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Primary and Secondary Amenorrhea

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1. Introduction

Puberty represents a particular period of life characterized by hormonal changes and physical and psychological modifications leading children from childhood to adolescence. During this period, menarche represents the most important event in females. Age of menarche is different among populations and has been recognized as an useful marker of socio-economic status, as well as dietary and environmental patterns (Chumlea et al., 2003; Swenson & Havens, 1987; Thomas et al., 2001). Generally, the first menstrual cycle takes place between 12 and 13 years of age, with 98% of girls having menarche by 15 years of age (Diaz, 2006). The normal range for menstrual cycles is between 21 and 45 days, with flow length varying from 2 to 7 days (Flug et al., 1984; World Health Organization Task Force on Adolescent Reproductive Health, 1986). During the first 2 years after menarche, menses length is often abnormal due to immaturity of the hypothalamic-pituitary-ovarian axis (Diaz, 2006); however, cycles range can be regular also in the first gynecologic year (Flug et al., 1984; World Health Organization Task Force on Adolescent Reproductive Health, 1986). Amenorrhea is defined as the complete absence or anomalous cessation of menstrual cycles in females during reproductive years. Just in three situations amenorrhea is considered physiological: during pregnancy, lactation and menopause. In all other situations, amenorrhea can be due to many pathological conditions and merits a careful assessment. Amenorrhea is classified as primary and secondary according to its occurrence before or after menarche, respectively (The Practice Committee of American Society for Reproductive Medicine, 2008). Amenorrhea is defined primary when menarche does not occur by the age of 16 years in a girl with complete secondary sexual development, or by the age of 14 years in a girl without secondary sexual development. Amenorrhea is defined secondary when menstrual cycles disappear for 6 consecutive months in a girl with irregular menses or for 3 consecutive months in a girl with regular menses (Deligeoroglou et al., 2010). According to the American Society for Reproductive Medicine, currently in literature many causes of amenorrhea have been recognized (The Practice Committee of American Society for Reproductive Medicine, 2008), including:

- anatomic defects of the genital tract
- hypothalamic/pituitary causes
- ovary insufficiency
- endocrinopathies
- chronic oligo- or anovulation

Treatment of amenorrhea depends on the aetiology and consists of specific diagnostic and therapeutic procedures. The aim of the present chapter is to summarize the most important and recent findings regarding primary and secondary amenorrhea.

2. Epidemiology of amenorrhea

It has been estimated that amenorrhea not due to physiological conditions has a prevalence ranging from 3% to 4% (Bachmann & Kemmann, 1982; Pettersson et al., 1973). The most frequent causes of amenorrhea are four: hypothalamic amenorrhea, hyperprolactinemia, ovarian failure, and polycystic ovary syndrome (The Practice Committee of American Society for Reproductive Medicine, 2008).

3. Causes of primary and secondary amenorrhea

The main causes of primary and secondary amenorrhea include anatomic defects of the genital tract, hypothalamic/pituitary causes, ovary insufficiency, endocrinopathies and chronic oligo- or anovulation (Table 1).

Anatomic genital defects	Hypothalamic causes	Pituitary causes	Ovary insufficiency	Endocrine diseases	Chronic oligo- or anovulation
Vaginal agenesis	Functional hypothalamic amenorrhea	Prolactinomas	Gonadal agenesis	Adrenal diseases	Polycystic ovary syndrome
Transverse vaginal septum	<ul style="list-style-type: none">• Psychogenic stress• Intensive physical activity• Nutritional disorders	Tumours secreting	Gonadal dysgenesis	<ul style="list-style-type: none">• 17αHydroxylase deficiency• 17,20Lyase deficiency• Aromatase deficiency	
Imperforate hymen	Isolated gonadotropin deficit	<ul style="list-style-type: none">• FSH• LH• GH• TSH• ACTH	Premature ovarian failure	Thyropathies	
Cervical agenesis or dysgenesis	<ul style="list-style-type: none">• Kallman syndrome• Idiopathic hypogonadotropic hypogonadism	Inflammatory and infiltrative disorders	Enzymatic deficits	Poorly controlled diabetes	
Endometrial hypoplasia or aplasia	Chronic diseases	Empty sella		Ovarian tumours	
Intrauterine synechiae	Infections	Panhypopituitarism			
Mayer-Rokitansky-Küster-Hauser syndrome	Tumours	Sheehan syndrome			
Androgen insensitivity syndrome					

Table 1. Etiopathology of primary and secondary amenorrhea

3.1 Anatomic defects of the genital tract

Anatomic genital defects include vaginal agenesis, transverse vaginal septum, imperforate hymen, cervical agenesis or dysgenesis, endometrial hypoplasia or aplasia, Mayer-Rokitansky-Küster-Hauser syndrome, and androgen insensitivity syndrome.

Vaginal agenesis should be suspected in all girls with primary amenorrhea suffering frequent abdominal and pelvic pain due to the anatomic barrier which obstacles blood flow. Furthermore, the amassing of blood in the uterus (hematometra) can provoke retrograde menstruation leading to the development of adhesences and endometriosis (The Practice Committee of American Society for Reproductive Medicine, 2008).

Transverse vaginal septum represents a congenital vaginal obstruction. There are two variety of transverse septum: partial and total; only the total variety is responsible for amenorrhea (Deligeoroglou et al., 2010). The obstruction can be located in the inferior (16%), central

(40%) or superior (46%) vaginal portion (Rock et al., 1982). Similarly to vaginal agenesis, also this defect is responsible for recurring abdominal and pelvic pain coming from blood accumulation in the uterus and vagina (hematocolpos) (Deligeoroglou et al., 2010).

Imperforate hymen has been estimated having an incidence of 1/1000 (Deligeoroglou et al., 2010). The diagnosis is uncommon during infancy because this condition is usually asymptomatic, although in rare cases neonates can suffer marked abdominal enlargement. More commonly, girls with amenorrhea will receive diagnosis of imperforate hymen after having abdominal pain, hematometra or hematocolpos during the pubertal period (Ameh et al., 2011).

Cervical anatomic defects represent another important cause of primary amenorrhea. There are two types of cervical abnormality: agenesis and dysgenesis. Both these defects can be associated with a normal development of the vagina. In details, while in the dysgenesis a partial cervical development is observed, in the agenesis patients are likely to present earlier with a history of primary amenorrhea and severe lower abdominal pain occurring at irregular intervals (Deligeoroglou et al., 2010).

Endometrial hypoplasia or aplasia represent the partial development or the congenital absence of endometrium.

Intrauterine synechiae, also named Ashermann syndrome, is a condition very unusual among adolescents, while represents the most frequent cause of secondary amenorrhea in women of reproductive age. In fact, abortion, postpartum curettage for haemorrhage, or postpartum endometritis can provoke the development of intrauterine synechiae leading to cessation of menses (Deligeoroglou et al., 2010).

Mayer-Rokitansky-Küster-Hauser syndrome is a congenital defect of the genital tract recognized as the more common cause of amenorrhea after gonadal dysgenesis, having an incidence of 1/5.000 (Fedele et al., 1996). This syndrome is also called “Müllerian agenesis” because is characterized by absence or hypoplasia of the Müllerian ducts derivatives. In fact, the main features of Mayer-Rokitansky-Küster-Hauser syndrome are the following: normal ovaries, anomalies of the uterine development ranging from absence to rudimentary residues of uterus and aplasia of the upper two thirds of the vagina. Furthermore, affected women show the development of secondary sexual characteristics with a female 46, XX karyotype (Bean et al., 2009; Morcel et al., 2007). There are two types of Mayer-Rokitansky-Küster-Hauser syndrome (Morcel et al., 2007): type 1 represents the isolated variety, while type 2 is associated with several organic abnormalities involving upper urinary tract (40% of cases), skeleton (10-12% of cases) (American College of Obstetricians and Gynecologist Committee on Adolescent Health Care, 2006), auditory system (10-25% of cases) (Cremers et al., 1995; Strübbe et al., 1994), and more rarely heart. The aetiology of Mayer-Rokitansky-Küster-Hauser syndrome is still uncertain: although at the beginning it was supposed that this syndrome was the result of sporadic abnormality, it has been recently assumed a genetic background on the basis of a growing amount of familial cases (Morcel et al., 2007). Clinically, the most common presentation is characterized by primary amenorrhea in adolescents with normal secondary female characteristics. Just in few cases, where patients have rudimentary residues of uterus with a normal endometrial function, there is a history of recurring severe lower abdominal pain; furthermore, some adolescents can suffer psychological distress from unsuccessful sexual life (Deligeoroglou et al., 2010). Endocrine evaluation shows normal levels of basal plasma gonadotropin and sex steroid (estradiol), without biochemical signs of androgen excess (Carranza-Lira et al., 1999).

Androgen insensitivity syndrome is a rare X-linked recessive androgen receptor defect having an incidence of 1/20.000-99.000 (Boehmer et al., 2001; Grumbach et al., 2003). The gene responsible for this condition has been mapped to chromosome Xq11-12 (Brinkmann et al., 1989), and about 30% of mutations are the result of sporadic anomalies (Hughes & Deeb, 2006). Nowadays, three variants of androgen insensitivity syndrome have been recognized based on the inactivity of androgen receptor: complete androgen insensitivity syndrome, with a phenotype characterized by normal female external genitalia; mild androgen insensitivity syndrome, with a phenotype characterized by normal male external genitalia; partial androgen insensitivity syndrome, with a phenotype characterized by partial masculinization of external genitalia (Hughes & Deeb, 2006). In details, complete androgen insensitivity syndrome has an incidence of 1/60.000 (Jorgensen et al., 2010) and is characterized by congenital agenesis of the uterus and absent or rudimentary vagina in women showing normal development of secondary sexual characteristics in presence of a 46,XY karyotype (Oakes et al., 2008). In addition, these patients present cryptorchidism, with gonads situated in the inguinal canal or abdominal cavity; testicles are functional and produce normal testosterone and dihydrotestosterone levels. Although usually patients affected by complete androgen insensitivity syndrome present primary amenorrhea together with scarce or absent pubic and axillary hair, girls can also present an inguinal hernia during infancy or childhood. In addition, since the incidence rate of complete androgen insensitivity syndrome has been reported to be 1%-2% in subjects with inguinal hernia, some authors have suggested to consider a karyotype in every girl with inguinal masses (Hughes & Deeb, 2006; Sarpel, 2005). The incidence of testes malignancy has been estimated to be 22%, although it is infrequent in subjects younger than 20 years of age (Manuel et al., 1976). Usually, endocrine evaluation shows high levels of basal plasma testosterone and luteinizing hormone, frequently in association to high levels of estradiol (Hughes & Deeb, 2006).

3.2 Hypothalamic causes

Hypothalamic diseases represent the most frequent cause of amenorrhea in adolescents (Deligeoroglou et al., 2010). In fact, girls with disorders of the hypothalamus are susceptible to the development of chronic anovulation, due to an insufficient secretion of gonadotropin-releasing hormone leading to low levels of basal plasma gonadotropins and estradiol. However, after stimulation with exogenous gonadotropin-releasing hormone, the secretion of gonadotropins is in the physiological range. Hypothalamic amenorrhea has frequently a dysfunctional origin, although in rare cases it can be due to other conditions including the isolated deficit of gonadotropins, chronic diseases, infections, and tumours (Deligeoroglou et al., 2010).

Dysfunctional causes of hypothalamic amenorrhea include psychogenic stress, excessive physical activity and nutritional disorders. Actually the precise mechanisms through which excessive stress and weight loss influence negatively gonadotropin-releasing hormone secretion are still uncertain (Golden & Carlson, 2008). However, in these girls the impaired production of gonadotropin-releasing hormone may have several implications on luteinizing hormone secretion, coming from absent or reduced pulses to normal or elevated pulses (Deligeoroglou et al., 2010).

Psychogenic stress seems to induce the secretion of high levels of corticotrophin-releasing hormone, which inhibits gonadotropin-releasing hormone pulses (Deligeoroglou et al., 2010).

Also girls performing excessive physical activity are prone to present hypothalamic amenorrhea and short luteine phases. These abnormalities are induced by the strenuous physical activity and the restricted caloric intake requested to maintain leanness. In fact, athletes show frequently a strong disproportion among nutritional intake and real energy expenditure, especially in disciplines where low body weight for performance and aesthetics is needed (Golden & Carlson, 2008). In particular, in athletes there is a risk of amenorrhea three times higher than in general population, with predominance between long-distance runners (Warren & Goodman, 2003). Interestingly, a peculiar condition called the "female athlete triad" has been recognized as the result of an inadequate caloric intake. This condition includes amenorrhea, eating disorders, and osteoporosis, and athletes can present one or more components of the triad. Therefore, all these alterations should be screened in order to perform an early diagnosis and to improve quality life of women involved in competitive sports (Mendelsohn & Warren, 2010).

Eating disorders represent another common cause of functional hypothalamic amenorrhea. Unfortunately, these disorders are increasing worldwide and the effects on reproduction are more than negative. In particular, in females the reproductive axis is strongly related to the nutritional status and is highly responsive to external stimuli due to the high energy expenditure during pregnancy and lactation. Therefore, in condition of undernutrition, the female reproduction can be interrupted and continued in better periods to preserve vital functions. In fact, a decrease of 10%-15% in normal body weight seems to be able to cause amenorrhea (European Society of Human Reproduction and Embryology Capri Workshop Group, 2006). Up to now, it has been estimated that about 1%-5% of women are affected by the "weight related amenorrhea" (Laughlin et al., 1998). Although the responsible mechanisms are not entirely clear, it has been proposed a minimal body weight of 47 kg for the onset or maintenance of menstrual cycles (Frisch & McArthur, 1974; Frisch, 1987). Among the most important eating disorders, anorexia nervosa and bulimia nervosa affect up to 5% of women of reproductive age causing amenorrhea and infertility (European Society of Human Reproduction and Embryology Capri Workshop Group, 2006). In details, anorexia nervosa has been defined as body weight less than 85% of expected weight or body mass index less than 17.5 kg/m², caloric restriction, fear of weight gain and an impaired perception of body image. Bulimia nervosa has been defined as binge eating followed by vomiting, intense physical activity and other compensatory actions (Becker et al., 1999). Approximately 15%-30% of girls affected by anorexia nervosa present amenorrhea (Miller et al., 2005; Watson & Andersen, 2003), while girls with bulimia may present oligoamenorrhea also in presence of a normal body mass index (European Society of Human Reproduction and Embryology Capri Workshop Group, 2006). The mechanisms underlying preservation or discontinuation of the physiological neuroendocrine regulation of ovarian function in girls with anorexia or bulimia are still unknown. However, it has been supposed the occurrence of impaired gonadotropin-releasing hormone secretion with alterations in dopaminergic and opioid systems. Recently, low levels of luteinizing hormone and estradiol have been demonstrated in women with hypothalamic amenorrhea, together with gonadotropins pulses insufficient to protract the development of follicles until ovulation (Welt et al., 2004). Furthermore, the lately discovered leptin, one of the most important adipose derived hormones which plays a key role in regulating energy intake and expenditure, seems to be strictly involved into the mediation of reproductive axis (Brennan & Mantzoros, 2006). In fact, low levels of leptin have been reported in women with hypothalamic amenorrhea (Welt et al., 2004). Although it is still unclear if leptin has direct

hypothalamic effects or augments the metabolic substrates availability, it is probable that this hormone mediates both these effects.

Isolated deficit of gonadotropins represents a rare cause of hypothalamic amenorrhea, including the Kallman syndrome and the idiopathic hypogonadotropic hypogonadism.

The *Kallman syndrome* represents a genetic heterogeneous developmental disease characterized by gonadotropin-releasing hormone deficiency and defective development of olfactory nerves, bulbs and sulci, with an incidence of 1/40000 girls and 1:8000 boys (Dodé & Hardelin, 2009). This disorder can be autosomal-dominant with incomplete penetrance, autosomal-recessive, X-linked recessive, or can have an oligogenic/digenic inheritance pattern (Dodé & Hardelin, 2009; Jana & Kumar, 2010). Up to now, five genes have been implicated into the pathogenesis of the disease: KAL1 (Franco et al., 1991; Hardelin et al., 1992), FGFR1 (Dodé et al., 2003), FGF8 (Falardeau et al., 2008), PROKR2 and PROK2 (Dodé et al., 2006). However, a smaller amount (around 30%) of affected subjects present mutations in any of these genes. Affected women present hypogonadotropic hypogonadism, amenorrhea and absence of secondary sexual characteristics together with hyposmia or anosmia (Seminara et al., 1998). Generally, the diagnosis is performed during adolescence on the basis of reproductive and olfactory disorders. However, patients with Kallman syndrome can present further characteristics as well as mental retardation, cerebellar ataxia, cardiovascular anomalies, cranio-facial alterations, renal agenesis, hearing impairment, and abnormal visual spatial alterations (Quinton et al., 2001).

The *Idiopathic Hypogonadotropic Hypogonadism* is a rare genetic disease caused by a deficiency of hypothalamic gonadotropin-releasing hormone release; however, this disorder can be also caused by an impaired action of gonadotropin-releasing hormone on gonadotropes cells in the pituitary (Bianco & Kaiser, 2009). Idiopathic hypogonadotropic hypogonadism has been suggested to be the result of isolated functional anomalies of the neuroendocrine signals for release of gonadotropin-releasing hormone or gonadotropins. In fact, in these subjects no developmental or anatomical alterations of the hypothalamus-pituitary-gonadotropin axis have been described; the affected patients present a normal olfaction in presence of a phenotype deriving from pre- and postnatal gonadotropins and sex steroid deficiency (Brioude et al., 2010). Hypogonadotropic hypogonadism may be also due to mutations in gonadotropin-releasing hormone receptor genes (Layman et al., 2001).

Active, uncontrolled or untreated chronic diseases responsible for hypothalamic amenorrhea include malabsorption, acquired immune deficiency syndrome, diabetes, and kidney disorders (The Practice Committee of American Society for Reproductive Medicine, 2008).

Infections include meningitis, encephalitis, syphilis, and tuberculosis (The Practice Committee of American Society for Reproductive Medicine, 2008).

Possible *tumours* causing hypothalamic amenorrhea include craniopharyngioma, Langerhans cell histiocytosis, hamartoma, germinoma, endodermal sinus tumor, teratoma, metastatic carcinoma (The Practice Committee of American Society for Reproductive Medicine, 2008).

3.3 Pituitary causes

The main pituitary disorders responsible for amenorrhea include tumours, inflammatory/infiltrative disorders, panhypopituitarism and empty sella syndrome (Deligeoroglou et al., 2010).

Possible pituitary *tumours* causing amenorrhea include prolactinomas, and other tumours secreting hormones such as adrenocorticotrophic hormone, thyrotropin-stimulating hormone, growth hormone, gonadotropins (luteinizing hormone, follicle-stimulating hormone).

Hyperprolactinemia represents the most frequent cause of amenorrhea of pituitary origin, being responsible for 1% of cases of primary amenorrhea (Patel & Bamigboye, 2007). In fact, high levels of prolactin suppress hypothalamic gonadotropin-releasing hormone release determining a reduction of estradiol levels. It is fundamental to recognize the origin of prolactin hypersecretion. In fact, in women with hyperprolactinemia it has been estimated a prevalence of pituitary tumours of approximately 50-60% (Brenner et al., 1985). However, it is important to rule out also any other cause responsible for rise in prolactin levels, including macroprolactinemia, hypothyroidism, stress, antipsychotics and masses reducing dopamine release; in fact, prolactin pituitary release is principally inhibited by dopamine (Asa & Ezzat, 2009). Furthermore, in women with mild prolactin increase it is common to find altered inhibiting systems (Deligeoroglou et al., 2010).

Among the pituitary disorders responsible for amenorrhea, Sheehan's syndrome represents a form of hypopituitarism resulting from ischemic pituitary necrosis caused by severe postpartum haemorrhage, especially in developing countries (Kelestimur, 2003). Up to now the pathogenesis of this syndrome is still unknown although it has been proposed that during pregnancy the enlarged pituitary gland, small sella dimension, autoimmunity and disseminated intravascular coagulopathy could play a pivotal role. A variety of signs and symptoms have been described in women affected by Sheehan's syndrome, including tiredness, weakness, agalactia, amenorrhea and partial to total hypopituitarism. The majority of affected women show empty sella on computer assisted tomography or magnetic resonance imaging. It has been recommended to consider primary empty sella syndrome and lymphocytic hypophysitis among differential diagnosis.

Systemic inflammatory/infiltrative diseases, like hemocromatosis and sarcoidosis, represent less frequent pituitary causes of amenorrhea (Deligeoroglou et al., 2010).

3.4 Ovary insufficiency

Ovary insufficiency includes a wide spectrum of diseases characterized by hypergonadotropic hypogonadism due to an insufficient production of sex steroids in presence of high follicle-stimulating hormone and luteinizing hormone levels. Hypergonadotropic hypogonadism can be due to several conditions including gonadal agenesis or dysgenesis, premature ovarian failure and enzymatic deficits; each of these conditions includes many other disorders (Deligeoroglou et al., 2010).

Gonadal dysgenesis includes those situations characterized by anomalous development causing streak gonads. These conditions can take place in patients with abnormal as well as normal karyotype.

Turner Syndrome represents the most frequent chromosomal abnormality responsible for gonadal dysgenesis, having an incidence of approximately 1/2500 live female births (Nielsen & Wohler, 1991). The diagnosis of Turner syndrome is performed on the basis of typical phenotypic characteristics in phenotypic girls females (Turner, 1938; Ullrich, 1930) having partial or total absence of one X chromosome, with or without mosaicisms (Ferguson-Smith, 1965). The key features of Turner syndrome are webbing of the neck, misshapen ears, broad chest, widely spaced nipples, cubitus valgus, cardiac malformations, renal diseases and short stature (Morgan, 2007). Furthermore, one of the most frequent characteristics of Turner syndrome is the lack of pubertal development. In fact, although the ovaries develop normally, they degenerate during intrauterine life and infancy, and more than 90% of females will present gonadal failure (Bondy et al., 2007). However, approximately 30% of these patients will present natural pubertal development (Boechat et

al., 1996; Pasquino et al., 1997), and menses will occur in 2-5% of girls having 46,XX/45,X mosaicism due to a normal oocytes amount; furthermore, about 5% of girls with Turner syndrome will present spontaneous pregnancy (Hovatta, 1999).

Gonadal dysgenesis can happen also in subjects with 46,XY or 46,XX karyotype. In particular, subjects with 46,XY karyotype are known to be affected by Swyer syndrome. These subjects present female external or ambiguous genitalia with normal development of vagina and uterus due to the absent or inadequate production of anti-Müllerian hormone and testosterone (Barbaro et al., 2007). It has been estimated that approximately 25% of subjects with diagnosis of Swyer syndrome develop gonadal tumours; for this reason, it is necessary to remove gonads at the diagnosis (Manuel et al., 1976).

Premature ovarian failure refers to primary ovarian defect occurring in women younger than 40 years of age. This condition can be responsible for primary amenorrhea, or secondary amenorrhea when there is premature oocytes depletion and/or reduced folliculogenesis (Santoro, 2003; Timmreck & Reindollar, 2003). It has been estimated a premature ovarian failure incidence of approximately 1/1000 women under the age of 30 years, 1/250 around the age of 35 years and 1/100 at the age of 40 years (Timmreck & Reindollar, 2003). Furthermore, it has been described a familial form of premature ovarian failure which accounts for 4-31% of cases (Conway et al., 1996; Cramer et al., 1995; Torgerson et al., 1997). Premature ovarian failure can have different causes: iatrogenic after surgery or treatment of cancer (Santoro, 2003), autoimmune, infective (mumps oophoritis, cytomegalovirus, herpes zoster) and metabolic (galactosemia) (Beck-Peccoz & Persani, 2006). However, the major part of all cases of premature ovarian failure is idiopathic, and a genetic aetiology has been suggested on the basis of candidate genes found in some families (Van Kasteren & Schoemaker, 1999). In fact, disorders of the X chromosome have been found to be related with premature ovarian failure in women with Turner syndrome, partial X deletions or translocation, or presence of an extra X chromosome (Goswami & Conway, 2007). In particular two genes, respectively POF1, localised on Xq21.3-Xq27, and POF2, localised on Xq13.3-q21.1, have been found to be associated with chromosomal anomalies responsible for POF development (Beck-Peccoz & Persani, 2006). However, numerous other genes have been implicated in females with premature ovarian failure, including BMP15, FMR1, FMR2, LHR, FSHR, INHA, FOXL2, FOXO3, ERa, SF1, ERb and CYP19A1 genes (Cordts et al., 2011). Clinically, the presentation is characterized by primary amenorrhea in adolescents without secondary female characteristics, or disappearance of menses in women with normal pubertal development, palpitations, flushes, tiredness and depression. Endocrine evaluation shows high basal gonadotropins levels and low estradiol and inhibin values (Beck-Peccoz & Persani, 2006).

3.5 Endocrinopathies

The spectrum of endocrinopathies is broad and includes adrenal diseases (including 17- α -Hydroxylase deficiency, 17,20-Lyase deficiency, aromatase deficiency), thyropathies, poorly controlled diabetes and ovarian disorders (Deligeoroglou et al., 2010).

3.6 Chronic oligo- or anovulation

Chronic oligo- or anovulation refers to *polycystic ovary syndrome*, an heterogeneous endocrinopathy characterized by a broad spectrum of clinical and biochemical features. In fact, this complex disorder requires the presence of several phenotypes, including

hyperandrogenism and/or hyperandrogenemia, and normoovulation or oligoovulation with or without polycystic ovaries (Azziz et al., 2006). This phenomenon has been described in at least 6% of women during the reproductive years (Rosenfield, 2007). However, it has been recently reported that using different diagnostic criteria the prevalence of polycystic ovary syndrome was approximately 18% (March et al., 2010). The etiopathogenesis of polycystic ovary syndrome is still unclear although it seems a combination of genetic and environmental factors. In particular, two conditions have been recognized as playing a major role: insulin resistance with hyperinsulinemia and hyperandrogenism (Teede et al., 2010). In addition, hypothalamic/pituitary disorders, ovarian disorders failure and obesity are implicated in the pathogenesis of polycystic ovary syndrome (Doi et al., 2005; Legro & Strauss, 2002). This syndrome becomes symptomatic already during adolescence (Azziz et al., 2004; Franks et al., 2006) with psychological, metabolic and reproductive symptoms, including depression, anxiety (Deeks et al., 2010), hirsutism, oligoamenorrhea or amenorrhoea, infertility (Boomsma et al., 2006), metabolic syndrome, type 2 diabetes and cardiovascular diseases (Apridonidze et al., 2005; Legro et al., 1999). In particular, 70% to 80% of women with polycystic ovary syndrome show oligoamenorrhea or amenorrhoea caused by chronic oligo-ovulation/anovulation (Brassard et al., 2008; Teede et al., 2010).

4. The assessment and investigation of amenorrhea

According to the American Society for Reproductive Medicine, the investigation of amenorrheic girls should be started by 15 years of age in girls with normal secondary sexual development as well as in girls presenting thelarche before 10 years of age but without menses within 5 years, and in girls without secondary sexual development until 13 years of age (The Practice Committee of American Society for Reproductive Medicine, 2008). Diagnostic features of primary and secondary amenorrhea are reported in Table 2.

4.1 Medical history

The first step in the evaluation of amenorrheic girl should be based on the *patient and family history* (Master-Hunter & Heiman, 2006). The physician should conduct a complete patient history including growth and pubertal pattern, congenital anomalies, preceding or existing chronic or autoimmune diseases, anosmia, galactorrhea, recurring abdominal and/or pelvic pain, headache, vomiting, nausea, visual changes or double vision, preceding central nervous system radiation or chemotherapy and/or pelvic radiation, legal or illegal drug utilize, psychological distress, nutritional and exercise pattern, menarche, menstrual history, sexual life. In particular, date of menarche and records of menses should be extremely accurate. The family history should include growth and pubertal pattern, menarche and menstrual history of mothers and sisters, infertility, genetic disorders, chronic or autoimmune diseases, disorders or signs of androgen excess, hypo/hypertrichosis of pubis.

4.2 Physical examination

A complete *physical evaluation* should be carefully performed (Master-Hunter & Heiman, 2006), including anthropometric measurements [height, height standard deviation score, weight, body mass index, body mass index standard deviation score, growth velocity], staging of pubertal development according to the criteria of Marshall and Tanner (Marshall & Tanner, 1969), signs of androgen excess (acne, hirsutism, deepening of the voice), signs or

	Clinical aspects	Laboratoristic features	Instrumental procedures
Anatomic genital defects	-Frequent abdominal and pelvic pain -Hematometra/hematocolpos -Normal secondary female characteristics, except in: <ul style="list-style-type: none">• mild androgen insensitivity syndrome (male external genitalia)• partial androgen insensitivity syndrome (partial masculinization of external genitalia) -Scarce or absent pubic/axillary hair, inguinal masses (complete androgen insensitivity syndrome)	-In Mayer-Rokitansky- Küster- Hauser syndrome: <ul style="list-style-type: none">• normal levels of basal gonadotropins and sex steroids• no hyperandrogenism• 46,XX karyotype -In complete androgen insensitivity syndrome: <ul style="list-style-type: none">• high levels of basal LH and testosterone, frequently with high levels of estradiol• 46,XY karyotype	-Pelvic ultrasonography and magnetic resonance imaging: <ul style="list-style-type: none">• anatomic defects -Hysteroscopy or salpingogram: <ul style="list-style-type: none">• intrauterine synechiae
Hypothalamic causes	-Low body weight (functional hypothalamic amenorrhea) -Absence of secondary sexual characteristics, hyposmia/anosmia (Kallman syndrome) -Normal olfaction with a phenotype deriving from pre- and postnatal gonadotropins and sex steroid deficiency (idiopathic hypogonadotropic hypogonadism)	-Insufficient secretion of GnRH leading to low levels of basal gonadotropins and estradiol -After stimulation with exogenous GnRH, gonadotropins secretion is in the physiological range -Low levels of leptin	Magnetic resonance imaging: <ul style="list-style-type: none">• normal or altered anatomy/ development of the hypothalamus
Pituitary causes	-Galactorrhea (prolactinomas)	-High levels of prolactin -Suppression of GnRH release -Reduction of estradiol levels	Magnetic resonance imaging: <ul style="list-style-type: none">• empty sella• normal or altered anatomy/ development of the pituitary gland
Ovary insufficiency	-Lack of pubertal development, webbing of the neck, misshapen ears, widely spaced nipples, cardiac malformations, renal diseases, short stature (Turner syndrome) -Female external or ambiguous genitalia with normal vagina and uterus (Swyer syndrome) -Primary amenorrhea without secondary characteristics, or secondary amenorrhea in girls with normal puberty (ovarian failure)	-High FSH and LH levels -Estrogen deficiency -Low inhibin levels -Karyotype: <ul style="list-style-type: none">• 46,XX• 45,X• 46,XX/45,X mosaicism• 46,XY	Pelvic ultrasonography: <ul style="list-style-type: none">• streak gonads• absent or reduced follicular activity
Chronic oligo- or anovulation	-Signs of androgen excess: acne, hirsutism, deepening of the voice -Obesity, metabolic syndrome, type 2 diabetes, cardiovascular diseases -Oligoamenorrhea or amenorrhoea	-Hyperandrogenemia -Insulin resistance -Hyperinsulinemia	Pelvic ultrasonography: <ul style="list-style-type: none">• polycystic ovaries

Table 2. Diagnostic features of primary and secondary amenorrhea

symptoms of systemic diseases or endocrine disorders (goiter, central obesity, purplish skin striae, muscle weakness), and stigmata of genetic anomalies (short stature, misshapen ears, broad chest, widely spaced nipples, cubitus valgus). Systolic blood pressure and diastolic blood pressure should be measured to exclude hypertension. Therefore, the physician should perform a careful examination of the external genitalia to assess clitoris, hymen permeability and vaginal and uterine development (Adams Hillard, 2008).

4.3 Laboratory evaluation

Laboratory evaluation of amenorrheic adolescents should include the measurements of basal plasma gonadotropins, estradiol, progesterone, free and total testosterone, dehydroepiandrosterone sulphate, delta4-androstenedione, 17-OHprogesterone, thyroid function tests (free triiodothyronine, free thyroxine, thyrotropin, anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies, anti-thyrotropin receptor antibodies), prolactin, fasting insulin and glucose, insulin resistance indexes, adrenocorticotrophic hormone, cortisol, markers of ovarian tumours. Because pregnancy represents the most frequent cause of secondary amenorrhea, urine or serum pregnancy test is obligatory in adolescents with irregular menses (Master-Hunter & Heiman,2006). It has been suggested to perform the “progesterone challenge test” in those females with secondary amenorrhea and androgen in the normal range in order to measure circulating estrogens values and identify an insufficient endometrial estrogenization (Deligeoroglou et al., 2010).

It can be also very important to detect peak plasma gonadotropins response to exogenous gonadotropin-releasing hormone to detect a defect of hypothalamic-pituitary axis. Karyotype should be requested in case of suspected genetic anomalies.

4.4 Instrumental evaluation

The *instrumental procedures* are crucial in the evaluation of primary and secondary amenorrhea. Pelvic transabdominal ultrasonography scanning should be performed by a trained and experienced operator to measure length, breadth, and depth of uterus and ovaries, and endometrial thickness. Furthermore, magnetic resonance imaging of the hypothalamus and pituitary gland, and magnetic resonance imaging of the pelvis are of pivotal importance. In some cases, it can be necessary to perform hysteroscopy or hysterosalpingogram to assess the presence of intrauterine synechiae (The Practice Committee of American Society for Reproductive Medicine, 2008).

5. Treatment of amenorrhea

Amenorrhea and the related disorders require appropriate treatments (Table 3).

Therapeutic approaches	
Anatomic genital defects	<div><div>- Surgical correction</div><div>- Gonadectomy followed by exogenous estrogens (complete androgen insensitivity syndrome)</div></div>
Hypothalamic causes	<div><div>- Estrogens and progestin replacement therapy</div><div>- Calcium and vitamin D supplementation</div><div>- Reduced physical activity, weight gain</div><div>- Surgical removal of tumours</div></div>
Pituitary causes	<div><div>- Dopamine agonists: cabergoline or bromocriptine (prolactinomas)</div><div>- Surgical removal (tumours)</div><div>- Estrogens and progestin replacement therapy</div></div>
Ovary insufficiency	<div><div>- Estrogens replacement therapy at approximately 12 years of age at low-doses, followed by a gradual augment over 2–4 years. Progestin should be started after at least 2 years or at uterine bleeding. Calcium supplementation (Turner syndrome)</div><div>- Estrogens replacement therapy after gonadectomy at approximately 11 years of age (Swyer syndrome)</div><div>- Estrogens replacement therapy until the normal age of menopause; for females having a whole uterus combined estrogens and progestin hormone therapy; physical activity, diet rich in calcium and vitamin D (premature ovarian failure)</div></div>
Endocrine diseases	<div><div>Appropriate therapy</div></div>
Chronic oligo- or anovulation	<div><div>- Increased physical activity, reduced food intake</div><div>- Estrogen replacement therapy at low doses combined with cyclic progestin</div><div>- Insulin-sensitising drugs (metformin)</div></div>

Table 3. Therapeutic approaches for primary and secondary amenorrhea

5.1 Treatment of the anatomic defects of the genital tract

Every anatomic defect of the genital tract requires appropriate surgical procedures. In particular, transverse vaginal septum require the excision, imperforate hymen necessitates the elimination of the tissue in a triangular form and intrauterine synechiae require their removal. Furthermore, cervical agenesis may require hysterectomy while cervical dysgenesis may necessitate cervical canalization (Deligeoroglou et al., 2010). Regarding to Mayer-Rokitansky-Küster-Hauser syndrome, patients may benefit by surgical formation of a neovagina; undeveloped uterus should be removed in presence of functional endometrium as it can be responsible for uterus swelling and recurrent lower abdominal pain. Finally, in girls with diagnosis of androgen insensitivity syndrome a vaginal length adequate for intercourse could be reached through non surgical dilatation. However, in

some cases surgical correction of genital tract anomalies should be performed in order to create a neovagina. Both in girls affected by Mayer-Rokitansky-Küster-Hauser syndrome and androgen insensitivity syndrome it is imperative to guarantee a constant psychological support (Deligeoroglou et al., 2010).

5.2 Treatment of hypothalamic and pituitary disorders

Hypothalamic amenorrhea should be treated according to its aetiology. In particular, treatment of functional hypothalamic amenorrhea should be finalised to the appearance or regulation of menstrual cycles by starting estrogens and progestin therapy. Furthermore, this therapy should prevent the development of osteoporosis. Respect to oral estrogens, it has been demonstrated that transdermal hormone replacement therapy has better effects on bone density than oral hormone replacement therapy due to the absence of the first-pass hepatic metabolism (Jayasinghe et al., 2008). In addition, calcium and vitamin D supplementation is highly suggested (Master-Hunter & Heiman, 2006). In particular, in athletes with the “female athlete triad” treatment targets to restore menses through reduced physical activity, weight gain, calcium supplementation and estrogen therapy (American Academy of Pediatrics Committee on Sports Medicine and Fitness, 2000).

Regarding to the Kallmann syndrome, the treatment targets to promote breast development through estrogens and progestin replacement therapy in girls and to promote virilization through testosterone replacement therapy in males. Furthermore, hormonal treatments can be offered as a valid method for restoring fertility in these patients. Both pulsatile gonadotropin-releasing hormone or gonadotropins administration have been utilized to stimulate ovulation in females and spermatogenic activity in males (Buchter et al., 1998). Also in the majority of subjects affected by idiopathic hypogonadotropic hypogonadism, long-term exogenous pulsatile gonadotropin-releasing hormone therapy has been proven to be efficient because it induces testicular growth and development of sperm in the ejaculate, favours sexual life and improves reproductive prognosis. However, a minor part of this population did not respond to gonadotropin-releasing hormone replacement, suggesting that pituitary and testicular defects in these subjects are improbable to be totally consequences of gonadotropin-releasing hormone deficiency (Sykiotis et al., 2010).

Regarding to prolactinomas, therapy should target to restore menses and guarantee fertility. Dopamine agonists are the favourite treatment of hyperprolactinemia because they are able to reduce prolactin levels, to decrease the tumor size and to restore gonadal function (Iyer & Molitch, 2011). Actually, two dopamine agonists are used to treat prolactinomas: bromocriptine and cabergoline. In particular, cabergoline has been shown to be more efficacious with less adverse effects than bromocriptine in females with microadenomas (Webster et al., 1994). Therefore, cabergoline represents the principal therapeutic approach. Also females with macroadenoma can benefit by dopamine agonists or, in some cases, they must underwent surgical removal of tumours (Master-Hunter & Heiman, 2006).

Sheehan’s syndrome requires the general standard of treatment of patients presenting with hypopituitarism, aiming to replace the endocrine deficits. In particular, because these patients are at increased risk of developing partial loss of feminization, amenorrhea and osteoporosis, they should start hormone replacement therapy (Kelestimur, 2003).

5.3 Treatment of ovary insufficiency-related diseases

Turner syndrome requires growth-promoting treatments aimed to obtain a normal progression of puberty and the achievement of a normal adult height. Growth hormone

represents the focus of growth-promoting therapy as this therapy is able to improve growth velocity and final height (Bondy et al., 2007). Regarding to the induction of puberty, it is opportune to dose gonadotropins levels before starting hormone replacement therapy to rule out a delayed puberty. Recent data have demonstrated that treatment with estrogens should begin at approximately 12 years of age to promote a normal pubertal development without interfering with growth hormone therapy on final height. Actually, oral estrogens as well as transdermal and injectable depot forms of estradiol are available (Ankarberg-Lindgren et al., 2001; Rosenfield et al., 2005). Estradiol therapy is generally initiated at low-doses (from 1/10 to 1/8 of the adult dose) followed by a gradual augment over 2–4 years, while progestin should be started after at least 2 years or when uterine bleeding happens to permit a regular uterine and breast development (Bondy et al., 2007). In addition, calcium supplementation has been highly suggested in Turner syndrome.

In Swyer syndrome, estrogens replacement therapy should be started after gonadectomy at approximately 11 years of age in order to allow a normal pace of puberty (Han et al., 2008).

Women with diagnosis of premature ovarian failure should undergo estrogens replacement therapy until the normal age of menopause to replace deficit of ovarian estrogens and to counter menopausal symptoms. In particular, for those females having a whole uterus it is preferable to start combined estrogens and progestin hormone therapy to avoid hyperplasia of the endometrium (Shelling, 2010). Due to estrogen deficiency, women with premature ovarian failure are also at risk of osteoporosis (Rebar, 2009); for this reason, physical activity, diet rich in calcium and vitamin D without smoking or alcohol consumption are mandatory.

5.4 Treatment of chronic oligo- or anovulation

Overweight or obese women with polycystic ovary syndrome presenting oligomenorrhoea or amenorrhoea should underwent structured lifestyle interventions, including increased physical activity and reduced food intake (Moran et al., 2009). In fact, it has been demonstrated that a weight loss of 5-10% is associated with beneficial effects on reproductive system (Huber-Buchholz et al., 1999). Regarding to pharmacological treatment, actually there is no therapy able to completely resolve hormonal disturbances in polycystic ovary syndrome. Furthermore, pharmacological treatments should not substitute the lifestyle interventions (Teede et al., 2010). Estrogen replacement therapy at low doses combined with cyclic progestin can be started leading to a reduction of hyperandrogenism. Furthermore, insulin-sensitising drugs represent a valid approach to reduce insulin resistance in polycystic ovary syndrome (Meyer et al., 2007). In particular, metformin has been proven to improve ovulation and regulate menstrual periods (Tang et al., 2009).

6. Conclusion

Future research is needed to clarify amenorrhea and the related endocrine disorders in order to make an early diagnosis and to identify the more appropriate strategies during reproductive years of life.

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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

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