmann DA, Schneider DJ, Sobel BE, Cavaghan MK, Imperial J, Rosenfield RL, et al. Troglitazone improves defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1997;82(7):2108–16.
58. Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, Gosman G, et al. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2005;1(2):77–80.
59. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millan JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab. 2005;90(12):6364–9.
60. Foecking EM, Szabo M, Schwartz NB, Levine JE. Neuroendocrine consequences of prenatal androgen exposure in the female rat: absence of luteinizing hormone surges, suppression of progesterone receptor gene expression, and acceleration of the gonadotropin-releasing hormone pulse generator. Biol Reprod. 2005;72(6):1475–83.
61. Witchel SF, Lee PA, Suda-Hartman M, Hoffman EP. Hyperandrogenism and manifesting heterozygotes for 21-hydroxylase deficiency. Biochem Mol Med. 1997;62(2):151–8.
62. Hensleigh PA, Woodruff JD. Differential maternal-fetal response to androgenizing luteoma or hyperreactive luteinalis. Obstet Gynecol Surv. 1978;33:262–71.
63. Meldrum DR, Frumar AM, Shamonki IM, Benirschke K, Judd HL. Ovarian and adrenal steroidogenesis in a virilized patient with gonadotropin-resistant ovaries and hilus cell hyperplasia. Obstet Gynecol. 1980;56(2):216–21.
64. Kaltsas GA, Mukherjee JJ, Jenkins PJ, Satta MA, Islam N, Monson JP, et al. Menstrual irregularity in women with acromegaly. J Clin Endocrinol Metab. 1999;84(8):2731–5.
65. Speiser PW, Susin M, Sasano H, Bohrer S, Markowitz J. Ovarian hyperthecosis in the setting of portal hypertension. J Clin Endocrinol Metab. 2000;85(2):873–7.
66. Herzog AG. Menstrual disorders in women with epilepsy. Neurology. 2006;66(6 Suppl 3):S23–8.
67. Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, et al. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(4):1105–20.
68. Barnes RB, Rosenfield RL, Ehrmann DA, Cara JF, Cuttler L, Levitsky LL, et al. Ovarian hyperandrogynism as a result of congenital adrenal virilizing disorders: evidence for perinatal masculinization of neuroendocrine function in women. J Clin Endocrinol Metab. 1994;79(5):1328–33.
69. Qin K, Rosenfield RL. Mutations of the hexose-6-phosphate dehydrogenase gene rarely cause hyperandrogenemic polycystic ovary syndrome. Steroids. 2010;76(1–2):135–9.
70. Glickman SP, Rosenfield RL, Bergenstal RM, Helke J. Multiple androgenic abnormalities, including elevated free testosterone, in hyperprolactinemic women. J Clin Endocrinol Metab. 1982;55(2):251–7.
71. Kaltsas GA, Korbonits M, Isidori AM, Webb JA, Trainer PJ, Monson JP, et al. How common are polycystic ovaries and the polycystic ovarian syndrome in women with Cushing's syndrome? Clin Endocrinol (Oxf). 2000;53(4):493–500.
72. Futterweit W, Krieger DT. Pituitary tumors associated with hyperprolactinemia and polycystic ovarian disease. Fertil Steril. 1979;31(6):608–13.
73. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science. 1974;185(4155):949–51.
74. National Centers for Health Statistics. National Health and Nutrition Examination Survey 2000 CDC Growth Charts: United States. 2000. Available at: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm.
75. Rebar RW, Connolly HV. Clinical features of young women with hypergonadotropic amenorrhea. Fertil Steril. 1990;53(5):804–10.
76. Ibanez L, Potau N, Zampolli M, Virdis R, Gussinye M, Carrascosa A, et al. Use of leuprolide acetate

response patterns in the early diagnosis of pubertal disorders: comparison with the gonadotropin-releasing hormone test. J Clin Endocrinol Metab. 1994;78(1):30–5.
77. Winslow KL, Toner JP, Brzyski RG, Oehninger SC, Acosta AA, Muasher SJ. The gonadotropin-releasing hormone agonist stimulation test—a sensitive predictor of performance in the flare-up in vitro fertilization cycle. Fertil Steril. 1991;56(4):711–7.
78. Zimmer CA, Ehrmann DA, Rosenfield RL. Potential diagnostic utility of intermittent administration of short-acting gonadotropin-releasing hormone agonist in gonadotropin deficiency. Fertil Steril. 2010;94(7):2697–702.
79. Buggs C, Rosenfield RL. Polycystic ovary syndrome in adolescence. Endocrinol Metab Clin North Am. 2005;34(3):677–705.
80. Rosenfield RL. Polycystic ovary syndrome in adolescents. 2008. Available at: http://www.uptodate.com/index.
81. Rosenfield RL. What every physician should know about polycystic ovary syndrome. Dermatol Ther. 2008;21(5):354–61.
82. Legro RS, Schlaff WD, Diamond MP, Coutifaris C, Casson PR, Brzyski RG, et al. Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. J Clin Endocrinol Metab. 2010;95(12):5305–13.
83. Escobar-Morreale HF, Sanchon R, San Millan JL. A prospective study of the prevalence of nonclassical congenital adrenal hyperplasia among women presenting with hyperandrogenic symptoms and signs. J Clin Endocrinol Metab. 2008;93(2):527–33.
84. Bidet M, Bellanne-Chantelot C, Galand-Portier M, Tardy V, Billaud L, Laborde K, et al. Clinical and molecular characterization of a cohort of 161 unrelated women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency and 330 family members. J Clin Endocrinol Metab. 2009;94(5):1570–8.
85. Lutfallah C, Wang W, Mason JI, Chang YT, Haider A, Rich B, et al. Newly proposed hormonal criteria via genotypic proof for type II 3{beta}-hydroxysteroid dehydrogenase deficiency. J Clin Endocrinol Metab. 2002;87(6):2611–22.
86. Valassi E, Klibanski A, Biller BMK. Potential cardiac valve effects of dopamine agonists in hyperprolactinemia. J Clin Endocrinol Metab. 2010;95(3):1025–33.
87. Lock J, Le Grange D, Agras WS, Moye A, Bryson SW, Jo B. Randomized clinical trial comparing family-based treatment with adolescent-focused individual therapy for adolescents with anorexia nervosa. Arch Gen Psychiatry. 2010;67(10):1025–32.
88. Miller KK, Lee EE, Lawson EA, Misra M, Minihan J, Grinspoon SK, et al. Determinants of skeletal loss and recovery in anorexia nervosa. J Clin Endocrinol Metab. 2006;91(8):2931–7.
89. Rosenfield RL, Devine N, Hunold JJ, Mauras N, Moshang Jr T, Root AW. Salutary effects of combining early very low-dose systemic estradiol with growth hormone therapy in girls with Turner syndrome. J Clin Endocrinol Metab. 2005;90(12):6424–30.
90. Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., Collaborative Study Group. J Clin Endocrinol Metab. 2000;85(7):2439–45.
91. Woodruff JD, Pickar JH. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. The Menopause Study Group. Am J Obstet Gynecol. 1994;170(5 Pt 1):1213–23.
92. Farmer RD, Lawrenson RA, Todd JC, Williams TJ, MacRae KD, Tyrer F, et al. A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. Br J Clin Pharmacol. 2000;49(6):580–90.
93. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case–control study. BMJ. 2010;340:c2519.
94. Rosenfield RL, Bickel S, Razdan AK. Amenorrhea related to progestin excess in congenital adrenal hyperplasia. Obstet Gynecol. 1980;56(2):208–15.
95. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. 2010;95(5):2038–49.
96. Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, et al. Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. J Clin Endocrinol Metab. 2008;93(4):1153–60.
97. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril. 2009;92(6):1966–82.
98. Ibanez L, Potau N, Marcos MV, de Zegher F. Treatment of hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism in nonobese, adolescent girls: effect of flutamide. J Clin Endocrinol Metab. 2000;85(9):3251–5.
99. Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. J Clin Endocrinol Metab. 2002;87(2):569–74.
100. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. J Clin Endocrinol Metab. 2000;85(1):139–46.

101. Eisenhardt S, Schwarzmann N, Henschel V, Germeyer A, von Wolff M, Hamann A, et al. Early effects of metformin in women with polycystic ovary syndrome: a prospective randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2006;91(3):946–52.

102. Salley KES, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. POSITION STATEMENT: Glucose intolerance in polycystic ovary syndrome—a position statement of the Androgen Excess Society. J Clin Endocrinol Metab. 2007;92(12):4546–56.