MANAGEMENT OF ENDOCRINE DISEASE

Diagnosis and management of primary amenorrhea and female delayed puberty

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Abstract

Puberty is the period of transition from childhood to adulthood characterized by the attainment of adult height and body composition, accrual of bone strength and the acquisition of secondary sexual characteristics, psychosocial maturation and reproductive capacity. In girls, menarche is a late marker of puberty. Primary amenorrhea is defined as the absence of menarche in ≥ 15 -year-old females with developed secondary sexual characteristics and normal growth or in ≥ 13 -year-old females without signs of pubertal development. Furthermore, evaluation for primary amenorrhea should be considered in the absence of menarche 3 years after thelarche (start of breast development) or 5 years after thelarche, if that occurred before the age of 10 years. A variety of disorders in the hypothalamus–pituitary–ovarian axis can lead to primary amenorrhea with delayed, arrested or normal pubertal development. Etiologies can be categorized as hypothalamic or pituitary disorders causing hypogonadotropic hypogonadism, gonadal disorders causing hypergonadotropic hypogonadism, disorders of other endocrine glands, and congenital utero–vaginal anomalies. This article gives a comprehensive review of the etiologies, diagnostics and management of primary amenorrhea from the perspective of pediatric endocrinologists and gynecologists. The goals of treatment vary depending on both the etiology and the patient; with timely etiological diagnostics fertility may be attained even in those situations where no curable treatment exists.

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Invited Author's profile

Raimo Voutilainen is a pediatric endocrinologist and emeritus professor in pediatrics at the University of Eastern Finland and Kuopio University Hospital in Kuopio, Finland. His research fields have included both translational and clinical studies on adrenal and gonadal function during fetal, childhood and adult life. Adrenal tumors, congenital adrenal hyperplasia, premature adrenarche, pubertal development, and later health consequences of small and large birth size, and maternal pre-eclampsia have been his clinical research areas. Hair steroids and their relationship to cardiovascular disease risk is one of his current research interests.

Normal puberty and pubertal markers

Puberty is the period of transition from childhood to adulthood characterized by the attainment of adult height and body composition, accrual of bone strength and the acquisition of secondary sexual characteristics, psychosocial maturation and reproductive capacity. Its biological control is complex involving multiple endocrine systems that interact in an ordered, progressive pattern beginning already in fetal life (1). During the first postnatal months, the human infant experiences a transient activation of the hypothalamic–pituitary–gonadal (HPG) axis described as minipuberty (2). Subsequently, the HPG axis is inactive until the beginning of puberty. The precise mechanisms underlying the reactivation of the HPG axis are not fully known. Although they are strongly determined by genetics, also environmental, nutritional and stress-related factors play a role (1, 3).

Reactivation of the HPG axis is characterized by a gradual increase in hypothalamic gonadotropin-releasing hormone (GnRH) secretion. Episodic GnRH boluses are secreted into the hypothalamic–pituitary–portal system to reach the anterior pituitary gland, where they stimulate the secretion of gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in a progressive fashion (1) (Fig. 1). LH stimulates ovarian follicular theca cells to produce androgens, which are converted to estrogens in granulosa cells by FSH-induced aromatase. Increasing estrogen levels in girls result in gradual breast tissue and uterine growth, pubertal growth

spurt, feminine adipose tissue distribution and accrual of bone strength. The endometrium proliferates and eventually bleeds marking menarche. During the first postmenarcheal years, about half of the cycles may be anovulatory and irregular menstruation may continue for several years after menarche. The gradual maturation of the hypothalamic neuronal circuits by estrogens results in generation of the GnRH and LH surge that induces ovulation and regular menstrual cycles (4).

Pubertal markers and timing

In girls, the first physical marker of puberty is thelarche, that is the transition from Tanner breast stage B1 (prepubertal stage) to B2 (glandular breast tissue) (1, 5, 6). Development of pubic hair, pubarche, is usually not regarded as a sign of pubertal onset because it may result from adrenarche being independent of HPG axis activation. Adrenarche refers to the morphological and functional development of the zona reticularis in the adrenal cortex resulting in increased production of adrenal androgen precursors in mid-childhood. It is associated with secondary sexual characteristics such as the development of pubic and axillary hair, acne and adult type body odor. Adrenarche may precede, overlap or follow gonadarche with a wide variation in timing, clinical signs and adrenal androgen secretion (reviewed in (7)). Menarche is regarded as a late marker of puberty in girls (6). Typically, it occurs within 2 to 3 years after thelarche at Tanner stage IV of breast development (5, 8, 9). It is rare before Tanner stage III of breast development (5). Pubertal development is completed approximately 1.5 years after menarche (reviewed in (10)).

Pubertal timing varies in the population, and 50 to 80% of this variation is genetically determined (1, 3, 10). In most populations, 95% of girls experience the onset of puberty between 8.5 and 13 years of age (1). However, a downward secular trend in the onset of breast development has been reported (8, 11, 12). According to a recent meta-analysis, the age at pubertal onset based on thelarche had decreased by almost 3 months per decade from 1977 to 2013 (12). The average age of menarche has decreased significantly between the 19th and the mid-20th centuries in many countries, due to improved general health, nutrition and lifestyle (reviewed in (1, 10)). After that, the median age at menarche has remained more stable across well-nourished populations in developed countries (11, 13, 14, 15), although a small but statistically significant decline has been reported (11, 16). A large study from the United States reported the median age at menarche to be

Figure 1

Hypothalamus–pituitary–ovarian (HPO) axis and secondary sexual characteristics. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

12.43 years (14). In that study, menarche was significantly earlier in non-Hispanic black girls compared with non-Hispanic white and Mexican–American girls. In a large Danish study, estimated age at menarche was 13.42 years in 1991 and 13.13 years in 2006 (11).

Definition of primary amenorrhea

Primary amenorrhea is defined as the absence of menarche in ≥ 15 -year-old females with developed secondary sexual characteristics and normal growth or in ≥ 13 -year-old females without signs of pubertal development (i.e. delayed puberty) (Fig. 1) (13, 17). Furthermore, evaluation of primary amenorrhea should be initiated 3 years post-thelarche (13), or within 5 years, if breast development has started before the age 10 years (17). Secondary amenorrhea is defined as the cessation of regular menses for 3 months or the cessation of irregular menses for 6 months. Oligomenorrhea is the absence of menstruation for longer than 45-day intervals in adolescents (18).

Although the majority of the causes of primary and secondary amenorrhea are similar, their relative proportions differ from each other (17). Etiologies of primary amenorrhea can be categorized as hypothalamic or pituitary disorders causing hypogonadotropic hypogonadism, gonadal disorders causing hypergonadotropic hypogonadism, disorders of other endocrine glands, and congenital utero–vaginal anomalies. Underlying causes of primary amenorrhea can lead to delayed or stalled puberty, or normal pubertal development with no menarche. The most common etiologies of primary amenorrhea have been reported to be gonadal dysgenesis, Müllerian agenesis, and hypogonadotropic hypogonadism (17, 19). However, to our knowledge, no recent reports on the European or American descent exists. Potential etiologies of primary amenorrhea are presented in Table 1. This review article is primarily targeted at pediatric endocrinologists and gynecologists. A comprehensive review targeted at primary care clinicians has been published recently (18).

Evaluation of the adolescent with primary amenorrhea

Evaluation of the adolescent with primary amenorrhea should include a thorough personal medical history with height and weight charts, trends in height and weight development, nutritional status, medications,

fractures, history or symptoms of chronic diseases, psychosocial functioning and the intensity of exercise. If pubertal development is delayed or stalled, a complete family history, including childhood growth patterns, age at pubertal onset of both parents and siblings, age of menarche of the close relatives, and any history of infertility, anosmia, midline abnormalities and chronic diseases should be included. Timing of possible breast and pubic hair development should be reviewed. A full physical examination is needed to consider the broad spectrum of differential diagnoses. Normal breast development and presence of secondary sexual characteristics indicate that circulating estrogens are or at least have been present. In most cases, the external gynecological examination with abdominal ultrasonography is sufficient to evaluate internal reproductive organs. Table 2 presents features or findings related to primary amenorrhea.

In the absence of signs of androgen excess, measurement of FSH, LH, prolactin, thyroid-stimulating hormone (TSH), free thyroxine (FT4), estradiol (E2), complete blood count and screening for celiac and inflammatory bowel disease will generally provide sufficient information to rule out organic causes of amenorrhea (20). Pregnancy test should be taken with low threshold. Signs of hyperandrogenism indicate measurement of serum (free) testosterone, DHEA or its sulfate (DHEA-S), androstenedione and 17-hydroxyprogesterone (17-OHP). Figure 2 represents an algorithm for the approach to the patient with primary amenorrhea and low or normal serum FSH and LH concentrations. In Fig. 3, an algorithm for hypergonadotropic etiologies is presented. Because hypoestrogenism is a significant risk factor for bone loss, bone mineral density (BMD) testing should be considered in hypoestrogenic states.

Etiologies causing hypogonadotropic hypogonadism

Hypogonadotropic hypogonadism is caused by disorders at hypothalamic or pituitary levels. Serum FSH and LH may be undetectable, very low or within the low-normal range.

Self-limited delayed puberty/constitutional delay of growth and puberty (CDGP)

Delayed puberty is characterized by the absence of the pubertal HPG axis activation. Constitutional delay of growth and puberty (CDGP) is the most common cause of

Table 1 Potential etiologies of primary amenorrhea.

Condition	Causes
Hypogonadotropic hypogonadism	
Constitutional delay of growth and puberty/self-limited delayed puberty	
Functional hypothalamic amenorrhea	Anorexia nervosa, other eating disorder, excessive exercise, stress, psychiatric illness, chronic disease (e.g. celiac disease, inflammatory bowel disease)
Congenital hypogonadotropic hypogonadism	GnRH deficiency and anosmia (Kallmann syndrome); isolated congenital hypogonadotropic hypogonadism
Syndromic congenital hypogonadotropic hypogonadism (often multiple pituitary hormone deficiencies)	CHARGE syndrome, Waardenburg syndrome, Hartsfield syndrome, congenital adrenal hypoplasia, 4H syndrome (hypomyelination, hypogonadotropic hypogonadism, hypodontia), septo-optic dysplasia, holoprosencephaly, encephalocele, Prader-Willi syndrome, Laurence-Moon syndrome, Gordon Holmes syndrome, Bardet-Biedl syndrome
Combined pituitary hormone deficiency	
Pituitary gland or stalk damage	Adenomas and other tumors (i.e., prolactinoma, Cushing's disease, germinoma, craniopharyngioma); cysts (Rathke's cleft cyst, arachnoid, dermoid, epidermoid, suprasellar cysts, mucocoele), Infiltrative disorders (autoimmune hypophysitis, hemochromatosis, sarcoidosis, Langerhans cell histiocytosis, granulomatous diseases); surgery, trauma, pituitary apoplexy, vascular lesions, empty sella syndrome, radiation therapy
Thyroid	Hypothyroidism or hyperthyroidism
Medications/drugs	Anesthetics, anticonvulsants, antipsychotics, gastrointestinal motility agents (metoclopramide, domperidone, ranitidine?), opiates; selective serotonin uptake inhibitors; Oral contraceptives, alcohol abuse, heroin, cocaine, marijuana, glucocorticoids (high dose), exogenous androgens (transgender care)
Hypergonadotropic hypogonadism	
Premature ovarian insufficiency	Turner syndrome, gonadal dysgenesis 46,XX -e.g., mutations in steroidogenic genes (17 hydroxylase deficiency, aromatase deficiency), FSH receptor gene, gonadal dysgenesis 46,XY -e.g., mutations in steroidogenic genes, SOX9, SRY, WT1, NR5A1, LH receptor gene, other genetic etiologies; autoimmune oophoritis, polyglandular autoimmune syndrome, irradiation or surgery, chemotherapy, infection
Normogonadotropic hypogonadism	
Pituitary	Hyperprolactinemia
Adrenals	Non-classic congenital adrenal hyperplasia, adrenal insufficiency, tumor (androgen-secreting)
Ovaries	Polycystic ovary syndrome; tumors (androgen- or estrogen-secreting)
Uterus	Müllerian agenesis; cervical agenesis, androgen insensitivity syndrome, pregnancy
Vagina	Agenesis, transverse septum, distal atresia
Hymen	Imperforate

FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

delayed puberty in girls comprising up to 30–56% of girls with pubertal delay (1, 21, 22). It can be considered as an extreme variant of normal pubertal timing (23). Many subjects with CDGP have had delayed maturation during early childhood, and consequently they may be shorter than their peers (1). Bone age is usually delayed compared to chronological age, but the developmental milestones are achieved at a normal bone age (i.e. the onset of signs of pubertal development by the bone age of 13 years in girls) (1). If adrenarche is also late in a girl with CDGP, the delay in the development of pubertal signs and growth acceleration is emphasized (7).

Although only a small number of genetic causes of self-limited delayed puberty are known (1), a genetic basis

is evident, since 50 to 75% of girls with CDGP have a family history of delayed pubertal onset (21, 24).

Evaluation reveals delayed pubertal development with prepubertal FSH and LH concentrations. However, CDGP can be diagnosed only after exclusion of other underlying causes (23). Differential diagnoses of CDGP and their evaluation are described in the following chapters of this review.

Expectant observation is appropriate in girls with milder forms of delayed puberty who are not predicted to have negative outcomes from their condition (1). If a girl elects to be treated, transdermal or oral 17 β -estradiol is preferred to ethinyl estradiol (23). Induction of pubertal development is described later in this review. Before

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Table 2 Summary of history and clinical evaluation in the work-up of primary amenorrhea.

Parameters evaluated	Parameters checked
History	
Family history of	Delayed puberty, infertility, early menopause
Changes in weight	Growth chart
Eating habits, diet	
Exercise	
Psychosocial distress	
Medications	
Chemotherapy	
Radiation therapy (brain, pelvis)	
Head trauma/surgery	
Sexual activity	
Specific symptoms	Headache, nausea, changes in vision, abnormal thirst, galactorrhea, anosmia, vasomotor symptoms (hot flashes, night sweats), abdominal pain, constipation/diarrhea
Clinical evaluation	
Growth charts	Weight loss, stunted growth
Pubertal development	Tanner staging
Thyroid examination	
Abdominal palpation	Tumor, hematometra
CHH-associated phenotypes	Midline abnormalities, mirror movements, dental agenesis, skeletal or cardiovascular defects, hearing loss, obesity
Turner syndrome stigmata	Short stature, webbed neck, low hairline, skeletal and cardiovascular defects
Signs of hyperandrogenism	Acne, male pattern baldness, hirsutism, clitoral enlargement, voice deepening
Signs of hypercortisolism	Striae, moon face, buffalo hump, hypertension, central obesity
Complete androgen insensitivity syndrome	Scanty axillary and pubic hair in association with (full) breast development
Eating disorder	Low BMI, lanugo, dry skin, cold extremities, bradycardia

CHH, congenital hypogonadotropic hypogonadism.

considering hormonal treatment of CDGP, life-style reasons causing functional hypothalamic amenorrhea (FHA) should be carefully excluded (presented in the next paragraphs).

Functional hypogonadotropic hypogonadism

Functional etiology is found in approximately 20% of females with delayed puberty or incomplete pubertal development (1, 22). The underlying pathophysiology is HPG axis suppression causing hypogonadotropic hypogonadism and delayed or arrested pubertal development (reviewed in (1)). Functional reduction in GnRH drive manifests as reduced LH pulse frequency and LH and FSH levels that are insufficient to maintain full folliculogenesis and ovulatory ovarian function thus causing hypoestrogenism (reviewed in (20)), which in turn leads to poor endometrial growth and amenorrhea. Furthermore, hypoestrogenism may lead to bone loss, inability to obtain peak bone mass and infertility. A longer duration of insult will result in a longer time to reversal. Functional hypothalamic amenorrhea (FHA) is a form of chronic anovulation that is not due to identifiable organic causes (20).

In addition to life-style causes, for example, stress, excessive exercise or restrictive eating habits, also chronic disease (e.g. anorexia nervosa, inflammatory bowel disease, celiac disease, chronic renal disease, sickle cell anemia and cystic fibrosis) may cause HPG axis suppression. Hypogonadotropic hypogonadism and FHA develop as an adaptive response to chronic metabolic energy deficiency (reviewed in (20)), but also hypercortisolism, and elevated levels of proinflammatory cytokines may have an impact on the HPG axis (1). An association between activation of the hypothalamic–pituitary–adrenal (HPA) axis and reduction in GnRH drive in women with FHA has been described (reviewed in (20)). Both corticotropin-releasing hormone (CRH) and cortisol suppress GnRH secretion. Glucocorticoids also inhibit the effects of E2 in the uterus (reviewed in (25)).

In athletic individuals, hypogonadotropic hypogonadism may develop even at normal weight with less fat and more muscle compared with nonathletic individuals. Sports in which leanness may confer an advantage (i.e. gymnastics, figure skating, cheerleading, running) are risk factors for amenorrhea (26). Certain genetic mutations may predispose to the development of functional hypogonadotropic hypogonadism, and there

Figure 2

Algorithm for the approach to the patient with primary amenorrhea and hypogonadotropic or normogonadotropic hypogonadism. CBC, complete blood count; CHH, congenital hypogonadotropic hypogonadism; E2, estradiol; FSH, follicle-stimulating hormone; FT4, free thyroxine; β -hCG, beta-human chorionic gonadotropin; LH, luteinizing hormone; NCAH, non-classic congenital adrenal hyperplasia; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone; 17-OHP, 17-hydroxyprogesterone.

Figure 3

Algorithm for the approach to the patient with primary amenorrhea and hypergonadotropic hypogonadism. FSH, follicle-stimulating hormone; LH, luteinizing hormone; POI, premature ovarian insufficiency.

is evidence for heterozygous overlap between the genetic bases of functional and congenital hypogonadotropic hypogonadism (CHH) (27).

In a suspicion of FHA, review of the growth curves (typically weight loss and sometimes stunted growth) and a careful evaluation for psychosocial influences are essential. Chronic diseases have to be ruled out. Laboratory parameters typically reveal low or low-normal serum LH and normal FSH (usually higher than LH) levels (Fig. 2). Serum E2 is typically < 50 pg/mL (184 pmol/L), but acute gonadotropin response to GnRH stimulation is preserved (defined as a two- or three-fold rise in LH and FSH compared with baseline levels). Usually, evaluation of basal pituitary hormones is sufficient to establish deficient gonadotropin secretion. However, in females with E2 consistently lower than 20 pg/mL (73 pmol/L), the response to GnRH is the only feature that may differentiate FHA from other types of hypogonadotropic hypogonadism (20). If no evident reason (e.g. weight loss) for amenorrhea exists, a GnRH stimulation test should be considered after an endocrinologist consultation. The Endocrine Society guidelines to assure E2 assay reliability and validity should be followed (28). In FHA, TSH and FT4 are in the lower range of normal, similar to that seen in any chronic illness. The increase in cortisol secretion is less than that seen in Cushing's syndrome, and the circadian pattern is preserved. In patients with FHA and underlying polycystic ovary syndrome (PCOS), LH and FSH may be normal, E2 low and LH/FSH ratio elevated (20).

Although recovery of normal weight will normalize most endocrine and metabolic functions, amenorrhea may persist for years. Treatment should restore HPO

axis function through behavioral changes and energy imbalance correction by improved nutrition, decreased exercise activity, stress reduction, and weight gain. Patients with bradycardia, hypotension, orthostasis, or electrolyte abnormalities may require inpatient treatment. The need for psychological support must be evaluated (20). In FHA, BMD measurement is recommended after 6 to 12 months of amenorrhea before considering hormone replacement therapy (HRT) (20). NICE guideline recommends bone density testing after 12 months of undernourishment (29).

After a reasonable trial of non-pharmacological therapy (12 months), short-term use of transdermal 17 β -estradiol may be tried. The Endocrine Society suggests against oral contraceptives for the purpose of gaining menses or improving BMD, as they may mask the underlying pathology and bone loss may continue. However, oral contraceptives should be considered for patients at risk for pregnancy because ovulation may precede menstruation. The Endocrine Society recommends against bisphosphonates, testosterone, and leptin to improve BMD in adolescents with FHA (20).

Congenital hypogonadotropic hypogonadism (CHH)

CHH is a rare genetic disorder caused by GnRH deficiency due to developmental defects in the GnRH neuron migration or in the maturation of the GnRH neuronal network. It is characterized by absent or incomplete puberty (10, 30) affecting approximately 10 to 20% of adolescent girls with pubertal delay (21, 22). CHH associated with an absent sense of smell is termed

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Kallmann syndrome. Kallmann syndrome is a result from abnormal fetal development of GnRH neurons; both GnRH and olfactory neurons originate from the olfactory placode and migrate together into the CNS during embryogenesis (31). With lower prevalence, other non-reproductive phenotypes associated with CHH are mirror movements (synkinesis), unilateral renal agenesis, eye movement disorders, sensorineural hearing loss, midline brain defects, cleft lip/palate, dental agenesis, skeletal defects, and cardiovascular defects (1, 10).

CHH is termed 'isolated' when no anatomical defects are found (10). Isolated CHH is typically associated with normal olfactory and GnRH neuronal development but impaired regulation of GnRH secretion (reviewed in (6)). Loss-of-function mutations within the GnRH receptor are the most frequent causes of autosomal recessive CHH, accounting for 16 to 40% of patients (1, 31). To date, mutations in over 30 genes have been identified to act either alone or in combination. However, the pathophysiological basis of CHH in approximately 50% of cases remains unclear (1). CHH can be challenging to diagnose, particularly in early adolescence when the clinical picture is similar to that in CDGP. Its penetrance is incomplete and expressivity variable probably due to oligogenicity (i.e. interaction of mutations in two or more genes) (1, 32). The spectrum of phenotypes is wide from complete hypogonadotropic hypogonadism to partial hypogonadism with an arrest of pubertal development, reversible hypogonadotropic hypogonadism in some patients (1, 10) or normal pubertal development with secondary amenorrhea (33). However, only few case reports concerning females with reversible CHH exist (32).

CHH may manifest as partial hypogonadism, leading to a variable degree of pubertal development in females carrying mutations in autosomal genes, for example, fibroblast growth factor 1 (*FGF1*), prokineticin 2 (*PROK2*) / prokineticin 2 receptor (*PROKR2*), and GnRH receptor (*GNRHR*) (34, 35, 36, 37). Biallelic, partial loss-of-function mutations in *GNRHR* cause a wide spectrum of reproductive phenotypes from CDGP to complete CHH (33, 38). In a series of twelve patients, ten (83%) had primary amenorrhea, eight had partial, three complete, and one no breast development (38). Amenorrhea is reported in nearly 90% of women with CHH. In most studies, absent breast development was observed in up to 50% of women (37, 39). Pubarche ranged from absent to almost normal (39, 40). Partial CHH may be underdiagnosed due to clinical presentation that resembles FHA (33, 39).

CHH-associated phenotypes

Several complex syndromes are associated with hypogonadotropic hypogonadism. Specific phenotypes, such as delayed cognitive development associated with obesity or dysmorphic features can lead to the diagnosis of syndromic forms of CHH. Syndromes associated with CHH are for example CHARGE (coloboma, heart malformations, atresia of the choanae, retardation of growth and development, genital anomalies, ear anomalies, olfactory bulb aplasia) syndrome, Waardenburg syndrome, and 4H (hypomyelination, hypogonadotropic hypogonadism and hypodontia) syndrome. Prader-Willi syndrome, frequently caused by imprinting disorders, is associated with absent or delayed puberty. Most undergo incomplete pubertal development expressed as lack of pubertal growth spurt, hypogonadotropic hypogonadism and underdeveloped genitalia. The minority of individuals with Prader-Willi syndrome undergo precocious puberty (reviewed in (1)). Nuclear receptor subfamily 0 group B member 1 (*NROB1*), alternatively known as DAX-1 orphan nuclear receptor gene (*DAX1*) is important for the development of the adrenal gland, gonads, ventromedial hypothalamus, and pituitary gonadotrope cells. Mutations in *NROB1* cause congenital X-linked adrenal hypoplasia that is associated with hypogonadotropic hypogonadism (41). Mutations in the leptin-receptor gene (*LEPR*) cause hyperphagia, severe obesity, alterations in immune function, delayed puberty and hypogonadotropic hypogonadism (42).

Evaluation for CHH

Similar to CDGP and FHA, CHH is an exclusion diagnosis. Although CHH cannot be distinguished from CDGP by growth rate, usually subjects with CHH have steady linear growth during childhood and become short for their age in adolescence with absence of pubertal growth spurt (1, 22). Moreover, basal gonadotropin levels are not useful in the differential diagnosis of CDGP and CHH (1). Serum FSH and LH may be undetectable low, or in those with partial pubertal development, serum gonadotropins and E2 (using sensitive E2 assays) may be within the low-normal range (10, 43). Genetic testing is recommended for diagnosis, prognosis and genetic counselling in CHH. Its work-up includes cranial MRI to rule out tumors or other lesions, ultrasonography to visualize the ovaries, uterus and unilateral renal agenesis, and a BMD measurement to evaluate bone health (30). In the evaluation of CHH, other pituitary hormone defects have to be ruled out by performing an exploration of the complete pituitary

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axis (30). Sense of smell should be tested with a standardized olfactory test, since 50% of those with CHH were anosmic or hyposmic despite self-reported normal sense of smell (44). Induction and maintenance of pubertal development are described later in this review.

Acquired causes of hypogonadotropic hypogonadism

Organic causes of hypogonadotropic hypogonadism may lead to delayed or stalled puberty depending on the onset of exposure. They can be classified into hormone-secreting or non-secreting tumors, infiltrative or systemic diseases, irradiation, surgery, pituitary apoplexy, and traumatic causes (reviewed in (45, 46) (Table 1, Fig. 2). Pathophysiology is usually mediated either by hypothalamus or pituitary stalk compression interfering with GnRH or gonadotropin synthesis or secretion, or by hyperprolactinemia via the interference of the inhibitory effect of dopamine on prolactin secretion (1, 25, 47). High prolactin concentrations inhibit normal hypothalamic GnRH pulse rhythm and secretion, resulting in disturbed gonadotropin secretion with normo- or hypogonadotropic hypogonadism (4). These conditions may be accompanied by multiple pituitary hormone deficiencies termed hypopituitarism (45).

As serum prolactin concentration may rise in response to stress or other factors, it should be measured more than once in cases of mild hyperprolactinemia. Mildly elevated prolactin levels are usually the result of dysregulation in the inhibitory mechanism of prolactin secretion. Macroprolactinemia, which is a cause of physiological hyperprolactinemia, has to be ruled out in subjects with asymptomatic hyperprolactinemia (25, 48).

Tumors and cysts

Pituitary adenomas are rare in children and adolescents representing 2–8.5% of pituitary tumors. In adolescents, functional adenomas are more common than non-functional. According to Guaraldi *et al.*, the most common adenomas in adolescence are prolactinomas (46–66%), followed by corticotropinomas (30%), somatotropinomas (5–15%), gonadotropinomas, thyrotropinomas and non-functioning adenomas (reviewed in (49)). Corticotropinomas are ACTH-producing pituitary adenomas that stimulate excessive cortisol secretion from the adrenal cortex (termed pituitary-dependent Cushing's syndrome or Cushing's disease). Other CNS tumors and

space-occupying lesions, such as craniopharyngiomas (50), germinomas, Rathke's cleft cyst, Langerhans cell histiocytosis, and dermoid or epidermoid cysts can cause hypogonadotropic hypogonadism via mass effect.

Brain MRI is indicated in a suspicion of a space-occupying lesion: severe or persistent headache, vomiting that is not self-induced, change in vision, lateralizing neurologic signs, thirst or urination not attributable to other causes, clinical signs or laboratory results suggesting pituitary hormone excess or deficiency, or if no other explanations for amenorrhea are found. In microprolactinomas, serum prolactin levels are usually between 100 and 250 ng/mL (~ 2000–5000 mU/L), in macroprolactinomas between 200 and 1000 ng/mL (~ 4000–20 000 mU/L), and in other adenomas between 25 and 100 ng/mL (~ 500–2000 mU/L) (reviewed in (51)).

Dopamine agonists cabergoline and bromocriptine are the primary treatment for microprolactinomas. In other pituitary adenomas and macroadenomas causing hyperprolactinemia, trans-sphenoidal resection is the initial treatment followed by medical therapy (reviewed in (49)).

Other acquired causes of hyperprolactinemia or hypogonadotropic hypogonadism

Primary hypothyroidism may cause moderate hyperprolactinemia via lack of negative feedback in the hypothalamus–pituitary–thyroid axis leading to increased thyrotropin-releasing hormone (TRH) secretion in the hypothalamus. Subsequently, TRH stimulates TSH and prolactin release causing hyperprolactinemia, which inhibits GnRH pulsation (25). Long-term or inadequately treated primary hypothyroidism can cause pituitary hyperplasia that may mimic a pituitary tumor (48). Renal insufficiency may cause moderate hyperprolactinemia due to impaired renal degradation and clearance of prolactin, and increased prolactin secretion (48). The latter may be due to reduced lactotroph responsiveness to dopamine suppression (25). Juvenile hemochromatosis (type 2) can present with delayed puberty or permanent hypogonadotropic hypogonadism with no additional pituitary deficiencies due to mutations in hemojuvelin (*HJV*) gene (type 2A) or hepcidin antimicrobial peptide (*HAMP*) gene (type 2B) (52). Treatment of the underlying pathology will usually result in the normalization of serum prolactin levels and the HPO axis.

Use of any medication or drug causing hyperprolactinemia or decreasing pituitary sensitivity to GnRH stimulation has to be reviewed (Table 1). Opiates

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suppress LH secretion, resulting in low sex steroid production and clinical hypogonadism (53). Neuroleptics have an antagonistic effect on pituitary dopamine receptors, which diminish the inhibitory effect of dopamine on prolactin secretion (reviewed in (20)). Typical antipsychotics have a more robust effect on elevating prolactin concentrations than atypical antipsychotics, with the exception of risperidone (54). Selective serotonin reuptake inhibitors such as fluoxetine may cause hyperprolactinemia. Certain gastrointestinal motility agents (such as metoclopramide and domperidone) and antihypertensives may cause hyperprolactinemia and amenorrhea through antidopaminergic mode of action (reviewed in (25)).

Hypopituitarism

Hypopituitarism refers to deficiency of one or more hormones produced by the anterior pituitary or released from the posterior pituitary. Hypothalamic–pituitary axis damage due to inflammation, infection, ischemia, hemorrhage or trauma may cause GnRH deficiency and hypopituitarism. Hypophysitis, an inflammatory infiltrate in the pituitary gland is very rare. Lymphocytic hypophysitis occurs typically during pregnancy but also case reports in adolescents with primary amenorrhea exist (55).

Combined pituitary hormone deficiency (CPHD)

Combined pituitary hormone deficiency (CPHD) can be either an acquired or congenital disorder characterized by impaired production of at least two anterior pituitary hormones. Its genetic basis comprises over 30 genes with a variety of syndromic and non-syndromic presentations (56). It may manifest as isolated pituitary hormone deficiencies, component of other syndromes, or pituitary stalk interruption syndrome with ectopic posterior pituitary gland (10). In some instances, hypopituitarism evolves over time, with the last deficiency presenting in adolescence (55).

Mutations in several transcription factors, such as *HESX1*, *LHX3*, *SOX2*, *PITX2*, *GATA2*, *ERG1*, *NR5A1*, *GLI2*, *POU1F1*, *LHX4*, *PITX1*, *OTX2* and *SOX3* can cause syndromic hypopituitarism with gonadotropin deficiency and a wide spectrum of craniofacial or other midline defects or with other clinical findings (1, 55, 57). Autosomal recessive mutations in *PROT1*, being important for the development of gonadotropin-secreting cells, are the most common causes for CPHD in humans (reviewed in (1)).

Empty sella is most often found by a coincidence in brain MRI without any symptoms or deficiencies in hormonal secretion. Primary empty sella syndrome is a rare disorder of the anterior pituitary region due to a congenital defect in the sellar diaphragm. It is characterized by herniation of the subarachnoid space within the sella and pituitary parenchyma compression against the sellar cavity walls causing pituitary dysfunction. Primary empty sella syndrome is rare in children and often associated with hypothalamic–pituitary dysfunction, perinatal complications, or genetic disorders. Secondary empty sella syndrome can occur after trans-sphenoidal neurosurgery, pharmacological or radiotherapy of pituitary tumors (reviewed in (58)).

Evaluation and treatment of hypopituitarism

If pituitary insufficiency is suspected, exploration of the complete pituitary axis (prolactin, FT4, TSH, morning cortisol, ACTH, insulin-like growth factor I), dynamic challenge tests and brain MRI should be performed (55). Management includes replacement therapy of hormonal deficiencies (thyroxine, sex steroids, GH, desmopressin and hydrocortisone), regular screening for the development of new pituitary hormone deficiencies, surveillance of the underlying cause, and management of bone and cardiovascular health and wellbeing of the patient (55). Treatment of gonadotropin deficiency is described later in this review.

Etiologies causing hypergonadotropic hypogonadism

Failure of the ovarian hormone production results in lack of negative feedback on the hypothalamic–pituitary unit and elevated gonadotropin levels. Since the development of phenotypic female genitalia does not require active gonadal function prenatally, and since ovarian hormone production is relatively quiescent during childhood, congenital ovarian failure/agenesis may go unrecognized until adolescence.

Premature ovarian insufficiency (POI)

Premature ovarian insufficiency (POI) is defined as menstrual absence or irregularity with elevated gonadotropin levels on two occasions separated at least 4 weeks apart and low E2 levels before 40 years of age (59). The diagnostic increase in FSH level varies according

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to source from >25 IU/L (58) to >40 IU/L (60). POI in adolescence or presenting as primary amenorrhea is rare and most often associated with chromosomal aberrations or iatrogenic causes such as previous cytotoxic treatment (chemotherapy or radiation therapy) (61, 62). In a large Chinese POI cohort of 955 women, primary amenorrhea was observed in 14% and chromosomal abnormality was found in 30.7% of them (63). Other less common etiologies include ovarian autoimmunity, infections, pelvic surgery and single gene mutations leading to syndromic or non-syndromic POI (reviewed in (64)) (Fig. 3). Family history of POI has been reported in 12–14% of POI women (63, 65). The genetic background is diverse and mutations in over 75 genes have been found in association with POI; however, its etiology still remains unknown in many cases (66).

In a suspicion of non-iatrogenic POI, chromosomal analysis is a key diagnostic test to rule out Turner syndrome and 46,XY gonadal dysgenesis. If chromosomal analysis is normal, screening of 21-hydroxylase antibodies (or adrenocortical antibodies) and thyroid peroxidase antibodies should be considered. Routine autosomal genetic testing is not recommended. Fragile-X premutation testing should not be obtained unless the significance and consequences of a positive result are discussed first (associated intellectual disability in family members) (59).

POI has a negative impact on bone health and lower BMD has been reported in women with POI presenting as primary vs secondary amenorrhea (65). In addition, POI is associated with cardiovascular, psychological, sexual and neurological sequelae, and follow-up of a multidisciplinary team is warranted. Diagnosis of POI and associated fertility issues may be emotionally devastating, and psychological support should be offered to all adolescents at the time of POI diagnosis.

Turner syndrome

Turner syndrome is the most common non-iatrogenic cause of POI in adolescents (61, 62). The incidence of Turner syndrome is approximately 50/100 000 females (67). In the most common form of Turner syndrome (40–50% of cases), the other X chromosome is missing completely (karyotype 45,X) (68). In mosaic forms, there is a cell line with X monosomy and a 46,XX cell line (45,X/46,XX; 15–25%), a 46,XY cell line (45,X/46,XY; 10–12%) or a cell line with three X chromosomes (3%) (68). Structural aberrations of the second X chromosome may be present (such as ring X chromosome).

Typical phenotypic features include short stature (95–100%), characteristic facial and skeletal signs, congenital heart disease (50%) and kidney anomalies, and milder phenotypes are seen in mosaic forms (68). Phenotypic features may lead to prenatal suspicion and diagnosis of Turner syndrome; however, the median age at diagnosis has been late (15.1 years in a Danish registry during 1961–2014) (67). Screening of associated features and morbidities should be commenced after diagnosis (presented in recent clinical practice guidelines (68)).

Accelerated loss of germ cells in Turner syndrome starts prenatally and depletion of the ovarian follicle pool results in POI prepubertally or during adolescence. In a recent systematic review including data from over 2500 girls with Turner syndrome (69), spontaneous thelarche was reported in 32% at the average age of 12.3 years, and spontaneous menarche in 20.8% at the average age of 13.2 years. In girls with 45,X karyotype, the rates of spontaneous thelarche and menarche were lowest, 13 and 9.1% respectively. In mosaic forms, the rate of spontaneous thelarche ranged from 31 to 88% and that of spontaneous menarche from 13 to 66%.

HRT in Turner syndrome should be optimized for linear growth. GH therapy is a standard treatment in short girls with Turner syndrome but in case of late diagnosis, the remaining growth potential (evaluated as the level of epiphyseal closure on an X-ray of the left hand and wrist, i.e. bone age) may be limited. In some cases with late diagnosis, treatment with oxandrolone (an anabolic steroid) may result in a better gain of height than growth hormone alone; however, associated symptoms of virilization are possible (68). If growth potential exists, estrogen replacement should be started with low doses to allow for a long period of other growth promoting therapies. FSH level over 10 IU/L at 10 years of age in Turner girls is considered to be a sign of ovarian failure and an indication for pubertal induction from the age of 11–12 years (70). In very short girls, the induction may be delayed, however, not past 14 years (71) and also longer time for induction could be used.

In rare cases, spontaneous pregnancies in women with Turner syndrome have been reported; however, in the majority of cases, assisted reproductive technologies are required to treat infertility. The risk of pregnancy complications, both maternal and fetal, is increased in Turner syndrome. It is recommended that counselling concerning the fertility issues is started at the time of diagnosis (68). In girls with Turner syndrome with Y-chromosomal material, gonadectomy is recommended because of the increased risk of malignant germ cell tumors (68).

46,XY differences of sexual development (DSD) presenting as delayed puberty or primary amenorrhea

Sometimes chromosomal analysis may reveal a male karyotype (46,XY) in an adolescent girl with either delayed puberty or primary amenorrhea (Figs 2 and 3). Since the embryonic development of phenotypic male external and internal genitalia requires active testicular hormone production, mutations in genes affecting early gonadal development (e.g. *WT1*, *NR5A1*) or gonadal differentiation (e.g. *SRY*, *SOX9*) may lead to failure in testis development and prevention of masculinization. Instead, genitalia develop into a typical female and the gonad develops into ovary, ovotestis or a streak. At least 16 genes have been described in association with 46,XY complete gonadal dysgenesis, sometimes with syndromic appearance involving for example, defects in renal and adrenal development (72).

The prevalence of 46,XY gonadal dysgenesis is 1.5/100 000 (73). The diagnosis is typically made in puberty due to pubertal delay or primary amenorrhea. Due to a significant risk of germ cell tumors, the recent consensus statement recommends gonadectomy at the time of diagnosis (74). Discussion between the family and multidisciplinary DSD team before gonadectomy is essential.

Defects in androgen production due to gonadotropin resistance (*LHCGR* mutation), mutations in steroidogenic enzymes (e.g. *CYP17A1*, *SRD5A2*, *HSD17B3*) or the androgen receptor (*AR*) may result in development of phenotypic female external genitalia with abdominal or undescended testes (sometimes misdiagnosed as inguinal hernias), and lack of Wolffian structures in genetic males with 46,XY karyotype. Because testicular anti-Müllerian hormone secretion remains intact in these conditions, Müllerian structures regress leading to absence of the fallopian tubes, uterus, cervix, and upper vagina. Distal vagina is of different embryonic origin (urogenital sinus) and normally fuses with the upper part but in these cases it develops into a vaginal pouch.

Androgen insensitivity syndrome (AIS) due to mutations in the *AR* gene is the most common genetic defect in 46,XY females with prevalence of 4.1/100 000 women (73). Testosterone levels are very high with normal or high LH levels. Presentation with inguinal hernia may lead to prepubertal diagnosis; however, typical presentation in an adolescent is primary amenorrhea with some or full breast development (aromatization of testicular androgens to estrogens) but scanty axillary or pubic hair (73). Mild clitoral enlargement may be

present depending on the degree of AR insensitivity. In the complete form of AIS (CAIS), the risk of developing a germ cell tumor is lower than in partial AIS (PAIS) and gonadectomy may be postponed after puberty allowing spontaneous breast development (74). Dilation of the vaginal pouch enables sexual intercourse, surgical vaginoplasty is rarely required (75).

46,XX DSD presenting as pubertal delay or primary amenorrhea

If no sex chromosomal aberration is detected, ovarian insufficiency may be caused by mutations in genes involved in gonadal development (ovarian dysgenesis) or ovarian estrogen production. The clinical presentation of ovarian dysgenesis is absent or incomplete pubertal development with normal female reproductive organs except for streak ovaries. In genetically heterogeneous Perrault syndrome, ovarian dysgenesis is associated with bilateral sensorineural hearing defect (64).

Ovarian estrogen production may be blocked by gonadotropin resistance (e.g. *FSHR* mutations) or mutations in steroidogenic enzymes (e.g. *CYP17A1*, *CYP19A1*). 17-hydroxylase deficiency (mutation in *CYP17A1*) blocks the production of C19 steroids in both gonads and adrenals and may present as an adolescent girl with lack of pubertal development, low-renin hypertension and hypokalemia (76). Adrenal crisis is prevented by high corticosterone levels that substitute cortisol. Aromatase deficiency (*CYP19A1* mutation) in a girl is usually detected already at birth due to virilization, which worsens at puberty and no breast development is observed (77). Ovarian cysts may be present in both conditions due to high gonadotropin stimulation. In contrast, ovaries in girls with *FSHR* mutations are small and follicular development is halted to primary stage due to the block in FSH action (64).

Etiologies causing primary amenorrhea with normogonadotropic hypogonadism

Primary amenorrhea and androgen excess

Androgen excess may present in adolescent girls as menstrual disturbances including primary amenorrhea in association with previous premature adrenarche, severe acne, hirsutism, androgenic alopecia (male pattern baldness), clitoral enlargement and voice deepening. If there is an evidence of clinical hyperandrogenism, serum

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(free) testosterone, DHEA-S, androstenedione and 17-OHP levels should be obtained (20).

Polycystic ovary syndrome (PCOS)

PCOS is the most common hyperandrogenic disorder in adolescent girls. PCOS may present as primary or more commonly secondary amenorrhea although oligomenorrhea is the most typical menstrual disturbance (78). The suggested diagnostic criteria for PCOS in adolescence are clinical or biochemical hyperandrogenism (calculated free testosterone, free androgen index or bioavailable testosterone using liquid chromatography–mass spectrometry or extraction/chromatography immunoassays) with menstrual irregularity or primary amenorrhea and exclusion of other conditions that mimic PCOS (79, 80). Polycystic ovarian morphology is not required for PCOS diagnosis in adolescents since multifollicular appearance is common for age (79). Obesity or overweight is a common feature but not required for diagnosis. In PCOS adolescents, primary amenorrhea has been associated with more severe metabolic disturbances such as higher testosterone, insulin and triglyceride levels, and higher prevalence of acanthosis nigricans in comparison to PCOS with secondary amenorrhea or oligomenorrhea (78, 81). Therefore, routine evaluation for type 2 diabetes, insulin resistance, dyslipidemia, and hypertension in PCOS patients with primary amenorrhea is justified. The treatment of PCOS includes life-style intervention, combined oral contraceptive pills and metformin (80).

Non-classic congenital adrenal hyperplasia (NCAH)

In non-classic congenital adrenal hyperplasia (NCAH) due to 21-hydroxylase defect (the most common form of CAH), the symptoms of androgen excess are not present until later in childhood or sometimes even in adulthood. Newborn screening rarely detects NCAH. It may present as premature pubarche/adrenarche, severe acne, hirsutism, primary amenorrhea/menstrual irregularity or clitoromegaly (82). The prevalence of NCAH varies between ethnicities and has been estimated to be from 1:100 to 1:2000 women (83). Non-stimulated, early morning level of 17-OHP >6 nmol/L is suggestive of NCAH and should be controlled with an ACTH stimulation test: stimulated 17-OHP level >30 nmol/L at 60 min is diagnostic for the disease. Genetic analysis of *CYP21A2* gene is recommended, and compound heterozygous forms

are typical. Other forms of NCAH (mutations in *CYP11B1* or *HSD3B2*) are extremely rare (83). Primary amenorrhea in an NCAH patient is an indication for hydrocortisone treatment to suppress androgen levels (82).

Rare causes of androgen excess or virilization in adolescence

Highly elevated DHEA-S and/or androstenedione levels are seen in androgen secreting tumors of adrenal (84) or ovarian origin. Cushing's disease may result in adrenal hyperandrogenism due to ACTH excess. Hypercortisolism may also be due to ectopic ACTH or CRH production by neuroendocrine neoplasms and ACTH-independent cortisol overproduction by adrenal adenomas or carcinomas. In addition to all above mentioned forms of hypercortisolism (representing 'endogenous Cushing's syndrome'), therapeutically used glucocorticoids may cause 'exogenous Cushing's syndrome' (85). If Cushing's syndrome is suspected, a 24-h urinary free cortisol, late-night salivary cortisol, or a 1-mg overnight dexamethasone suppression can be used as screening tests. Additional positive test is needed to confirm the diagnosis (86).

Mutations in genes encoding 5 α -reductase-2 (*SRD5A2*) and 17 β -hydroxysteroid dehydrogenase 3 (*HSD17B3*) cause 46,XY DSD presenting with female/ambiguous genitalia at birth but progressive virilization during puberty. Aromatase deficiency due to *CYP19A1* mutations in 46,XX DSD is associated with ambiguous genitalia at birth and virilization during puberty.

Anatomical causes of primary amenorrhea

Primary amenorrhea with otherwise normal pubertal development and normogonadotropic hypogonadism may be caused by congenital anomalies of the derivatives of the Müllerian ducts (uterus, cervix, upper vagina) or urogenital sinus (hymen, distal vagina) or a defect in their fusion. In this scenario, the approach is a gynecological examination with imaging of the internal reproductive organs with ultrasonography and MRI (87) (Fig. 2). A genital examination is abnormal in approximately 15% of women with primary amenorrhea (17).

Imperforate hymen

Imperforate hymen may present as a bulging mass in blueish or dark color caused by the retained blood in the vagina (hematocolpos). Cyclic or acute pelvic or

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abdominal pain and urinary retention may present. On examination, imperforate hymen should be differentiated from labial adhesions, distal vaginal atresia and transverse vaginal septum. If these can be excluded, the management is by a surgical incision, and long-term sequelae are not expected (88).

Distal vaginal atresia

In distal vaginal atresia, evaluation of external genitalia shows pink mucosa without hymenal tissue or a bulge. Urologic or anorectal anomalies may be associated (89).

Transverse vaginal septum

Failure of fusion of the vaginal plate and the urogenital sinus result in transverse vaginal septum. If the septum is imperforate, the obstructed menstrual blood may cause vaginal and uterine enlargement (hematometrocolpos) and abdominal or pelvic pain. The mean age of diagnosis of imperforate transverse septae was 14.3 years in a patient series from a specialized center for Müllerian anomalies in Britain (90). The management is operative and presurgical evaluation should include the location and thickness of the septa (89, 91). The location of the septa has been defined as low (<3 cm from the introitus, 72%), mid (3–6 cm, 22%) and high (>6 cm, 6%), and the thickness (determined by MRI as thick (> 1 cm, 46%) or thin (<1 cm)) (90). A careful presurgical evaluation aids in choice of the best surgical approach (laparotomy, laparoscopy or vaginal approach) to minimize the risk of complications. A surgical management should be performed in specialized centers. High and thick septae are associated with the higher rate of post-operative complications and need for re-surgery (90). Prior to operative treatment, continuous combined oral contraceptive pills or GnRH analogs can be used to prevent further uterine bleeding (89). Obstruction and retrograde menstruation are associated with endometriosis (89).

Cervical agenesis

Cervical agenesis may be isolated but is often associated with vaginal agenesis. Obstruction of the menstrual flow results in hematometra, retrograde menstrual flow, endometriosis and pelvic adhesions which may complicate surgical treatment. Different treatment modalities exist (92).

Müllerian agenesis

Müllerian agenesis, also known as Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome is a failure of the Müllerian duct development resulting in agenesis of the uterus and upper two-thirds of vagina in women with 46,XX karyotype. Estimated prevalence is 1:5000 women. Secondary sexual characteristics develop normally, and external genitalia are typical female but the vagina is short and blind-ended and primary amenorrhea is a typical complaint leading to diagnosis. Chromosomal analysis aids in differentiating Müllerian agenesis from 46,XY DSD with similar presentation (Fig. 2). Renal, skeletal, hearing and cardiac complications may be associated. The genetic background is not clear. Vaginal agenesis is treated by non-invasive vaginal dilatation (first-line therapy) or vaginoplasty. Genetic motherhood is possible by using gestational surrogacy. As a result of uterine transplantation and embryo transfer, women with MRKH have been able to give birth (93).

Induction and maintenance of pubertal developmentThe induction and maintenance of pubertal development in girls is similar in both hypogonadotropic and hypergonadotropic hypogonadism and aim at physical and psychosocial development at a similar tempo and magnitude as in peers. More specifically, the aims are to induce proper breast development, adult-sized and -shaped uterus enabling possible later pregnancies, growth spurt that results in adult height close to expected, and achievement of normal peak bone mass.

Estrogen replacement is initiated with small doses and gradually increased over 2–3 years to full adult dose. Detailed instructions for either transdermal or oral estrogen administration have been described in recent review articles for girls with Turner syndrome (70, 71) or hypogonadal girls, in general (94, 95). In general, transdermal route and natural 17 β -estradiol instead of synthetic ethinyl estradiol is preferred. The dose may be titrated for body weight (70) or fixed increments for every 6 months could be used (71). The availability of hormonal preparations varies from country to country and influences the choice of treatment. Individualization of the treatment may result in better compliance and benefits of the treatment should be explained carefully. Progestin is added when breakthrough bleeding occurs or after 2–2.5 years of unopposed estrogen replacement. The thickness of endometrium may be evaluated by transabdominal ultrasonography to optimize the initiation of cyclic progestin. Ten days of progestin for every 1–3 months protects from estrogen-induced endometrial hyperplasia and irregular bleeding.

Since permanent hypogonadotropic hypogonadism may not be indistinguishable from CDGP, temporal withdrawal of hormone replacement and observance of spontaneous HPO axis function should be performed to confirm the diagnosis and need for permanent HRT. Finally, BMD should be measured after a full dose of HRT has been used for 1 to 2 years.

Conclusions

Multiple etiologies affecting the HPO axis and outflow tract may underlie primary amenorrhea. Its long-term health risks vary depending on its cause and include innate problems of the underlying etiology, hypoestrogen-related problems, feelings of defeminization, sexual dysfunction and infertility. Diagnostics of primary amenorrhea in teenagers often needs collaboration between the pediatric endocrinologist and gynecologist. Especially in younger females with primary amenorrhea despite normal pubertal development, the first-line approach is external gynecological examination with transabdominal sonography of the internal reproductive organs. Gene discoveries are expanding in several fields underlying primary amenorrhea. However, genetic testing should be used cautiously; although it is recommended in the diagnosis of CHH and NCAH, in POI, genetic testing is not yet as advanced, and therefore, routine autosomal genetic testing is not recommended.

The psychosocial impact of primary amenorrhea should not be neglected. Early diagnosis, timely HRT (if needed), and psychological support alleviate the psychological burden associated with delayed or arrested sexual maturation or infertility. Treatment involves medication to recompense the lack of estrogen and progesterone, and later more complex management in patients with permanent hypogonadism. In central pathologies in the absence of a male factor of infertility, reproductive capacity is quite good, whereas in POI, fertility is always threatened. However, with timely diagnosis fertility may be attained even in those situations where no curable treatment exists.

Declaration of interest

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