Adolescent Menstrual Disorders

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The hallmark of the adolescent years is the initiation and completion of the pubertal process. Neuroendocrine maturation, which results from a multitude of environmental and physiologic factors, is responsible for converting the sexually infantile girl into a mature adolescent capable of reproduction. Reassuring signs of a normal transition into puberty are the budding of the breasts, the growth of pubic hair, and the acceleration of growth velocity. Menarche and the initiation of regular menstrual cycles signal an uneventful completion of the pubertal process.

The development of normal menstrual function is documentation that the neuroendocrine, gonadal, and anatomic components of the reproductive system are intact and mature. It is also evidence of nonreproductive physiologic homeostasis. In contradistinction, adolescent menstrual dysfunction may be the first obvious sign of an abnormality in both reproductive and nonreproductive systems.

Normal menstrual function begins with menarche, which occurs at an average age of 12.8 years for American girls. Until the positive feedback system develops, cycles subsequent to menarche are usually anovulatory. During the first year of menstrual life, 55.7% of the cycles are anovulatory.[1] It takes approximately 15 months for completion of the first 10 cycles and an average of 20 cycles before ovulation occurs on a regular basis. Once ovulatory function is established, the menstrual cycle averages 29.5 days in length, with a range of 21 to 40 days. The menstrual flow lasts from 3 to 8 days. Quantitative blood loss of 40–100 ml of blood is normal for these ovulatory cycles.[1]

Adolescent menstrual disorders occur through the first 10 years following menarche; they include the absence of menarche by age 15, amenorrhea of 6 months' duration or greater, the persistence of irregular cycles of less than 21 days or greater than 40 days in length, and cyclic or acyclic hypermenorrhea. Menstrual blood loss is subjective and difficult to quantitate.[2] The use of eight or more sanitary napkins per day is considered evidence of excessive blood loss. Severe dysfunctional bleeding is associated with a hemoglobin less than 10 g/100 ml blood. Menses lasting longer than 8 days on a repetitive basis are also considered abnormal.

Many causes of adolescent menstrual dysfunction are directly associated with the pubertal process. These disorders result

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from aberrations of pubertal maturation. Some causes of menstrual disorders of adolescence are only temporally related to puberty. Such abnormalities are not directly associated with pubertal aberrancy. Adolescent menstrual disorders will be discussed in relation to both pubertal and nonpubertal causes. Except for a few patients with dysfunctional bleeding, most girls with pubertal abnormalities present with forms of amenorrhea. Most girls with disorders unrelated to pubertal maturation will have bleeding abnormalities. Some of these patients may also present with amenorrhea. Table 1 outlines the classification of these adolescent menstrual disorders.

Pubertal Menstrual Disorders

Aberrations of the pubertal process are responsible for most adolescent menstrual disorders (Table 1). Such abnormalities of pubertal development occur in patients whose gonads are not functioning (hypogonadism) as well as in girls whose gonads are undergoing normal steroidogenesis (eugonadism).[3] Hypogonadism may be secondary to a hypothalamic-pituitary problem in which maturational changes responsible for pubertal gonadotropin release do not occur. More often, the lack of steroidogenic activity in the adolescent gonad may be the result of primary gonadal failure. Menarchal delay, or abbreviated menstrual function of 6 months or less, is a common conclusion of these hypogonadal disorders. Sexual infantilism often accompanies this state of hypogonadism. Eugonadal menstrual disorders are less frequently observed. Patients with eugonadal menstrual disorders present with phenotypic evidence of sex steroid production. Anatomic abnormalities may prevent either total menstrual function or menstrual outflow. Other eugonadal girls demonstrate menstrual disorders that are associated with a state of chronic anovulation. Eugonadal girls often present with amenorrhea. The adolescents with delayed sexual development and chronic anovulation may also present with significant and occasionally life-threatening bleeding disorders.

TABLE 1. Classification of Patients Presenting With Adolescent Menstrual Disorders

Pubertal adolescent menstrual disorders
Hypogonadal pubertal defects
Hypothalamic-pituitary problems (hypogonadotropism)*
Reversible†
Irreversible
Gonadal failure (hypergonadotropism)*†
Chromosomally incompetent ovarian failure (CIOF)
Chromosomally competent ovarian failure (CCOF)
Eugonadal pubertal defects*
Anatomic genital abnormalities
Inappropriate positive feedback (PCOD)†
Androgen insensitivity syndrome
Adolescent menstrual disorders unrelated to pubertal maturation
Organic causes
Ovulation disturbances
Pregnancy disorders

*Amenorrhea.

†Abnormal bleeding.

Table 2 presents an etiologic breakdown of 252 patients with pubertal abnormalities studied at the Medical College of Georgia.[3] The study was limited to individuals who presented with sexual infantilism and primary amenorrhea or with less than 6 months of menstrual function followed by secondary amenorrhea. Patients with pubertal ovulation disorders who presented with dysfunctional bleeding were not included in this study of delayed sexual development.

Hypothalamic-Pituitary Maturation Arrest (Hypogonadotropic Hypogonadism)

It appears that the initial changes associated with the pubertal process occur in the hypothalamus and pituitary. Dynamic maturation processes of both hypothalamic-pituitary-adrenal and hypothalamic-pituitary ovarian circuits have been identified. Adolescent menstrual disorders may result from a delay in these maturational changes, an interference with these processes, or the total incapacity for gonado-

TABLE 2. Etiologic Breakdown of 252 Patients Presenting With Pubertal Aberrancy

	Group Total	Number	%
Hypergonadotropic hypogonadism			
CIOF	69		27
CCOF	40		16
46,XX		34	14
46,XY		6	2
Total	109		43
Hypogonadotropic hypogonadism			
Reversible	48		19
Physiologic delay		35	14
Weight loss/anorexia nervosa		6	2
Primary hypothyroidism		3	1
Congenital adrenal hyperplasia		3	1
Cushing's syndrome		1	0.5
Irreversible	29		12
Congenital deficiency syndromes			
Isolated GnRF deficiency		13	5
Forms of hypopituitarism		6	2
Congenital CNS defects		2	1
Acquired anatomic lesions			
Prolactin-secreting adenoma		3	1
Unclassified pituitary adenoma		2	1
Craniopharyngioma		1	0.5
Unclassified malignant pituitary tumor		1	0.5
Postoperative hypopituitarism (craniopharyngioma)		1	0.5
Total	77		31
Eugonadism			
Anatomic	46		18
Rokitansky syndrome		37	15
Transverse vaginal septum		7	3
Imperforate hymen		2	1
Inappropriate positive feedback	17		7
Androgen insensitivity syndrome	3		1
Total	66		26

From Reindollar et al.[3] By permission.

tropin release. Approximately 30% of the 252 patients studied with pubertal menstrual abnormalities are identified with reversible or irreversible forms of hypogonadotropic hypogonadism (Table 2).[3] The gonads of such patients have the full potential for endocrine and exocrine activity but lie dormant until a stimulatory gonadotropin signal is produced.

Reversible Hypothalamic-Pituitary Disorders

Physiologic, or constitutional, delay represents the most common cause of reversible hypogonadotropism and one of the most frequent diagnoses assigned to patients with pubertal aberrancy. Fourteen percent of the patients with delayed sexual development and 45% of the patients with hypogonadotropism have physiologic delay.[3] The only abnormality of puberty in these patients is its slow start, and the cause at the present time is considered idiopathic. These patients present with early pubertal changes, generally short stature, and menarchal delay.[4] Once menarche occurs, subsequent menstrual function follows the normal adolescent menstrual course.

Systemic processes have been reported to interfere with hypothalamic-pituitary ma-

turation and cause both delayed sexual development and pubertal menstrual dysfunction. Gastrointestinal malabsorption disease processes (e.g., regional enteritis, ulcerative colitis), chronic renal failure, chronic pulmonary disease, hemoglobinopathies, neoplasia, and cardiovascular diseases have all been implicated as causes of these dysfunctions.[4] Rigorous exercise, dietary restrictions, and emotional distress may have the same effect on hypothalamic-pituitary maturation. The degree of pubertal development and the type of menstrual dysfunction are variable. They are dependent on the nature and the time of onset of the specific cause of the disorder. In our series, the reversible systemic processes diagnosed are anorexia and less severe forms of weight loss (Table 2).[3] These patients presented with amenorrhea. Whereas a few of them were sexually infantile, most of them had partial pubertal development. Still others had completed puberty and had several menses before developing amenorrhea. Menstrual disorders that include the persistence of irregular cycles during the adolescent years have also been reported in association with these systemic processes, as well as with rigid exercise programs (see Spellacy, this symposium).[5,6]

Endocrine disease processes may interfere with the normal pubertal maturation of hypothalamic-pituitary gonadotropin release. Primary hypothyroidism and, less frequently, congenital adrenal hyperplasia and Cushing's syndrome are observed (Table 2).[3,4] The hypothyroid patients present with menarchal delay as well as sexual infantilism, short stature, and associated bone-growth arrest.[4] These patients may show only subtle signs and symptoms of hypothyroidism. The conditions of hyperprolactinemia and enlarged sellar size, both the result of thyrotropin-releasing factor (TRF) overproduction, may confuse this diagnosis with that of prolactin-producing pituitary microadenomas. Menarchal delay in the patients with congenital adrenal hyperplasia is associated with masculinization, which is secondary to adrenal gland androgen overproduction. These patients occasionally present with good secondary sexual development, and misdiagnoses of forms of polycystic ovarian disease (PCOD) may be made. Patients with Cushing's syndrome demonstrate classic features of this condition in association with delayed menarche. Normal menstrual function follows appropriate treatment in all of these adolescents with endocrine disease processes.

Irreversible Hypothalamic-Pituitary Disorders

Congenital deficiency syndromes and acquired anatomic lesions may prevent normal pubertal changes in the hypothalamus and pituitary.[3] These irreversible forms of hypogonadotropic hypogonadism have a serious effect on future menstrual function and reproductive potential.[3]

Congenital deficiency syndromes are identified in 72% of the adolescents with irreversible disease and in 8% of all patients with delayed puberty (Table 2).[3] These patients are unable to produce sufficient quantities of hypothalamic or pituitary protein hormones because of genetically determined syndromes (e.g., Kallmann's, Laurence-Moon-Biedl, Prader-Willi), congenital central nervous system defects (e.g., congenital encephalocele, congenital hydrocephalus), certain forms of hypopituitarism, and possibly perinatal asphyxia or trauma. Most of these patients present with sexual infantilism and menarchal delay.[3,4] Somatic anomalies associated with the specific disorder and other evidence of diminished pituitary function are often present. Kallmann's syndrome, or isolated deficiency of luteinizing hormone-releasing hormone, is identified more frequently than the other congenital deficiency syndromes (Table 2).[3]

Acquired anatomic lesions of the central nervous system (CNS) are the most important identifiable causes of pubertal menstrual disorders. They may present immediate neurologic compromise and infrequently have life-threatening potential. Other pos-

sible causes of pubertal menstrual disorders include CNS infection (e.g., tuberculosis, encephalitis, meningitis), newborn kernicterus, histiocytosis-X, sarcoidosis, trauma, and acquired hydrocephalus.[3,4] Pituitary tumors are most commonly diagnosed, with prolactinomas occurring more frequently than craniopharyngiomas (Table 2).[3] Pubertal development and menstrual function are also variable in patients with these syndromes, and dependent on the time of onset of the acquired lesion as well as the aggressiveness of the particular defect. For example, craniopharyngiomas usually develop in the late childhood years before pubertal onset and exhibit extremely aggressive behavior. Prolactinomas are more benign in growth and usually appear during the late pubertal years or after pubertal completion. Patients with craniopharyngiomas tend to present with sexual infantilism and menarchal delay. Girls with prolactinomas usually demonstrate partial or complete pubertal development in association with delayed menarche or abbreviated menstrual function.

Gonadal Failure (Hypergonadotropic Hypogonadism)

The single largest category of patients presenting with pubertal menstrual disorders have ovarian failure.[3] The cases of 44% of the 252 patients with pubertal aberrancy are correctly diagnosed (Table 2).[3] Ovarian function is dependent upon the presence of ovarian determinant genes located on both arms of both X chromosomes and probably on autosomes as well. Ovarian failure is most commonly caused by chromosomal accidents such as anaphase lag or meiotic/mitotic nondisjunction. These accidents cause the deletion of ovarian determinant genes. Patients who lack X-chromosomal material have chromosomally incompetent ovarian failure (CIOF) and represent 63% of the patients with ovarian failure.[3] Patients with gonadal failure whose sex chromosomes are intact represent 37%[3] of the patients with ovarian failure and have chromosomally competent ovarian failure (CCOF).

CIOF

The Turner phenotype associated with a 45,X karyotype represents the prototype of the CIOF patient, but is not the most common form of this entity. Mosaic cell lines are more frequently encountered in these patients than are single cell lines.[3] Mixed gonadal dysgenesis (45,X/46,XY karyotype) is the most common mosaic form of Turner's syndrome observed. Structural abnormalities of the X chromosome (e.g., isochromosome for the long arm of the X) occur in approximately one-third of these individuals.

All CIOF patients lack X-chromosomal genetic material. Gonadal development is originally initiated with a full complement of germ cells. The privation of ovarian determinant genes is associated with unarrested meiotic activity and depletion of most of these germ cells. Most CIOF patients present with sexual infantilism and menarchal delay.[3,7] Occasionally a variable number of follicles remain in these dysgenetic gonads. At puberty stimulation of the dysgenetic gonads may produce partial or complete secondary sexual development.[8] CIOF patients may present during the adolescent years with regular menses, irregular menses, and dysfunctional uterine bleeding.[8,9] Pregnancy rarely occurs. Ultimately, the depletion of germ cells occurs in all such patients and results in ovarian failure and amenorrhea. Privation of statural genes, also present on both arms of both X chromosomes, is responsible for altered growth in utero and throughout adulthood. All CIOF patients are less than 63 inches in height.[3] Stigmata associated with the Turner phenotype are variably present. Associated cardiovascular-renal anomalies occur in 30% of the patients.[3] Such somatic and visceral anomalies may be related to the deletion of other important X-linked somatic genes or may stem from the same alterations in cell generation dynamics described in association with short stature.[10]

Patients with mixed gonadal dysgenesis differ from the other CIOF individuals because they have mosaic cell lines that in-

clude a Y chromosome. Sexual ambiguity may be noticed at birth or become apparent at puberty in some of these patients.[11] Most of these adolescents present at puberty with phenotypes not unlike the other Turner patients. Y germ cells appear to proliferate more rapidly than do X germ cells in utero. This may be one explanation for the predisposition for gonadal ridge tumors in these patients.[12] Y germ cell proliferation may also explain the increased meiotic activity in utero and total germ cell depletion. Spontaneous menstrual function never exists in these patients. Gonadoblastomas rarely secrete estrogen that mounts a pubertal development response.

CCOF

Factors other than the lack of X-chromosomal material are responsible for the depletion of ovarian follicles and ovarian failure in most patients. Such factors may include an autosomal recessive gene,[3,13] environmental agents (e.g., mumps oophoritis), neoplastic therapy, autoimmune disease, or ovarian infiltrative processes (e.g., tuberculosis and mucopolysaccharidosis).[4] Such systemic disorders as myotonia dystrophica,[14] ataxia-telangiectasia,[15] and galactosemia[16] have also been associated with ovarian failure. Individuals with CCOF are more likely to have residual follicles in their gonads at the time of puberty. As many as 46% of the patients will have a brief period of ovarian function before ovarian failure ensues.[3] Eighteen percent of the patients with 46,XX ovarian failure present with 6 months or less of menses following pubertal development.[3] Others may have menses for a number of years before ovarian failure. Corpus luteal deficiency is common as the follicles become depleted and may be associated with dysfunctional bleeding episodes. Ovarian malfunction, interpreted as ovarian failure, is seen in the rare patients with either 17α-hydroxylase deficiency or ovarian-gonadotropin-receptor deficiency. Most patients with CCOF are tall, because their epiphyses remain open in the absence of sex steroid production. Somatic and visceral anomalies are rare.

Patients with 46,XY gonadal dysgenesis are also placed in the category of CCOF.[3,13] Defective development of the testes occurs very early in embryogenesis. The gonads develop along ovarian streak lines, producing neither androgens nor müllerian inhibiting factor. These patients do not masculinize in utero or at puberty. They develop as phenotypic females with normal müllerian systems. The presence of a Y chromosome is responsible for the total depletion of germ cells in these patients. As a result, they will never have spontaneous pubertal development or menstrual function.[3] The presence of this Y chromosome places them at high risk for tumor formation, and this necessitates gonadal streak extirpation.[12]

Eugonadal Pubertal Defects

As many as one-fourth of the patients with pubertal aberrancy present with evidence of gonadal steroidogenesis and concomitant menstrual dysfunction (Table 2).[3] The adolescents in this heterogenous group experience anatomic abnormalities of the genital tract, ovulation disorders, and, rarely, androgen insensitivity syndrome (Table 2).[3,4]

Anatomic Abnormalities

Eighteen percent of the patients with pubertal aberrancy present with anatomic amenorrhea (Table 2).[3] The congenital absence of the uterus and vagina (Rokitansky-Kuster-Hauser syndrome) is most commonly diagnosed and represents the second most frequent pubertal abnormality. Environmental factors and possibly multifactorial inheritance are considered the causes for this condition as well as associated renal, cardiovascular, and skeletal anomalies found in some of these individuals.[3,17] Ovarian anatomy and function are preserved and allow for normal pubertal development. Menstruation is impossible from the hypoplastic uterine remnants of most Rokitansky patients. In the few patients reported to have enough endometrium to allow for cyclic shedding, menstruation has been concealed,

with hematometra developing above the absent vaginal plane.[17]

The obstructed genital tract is a rare cause of menstrual disorders in the adolescent. Four percent of patients with abnormalities of puberty have either a transverse vaginal septum or an imperforate hymen.[3] Genetic causes have been identified in some of these patients.[3,4] Most cases are random and may result from environmental agents. With either a transverse vaginal septum or an imperforate hymen, the functional uterus begins menstrual shedding at the normal time for menarche. Concealed menses produce a proximal hematocolpos and a hematometra. The reflux of blood into the pelvis may cause an aseptic inflammatory process and severe endometriosis. The first obstructive symptom is cyclic pain, which may become continuous in nature. Bladder and rectal discomfort may develop. Adolescents with duplicated müllerian systems and unilateral obstruction may present with cyclic menses and severe dysmenorrhea. Hematometra may develop on the obstructed side. If a communication or a small fistula exists between the two uteri, the unilateral hematometra may empty throughout the cycle and be noticed as dark intermenstrual bleeding.

Inappropriate Positive Feedback

Seven percent of the patients with delayed sexual development failed to develop the mature positive feedback mechanism necessary for ovulation (Table 2).[3] The negative feedback system matures at the appropriate time for these patients. Subsequent increased steroidogenic activity allows for the normal onset of pubertal development. Tonic elevations of luteinizing hormone (LH) may produce androgen overproduction and hirsutism. Most adolescents with PCOD will experience irregular and occasionally extremely heavy estrogen withdrawal bleeding beginning at menarche and continuing into the adult years. In adolescence most dysfunctional uterine bleeding occurs in this setting of unopposed estrogen production. The adolescents in our series with inappropriate positive feedback presented either with menarchal delay or brief menstrual lives following menarche and subsequent prolonged amenorrhea (Table 2). The patients with amenorrhea are relatively easy to evaluate and to treat appropriately. In contradistinction, dysfunctional bleeding in other girls may be difficult to control and may require hospitalization with medical or surgical curettage followed by long-term administration of cyclic hormonal agents (see Spellacy, this symposium).

Androgen Insensitivity

Only 1% of the adolescents with pubertal aberrancy will present with the triad of completed thelarche, absent pubarche, and delayed menarche.[3] Normal gonadal steroidogenesis is present in patients with testicular feminization syndrome. Unlike the other eugonadal individuals, these patients have 46,XY karyotypes and testes. An X-linked recessive trait is responsible for defective production of androgen cytosol receptors in this rarely diagnosed disorder. Unlike the dysgenetic testes in other phenotypic female patients, the risk for tumor formation becomes significant only after the pubertal years.[18]

Adolescent Menstrual Abnormalities Unrelated to Puberty

The adolescent may present with a menstrual dysfunction that is not directly associated with abnormalities of the pubertal process (Table 1). The first menses is often the initial test of competency of these nonpubertal systems. As a result, presenting complaints often center around abnormalities of menstruation that may begin at menarche.[19] Organic causes are the most significant of such abnormalities because of their occasional life-threatening potential.[1,2,20] Ovulation disorders that occur after development of the positive feedback system may be

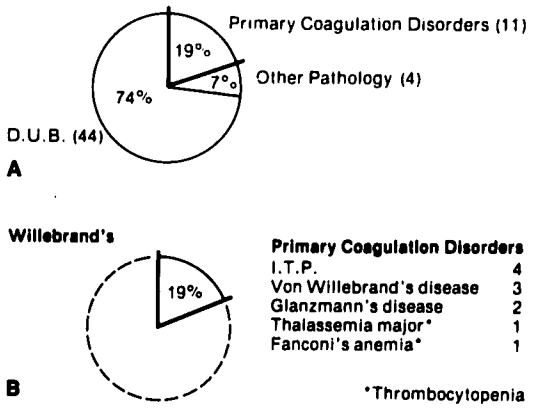

FIG. 1. A. *Etiologic breakdown of 59 patients with acute adolescent menorrhagia.* **B.** *Specific diagnoses given to 11 of these patients with primary coagulation disorders. (From Claessens E et al.[20] By permission.)*

similar to the defects that develop during the pubertal process. Finally, gestational disorders are a not infrequent cause of abnormal uterine bleeding that occurs during the adolescent years.[1,2] Figure 1 depicts an etiologic breakdown of abnormalities described by Claessens and Cowell in a series of 59 patients with acute adolescent menorrhagia.[20] This study is helpful because it presents a breakdown of many of the etiologies that are generally unrelated to the pubertal process. It does exclude patients with genital tract disease, and, like our series, represents a tertiary center bias.

Organic Causes of Adolescent Menstrual Disorders

The most significant finding in the study of Claessens and Cowell was the discovery of coagulation disorders in nearly 20% of the patients (Fig. 1).[20] Coagulation disorders, including leukemia and aplastic anemia, presented with significant blood loss during the initial menstrual years. Twenty-eight percent of the patients with hemoglobins less than 10g/100 ml on admission and 35% of those patients requiring blood component therapy had a coagulation defect.

Neoplastic processes of the genital tract are the most potentially serious causes of adolescent menstrual disorders. Clear cell carcinoma of the vagina or cervix heads the list. Three-fourths of these patients have had in utero exposure to diethylstilbesterol (DES).[1,2,21] The reported incidence of 0.14–1.4 cases/1000 women exposed to DES makes this a rare condition.[21] Other neoplasms reported in adolescents with abnormal bleeding have included ovarian tumors, cervical or endometrial polyps, submucous uterine myomas, and, rarely, sarcoma botryoides of the cervix.[1,2] Abnormal bleeding may occur in the setting of rhythmic menses and ovulation as documented by the basal body temperature graphs of these patients. Intermenstrual bleeding patterns are most common. Patients with submucous myomas may have menses which are normal for the first 1–3 days followed by heavy menstrual flow for 3 or more days.

Infectious processes (e.g., pelvic inflammatory disease, tuberculosis), forms of contraception (e.g., intrauterine devices, birth control pills), trauma, foreign bodies, and endometriosis are also causes of adolescent menstrual dysfunction.[1,2,22] Except for those patients whose bleeding disorders are secondary to exogenous hormones, abnormal bleeding patterns may be associated with cyclic ovulatory menstruation in all of the other adolescents.

Ovulation Disturbances Occurring After Puberty

Whereas approximately 50% of the cycles during the first several years of menstruation are anovulatory, most adolescents do not develop menstrual dysfunction.[1] Inappropriate pubertal maturation of the positive estrogen-feedback mechanism and persistent anovulation (i.e., PCOD) are responsible for most of the ovulation disturbances that result in adolescent menstrual disorders. PCOD may occasionally develop after the establishment of normal regular cycles. Adolescents with persistent tonic LH

may have amenorrhea. More typically they have infrequent episodes of prolonged heavy bleeding (see Dawood and Marut, this symposium). Anovulation that occurs after puberty is also frequently caused by hypothalamic suppression with both negative and positive estrogen feedback systems usually affected. The causes that are responsible for similar pubertal aberrancy may be operative in these patients (see pubertal-related hypothalamic suppression). Anovulation related to hypothalamic suppression is often associated with hypogonadism and secondary amenorrhea. Sometimes these patients present with oligohypomenorrhea. Finally, ovulatory disturbances that develop after pubertal maturation have also been related to ovarian failure. CIOF and CCOF patients with menstrual function will eventually develop amenorrhea.[3] These patients may ovulate and have relatively regular menses for a number of years before follicular depletion. Anovulatory cycles and occasionally dysfunctional bleeding may develop during the last years of menstruation.[3]

Disorders of Pregnancy

Occasionally, pregnancy is diagnosed for adolescents who have never experienced menarche. Other individuals present with secondary amenorrhea. Abnormal bleeding associated with incomplete abortion, ectopic pregnancy, trophoblastic disease, or complication of late gestation may develop before pregnancy is suspected as well as after it has been diagnosed.

Significance of Adolescent Menstrual Disorders

Investigators have shown that the adolescent years constitute a period of time when girls are vulnerable to the development of menstrual dysfunctions.[6] The ability to restore normal menstrual function after correction of the specific cause appears also to be adversely affected by occurrence of such menstrual dysfunction during these years of neuroendocrine maturation.[3,23,24] Furthermore, a known association exists between adolescent menstrual disorders and poor outcome.[3,23] Morbidity, mortality, and a significant compromise of reproductive potential have been demonstrated for both pubertal and nonpubertal adolescent abnormalities. The large series of Reindollar et al. and Southam and Richart clearly point out the dramatic significance of adolescent menstrual disorders.[3,33]

Evaluation and Treatment of Adolescent Menstrual Disorders

Adolescent menstrual disorders have been presented as a spectrum of disease processes that includes pubertal and nonpubertal conditions. Whereas this distinction is helpful in separating and understanding general categories of patients, it is not as important in establishing guidelines for evaluation and treatment. Menstrual disorders are similar in both groups of adolescents. They consist of various forms of amenorrhea and abnormalities of bleeding. Subsequent discussion will center around an approach to the adolescent patient presenting with amenorrhea. The evaluation and management of bleeding abnormalities will not be discussed, because it is outlined in detail in articles by Spellacy, Hale, and Chang in this symposium.

Adolescent Amenorrhea: Evaluation and Management

Evaluation of the adolescent with amenorrhea has previously been described in detail.[4,8,25] The initial history-taking and physical examination will produce information that indicates the patient's developmental relationship to the normal sequence and timing of pubertal events. Linear and velocity growth charts should be utilized. A pubertal development chart can be constructed by superimposing the onset of pubertal landmarks onto a growth velocity chart.[25] The patient can be classified as hypogonadal or eugonadal within two visits. Breast development and the presence

of superficial cells in the vaginal smear or a progestin-provoked withdrawal bleed identifies eugonadal patients. Sexual infantilism or breast development not associated with superficial cells or withdrawal bleeding signifies a state of hypogonadism.

Hypogonadal patients can be further classified according to gonadotropin assays. Serum follicle-stimulating hormone and LH values will separate adolescents with ovarian failure from those with hypothalamic and pituitary abnormalities. In patients whose gonadotropins are repeatedly greater than 50 mIU/ml, identification of chromosomal incompetency and especially Y cell lines is mandatory. It requires the use of both a peripheral blood karyotype and a buccal smear. Occasionally it may be necessary to karyotype other tissues and to consider H-Y antigen assays so that one can be assured that these important forms of mosaicism have not been overlooked in the initial screening process. Hypogonadotropic adolescents must be screened with a prolactin assay, a sella roentgenogram and with thyroid studies in order to rule out pituitary tumors and subtle forms of hypothyroidism. Other endocrine screening tests and dynamic pituitary function studies are sometimes necessary for elucidation of specific disorders (e.g., Kallmann's syndrome, physiologic delay, congenital adrenal hyperplasia, and Cushing's syndrome). Patients diagnosed with reversible forms of hypogonadotropism should be reevaluated if spontaneous pubertal development does not occur after appropriate therapy. Girls with physiologic delay, diagnosed, either by exclusion or by gonadotropin-releasing factor (GnRF) function studies, should be followed through the completion of puberty. Reevaluation is also in order, if pubertal development does not progress to completion.

Eugonadal pubertal defects may become apparent at the time of the first visit. Anatomic abnormalities of the genital tract may be identified. A history of pelvic pain and the presence of an anterior midline mass on rectal examination will usually identify outlet obstruction either by a transverse vaginal septum or an imperforate hymen. Patients with androgen insensitivity syndrome can often be distinguished from individuals with congenital absence of the uterus and vagina because they usually lack pubic hair. A buccal smear stained for Y-chromatin is sufficient to confirm this suspicion. A laparoscopy is seldom necessary for any of these individuals. Pelvic ultrasonography is a sufficient test for identification of a hematocolpos or a hematometra in patients with outlet obstruction.[4] It can demonstrate the presence of ovaries and the absence or hypoplasia of müllerian elements in Rokitansky patients. The motivated adolescent with Rokitansky syndrome may further confirm the diagnosis by demonstrating a thermogenic basal body temperature rise during a 40-day time period. Eugonadal patients with a normal müllerian system have chronic anovulation, which is usually a form of PCOD. A prolactin assay and a sella roentgenogram should be performed to prove that the patients do not have a pituitary tumor instead.

Once the diagnosis is made, identification of anomalies associated with these aberrant processes is in order. Patients with CIOF and girls with müllerian anomalies should have an intravenous pyelography performed to diagnose renal abnormalities. Cardiovascular evaluation is also important. Turner syndrome patients with isochromosome for the long arm of X are at risk for Hashimoto's thyroiditis and need thyroid autoimmune and function surveillance. All CIOF patients should be kept under close surveillance for gonadal tumors in case a Y-cell line was overlooked in the standard cytogenetic studies. Abdominal flat-plate roentgenograms may identify calcification of such tumors. Oral glucose tolerance tests are sometimes performed on high-risk patients with Cushing's syndrome, growth-hormone-producing tumors and Turner's syndrome. Patients with unopposed estrogen should have endometrial biopsies per-

formed for the diagnosis of endometrial hyperplasia. Prolactin assays should be performed annually in all patients who do not subsequently develop spontaneous rhythmic menses.

Treatment of adolescent amenorrhea involves specific medical or surgical therapy in some patients (e.g., hypothyroidism, Cushing's syndrome, pituitary tumors, anatomic genital tract abnormalities). Treatment includes hormonal replacement in other adolescents and the avoidance of unopposed endogenous estrogen production in anovulatory girls. Near normal pubertal development should occur with appropriate medical treatment in the sexually infantile adolescents with endocrine or systemic disease processes. Immediate surgical therapy is necessary if outlet obstruction is present to prevent pelvic reflux and an associated aseptic inflammatory process or endometriosis. Needle aspiration should be reserved for incision and drainage so that a hematocolpos is not converted into a pyocolpos. Neovaginas can be created for patients with congenital absence of the uterus and vagina and testicular feminizing individuals by persistent coitus and the use of dilators. Surgical creation of a perineal pouch or artificial vagina is often necessary. Surgery includes gonadectomy in gonadal dysgenesis patients with Y cell lines and after pubertal development in individuals with androgen insensitivity. A combination of surgical and medical therapy may be necessary for adolescents with pituitary tumors. Estrogen replacement therapy is reserved for patients who will never spontaneously undergo pubertal development (e.g., ovarian failure, Kallmann's syndrome), adolescents whose gonads will be removed after puberty (e.g., androgen insensitivity), and temporarily for those girls whose sexual infantilism is detrimental to their emotional well-being (e.g., physiologic pubertal delay). Ethinyl estradiol (Estinyl), 20 mcg for the first 25 days of each month, and medroxyprogesterone acetate (Provera), 10 mg daily from the 15th through the 24th day of each cycle is sufficient. Monthly progestin withdrawal is considered essential in euestrogenic anovulatory patients so that endometrial hyperplasia can be avoided.[26] Occasionally oral contraceptives are utilized for control of hirsutism or contraception in these individuals. Ovulation induction with clomiphene citrate or menotropins may be necessary for achieving pregnancy in all onovulatory patients. Education and counseling are considered essential for all adolescents with amenorrhea.

Summary

The adolescent years present a vulnerable period of time during which menstrual abnormalities may arise. These abnormalities may be related to the maturational processes of the neuroendocrine, gonadal, and anatomic components of the reproductive system. Adolescent menstrual disorders may be totally unrelated to these maturational changes or may occur after puberty is completed. Manifestation of pubertal and nonpubertal conditions is variable. Most patients with aberrations of puberty present with amenorrhea, and most adolescents with disorders unrelated to puberty present with abnormal bleeding. However, amenorrhea and bleeding problems may occur in both groups of patients. All adolescents with menstrual disorders must be treated aggressively because of the known association with these conditions and poor outcome. Morbidity, mortality, and reduced reproductive potential have been demonstrated for all such adolescents.

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