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Frontiers in Gynecological Endocrinology

Volume 1
From Symptoms to Therapies

INTERNATIONAL SCHOOL OF GYNECOLOGICAL AND REPRODUCTIVE ENDOCRINOLOGY
THE EDUCATIONAL BRANCH OF ISGE

Springer

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Editors

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Volume 1: From Symptoms to Therapies

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Part I

Menstrual Dysfunction in Young Women

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Pathophysiology and Clinical Assessment of Primary Amenorrhea

1

George K. Creatsas and Maria Creatsas

A significant number of adolescents present menstrual irregularities during the first 2 gynecological years. The absence of menses is defined as amenorrhea and is classified as primary or secondary. Primary amenorrhea (PA) is the absence of menstruation in 16-year-old girls with developed secondary characteristics or in 14-year-old girls with no presence of secondary characteristics. Secondary amenorrhea is defined as the absence of menstrual period, for 6 months or more, in women who had previously normal or irregular menses [1–4, 11].

The classification of PA, in relation to the etiology of the disease, includes the uterovaginal aplasia or congenital uterovaginal anomalies with obstruction, endocrine disorders, chromosomal anomalies, as well as stress and psychological problems [5–7].

Uterovaginal anomalies with obstruction needs immediate repair following excision or/and reconstruction of the obstructive area (vaginal diaphragm or imperforate hymen).

Endocrine disorders presented with PA include cases of congenital adrenal hyperplasia, hypothalamic or pituitary amenorrhea, the premature ovarian failure, and the polycystic ovarian syndrome (PCOS) [8, 9].

PA due to chromosomal anomalies includes cases of gonadal dysgenesis, hermaphroditism, etc. (Fig.1.1) [1, 2]. Gonadal dysgenesis (streak gonads) may be present either with normal XX and XY karyotypes or abnormal karyotypes. The Turner syndrome (45X0) is usually diagnosed in early childhood because of the well-known phenotypic characteristics (short stature, webbed neck, and low hairline), and therefore many patients do not present for assessment of PA.

Stress and psychological problems are common causes of PA in young girls including cases of athletic amenorrhea.

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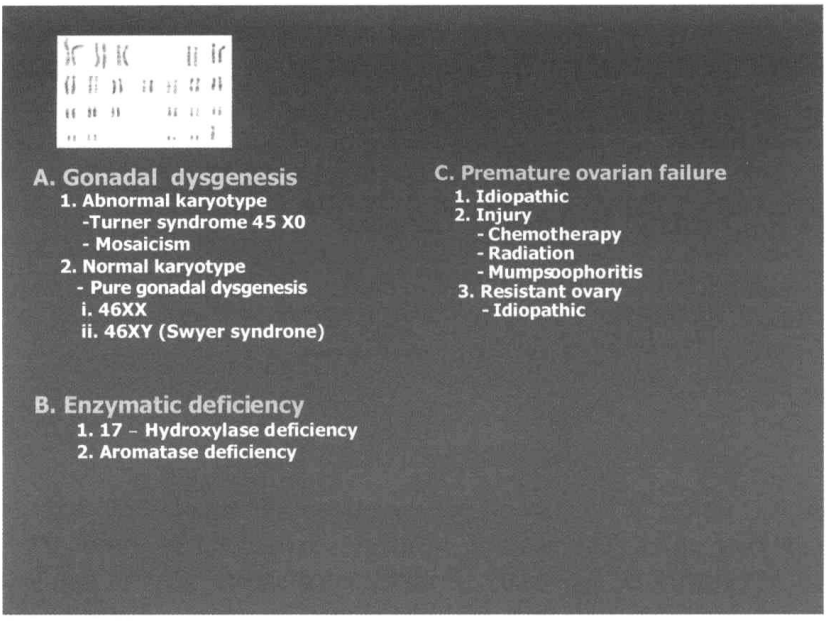

Fig. 1.1 Primary hypogonadism ([2], modified)

Another classification, including the relative incidence of PA causes, is presented in Table 1.1 [1–3, 5, 10–14].

Delayed puberty (DP) is the absence of onset of puberty by >2 SD, later than the average age of menarche. DP is also the absence of menstruation in 13–14-year-old girls who have no secondary sexual characteristic development. The causes of DP are (1) general: constitutional delay of growth and puberty, underweight, and other chronic diseases; (2) gonadal origin (hypergonadotropic hypogonadism): prodromal premature ovarian failure—karyotypically normal, Turner's syndrome, and pure gonadal dysgenesis; (3) autoimmune oophoritis; (4) 17,20-desmolase deficiency; (5) radiation or chemotherapy; (6) FSH receptor mutation; (7) galactosemia; (8) congenital hypogonadotropic hypogonadism; (9) gonadotropin deficiency; and (10) hypothalamic/pituitary lesions [3, 5, 11–14].

Patient's evaluation includes information taken by the clinical history, gynecological and physical examination, X-rays, ultrasonography (US), the hormonal profile of the patient, and rarely endoscopic evaluation (Fig. 1.2).

1.1 Case Presentations

1. Two girls 16 and 18 years old, presented with PA and periodic pelvic pain. The second girl also reported difficulty in sexual intercourse. Both had normal secondary sexual characteristics. The gynecological examination and the ultrasonography revealed *vaginal aplasia and atresia of the hymen, respectively.* Both were surgically treated.

Table 1.1 Classification and incidence of PA cases

• No breast development and low follicle-stimulating hormone (FSH) (30 % of PA cases)
– Constitutional delay (10 %)
– Prolactinomas (5 %)
– Kallmann syndrome (2 %)
– Other central nervous system lesions (3 %)
– Stress, weight loss, and anorexia (3 %)
– PCOS (3 %)
– Congenital adrenal hyperplasia (3 %)
– Other reasons (1 %)
• No breast development: high FSH (40 % of PA cases)
– 46 XX (15 %)
– 46 XY (5 %)
– Abnormal (20 %)
• Breast development (30 % of PA)
– Mullerian agenesis (10 %)
– Androgen insensitivity (9 %)
– Vaginal septum (2 %)
– Imperforate hymen (1 %)
– Constitutional delay (8 %)

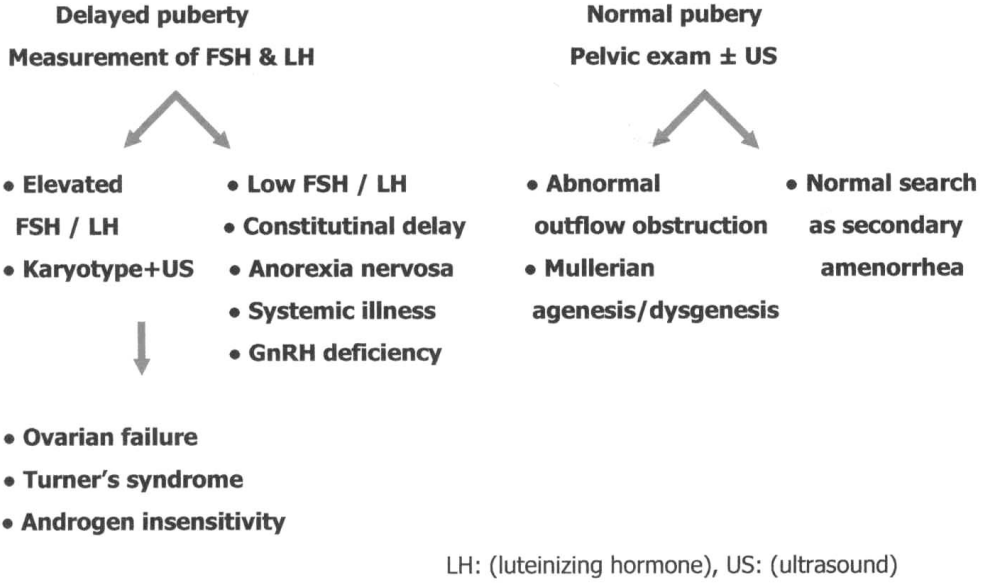

Fig. 1.2 Approach to adolescent PA [3, 4, 11, 13]

2. A young girl 16 years old presented with PA and short stature. The examination showed absence of secondary sexual characteristics. *The karyotype revealed XO—gonadal dysgenesis*. Management: hormone replacement therapy (HRT).
3. Adolescent 18.5 years old. Personal history: hypotonia, congenital cataract. Family history: Hashimoto's thyroiditis and endometrial polyp (mother). Height: 1.54 m (8th percentile), weight: 59 kg (58th percentile). Body mass

index (BMI): 24.8 kg/m^2. Breast: Tanner III, pubic hair: Tanner IV. US: small uterine volume. FSH: 46.6 mIU/mL, LH: 15.3 mIU/mL, 17 estradiol (E2): <9 pg/mL and anti-Mullerian hormone: 0.2 pmol/L. Karyotype: normal (46, XX). DEXA scan: osteoporosis. US evaluation: ovarian volume: 1.6 mL and 1.89 mL, respectively, endometrium not visible, uterus small. Diagnosis: primary ovarian insufficiency (POI) or failure (*The combination of POI, congenital cataract and hypotonia poses suspicion of Marinesco–Sjogren syndrome, a rare genetic disease*). Management: HRT, calcium plus vitamin D supplement. Recommendation: light weight lifting exercise.

4. Adolescent 16 years old. Free family history. Athlete. Exercise >2 h/day. Height: 1.56 m, weight: 39 kg, BMI: 16.02 kg/m^2. Gynecological and physical examination: Breast: Tanner V, pubic hair: Tanner V. Gynecological examination: normal. Laboratory tests: normal. PRL, testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEA-S), 17-OH progesterone (17-OH-prog), sex hormone binding globulin (SHBG), thyroid-stimulating hormone (TSH): normal. FSH: 0.3 mIU/mL, LH: 0.7 mIU/mL, E2: 12.3 pg/mL. Luteinizing hormone releasing test (LH-RH test): positive. DEXA scan: osteopenia. US evaluation: ovarian volume: 3 mL and 4 mL, respectively, endometrium: 1 mm, uterus: small. *Diagnosis*: *functional hypothalamic amenorrhea*. Management: HRT. Consultation: to improve body weight.
5. Adolescent 14 years old. Height: 1.49 m (5th percentile), weight: 50 kg (50th percentile), BMI: 22.52 kg/m^2, breast: Tanner I, pubic hair: Tanner I. Gynecological examination: normal. PRL, DHEA-S, 17-OH-progesterone, SHBG, TSH: normal. FSH: 1 mIU/mL, LH: <0.5 mIU/mL, E2: 10 pg/mL, LH-RH test: poor response. Magnetic resonance imaging (MRI)—pituitary: normal. US evaluation: small uterine and ovarian volume. *Diagnosis*: *Idiopathic hypogonadotropic hypogonadism, GnRH deficiency, and GnRH insensitivity*. Anosmia not present. Management: HRT.
6. Adolescent 15 years old. Free family and personal history. Height: 1.76 m, weight: 60 kg, BMI: 19.3 kg/m^2. Breast: Tanner III, pubic hair: Tanner IV, gynecological exam: normal. FSH, LH, E2, Testo, DHEA-S, 17-OH-Prog, SHBG, TSH: normal. PRL (0′, 30′): 50 ng/mL and 45 ng/mL. MRI: pituitary microadenoma. US evaluation: ovarian volume: 5.3 mL and 4.15 m, respectively, endometrium: 7 mm. *Diagnosis*: *hypophyseal microadenoma*. Management: bromocriptine 1.25 mg × 2.
7. Adolescent 16 years old. *Athlete*. Gynecological and physical examination: Normal. US evaluation: atrophic endometrium. FSH, LH: 10.5 mIU and 15.3 mIU/mL, respectively. E_2: 5.3 pg/mL. Treatment COCs.
8. Adolescent 15 years old. Low BMI <18 kg/m^2, gynecological examination: normal, physical examination: No acne or hirsutism, breast: Tanner II, hormonal evaluation: FSH: 16.3 mIU/mL, LH: 18.6 mIU/mL, PRL: normal, E2: 5.6 pg/mL. *Diagnosis: anorexia nervosa*. Management: psychiatric consultation and COCs.

Each patient should be individually treated, avoiding unnecessary tests and overtreatment. In cases presented with obstruction of the genital route immediate

surgery is advised. If hormonal treatment is scheduled, the low-dose, new-generation 17β-estradiol COCs are recommended. Explanation, reassurance, and emotional support are necessary tools for the management of the disease, as in many cases treatment is advisable for a long period of time.

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