Delayed Puberty: Impact on Female Fertility

11

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11.1 Introductory Remarks

Puberty is the period of life that leads to adulthood through complicated and sometimes painful physiological and psychological changes. The hypothalamic-pituitary-gonadal axis undergoes an active phase during foetal and neonatal development and then enters a resting phase that lasts for the rest of childhood until puberty. Puberty begins with an activation of the hypothalamic-pituitary-gonadal system. It occurs today earlier than a century and even earlier than 20 years ago. Delayed puberty may have a dramatic impact on the mental and social development of an adolescent. In the literature, different definitions for "delayed puberty" can be found and there are no guidelines indicating when in the absence of pubertal signs an investigation should be started. Usually, in girls, a first evaluation should be done not later than at the age of 13. However, the initiation of a first evaluation has to be earlier in some cases: it depends on the psychosocial pressure exerted on a child by her personal delay when it is compared to the pubertal development of the pair group of schoolmates and friends. One aspect that quite often worries the patient and her parents the most is the impact of delayed puberty might have on later fertility.

This chapter intends to give a short overview for non-specialized endocrinologists over normal puberty, the practically most important forms of delayed puberty and the measures to be taken.

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11.2 Normal Puberty

11.2.1 Clinical Aspects

The clinical onset of external pubertal development is announced by the appearance of secondary sex characteristics. In females, these signs are the appearance of breast buds and of pubic and axillary hair.

The development of secondary sex characteristics is rated into five stages according to Tanner's criteria [1–5]. They evolve progressively over several years until adulthood is reached and are designated as Tanner stages B1 through B5 for breast development and PH1 through PH6 for pubic hair growth (Figs. 11.1 and 11.2). A detailed description of the Tanner stages can be found in standard textbooks of paediatrics and paediatric or gynaecological endocrinology [1–3].

In girls, pubertal growth spurt occurs during Tanner stages 2 and 3. In girls, it occurs 2 years earlier than in boys. Girls do not show the same slowing down of growth velocity as boys before puberty and increase their growth velocity to 6 cm/year during the first year of puberty, and to 8 cm/year on average during the second year [6].

Menarche A variety of environmental and genetic factors are involved in the regulation of menarche. The first menstrual period (menarche) occurs at an average age of 13.4 years, according to the longitudinal data obtained by Largo et al. [4].

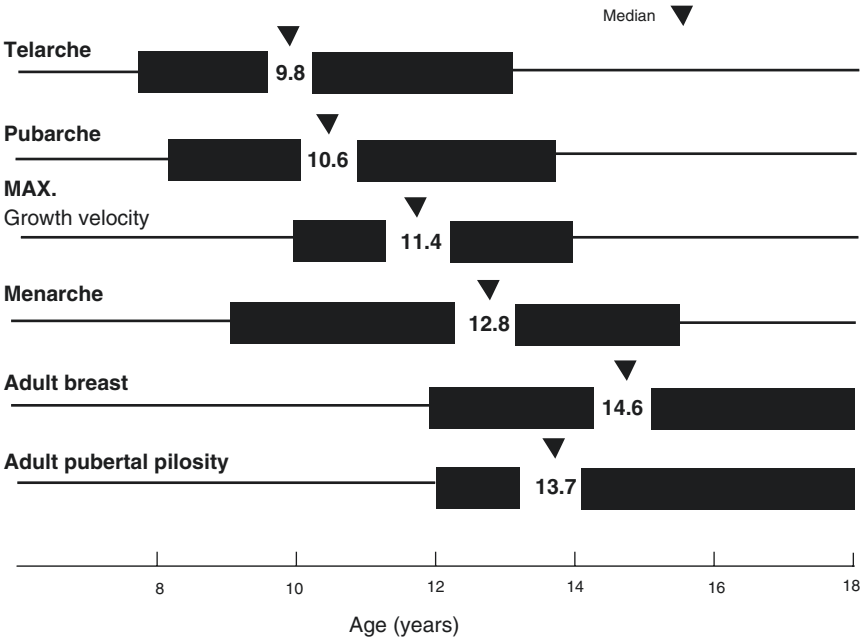

Fig. 11.1 The sequence of events during puberty in girls. Breast bud appearance is usually before pubic hair growth; in the meantime growth velocity increases reaching the peak at Stage 4 of puberty. At this time menarche may appear [4]

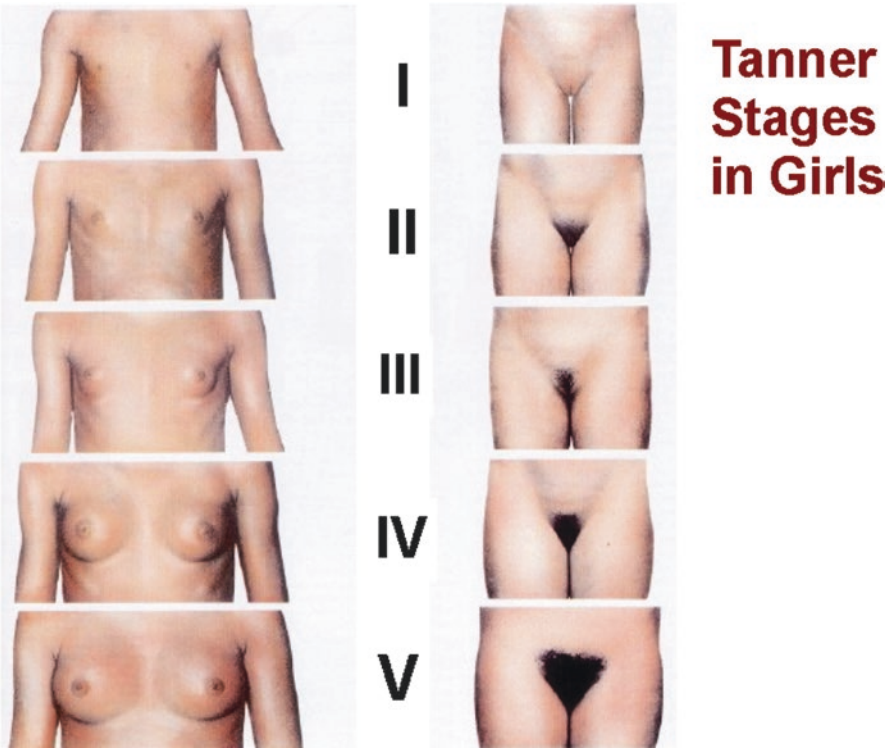

Fig. 11.2 Breast development in girls. The mammary gland grows from a breast bud that can be palpated under the nipple (Tanner stage B2) to a fully developed female breast (Tanner stage B4 or B5) over a period of 3.6 years, on average [4]

Menarche occurs generally at Tanner stage 4. The mean age at menarche is highly correlated within families, between monozygotic twins, and within ethnic groups [7]. Twin analyses suggest that 53–74 % of the variation in age of menarche may be attributed to genetic effects [7].

11.2.2 Endocrinological Aspects of Normal Puberty

11.2.2.1 Adrenarche

Endocrinologically, the first signal for puberty is given by the adrenals (adrenarche). The onset of DHEA-S production from the adrenal zona reticularis leads to the phenomenon of adrenarche.

During infancy and early childhood, adrenal androgens (androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone-sulphate) are secreted in small amounts. Their secretion increases gradually with age. This increase in androgen levels is responsible for the appearance of body odour, pubic hair and axillary hair. Therefore, pubic hair develops independently of the activation of the hypothalamic-pituitary-gonadal pathways.

Adrenarche is marked by the growth of the zona reticularis [8] and a parallel increase in the adrenal androgen levels. This phenomenon is only seen in the human beings and in some old world primates, such as the chimpanzee [9]. Plasma concentrations of the adrenal androgens increase, whereas those of cortisol remain stable, suggesting that factors other than corticotropin are involved. Hormones postulated for this role are the yet undefined androgen-stimulating factor, Corticotrophin Releasing Hormone (CRH) and more recently hormones related to body mass, such as insulin and leptin [10–13]. Although the temporal relation between adrenarche and the onset of puberty suggests that adrenal androgens might have a regulatory influence on the timing of puberty, it is now accepted that the two events are independent processes.

11.2.2.2 Regulation of the Hypothalamo-Hypophyseal-Gonadal Axis

Gonadotropin releasing-hormone Gonadotropin releasing-hormone (GnRH), a decapeptide secreted by approximately 1000 neurons located in the basal forebrain and extending from the olfactory bulbs to the mediobasal hypothalamus, is responsible for the gonadotropin secretion by the pituitary gland. GnRH stimulates the release of LH and FSH from the pituitary which in turn stimulate the gonads. LH and FSH have negative feedback effects on the hypothalamus, whereas testosterone (T) and Androstenedione (A) produced by the testis, and Estradiol (E2) produced by the ovary, inhibit both the hypothalamus and the pituitary gland. Inhibin, activin, and follistatin have also feedback effects at both levels. GnRH secretion by the hypothalamus is under the control of a great amount of central and peripheral signals: excitatory amino acids and other neurotransmitters such GABA, gonadal sex steroids, adrenal and thyroid hormones, the GH-IGF-IGFBP axis, nutrition and related hormones such as leptin and insulin (Fig. 11.3).

Two types of GnRH neurons have been identified to date, GnRH neuron I and II. GnRH neurons II have no known function in humans and are not involved in reproductive function, as inferred from Kallmann's syndrome patients in whom GnRH neurons I only are affected. GnRH neurons I originate in the embryonic period and exhibit an endogenous secretion very early in development. After birth, their activity is "turned-off" by the low circulating levels of androgens/oestrogens released by the gonads, by means of a negative feedback mechanism. At puberty, the reactivation of this "gonadostat" is independent of the effect exerted by the steroids and is related to a reduced sensitivity to their action [14–17].

Transcriptional factors Recently three *transcriptional factors*, Oct-2, TTF-1, and EAP-1, have been identified as potential regulators of the cell network, which controls the GnRH secretion ("Upstream control"). They regulate the expression of genes involved in cell function and cell-cell communication (for details, see [18–21]. In the mammalian, hypothalamic lesions that induce sexual precocity activate both Oct-2 and TGF <61537>expression in astrocytes near the lesion site [18], suggesting that TGF <61537>is one of Oct-2 target.

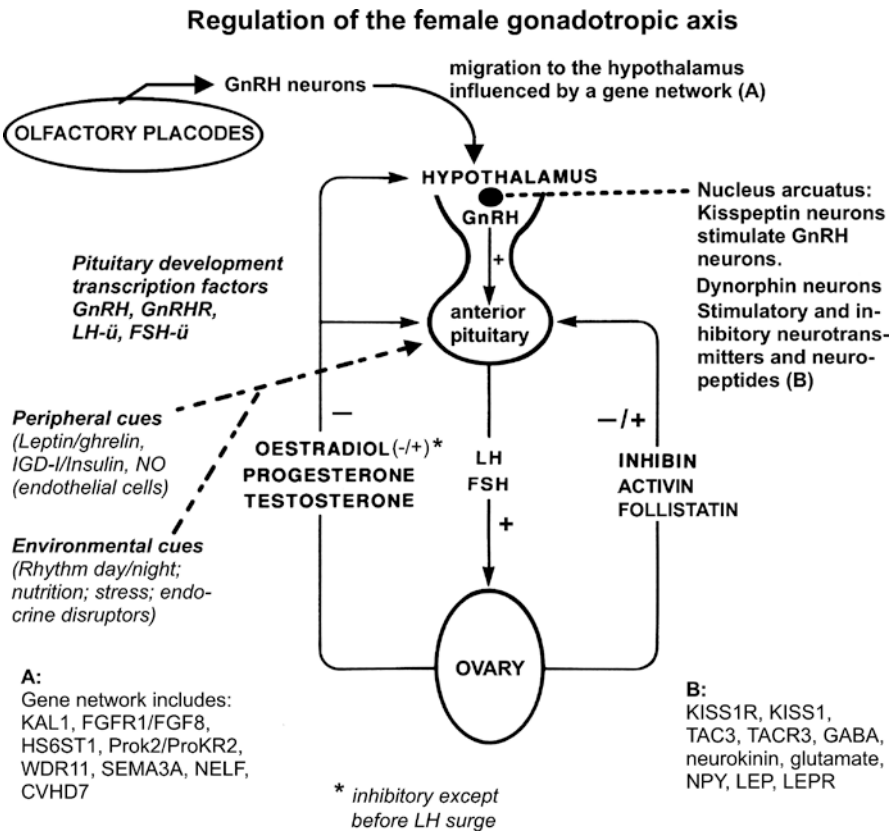

Fig. 11.3 Principals of the development and the regulation of the female gonadotropic axis (see text)

The second candidate is TTF-1 (thyroid transcriptional factor-1), another homeobox gene. After birth, it remains expressed in selected neuronal and glial population of the hypothalamus. At the onset of puberty, TTF-1 enhances GnRH and erbB2 and KiSS-1 gene transcription but inhibits preproenkephalin promoter activity [19].

The third candidate is EAP-1, earlier known as C14ORF4. Like TTF-1, EAP-1 transactivates the promoter of genes involved in facilitating the advent of puberty while suppressing the expression of genes inhibitory to the pubertal process. Knocking down hypothalamic EAP-1 expression causes delayed puberty and disrupted oestrous cyclicity, both in rats and monkeys [20, 21].

KiSS-1/GPR54 system Kisspeptin/metastin (KiSS-1) is a 53-amino-acid-peptide, earlier known as a suppressor of tumour metastases [22, 23]. The proteolitic cleavage of the primary KiSS-1 protein product originates the decapeptide kisspeptin-10 (KiSS-10), whose target is GPR54 receptor. GPR54-containing cells are diffusely distributed [24, 25]. Kiss neurons are important for the gonadal axis. They are located in

discrete neuronal subsets of the preoptic area and the nucleus arcuatus [24, 26]. These cells include GnRH neurons and the anterior pituitary [27, 28].

The KiSS-1/GPR54 system has been recognized recently as the director of central functional network and peripheral signals. Genetic, physiological and clinical data strongly indicate that the KiSS-1/GPR system is an essential gatekeeper of GnRH function, and not just one more element in the cascade of signals controlling the gonadotropic axis. It allows the integration of central and peripheral inputs and plays therefore a decisive role in the control of reproductive function [29].

Both in rats and in primates, a marked increase in KiSS-1 and GPR54 mRNA levels coincide with the onset of puberty [24, 30]. Moreover, the sensitivity of GnRH system to kisspeptin is dramatically enhanced in adult versus juvenile mice [42]. Thus, the developmental activation of the GnRH axis by KiSS-1 at puberty reflects a dual phenomenon involving, not only the increase of kisspeptin tone, but also the enhancement of its efficiency to activate GnRH neurons, probably through post-transcriptional changes in GPR54 signalling [31].

Hypothalamic KiSS-1 system also plays an essential role in relaying the negative feedback input of sex steroids onto GnRH neurons. In male and female rats, bilateral gonadectomy evoked a consistent increase in KiSS-1 mRNA at the hypothalamus. Recent studies added further elements to the role of kisspeptin in the feedback control of gonadotropins by showing that negative regulation of hypothalamic KiSS-1 gene expression by oestrogen appears to be restricted to the nucleus arcuatus (Arc), known to be pivotal for negative feedback of sex steroids. In contrast, at the anteroventral periventricular nucleus (AVPN), KiSS-1 mRNA decreased after gonadectomy and increased after sex steroid replacement [32, 33]. AVPN is involved in mediating the positive feedback effects of oestrogen upon GnRH and LH surges. Therefore, via positive regulation of GnRH secretion, KiSS-1 neurons might be involved also in generation of the pre-ovulatory gonadotropin surge.

New strong evidence indicates that hypothalamic KiSS-1 may participate also in delivering information regarding the nutritional status of the organism to GnRH-neurons. Kiss-1 may therefore contribute to the link between energy stores and fertility [34, 35]. It has been shown that the permissive actions of leptin on the reproductive axis are mediated through modulation of GnRH secretion. Because GnRH neurons do not express leptin receptors, [35] kiss peptins might explain badly understood metabolic processes, signalled onto GnRH neurons via peripheral hormones such as leptin. However, several key aspects of the physiology of this system still remain open [36].

In conclusion, KiSS-1 system is an essential downstream element in the negative and (probably) positive feedback loops controlling gonadotropin secretion [37]. In addition, it may participate in the signalling to GnRH neurons of peripheral inputs from hormones such as leptin [38].

Leptin Leptin is a 16-kDa peptide secreted by adipocytes. It is supposed to signal to the brain the critical amount of fat stores necessary for LHRH secretion, which in turn activates the hypothalamic-pituitary-gonadal axis [38]. Leptin was recently

shown to suppress neuropeptide Y (NPY) expression in the nucleus arcuatus. NPY stimulates appetite, has an inhibitory effect on the gonadotropin axis and is involved with the inhibition of puberty in conditions of food restriction. Therefore, it has been hypothesized that leptin might exert its effects by acting on NPY. Under favourable nutritional conditions, the rise in leptin levels would suppress NPY, and in turn release the inhibitory effect of NPY neurons on the GnRH-LH/FSH axis, allowing the initiation of puberty [39].

On the other hand, there might be a direct peripheral negative effect of leptin on gonadal function through inhibition of the steroidogenic enzymes [39, 40].

In humans and animals, leptin blood concentrations rise with the onset of puberty. In adolescents of both sexes, the gradual rise in serum leptin levels before puberty together with a decline in circulating levels of soluble leptin receptor suggest that these changes may serve as one of the signals to the central nervous system that metabolic conditions are adequate to support pubertal development and trigger puberty [41].

No gender differences were detected in the relationship between leptin serum levels and fat mass in pre-pubertal and early pubertal subjects. In contrast, at Tanner stages IV and V, the serum hormone concentrations decrease in males and increase in females. In addition, a significant negative correlation between circulating concentrations of testosterone and leptin was described in males only [38].

Finally, it has been shown that normal leptin levels are necessary for the maintenance of menstrual cycles and normal reproductive function in adolescents of both sexes.

In conclusion, leptin seems to exert a positive central effect on the hypothalamic-pituitary-gonadal axis and a negative peripheral one on the gonads. Leptin might signal that the metabolic conditions are adequate to support pubertal development and trigger puberty.

Inhibin, activin, and follistatin Inhibin and follistatin inhibit, and activin stimulates the expression, biosynthesis, and secretion of FSH [42–44]. They are synthesized mainly in the gonads. Inhibin, follistatin and activin are all three involved in the modulation of the hypophyseal-gonadal axis function. Inhibin and follistatin are both negative regulators of FSH secretion.

Inhibin, a heterodimeric glycoprotein, belongs to the TGF-b super family produced by ovarian granulosa cells. It is composed of an alpha and one or two beta subunits. These form two different products, inhibin A and B, respectively. FSH stimulates the synthesis and secretion of inhibins by the gonads, which in turn are involved in the feedback regulation of FSH secretion. In girls, inhibin A concentrations increase between stage 2 and 3 of puberty, remain constant throughout stages 4 and 5, and correlate positively with bone age, inhibin B and oestradiol serum levels [45, 46]. Inhibin B blood concentrations increase further similarly to inhibin A levels, reaching a plateau at 12–18 years. They correlate with oestradiol [45, 46] and FSH serum levels [48].

Blood concentrations of follistatin decrease slightly from stage 1–4 and 5 of puberty in girls [46]. Blood levels of activin A were shown to remain unmodified from stage 1–3 of puberty in females [48].

In conclusion, at puberty the concentrations of the two negative regulators of FSH secretion, inhibin and follistatin, change in opposite directions [46], whereas the blood levels of a positive regulator, activin A, increase, at least in females. All together, these alterations in serum concentrations of FSH-regulatory peptides lead to an increase in FSH secretion.

Melatonin The marked increase in LH amplitude at night observed in early puberty occurs at the same time of melatonin secretion. On the other hand, precocious puberty associated with pineal tumours and due to ectopic secretion of gonadotropins is independent of melatonin [14]. The role of melatonin in puberty is questioned.

Other hormones Growth hormone (GH), insulin, insulin-like growth factor (IGF)-I, and its major binding protein, IGFBP-3, normally rise at puberty [49]. The increase in growth hormone and IGF-I concentrations is probably responsible for most of the metabolic changes observed during puberty, including insulin-resistance, increased beta-cell response to glucose, and growth spurt. GH, and not androgens, may directly affect insulin sensitivity regulating the glucose-insulin homeostasis at the time of puberty [50]. Adiponectin, an adipocytokine with antidiabetic and antiatherogenic effects, were recently shown to progressively decline in parallel with pubertal development in boys [51]. It is inversely related to serum testosterone and dehydroepiandrosterone sulphate levels [51].

11.2.3 Pubertal Maturation of the Hypothalamo-Hypophyseal-Gonadal Axis (Fig. 11.5)

The hypothalamic-pituitary-gonadal axis undergoes an active phase during foetal and neonatal development and then enters a resting phase that lasts for the rest of childhood until puberty.

Puberty begins with an activation of the hypothalamic-pituitary-gonadal system. Changes in GnRH pulsatility during puberty are reflected by the peripheral LH- and FSH-Levels. Qualitative and quantitative changes in LH secretion resulting from pulsatile GnRH secretion, occur approximately 2 years before the appearance of secondary sexual characteristics. At puberty, LH pulsatile secretion is characterized by a 28-fold increase in the pulse amplitude, whereas pulse frequency increases only 1.8-fold. During prepubertal years, both LH and FSH secretions are preponderant during night-time. In the peripubertal period the secretion of gonadotropins increases during sleep, and stimulation with exogenous GnRH shows an enhanced release of LH from the pituitary gland that may be useful in differentiating a pubertal from a pre-pubertal response. Throughout puberty then, gonadotropin pulses further increase becoming apparent during daytime also.

Several studies have been published suggesting that the mechanisms underlying the onset of puberty are different in girls and boys, and different modes of transmission of induction of puberty in boys and girls were revealed [52]. Among other differences, in girls, FSH levels increase during the early stages, and LH levels during the later stages of puberty with a 100-fold increase in hormone concentrations. In contrast, in boys, FSH levels rise progressively through puberty with an increase in amplitude only, whereas LH levels increase in early puberty reaching a plateau shortly [14, 17].

11.2.4 Acceleration of Puberty

Puberty occurs today earlier than a century and even earlier than half a century or 20 years ago. In Tanner's original report [1, 5] white girls had a mean age at onset of breast development and pubic hair of 11.2 and 11.7 years, respectively. The normal mean age at onset of pubertal characteristics in young girls has been revised in 1997 in a considerable population of 17,000 girls evaluated in a cross-sectional study [53]. It has been shown to vary with race, ethnicity, geographical location, and environmental and nutritional conditions.

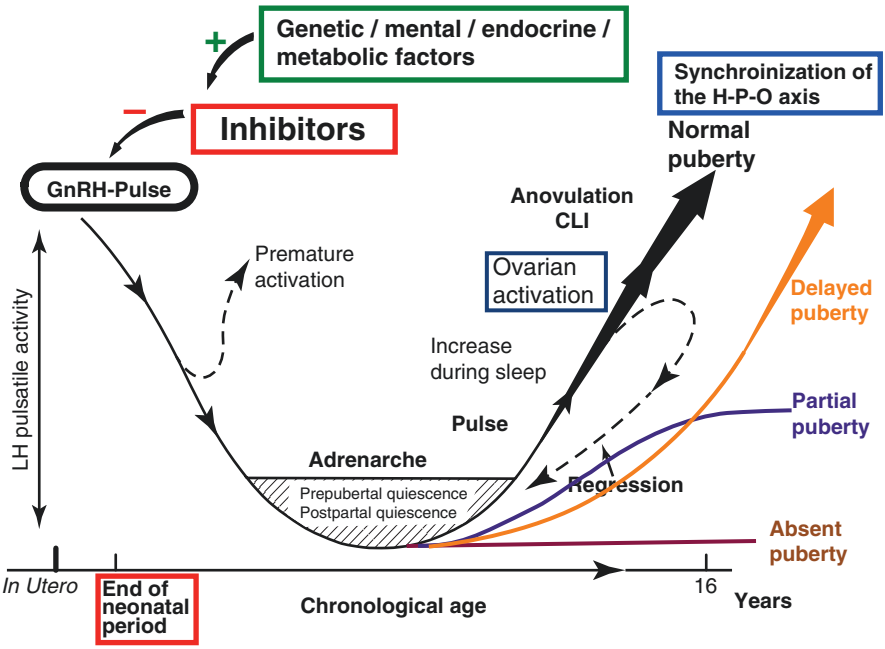

Fig. 11.4 Normal and delayed maturation of the hypothalamo-hypophyseal-gonadal axis (H-P-O-axis). Onset of puberty implies the regression of the inhibitory factors blocking the gonadal axis in childhood. Maturation and activation of the ovarian axis can be interrupted at each stage and may even regress to prepubertal quiescence

Compared to Tanner's original report, pubertal development appears to begin up to 1 year in advance in white and up to 2 years in African-American girls. Breast stage 2 is reported to occur in white girls at 9.96 ± 1.82 years (mean ± SD) with upper and lower limits of 7 and 13 years, and in African-American at 8.87 ± 1.93 years with limits between 6 and 13 years. Pubic hair would occur at 10.51 ± 1.67 and 8.78 ± 2.00 year in white and African-American girls, respectively [54]. In the US white girls puberty would begin by 10 years of age on average, and African American between 8 and 9 years [1, 5, 54, 55].

The age of menarche has been shown to decrease significantly since the nineteenth century. With respect to the first data published by Tanner [5] and Largo [4] 50 and 30 years ago, respectively, it continues to decrease. Menarche seems to occur earlier in white British girls (13.5 years) in 2004 [56] than in 1962 [5] and is reported to occur at 12.88 ± 1.2 years in white and at 12.16 ± 1.21 year in African-American girls [54]. In 2006, a large German survey found the median age at menarche to be 12.8 years [57], suggesting that the secular trend to an earlier menarche is continuing.

11.3 Delayed Puberty

11.3.1 Definition

Puberty is the period of life that leads to adulthood through complicated and sometimes painful physiological and psychological changes. Delayed puberty may have a dramatic impact on the mental and social development of an adolescent.

In the literature, different definitions for "delayed puberty" can be found.

The classical endocrinological definition and the current paediatric definition are identical for girls, but slightly different for boys:

Endocrinological definition (Grumbach and Styne [42])
: Delayed puberty is defined as the absence of signs of puberty in healthy girls at age 13 years and in healthy boys at the age 13.5 years (2 SD above the mean age at start of puberty).

Paediatric definition: Delayed puberty is defined as the absence of signs of sexual maturation by an age more than 2–2.5 SD values above the mean of the population (traditionally breast development by 13 years in girls and testicular development by 14 years in boys) (Marshall and Tanner [1]; Lee [2]; Brämswig and Dübbers [55]).

11.3.2 Incidence

Delayed puberty is a rare condition, occurring in only approximately 2.5 % of the population. [1, 2, 42, 55]. The relative incidence of the different forms of hypogonadism in delayed puberty is shown on Table 11.1. In the series of Reindollar et al. [58], hypogonadotropic hypogonadism is found in 31 %, hypergonadotropic

Table 11.1 Relative incidence of observed hypogonadism in delayed puberty [58]

Hypogonadotropic Hypogonadismus	*31 %*
Idiopathic	10 %
GnRH-deficiency	7 %
Anorexia	3 %
Other endocrinopathies	4 %
Organic	13 %
Hypergonadotropic Hypogonadismus	*43 %*
Abnormal karyotype	26 %
Normal karyotype	17 %
Eugonadotropic hypogonadism[a]	*26 %*
Rokitansky-Kuster and similar	17 %
Testicular feminization	1 %

[a]Primary amenorrhea in presence of partial or complete development of secondary sex characteristics

hypogonadism in 43 % and eugonadotropic hypogonadism leading to primary amenorrhea in presence of partial or complete development of secondary sex characteristics in 26 %.

11.3.3 When and How to Investigate?

There are no guidelines indicating when in the absence of pubertal signs an investigation should be started. Following both definitions listed above, in girls, a first evaluation should be done not later than at the age of 13.

Important is empathetic counselling to counteract the mostly deep anxiety due to the fact of being different from other girls at the same age. The child and the parents have to be fully and accurately informed and reassured that an underlying pathological process is rare and that the delay of the onset of puberty is mostly due to a benign, often familiar, deviation from the normal time course.

In most recommendations, a precise diagnostic evaluation is recommended in girls with persisting absence of the onset of puberty at the age of 14.5 years (mean + 3 standard deviations). However, a further evaluation is recommended earlier if a girl without onset of puberty starts to suffer because she becomes socially isolated among her classmates because of her physical retardation. Therefore, acceleration of puberty has to be taken into account for the decision when to start clinical evaluation in absence of pubertal signs.

In conclusion, investigation has to be started earlier than it has been recommended 20 years ago. It depends on the psychosocial pressure exerted on a child by the pubertal development of the pair group of schoolmates and friends.

Figure 11.5 presents a simplified flow chart of the assessment of delayed female puberty. It describes schematically the process for the investigation of adolescent girls presenting with lack of spontaneous pubertal development. Shaded boxes show the major differential diagnoses of constitutional delay of growth and puberty,

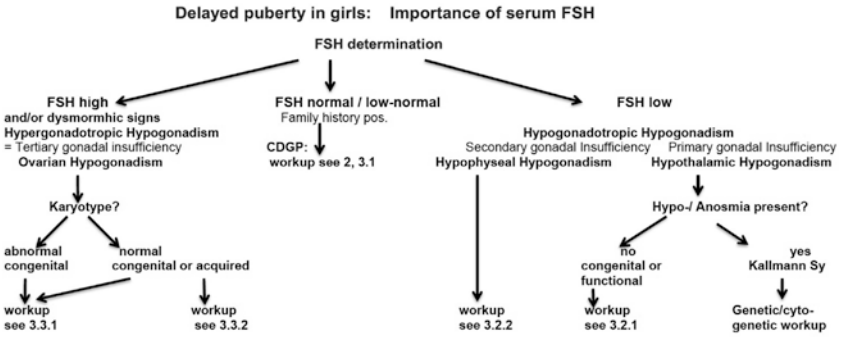

Fig. 11.5 The determination of serum FSH, together with family history and clinical signs, allows in a simple way a first preliminary classification of girls suffering from delayed puberty. Workup numbers relate to the chapters of this review

hypogonadotropic hypogonadism, and hypergonadotropic hypogonadism. However, no clinical algorithm can fully meet the requirements of all individual cases. Thus, adapted clinical decision–making is important at each stage.

11.3.3.1 Hormone Measurements

Gonadotropins

- Basal levels of FSH and LH are low in patients with HH or constitutionally delayed puberty and elevated in hypergonadotropic hypogonadism.
- Levels of FSH and LH remain low after one GnRH injection in hypothalamic and in hypophyseal hypogonadism.
- Levels of LH and FHS increase in hypothalamic hypogonadism with intact pituitary function (but not in hypophyseal hypogonadism) after repeated pulsatile administration of GnRH (0.1 mg GnRH per injection).
- When 0.1 mg of GnRH is injected, pubertal onset is characterized by LH/FSH >1.

Oestradiol

In girls, at pubertal onset, oestradiol levels are >40 ng/ml (<10 ng/ml before puberty).

Inhibin B and Anti-Müllerian Hormone (AMH)

The distinction between constitutional delay of growth and puberty (CDGP) and idiopathic hypothalamic or hypophyseal hypogonadism (IHH) is still a difficult clinical issue. Harrington and Palmer conclude that basal inhibin B may offer a simple, discriminatory test if results from recent studies are replicated: very low levels indicate a high likelihood of IHH [59]. However, current literature does not allow today for recommendation of any diagnostic test for routine clinical use. This applies, too, to the clinical use of AMH in the investigation of delayed puberty [60].

Other Hormones to be Checked
Pituitary deficits should be evaluated by measuring IGF-I, T4, TSH and cortisol.

11.3.3.2 Bone Age
A bone age <11 years in girls with growth failure is encountered in constitutionally delayed puberty.

Bone ages >11 years in girls require further investigation to eliminate hypogonadism.

11.3.3.3 Pelvic Abdominal Ultrasonography
In case of hypergonadotropic hypogonadism, gonads may be small or absent. At the onset of puberty, the ovaries develop follicular cysts long before menarche. Multicystic ovaries with more than six cysts are a normal phenomenon and are already observed in the early stages of puberty [61, 62]. At that stage, these normal cysts should not be confounded with an early expression of a later PSO-syndrome. If ovarian volume is >2 ml and the uterus >35 mm, puberty is imminent [63].

The uterine volume increases at first without, and then with, a visible layer of uterine mucosa. This mucosa layer is induced by the slowly increasing oestrogen secretion.

11.3.3.4 Karyotype
Independent of dysmorphic features suggestive of Turner syndrome, a karyotype should be performed in hypergonadotropic hypogonadism if the patient's history (e.g., chemotherapy, X-ray treatment) cannot explain the gonadal pathology.

11.3.3.5 Brain Magnetic Resonance Imaging (MRI)
In presence of unexplained low levels of LH and FSH, organic pituitary or hypothalamic disease should be eliminated. MRI is the most efficient imaging examination. Agenesis of the olfactory bulbs is typical for Kallmann syndrome. Measurement of the pituitary and pituitary stalk is fundamental.

An elaborate discussion of the investigational process is presented by the specialized literature [55, 59, 64, 65].

11.4 Impact on Fertility of the Different Forms of Delayed Puberty

11.4.1 Constitutional Delay of Growth and Puberty

Constitutional delay of growth and puberty (CDGP) is the most common cause of delayed puberty in girls with 30 % of cases, as it is in boys [66]. CDGP is defined as a delay of growth occurring in otherwise healthy adolescents with stature reduced

for chronological age, but generally appropriate for bone age and stage of pubertal development, both of which are usually delayed. It is more frequent in boys than in girls with a 10:1 ratio and is the most common cause of delayed puberty (80–90 %).

In most cases delayed puberty is not due to any underlying pathology, but instead represents an extreme end of the normal spectrum of pubertal timing, a developmental pattern referred to as constitutional delay of growth and maturation [66]. The characteristically retarded linear growth occurs during the early years of life and is followed by regular growth paralleling the normal growth curve throughout the rest of prepubertal years. Pubertal growth spurt is attenuated and occurs after the usual expected time. In girls, exclusive maternal inheritance seems to be the major mode of inheritance whereas for boys the mode of inheritance is almost equally maternal, paternal or bilineal [52]. The majority of cases (70–80 %) are familial. Sedlmyer & Palmert classified family histories of pubertal timing among primary relatives in 95 of 122 of the CD and in 25 of 45 of the functional hypogonadotropic hypogonadism (FHH) cases. Analysis revealed at least a tendency to pubertal delay in 77 % of the CDGP and in 64 % of the FHH families and a diagnosis of delay in 38 % of the CDGP and 44 % of the FHH families. Both parents contributed to the positive family histories. The rates of positive family histories among the CDPD and FHH groups were approximately twice those seen among the other subjects in our case series [66]. Bone mineral density can be compromised by the low serum steroid concentrations measured [67, 68]. Specifically, the attainment of peak bone mass may be impaired, although recent data do not indicate significant changes in volumetric bone mineral density in young men with previous CDGP compared with appropriate controls [69].

The sleep-related increase in LH concentrations that characterizes the onset of puberty, is normally present in CDGP children. As a consequence of inadequate production of gonadal steroids, acute provocative tests may show a GH response wrongly consistent with partial GH deficiency [70]. Pre-treatment with oestrogens in girls results as expected in the normalization of the GH responses. The LH response to the LH-RH analogue leuprolide acetate is intermediate between that of hypogonadal patients and normal pubertal children, and is therefore useful in differentiating CDGP from hypogonadotropic hypogonadism. Recently, a critical appraisal of available diagnostic tests has been published [59].

Supportive care is essential. Although no specific treatment is required, the psychosocial problems faced by CDGP children may force physicians to substitute [55, 64, 71]. In girls, oestrogen therapy is recommended only after statural considerations have been carefully taken into account. Ethinylestradiol should be avoided. The administration of oestrogen, even in small amounts, leads to progressive skeletal maturation, and ultimately to epiphyseal fusion. The use of anabolic steroids or growth hormone to stimulate growth is highly controversial [72–75] and is not recommended in most reviews [66].

The inheritance patter of CDGP has been recently analysed by Winter et al. [52]. In girls, exclusive maternal inheritance seems to be the major mode of inheritance.

Impact on fertility There are no published data suggesting that compared to children with normal puberty, fertility may be decreased in adulthood in individuals who had lived a constitutionally delayed puberty.

11.4.2 Other Forms of Hypogonadotropic Delay of Growth and Puberty

Table 11.1 lists the most important causes of delayed puberty other than constitutional delay of puberty and growth. These causes are usually grouped in four categories:

- Delayed puberty due to congenital hypothalamic hypogonadotropic hypogonadism
- Delayed puberty due to functional hypothalamic hypogonadotropic hypogonadism
- Delayed puberty due to hypophyseal hypogonadotropic hypogonadism
- Delayed puberty due to congenital or acquired hypergonadotropic hypogonadism

The characteristic endocrine pattern for hypothalamic hypogonadotropic, hypophyseal hypogonadotropic and hypergonadotropic hypogonadism is presented on Fig. 11.6.

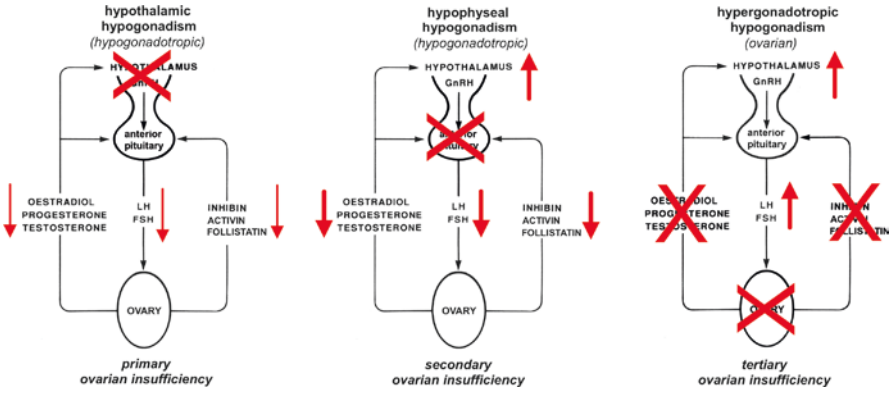

Fig. 11.6 Schematic presentation of the classical endocrine defects in primary, secondary and tertiary ovarian insufficiency

11.4.2.1 Hypothalamic Hypogonadotropic Hypogonadism (Primary Ovarian Insufficiency)

Delay of Puberty in Organic Hypothalamic Hypogonadotropic Hypogonadism (HH) (Table 11.2a)
In girls, HH is proposed when plasma gonadotropins are normal or low, with lack of pubertal signs at 13 years of age. Puberty is absent or partial (congenital and early acquired forms), or arrested in an intermediate stage (acquired forms), depending on the appearance of the pathology in relation to the onset of puberty. Serum gonadotropin levels are low or inappropriately low-normal, sex steroids are low.

Isolated GnRH Deficiency
Congenital isolated hypothalamic hypogonadism (CHH) is clinically characterized by a partial or complete lack of puberty and a primary infertility due to a deficient GnRH-induced gonadotropin secretion, in the absence of anatomical abnormalities in the hypothalamic and pituitary region, and by normal basal and reserve testing of the remaining pituitary hormones.

Biologically, CHH is defined by low or normal serum levels of LH and FSH in the setting of low sex steroids. All other hypophyseal functions are normal as is the

Table 11.2a Classical causes of Hypothalamic Hypogonadism (primary ovarian insufficiency) [55, 64, 65, 77, 80]

Congenital (permanent) hypothalamic hypogonadism
Isolated GnRH deficiency
With ansomia (Kallmann syndrome)
Without ansomia
Associated with a syndrome such as
Prader-Willi
Laurence–Moon
Bardet–Biedl
etc.
Acquired hypothalamic hypogonadism
CNS tumours (cranyopharngeoma, germinoma etc.)
Metastases from non-CNS-tumours
Infections of the central nervous system
Systemic infections, such as tuberculosis, syphilis, Trypanosomiasis
Infiltrating processes ans storage diseases such as haemochromatosis (Thalassaemia major!), histocytosis, granulomas,sarcoidosis, M. Wilson
Multiple sclerosis
Head injury
Stroke, rupture of anevrysm
Cerebral surgery
Chemotherapy/radiotherapy

imaging of the hypothalamo–pituitary region. Patients with CHH typically present in adolescence or early adulthood with delayed onset of puberty, primary amenorrhea, poorly developed sexual characteristics, and/or infertility.

There exist two clinical variants of congenital GnRH deficiency: the form without anosmia and the GnRH deficiency with anosmia. When CHH is associated with anosmia or hyposmia it is termed Kallmann syndrome [76–78]. The Kallmann syndrome is the classic example of congenital hypothalamic hypogonadism. The first description of the so-called Kallmann syndrome has been published by de Morsier [79]. It is due to an impairment of the normal migration of the GnRH neurons from the region of the olfactory nerve to the ventral hypothalamus through the cribriform plate (Fig. 11.4). The clinical features of Kallmann syndrome are variable, with X-linked and autosomal-dominant and -recessive causes and variable penetrance described. Renal anomalies and syncynesia may exist. Its prevalence is 1/8000–1/10,000 in men and 1:50,000 in women. MRI confirms aplasia or hypoplasia of the olfactory bulbs.

Most cases of Kallmann syndrome seem to be sporadic as a consequence of mutations in at least two autosomal genes.

Mostly, genetic mutations are responsible for CHH [55, 64, 80, 81]. Mutations in the KAL1 gene on the short arm of the X chromosome (Xp22.3) are responsible for the X-chromosomal recessive form, while mutations in the FGFR1 (fibroblast growth factor receptor 1) gene on the short arm of chromosome 8 (8p11.2–p11.1) are responsible for the autosomal dominant form (e12). At present, in human, the only type of hypothalamic hypogonadism attributed to a single gene defect is the alteration of GPR54 [76] where KiSS-1 is involved (see above). Subjects with mutations in the human leptin receptor gene have no pubertal development. Table 11.2b lists the classical genetic mutations leading to permanent hypothalamic hypogonadism, with and without anosmia. Gene mutations with normosmic congenital hypogonadal hypodonadism are shown on Table 11.3. In all six listed

Table 11.2b Gene mutations leading to congenital permanent hypogonadal hypogonadism [55, 64, 76, 80–83]

Migration disorder of the GnRH neurons (Kallmann syndrome) due to mutations in (e12):
The KAL1 gene (chromosome Xp22.3)
The fibroblast growth factor receptor 1 (FGFR-1) gene (chromosome 8p11.2–p11.1)
The prokineticin 2 gene (e13)
The prokineticin 2 receptor gene
Nasal embryogenic LHRH factor (NELF)
Disturbances of GnRH secretion without anosmia or hyposmia (e19)
Mutations of the GnRH receptor gene
Mutations of the leptin gene
Mutations of the leptin receptor gene
Mutations of the G-coupled protein receptor 54 gene (GPR54) (e18)

mutations, heredity is recessive. This explains why expression of the anomaly is rare although the frequency of the abnormal gene GnRH1 in Europe is quite high (1/50) [80].

Additional developmental anomalies can occur with CHH including unilateral renal agenesis, synkinesia (mirror movements), cleft lip and/or palate, sensorineural hearing loss, dental agenesis, and skeletal malformations [81]. In some forms of CHH, additional defects are observed. These specific phenotypes are known as syndromes with CHH and additional abnormalities such as coloboma, heart defect, atresia of nasal choanae, retarded growth/development or genital abnormalities. The best known of these clinical syndromes are the Prader-Willi, the Laurence-Moon and the Bardet-Biedl syndrome. CHH and ear abnormalities up to deafness is known as the CHARGE syndrome [82, 83].

Delay of Puberty in Functional Hypogonadal Hypogonadism (Primary Ovarian Insufficiency)

It has been estimated that 10–20 % of all women suffer at least once in their life from functional hypothalamic disorders, mostly stress [17]. If such a functional disorder occurs before the normal age of puberty, puberty may be delayed.

Transient hypogonadal hypogonadism is seen in systemic conditions such as anorexia starting before or around puberty, excessive exercise (athletic triad) in

Table 11.3 Genes responsible, frequency and phenotype in normosmic hypothalamic hypogonadism. Heredity is in all six listed mutations *recessive* [80]

Gene responsible of hypogonadism	Frequency of gene	Phenotype
GnRH1	Europe: 1/50	Complete HH
	USA: 1/310	
GnRH-R	40 % of cases of familial normosmic HH	Complete HH
	Sporadic mutations: 6–17 % of cases of hypogonadism	
KiSS-1	Rare, no sporadic mutations described	Severe gonadotropic deficiency, absence of puberty
KiSS-R	Rare, sporadic or familial idiopathic HH: 26 cases from 9 different families described	Severe gonadotropic deficiency, absence of puberty
TAC3 neurokinin B	Rare, no sporadic mutations described	2 of the 4 sisters with TAC3 mutations had spontaneous pregancies, another has regular cycles and the forth had an early miscarriage
TAC3-R	Rare, no sporadic mutations but rare variant described in sporadic cases	6 of the 7 males and 4 of the 5 females demonstrated evidence for reversibility of their hypogonadism

pubertal girls, in severe chronic diseases of any origin, in malnutrition and in emotional deprivation [66, 84–88]. Sedlmeyer et al. [66] and other groups [84, 85] listed over 25 different underlying chronic diseases in their analysis of children investigated for functional delayed puberty. Among them, in addition to eating disorders and intense exercise, endocrine diseases (GH deficiency, hyperprolactinemia (see above), hypothyroidism), diabetes mellitus, cystic fibrosis, Crohn's disease, celiac disease, severe asthma, nephrotic syndrome, rheumatoid arthritis, systemic lupus erythematodes, sickle cell disease and thalassemia major, congenital heart disease, focal segmental glomerulosclerosis, glycogen storage disease type 1A, several oncological diseases (Hodgkin's disease, leukaemia etc.), CNS disorders (particularly seizure disorders) and poor nutrition.

Acquisition of fat mass is involved in pubertal development. During starvation, in stress-induced amenorrhea with weight loss, in subjects with anorexia nervosa, and in strenuously exercising athletes, leptin and E2 levels fall concomitantly. By limiting the apposition of adipose tissue, chronic diseases affect the development of puberty and fertility by the same mechanism relayed through the hypothalamus, apart from the specific impact of their molecular alteration. As the effect of the drugs used to treat chronic diseases (e.g., corticosteroids) are undistinguishable from the chronic disease itself, pharmacological side effects have to be considered, too [85].

As long as these conditions persist, the onset of puberty remains blocked or its normal continuation stays arrested. In severe cases, a functional regression to prepuberty equivalent with the prepubertal quiescence of the ovarian axis may occur (see Fig. 11.4).

11.4.2.2 Delay of Puberty in Hypophyseal Hypogonadotrophic Hypogonadism (Secondary Ovarian Insufficiency)

Congenital or permanent hypophyseal hypogonadism is rare (Table 11.4). Intracranial tumour is a common cause of acquired hypogonadism in adolescence. Among these, craniopharyngeoma, a typical CNS tumour in adolescents, may lead to destructions in the hypothalamo-hypophyseal region [89]. If the pituitary stalk is compressed which is not rare in extrapituitary tumours such as craniopharyngeomas or metastases from non-CNS-tumours, other hypothalamo-hypophyseal axes in addition to the gonadal axis are affected. Neurosurgery for craniopharyngeoma is mostly followed by radiotherapy. In some other tumours, too, surgical resection may be complemented with radiotherapy and/or chemotherapy leading to secondary damage [90, 91].

In presence of an adenoma of the pituitary including makroprolactinoma, hypogonadotropic hypogonadism can result from the compression of pituitary tissue. In the case of prolactinoma or Cushing's disease, delayed puberty may be secondary to the inhibition of GnRH secretion by the hormones secreted by the endocrine active hypophyseal adenoma, even it is small.

Table 11.4 Classical causes of hypophyseal hypogonadotrophic hypogonadism (secondary ovarian insufficiency)

A. Congentital or permanent hypophyseal hypogonadism
Classical congenital forms are:
Isolated LH and FSH deficiency ("idiopathic isolated gonadotropin deficiency")
Panhypopuitarism (complete or partial)
Congenital (genetic, "idiopathic")
Associated with a lesion of the midline/Rathke's pouch
Syndromes, such as CHARGE syndrome: combined pituitary hormone deficiency (coloboma, heart defect, atresia of nasal choanae, retarded growth/development, genital abnormalities, and ear abnormalities/deafness)
B. Acquired hypophyseal hypoginadotropic hypogonadism
Panhypopituitarism (partial or complete)
CNS tumours, such as craniopharyngioma, hamartoma, germinoma etc.
Metastases from non-CNS-tumours
Prolactinomas
Non-prolactin secreting pituitary adenomas
Hypophysitis
Infections, such as tuberculosis, syphilis, trypanosomiasis
Sarcoidosis
Eosinophilic granuloma
Haemochromatosis (Thalassaemia major!)
Multiple sclerosis
Trauma
Chemotherapy/radiation therapy

A rare cause of hypophyseal hypogonadotropic hypogonadism is the empty sella syndrome. Primary ES occurs when CSF enters the sella through a rent in the sellar diaphragm that may or may not be associated with increased intracranial pressure. Secondary ES is a result of an injury to the pituitary itself or the consequence of surgical or radiation treatment. The incidence of ES in children varies greatly depending on the population surveyed, ranging from 1.2 % (children without endocrine symptoms) to 68 % (children with known endocrinopathy) in the survey of Lenz and Root [92].

In adenomas of the pituitary, in empty sella and in craniopharyngeoma, clinically, visual disturbance or headaches may accompany pubertal arrest. It is essential that all patients with intra- or extrahypophyseal tumours undergo a complete evaluation of anterior and posterior pituitary function.

11.4.2.3 Impact on Fertility

Hypogonadotropic hypogonadism due to congenital hypothalamic disorders have very rarely and only in very light partial forms the chance to get later spontaneously

pregnant. However, with the adequate treatment, the possibility to live later a normal pregnancy is excellent even in complete forms of hypothalamic hypogonadism (see below).

Hypogonadotropic hypogonadism resulting from hyperprolactinaemia can be treated medically by dopamin agonists [93]. Because the normalization of prolactin secretion by dopamin agonists allows not only the onset of normal pubertal development but also the uptake of a normal fertility, adolescents have to be informed that in case of intercourse without the desire of a child they need an adequate and efficient contraception.

In non-prolactin-secreting adenomas of the pituitary and in most other CNS tumours, surgical intervention is the usual first line treatment [94–96], followed frequently by radiotherapy or chemotherapy. These treatments per se may lead in survivors to permanent hypogonadism [90, 91]. Later spontaneous fertility depends on the destructions left by the tumour itself or by its treatments. As long as the ovaries are intact and have not suffered by chemotherapy or radiotherapy, the chances to become pregnant through ovulation induction remain intact.

In women, where the delay of puberty has been due to functional hypothalamic hypogonadism, the successful treatment of the underlying disease decides on later fertility. Particularly, in women with eating disorders, a complete remission is the *conditio sine qua non* if normalization of fertility is intended. However, the few longitudinal studies on later fertility show that the risk of a subnormal fertility pattern remains increased, as it has been observed in the "*Avon Longitudinal Study of Parents and Children Fertility and prenatal attitudes towards pregnancy in women with eating disorders*" [97]. In this study, Singleton and live births were included across four groups of women suffering from lifetime eating disorders:

- Lifetime anorexia nervosa (AN; $n=171$)
- Lifetime bulimia nervosa (BN; $n=199$)
- Lifetime anorexia nervosa and bulimia nervosa (AN + BN; $n=82$)
- General population ($n=10{,}636$).

The results show that women with AN (OR 1.6, 95 % CI 1.1–2.5; $P<0.021$) and women with AN + BN (OR 1.9, 95 % CI 1.1–3.4; $P<0.020$) were more likely to have seen a doctor for lifetime fertility problems than women from the general population. Furthermore, women with AN + BN were also more likely to take >6 months to conceive (OR 1.9, 95 % CI 1.0–3.5; $P<0.04$) and to have conceived the current pregnancy with fertility treatment.

All eating disorders groups experienced more frequently negative feelings upon discovering their pregnancy. Negative feelings remained still higher in the AN + BN group at 18 weeks of gestation. Finally, in spite of the longer time the AB women needed to get pregnant, unplanned pregnancies were more common in the AN group

compared with the general population. This points to the persistence of an increased ambivalence against pregnancy in women with eating disorders. These last two findings have been confirmed by a second study [98, 99].

Women with lifetime AN had a higher prevalence of twin births compared with those without the disorder (3.5 versus 1 %), as did women with BN and women with AN + BN, albeit to a lesser extent [99]. All eating disorders taken together were associated with increased odds of having twins (OR 2.7, 95 % CI 1.0–7.9; $P = 0.06$). These associations persisted after adjustment for potential confounding factors such as lifetime AN, OR 2.7, 95 % 1.0–8.0, lifetime BN, OR 2.7 (95 % CI 1.1–6.4) and lifetime AN + BN, OR 3.9, (95 % CI 1.3–11.1). Interestingly enough, women with other lifetime psychiatric disorders had similar odds as women without psychiatric disorders.

11.4.2.4 Profertile Measures: Ovulation Induction in Hypogonadotropic Hypogonadism (Primary and Secondary Ovarian Insufficiency)

In the absence of the uptake of normal menstrual cycles, as it is the case in all forms of delayed puberty with permanent hypogonadal hypogonadism, ovulation induction should be used to induce pregnancy. It has to be stressed that the administered hormones have to be considered and handled as a substitution. Therefore, the lowest efficient dose of GnRH/pulse or of HMG resp. FSH/LH per day has to be used to obtain a monofollicular response of the ovary.

To decide on the optimal treatment in hypogonadal hypogonadism, the grading system described by Leyendecker (Table 11.5) is recommended. Finally, it has to be remembered that the administration of pure FSH does not make sense in the absence of endogenous LH secretion.

Considering the risk/benefit ratio, in primary ovarian insufficiency the best results are obtained by the pulsatile administration of GnRH (Table 11.6). The pregnancy rate within 1 year is identical to the one of a healthy fertile couple of the same age with a normal fertility (Fig. 11.8). The incidence of hyperstimulation and the number of multiple pregnancies are close to normal. The success rate in patients < 35 years is above 90 % [15–17, 100, 101]. However, pregnancy rate is age dependent: Fig. 11.8 lists the results in women aged < 35 years, Table 11.7 the results in women with a mean age > 35 years (own data). The same age-dependency has been shown for the pregnancy rate with HMG treatment in hypogonadotropic women [102]. The cumulative pregnancy rate has been after six treatment cycles 97 % in women < 35 years and 63 % in women > 35 years.

Therefore, in women with hypothalamic hypogonadism, first line treatment of infertility is the pulsatile administration of GnRH, with one exception: in partial hypothalamic insufficiency (Table 11.6), the more economic ovulation induction by oral Clomiphene may be used first although its success rate is lower (Fig. 11.7).

Table 11.7 shows the results of ovulation induction by pulsatile GnRH (i.v.) in 17 patients with hypothalamic amenorrhea grade 3c needing a higher dosage of GnRH per pulse (15–20 GnRH µg/pulse). In spite of the severity of the hypothalamic deficiency and a mean age > 35 years, the pregnancy rate was 53 %.

Table 11.5 Grading of hypothalamic amenorrhea on the basis of the progestogen, clomiphene, and Gn-RH tests, respectively [156]

1	Clomiphene positive with bleeding following
1a	Normal luteal phase
1b	Insufficient luteal phase
1c	Anovulatory cycle
2	Progestogen positive
	Clomiphene negative
3	Progestogen negative with pituitary response to 100 μg of Gn-RH i.v.
3a	"Adult response"
3b	"Prepubertal response"
3c	No response

Table 11.6 Ovulation induction in hypothalamic and hypophyseal hypogonadism

Wish for a child positive	Grading (see Table 11.3)	Doses
In presence of a potentially normal pituitary function:		
Pulsatile GnRH [15–17, 100, 101]	Grade 1 or 2	5 μg GnRH/pulse every 90 min in the follicular phase
		5 μg GnRH/pulse every 4 h in the luteal phase (or HCG)
Pulsatile GnRH [15–17, 100, 101]	Grade 3	10–20 μg GnRH/pulse every 90 min in the follicular phase
		10–20 μg GnRH/pulse every 4 h in the luteal phase (or HCG)
In presence of normal pituitary and hypothalamic structures:		
Clomiphene [17]	Grade 1	50–100 mg/day day 5–9 after progestin-induced bleeding
Naltrexon [103]	Grade 1–3	25 mg/day in the evening day 1–3, then 50 mg/day in the evening (until pregnancy is confirmed, then stop)
In presence of an absent or deficient gonatropin secretion:		
HMG or FHS/LH		Begin low-dose (37.5–50 IU/day), individual increase of the dose
First line treatment in pituitary hypo-gonadism (secondary ovarian insufficiency)		Ovulation induction: 5000–10,000 IU HCG
Second line treatment in hypothalamic hypo-gonadism (primary ovarian insufficiency)		

In presence of a congenital defect or an acquired lesion of the pituitary, ovulation induction by HMG or FSH/LH has to be used (Table 11.6). To avoid hyperstimulation and multiple pregnancies in ovulation induction by gonadotropins, the classical

Table 11.7 Results of ovulation induction by pulsatile GnRH (i.v.) in hypothalamic amenorrhea grade 3c (15–20 GnRH µg/pulse, own data)

49 treatment cycles in 17 patients (1 Kallmann syndrome, 16 IHH.), mean age 37.2 years (range 32–39 years)	
Spermiograms have been normal in all male partners. All patients had been treated without success by Clomiphene and/or by HMG during a period of at least 1 year.	
Results per cycles:	
Ovulatory cycles	40 cycles (83 %)
Clinical pregnancies	10 cycles (21 %)
Biochemical pregnancies	6 cycles (13 %)
Clinical abortion	1 cycle (2.1 %)
"Take home babies"	9 cycles (18 %)
53 % of all patient became pregnant.	
No patient developed a hyperstimulation syndrome	
No multiple pregnancies have been seen.	
Complications: Two cycles were interrupted due to two superficial phlebitis	

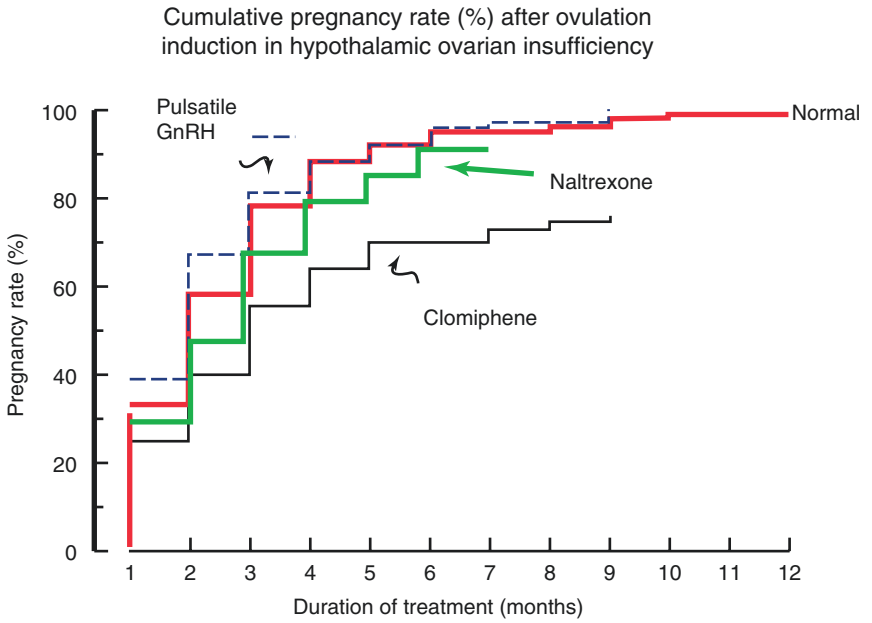

Fig. 11.7 Cumulative pregnancy rate (%) after ovulation induction in hypothalamic ovarian insufficiency by Clomiphene, pulsatile GnRH and Naltrexon compared to normal fertility within 12 months
Doses used:
– Clomiphenen citrate 50–100 mg/day from day 5–9 after a progestin-induced bleeding.
– Pulsatile GnRH s.c.: 5–10 µg/puls every 90 min in the folllicular phase and every 4 h in the luteal phase.
– Naltrexon 25 mg/day in the evening day 1–3, then 50 mg/day in the evening (until pregnancy is confirmed, then stop) (Adapted from Beier et al. [155])

rules have to be observed, meaning administration of the lowest efficient dose and regular supervision by serum oestradiol determination and sonographic control of follicular growth.

Naltrexone, an opioid antagonist, has been used in functional hypothalamic hypogonadism if there was a suspected deregulation of the endogenous opioid system [103]. However, success rate is inferior to pulsatile GnRH (Fig. 11.7); 20–30 % of all patients do not respond sufficiently or at all to Naltrexone. Side effects (mainly nausea, restlessness, sleep problems) are frequent in the first days of treatment.

11.4.3 Delay of Puberty in Hypergonadotropic Hypogonadism (Table 11.8)

11.4.3.1 Congenital Forms

Gonadal Dysgenesis: Phenotypic Female Variants

The term "gonadal dysgenesis" is generally used to describe a variety of clinical conditions. Their common denominator is an abnormal development of the foetal gonads. Gonadal dysgenesis includes Turner syndrome (45/X0, mosaics), mixed gonadal dysgenesis (45X/46, XY), female 46/XY dysgenesis ("pure gonadal dysgenesis, XY type", Swyer's syndrome) and the combination of a normal female sex chromosome constitution and hypergonadotropic hypogonadism (female 46/XX; "pure gonadal dysgenesis, XX type" or "XX gonadal dysgenesis").

Turner Syndrome

Definition, incidence [104] The most frequent disorder in the category of gonadal dysgenesis is Turner syndrome and its variants. Turner syndrome (TS) affects approximately one in 2500–3000 live-born females; in abortions the incidence is 1:270. Girls and women confront the clinician with a challenging array of genetic,

Table 11.8 Delay of puberty in hypergonadotropic hypogonadism

Congenital forms
Turner syndrome
Disorders of sexual development (gonadal dysgenesis and androgen resistance)
Mutations in LH or FSH receptor
Galactosemia
Acquired forms
Chemotherapy/radiotherapy
Endocrine disruptors
Ovarian torsion
Gonadectomy
Autoimmune disease

developmental, endocrine, cardiovascular, psychosocial, and reproductive issues. Intelligence is usually normal, but it may be limited in some cases.

Karyotype All individuals with suspected TS (see below) should have a karyotype performed. A standard 30-cell peripheral blood karyotype is recommended. It identifies at least 10 % mosaicism with 95 % confidence [104]. If there is a strong clinical suspicion of TS, despite a normal blood karyotype, a second tissue, such as skin, may be examined.

TS is a chromosomally determined disorder where complete ovarian agenesis is present with deletion of one X chromosome (karyotype 45 X0). Incomplete forms may be seen in patients with mosaicism (X0/XX, XO/XXX, X0/XX/XXX, 45X0/46XF etc.), in which case the patient may be chromatin positive.

Mosaics may present with a Y chromosome (45X0/46XY). The presence of Y chromosome material is associated with an approximately 12 % risk of a gonadoblastoma which may transform into malignant germ cell neoplasms. Therefore, prophylactic laparoscopic gonadectomy is recommended [105]. The patient and/or her parents should be informed of the finding of Y chromosome material with the utmost sensitivity regarding gender identity issues to minimize psychological harm.

Clinical presentation The phenotype may be oligosymptomatic, dominated by short stature. The diagnosis of TS should be considered in any female with unexplained growth failure or pubertal delay or any constellation of the following clinical findings: oedema of the hands or feet, nuchal folds, left-sided cardiac anomalies, especially coarctation of the aorta or hypoplastic left heart, low hairline, low-set ears, small mandible, short stature with growth velocity less than the 10th percentile for age, markedly elevated levels of FSH, cubitus valgus, nail hypoplasia, hyperconvex uplifted nails, multiple pigmented naevi, characteristic facies, short fourth metacarpal, high arched palate or chronic otitis media.

Absent or delayed puberty Absent pubertal development is one of the most common clinical features of TS, although up to 30 % or more of girls with TS (mosaicisms included) will undergo some spontaneous pubertal development. Ultimately, over 90 % of individuals with TS will have gonadal failure. Therefore, the critical importance of oestrogen treatment for feminization and for bone health during the adult years has to be emphasized. Today, it is accepted that induction of puberty should not be delayed from the age of 12 years until the age of 15 years as recommended earlier to promote statural growth by GnRH treatment first: the positive effect of GnRH administered today to most patients to promote adult height is not hindered by a prudent start of oestrogen substitution at the age of 12 [104].

Impact on fertility Most women with TS are infertile. Only 2–5 %, including forms with mosaicism, achieve spontaneous pregnancy [104]. In a review from 1993 [106], the literature contained reports of 28 spontaneous pregnancies in 16 women

with 45, X karyotype and 106 pregnancies in 48 women with mosaicism. Miscarriages, stillbirths and malformations were common. Since then, more spontaneous pregnancies have been known.

Today, various assisted reproductive techniques, particularly egg or embryo donation, are now legally available in many countries for achieving pregnancy. Recent studies show that using these techniques, women with TS become pregnant as easily as women with other types of infertility and carry their pregnancies to term without an increased miscarriage rate [104] if the uterus has been prepared adequately. Oestrogen/progestogen-substitution should be started at least 1 year before assisted reproduction. To be ready for donation, the thickness of the endometrium should reach 7 mm. TS women do have an increased rate of maternal complications, in part because of their small size. Only one embryo should be transferred to avoid the additional risks of a multiple pregnancy.

Reports of fatal aortic dissection during pregnancy and the postpartum period have raised concern about the safety of pregnancy in TS. Therefore, spontaneous or assisted pregnancy in TS should be undertaken only after thorough cardiac evaluation. It is recommended to consider a history of surgically repaired cardiovascular defect, the presence of BAV, or current evidence of aortic dilatation or systemic hypertension as relative contraindications to pregnancy. The possibility of prenatal genetic testing has to be offered.

Women with TS who have spontaneous menstrual cycles and ovulate normally should not postpone the timing of pregnancies without good reason because of the increased risk of premature ovarian failure. They have to be informed about the possibility of oocyte or embryo cryopreservation [107, 108], although these techniques are far from being an established method in TS.

Other Forms of Gonadal Dysgenesis

Mixed gonadal dysgenesis (45X/46, XY), female 46/XY gonadal dysgenesis (“pure” gonadal dysgenesis “XY type”, also called “XY females”) and “pure” gonadal dysgenesis (“XX type” or “XX gonadal dysgenesis”) are rare. They have no Turner stigmata. Complete and partial forms are observed. Pure 46/XX is at least in part due to ODGI gene mutation, inherited as an autosomal recessive, female-limited disorder [109]. SRY Mutations in XY females may lead to complete 46,XY gonadal dysgenesis or “pure” gonadal dysgenesis (also called “XY females”). These individuals suffer rapid and early degeneration of their gonads (gonadal dysgenesis), which are present in the adult as streak gonads consisting mainly of fibrous tissue and variable amounts of ovarian stroma. The external genitalia in these subjects are completely female, and Müllerian structures are normal. The frequency of SRY mutations in XY females (“pure” gonadal dysgenesis) seems to be higher than current estimates [110]. By contrast, subjects with 46,XY partial gonadal dysgenesis have ambiguous genitalia, a mix of Müllerian and Wolffian structures, and dysgenic gonads. These gonads usually consist of disorganized seminiferous tubules admixed with ovarian stroma. Again, the presence of Y chromosome material is associated with an increased risk of germ cell neoplasms so that prophylactic gonadectomy is recommended [105].

There are no practical guidelines for the clinical handling of these patients and no statistics about their later fertility available. It seems therefore logical to counsel and to treat them in analogy to the Turner Syndrome, after a full clinical and laboratory work-up including a full karyotype.

Impact on fertility There are no data pointing to the possibility of a spontaneous pregnancy. However, as long as a normal uterus is present, fertility can be reached through egg or embryo donation as clinical data confirm, describing pregnancies in pure 46/XX and pure 46/XY gonadal dysgenesis following ovum donation. Pregnancy rate per transfer was normal [111].

Noonan Syndrome

Noonan syndrome (NS) is a rare autosomal dominant disorder characterized by a phenotype [112] including short stature, facial dysmorphology and congenital heart defects.

Karyotype is normal. Noonan syndrome affects both sexes. In both sexes, there is a delay in pubertal development.

Other associated features are webbed neck, chest deformity, mild intellectual deficit, cryptorchidism, poor feeding in infancy, bleeding tendency and lymphatic dysplasias. The incidence of Noonan syndrome has been estimated to be between 1 in 1000 and 1 in 2500 live births [113]. In about 50 % of cases, NS is caused by mutations in the PTPN11 gene on chromosome 12, in a small proportion of patients by mutations in the KRAS gene. The aetiology of NS in individuals without mutations in PTPN11 or KRAS (together almost 50 % of cases) is still unknown.

NS should be considered in all foetuses with polyhydramnion, pleural effusions, oedema and increased nuchal fluid with a normal karyotype. With special care and counselling, the majority of children with NS will grow up and function normally in the adult world.

Impact on fertility Fertility appears to be normal in Noonan females but has been reported to be decreased in males, although male transmission of the disorder to the next generation is not uncommon.

Androgen Insensitivity Syndrome, Testicular Feminization ("Hairless Women")

Androgen resistance is a broad continuum reaching from male infertility to testicular feminization. Complete testicular feminization is a highly distinctive disorder where genotypic males (46/XY) are phenotypically female.

Androgen insensitivity syndrome (AIS) is a genetic condition carried on the X chromosome. Although it is inherited in an X-linked, recessive fashion in 70 %, up to 30 % of mutations are sporadic de novo mutations [114]. The estimated prevalence of AIS is between 1 in 20,000 and 1 in 99,000 genetic males. If one examines phenotypic females with inguinal hernias, the prevalence is noted to be 0.8–2.4 %.

In androgen insensitivity syndrome, there is a no activity at the androgen receptor leading to a tissue resistance to androgens. Wolffian structures are poorly (although partially) developed. Since AMH (anti-Müllerian hormone, or Müllerian inhibiting substance) is produced normally by the testes, there is a complete involution of the Müllerian ducts.

Clinical presentation [114] The typical presentation is that of primary amenorrhea in a phenotypic female adolescent. However, in an infant or child, the presentation may be of an inguinal hernia in a phenotypic female. Recent data shows a 1.1 % incidence rate of complete AIS in a child with a premenarcheal inguinal hernia, while 80–90 % of girls with complete AIS eventually develop an inguinal hernia

The external genitalia are female, breasts are developed. The "vagina" ends in a blind pouch; its average length is 2.5–3.0 cm. The testes are found in the labia majora, the inguinal canals or intra-abdominally, and should be prophylactically removed after puberty because of the risk of malignancy. Gonadectomy has to be followed by oestrogen substitution. Rates of dysgerminoma and gonadoblastoma in XY gonadal dysgenesis can rise as high as 15–30 %, but might be lower in AIS. Tumours prior to puberty are rare.

At the time of puberty (usually not delayed), testosterone levels increase in presence of abnormally high LH. Female secondary sex characteristics develop as a result of increased oestrogen levels. Sexual hair is scanty or absent because of the androgen resistance. The final diagnosis is given by the XY-karyotype.

Differential diagnosis The Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome or Müllerian Agenesis is part of the differential diagnosis. MRKH is a more common cause of primary amenorrhea. Its incidence rate is 1 in 5000 [119]. MRKH, too, has a normal breast development and an underdeveloped vagina, but it has normal axillary and pubic hair and a normal female karyotype (46/XX).

Impact on fertility To enable sexual intercourse, there are different options for vaginal creation (dilatation, surgical creation). Today, there is no reasonable way to treat infertility.

Mutations in LH or FSH Receptor

Today, several different homozygous or compound heterozygous inactivating mutations of the LH receptor known. Inactivating mutations of LH receptors can be a very rare cause of delayed puberty and primary hypergonadotropic amenorrhea or premature ovarian failure [115–118]. Clinically, these patients are characterized by female external genitalia, spontaneous breast and pubic hair development at puberty, and normal or late menarche followed by oligo-amenorrhea and infertility. Oestradiol and progesterone levels are normal for the early to midfollicular phase, but do not reach ovulatory or luteal phase levels, confirming lack of ovulation. Notably, serum LH levels are high in patients with LH receptor mutations, whereas follicle-stimulating hormone levels are normal or only slightly increased. Pelvic

ultrasound has demonstrated a small or normal uterus and normal or enlarged ovaries with cysts [118].

Mutations of the LH receptor gene may cause primary or secondary amenorrhea and infertility in sisters of male pseudohermaphrodites [115]. Clinically, they present a phenotype of hypergonadotropic hypogonadism ("LH resistance").

On the other hand, only few mutations of FSH receptor were discovered so far. Mutations of the FSH-receptor gene [116, 117, 120–122] cause ovarian dysgenesis leading to delayed puberty, primary or secondary hypergonadotropic amenorrhea and small ovaries with variable development of female secondary sex characteristics and infertility.

Impact on fertility In the different syndromes of inactivating mutations of gonadotropin receptors, no pregnancies have been described. In contrast to the clinically similar women harbouring inactivating mutations in luteinizing hormone (LH) beta subunit that may be treated with hCG (human chorionic gonadotropin) or LH, those with mutations in LH receptor are resistant.

Galactosemia

Galactosemia is a rare inborn error of metabolism that results from impaired activity of any of the three enzymes of the Leloir pathway: galactokinase (GALK, EC 2.7.1.6), galactose-1-phosphate uridylyltransferase (GALT, EC 2.7.7.12), or UDP-galactose 4′ -epimerase (GALE, EC 5.1.3.2). Classic galactosemia (OMIM 230400), the most common clinically severe form of the disorder, results from profound impairment of GALT. Classic galactosemia impacts about 1/60,000 live births, although prevalence differs substantially among populations [123].

Sequelae include cognitive and/or behavioural impairment in close to half of all patients, speech difficulties in at least half of all patients, low bone mineral density in many patients, ataxia or tremor in some patients, absent or delayed puberty and primary or premature ovarian insufficiency (POI) in at least 80 % of all girls and women. Neonatal diagnosis with immediate dietary galactose restriction prevents or resolves the acute symptoms of classic galactosemia. However, despite presymptomatic diagnosis and strict lifelong dietary intervention, a majority of patients go on to experience a constellation of troubling long-term complications

Impact on fertility [124] In imaging studies of girls with POI examined at pubertal age or later, the ovaries are invariably abnormal and usually described as hypoplastic or "streak-like." Histological examination most often shows few if any follicles; in the cases where follicles have been observed they did not appear to have matured beyond the primordial stage. The streak-like transformation of the ovaries may be related to accumulated galactose ootoxicity over time. One study of a small cohort of galactosemic women looked at spontaneous fertility outcomes (Gubbels et al. 2008) and reported that galactosemia patients with a diagnosis of POI may be more likely to conceive than women who have POI due to other causes. In a study, [124] 22 galactosemic women were followed. Nine women have tried to conceive, of which four were successful. Three mothers were diagnosed with POF before the

first pregnancy and/or in between pregnancies. In the literature, 50 pregnancy reports were found. The genotype and GALT-activity do not seem to predict the chance of becoming pregnant, whereas the occurrence of spontaneous menarche might. For those women with galactosemia who do achieve pregnancy, evidence from studies of small cohorts suggests that there are no adverse effects on the galactosemic mother or her infant.

Options to preserve endogenous fertility in galactosemia need to be explored further. For postpubertal women, freezing embryos after in vitro fertilization is an option.

11.4.3.2 Acquired Forms

Delayed Puberty and Reduced Fertility After Cancer Treatment

Childhood cancer is relatively rare, with an incidence of around 110 cases per million children per year [125, 126]. The Belgian Society of Pediatric Haematology and Oncology (unpublished date, in [108]) estimated childhood cancers are to occur in approximately 13 of 100,000 children under 15 years of age, with 45 % being cases of leukaemia and lymphoma, 20 % craniospinal tumours, 8 % neuroblastomas, 8 % soft tissue tumours, 7 % nephroblastomas, 3 % retinoblastomas and 9 % other rare tumours. The majority of children diagnosed with cancer are expected to be cured and become long-term survivors. The remarkable success in improving childhood cancer survival is exemplified by the 5-year survival rate for all leukaemias approaching 80 % (Office for National Statistics, 2004, UK) [125]. In 2010, in the USA, a total of 10,700 children and adolescents under the age of 14 were diagnosed with cancer. More than 80 % will survive the disease. For some common paediatric cancers such as Wilms' tumour, Hodgkin's disease (HD), and B-cell non-Hodgkin lymphoma (B-NHL) cure rates approach 90 % [127]. As such, it has been estimated that at the start of the twenty-first century, one in 1000 young adults in their third decade is a survivor of childhood cancer [126].

The results from the large and important *Childhood Cancer Survivor Study* (CCSS; [128]) show the natural outcome, without fertility preservation measures, of treatment for cancer diagnosed during childhood or adolescence on ovarian function and reproductive outcomes. The frequency of acute ovarian failure, premature menopause, live birth, stillbirth, spontaneous and therapeutic abortion and birth defects in the participants have been reviewed in the CCSS. Acute ovarian failure (AOF) occurred in 6.3 % of eligible survivors. Exposure of the ovaries to high-dose radiation (especially over 10 Gy), alkylating agents and procarbazine, at older ages, were significant risk factors for AOF. Premature nonsurgical menopause (PM) occurred in 8 % of participants versus 0.8 % of siblings (rate ratio = 13.21; 95 % CI, 3.26–53.51; $P = .001$). Risk factors for premature menopause included attained age, exposure to increasing doses of radiation to the ovaries, increasing alkylating agent score, and a diagnosis of Hodgkin's lymphoma. 1915 female survivors reported 4029 pregnancies. Offspring of women who received uterine radiation doses of more than 5 Gy were more likely to be small for gestational age (birth weight < 10

percentile for gestational age; 18.2 % v 7.8 %; odds ratio = 4.0; 95 % CI, 1.6–9.8; $P = .003$). The CCSS did not reveal any differences in the proportion of offspring with simple malformations, cytogenetic syndromes, or single-gene defects.

The CCSS demonstrates that women treated with pelvic irradiation and/or increasing alkylating agent doses were at risk for acute ovarian failure, premature menopause, and small-for-gestational-age offspring. There was no evidence for an increased risk of congenital malformations.

Based on these data, although problems with fertility do not become apparent until after puberty, it is clear that many treatments for childhood cancer can lead to infertility and subfertility in later life. Having survived cancer as a child, it can be very difficult for many patients to accept that they cannot produce their own children because of the treatment they received during childhood.

How can this outcome after cancer treatment be improved? Fertility preservation is becoming increasingly important to improve the quality of life in cancer survivors. Despite guidelines suggesting that discussion of fertility preservation should be done prior to starting cancer therapies, there is a lack of implementation in this area. The need for fertility preservation has to be weighed against morbidity and mortality associated with cancer. Thorough psychological counselling is required. Recommendations should be individualized and should not violate the ethical principles.

Particularly in young girls and in adolescents, there is a need for a multidisciplinary collaboration between oncologists, paediatrician and reproductive specialists to improve awareness and availability.

Effect of Chemotherapy and Radiotherapy

Children that undergo treatment for cancer are at risk of suffering from primary amenorrhea, delayed puberty, hormonal dysfunction and subfertility. Both chemotherapy and radiotherapy have a major impact on the gonadal axis and its hormonal and reproductive potential.

The oocyte has been in an arrested stage of meiosis since before birth and remains so until the onset of puberty, and this does not advance until ovulation. Chemotherapy, radiotherapy and surgery can all have adverse affects on reproduction. It is the effects on the nongrowing stockpile of primordial follicles that is of particular importance for future reproductive potential (Fig. 11.8) [129]. The mechanism by which chemotherapy causes loss of primordial follicles is, however, poorly understood. At present, it is impossible to predict the functional life span of the chemotherapeutically damaged ovary and the reproductive potential of patients with cancer.

It is important to emphasize that there is no evidence to suggest that the prepubertal female (or male) reproductive tract is protected from the adverse effects of cancer therapies. The danger of pelvic radiotherapy is significantly greater than the risk of all kinds of chemotherapy. The susceptibility of the prepubertal uterus to radiotherapy is also clearly demonstrated [108, 129].

Chemotherapy

Chemotherapeutic drugs act by interrupting vital cell processes and arresting the normal cellular proliferation cycle. They cause DNA abnormalities as well as

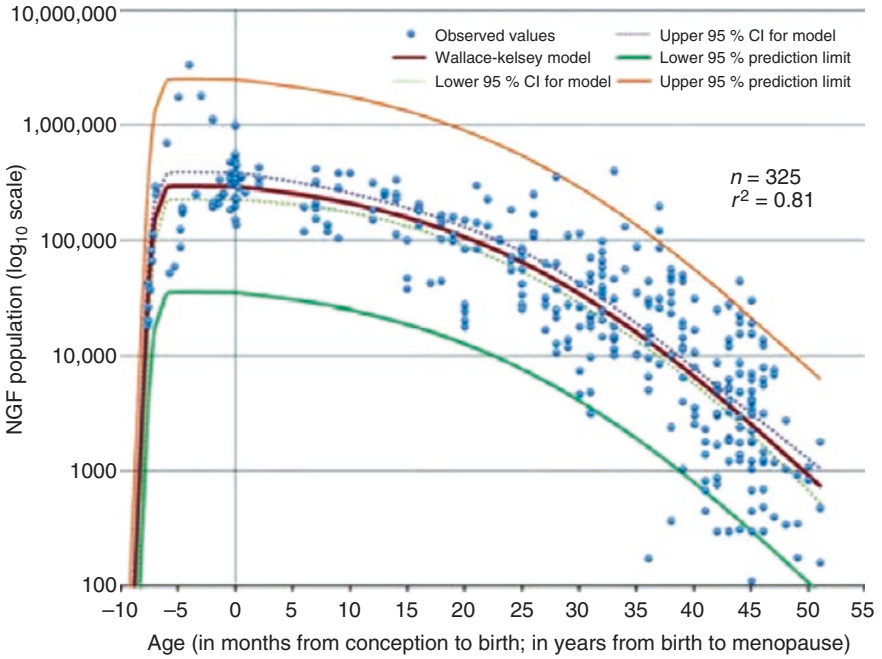

Fig. 11.8 The number of nongrowing follicles in the ovary is increasing as a function of time. Inversely, the number of potentially fertile promordial follicle available for recruitment is decreasing already before birth

oxidative damage in somatic and germ cells. Persistent unrepaired DNA double-strand breaks activate apoptotic death in oocytes. Genetic effects on the oocyte result in aneuploidy and early embryonic mortality.

In contrast to the effects on male fertility, females are, in general, less susceptible to the gonadotoxic effects of chemotherapy [130]. The clinical impact of chemotherapeutic drugs on the ovary is variable, ranging from no effect to complete ovarian atrophy. The degree of damage is dependent upon the type of the chemotherapeutic agent used, dose given, age of the patient and her baseline ovarian reserve. The prepubertal ovary is less susceptible to damage by chemotherapeutic agents. Compared to older women, early postpubertal adolescents have a higher ovarian reserve and are less susceptible to premature ovarian failure (POF). Fibrosis of stromal blood vessels adds to the ovarian damage.

Depending on the chemotherapy used, the clinical manifestation of the follicular loss ranges from a complete amenorrhea to POF and to varying degree of infertility (Table 11.9) [131]. Some paediatric chemotherapy regimens such as MOPP (mustagen, oncovin, procarbazine, and prednisone) for Hodgkin's disease, and high-dose cyclophosphamide and busulfan for bone marrow transplantation, cause sterility in a significant number of patients. Other regimens such as high dose cyclophosphamide for B-NHL and Ewing sarcoma are associated with a significant risk for fertility impairment [131]. Because no systematic comprehensive data exists on the exact

rates of fertility impairment associated with current paediatric oncology therapeutic regimens, the following grading of the damaging potential is derived from adult data [125, 132]:

Alkylating agents such as cyclophosphamide and procarbazine are high risk drugs with the highest age-adjusted odds ratio of ovarian failure rates.
Platinum-based compounds such as cisplatin cause DNA damage. They carry a medium risk of amenorrhea.
Anthracycline antibiotics such as doxorubicin (DXR) induce oxidative stress. The amenorrhea and fertility risk is medium to low with this group of drugs. DXR administration in female mice caused dominant lethal mutations and aneuploidy in maturing/preovulatory oocytes.
Vinca alkaloids do not seem to increase the risk of ovarian failure though animal experiments show a high rate of oocyte aneuploidy.
Anti-metabolites like methotrexate and 5-fluorouracil do not seem to affect the ovary based on the limited current data available. Methotrexate is commonly used to treat the ectopic pregnancy without any effect on subsequent fertility.
Taxanes: The data available for taxanes are controversial. Some studies show increased risk of ovarian failure, others suggest that there is no increased risk.
Biological targeted therapies (herceptin, tamoxifen, rituximab) are designed to interfere with specific receptors or molecules expressed by tumours (herceptin or tamoxifen), or act via the immune system (rituximab). Fertility risk data for these drugs are limited. Since they target specific cells, it is believed that the risk should be low.

The risk of POF with polyagent adjuvant chemotherapy has been reported to range from 53 to 89 %. The risk of POF is related to the patient's age, treatment protocol and type of malignancy [125]. Restoration of menstruation after CRA is possible. Again this is influenced by age and duration of follow-up and has been estimated at 39–55 % in younger women (<40 years) and 0–11 % in older patients (>40 years) [133]. However, women who maintain normal menses throughout

Table 11.9 Gonadotoxic chemotherapy agents

Alkylating agents
Cyclophosphamide
Ifosfamide
Nitrosureas, e.g., carmustine and lamustine
Chlorambucil
Melphalan
Busulphan
Vinca-alkaloids
Vinblastine
Antimetabolites
Cytarabine
Others
Cisplatin
Procarbazine

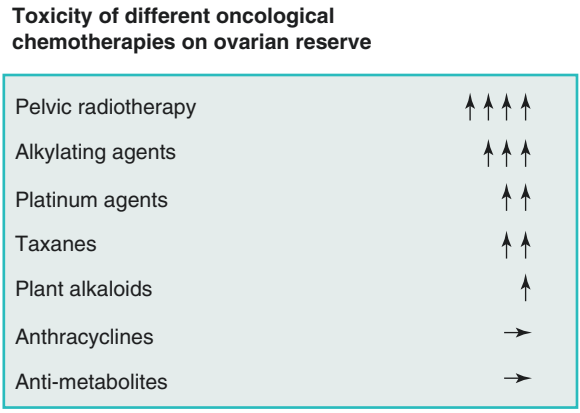

Fig. 11.9 Comparison of the ovarian toxicity exerted by the main groups of cytotoxic drugs with the damaging effect of pelvic radiotherapy. The number of *arrows* indicates their relative potency. No particular risk is known for substances marked by a *horizontal arrow* (Modified from Meirow et al. [131])

chemotherapy remain at risk for developing POF. This is evident from the high rates of POF seen in adolescents receiving alkylating agents for cancer [134]. There are no reports of uterine damage after chemotherapy [135] (Fig. 11.9).

Effect of Radiotherapy

Unlike chemotherapy, radiotherapy affects both the ovary and the uterus [129].

Human oocyte is sensitive to radiation, with an estimated median lethal dose (LD) of <2 Gy. Damage to the ovary by radiotherapy is dependent on the age of the patient and dose of the ovarian exposure. The effective sterilizing dose (ESD) is the dose of fractionated radiotherapy (Gy) at which POF occurs immediately after treatment in 97.5 % of patients. The degree of damage depends on the radiation dose and field, fractionation schedule, and the patient's age. A radiation dose of 2 Gy is estimated to damage 50 % of ovarian follicles irreversibly; doses ranging from 5 to 20 Gy cause complete loss of ovarian function resulting in sterility [136]. The number of primordial follicles present at the time of treatment and the dose of radiation received by the ovaries determines the fertility "window." In females, it has been shown that for a given dose of radiation, the younger the patient at the time of treatment, the later the onset of premature menopause, and inversely, the higher ESD to cause permanent ovarian failure [131, 132, 136, 137]: ESD is 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, and 14.3–16 Gy at 30 years, with only 6 Gy being required in women over 40. With total body irradiation, the location of the radiation field impacts the degree of ovarian damage (10–15.75 Gy) observed to result in ovarian failure in 90 % of patients in long-term follow-up. After abdominal radiation, ovarian failure rates may be as high as 97 %. [131].

After abdominal, pelvic, or TBI, the uterus is at risk of damage in a dose- and age-dependent manner [135]. Uterine growth and uterine blood flow start at puberty and are completed almost 7 years after menarche. Exposure to radiation leads to reduced vascularity, damage to myometrium leading to fibrosis and hormone dependent endometrial insufficiency. These uterine damages result in adverse reproductive outcomes such as increased rates of infertility, miscarriage, preterm labour, intra-uterine growth retardation and low birth weight.

Uterine function may be impaired after radiation doses of 14–30 Gy as a consequence of disruption to the uterine vasculature and musculature elasticity. In adults, an exposure to TBI of 12 Gy is associated with significant uterine damage. In childhood, radiation doses of >25 Gy directly to the uterus appears to induce irreversible damage. However, even lower dose of irradiation, as in total body irradiation, have been reported to cause impaired growth and blood flow. There is no agreement on the dose of radiation to the uterus, above which a pregnancy would not be sustainable.

Efforts to improve uterine function have been tried. However, there was no significant difference noted with regard to uterine volume, endometrial thickness, or uterine artery blood flow after high dose oestrogen replacement.

Preventive measure Ovarian transposition has been recommended to get the ovary out of the radiation field (laparoscopic "ovarian suspension" or "oophoropexy"; [132]).

Estimation of the Damage Induced by Chemotherapy and Radiotherapy by Biological Markers and By Sonography

In a prospective cohort study on girls treated for cancer, AMH, inhibin B, and FSH have been measured before, during, and after completion of treatment [138]. The aim of our study was to evaluate these biochemical measures as potential markers of early gonadotoxicity in young girls treated for cancer. As a result, AMH has been shown to be a clinically useful marker of damage to the ovarian reserve in girls receiving treatment for cancer. AMH is detectable in girls of all ages and falls rapidly during cancer treatment in both prepubertal and pubertal girls [138, 139]. Both the fall during treatment and recovery thereafter varied with risk of gonadotoxicity. In medium/low risk patients, AMH recovery is highly significant and reaches pretreatment levels [139]. The value of FSH and Inhibin B as markers of ovarian activity is limited by very low/undetectable concentrations before puberty and the need for measurement in the early follicular phase thereafter [129, 138].

The number of small antral follicles within the ovary (AFC) counted by transvaginal ultrasound, too, provide substantially more accurate indicators than FSH (or inhibin B) of what is known as the ovarian reserve. AFC allows to mean the number of primordial follicles remaining in the ovary. Both AMH and AFC show very good correlation with oocyte yield following superovulation needed for mature oocyte preservation, with a very high correlation between the two [129]. Today, this elegant method is not yet validated for abdominal transvesical ultrasound in prepubertal children.

The assessment of ovarian reserve in the prepubertal girl who has been successfully treated for cancer remains difficult. Larsen et al. evaluated ovarian function in 100 childhood cancer survivors and 21 controls of similar age [140]. Survivors with spontaneous menstrual cycles ($n=70$) were found to have smaller ovarian volume per ovary compared with controls (median, 4.8 cm^3 vs. 6.8 cm^3; $P<.001$) and a lower number of antral follicles (AFC) per ovary (median, 7.5 AFC vs. 11 AFC; $P<.001$). A regression analysis was performed to predict the total AFC number per ovary, which demonstrated a reduced number in women who were treated with ovarian irradiation (beta=−.40; $P<.001$),

alkylating chemotherapy (beta=−.25; P=.01), older age at diagnosis (beta=−.25; P=.01), and longer time period off treatment (beta=−.19; P=.044) [140].

Fertility Preservation in Young Girls and in Adolescents

Oncological Indications

In general, fertility preservation before cancer treatment is strongly recommended if the chance of losing fertility is over 30 % with cancer therapy. In adult patients that have a partner, cryopreservation of embryos remains the most reliable method to preserve fertility in women < 35 years of age. Another efficient option is vitrification of mature unfertilized oocytes. Today, an extensive database is available for adult cancer patients [107, 141].

Children and adolescents represent a special patient group. Jadoul et al. published in 2010 an important review of ovarian cryopreservation in adults and, more specifically, in children using the PubMed databases and added their own experience with cryopreservation in children [108]. They conclude that ovarian cortex cryopreservation is feasible and as safe as comparable operative procedures in children. However, the absence of consensus on the indications for fertility preservation, as well as the optimal timing and quantity of ovarian cortex for cryopreservation, should be taken into consideration when discussing fertility issues with girls at risk of POF and their parents.

Cryopreservation of embryos and vitrification of mature unfertilized oocytes require both hormonal stimulation and delay of treatment; thus, they cannot be offered to prepubertal patients and to adolescents that must receive urgent treatment. Therefore, cryopreservation of gonadal tissue is the only option today to be offered to young prepubertal girls with malignancies that require gonadotoxic therapy [108, 129], although no births have yet resulted from freeze-thawing of prepubertal ovarian cortex.

Wallace et al. recommended the following risk assessment for fertility preservation in girls [146]:

- Intrinsic factors
  Health status of patient
  Consent (patient/parent)
  Assessment of ovarian reserve in girls/young women
- Extrinsic factors
  Nature of predicted treatment (high/medium/low/uncertain risk)
  Time available
  Expertise available

A series of women having undergone ovarian cryopreservation has shown that these patients did not necessarily need reimplantation of the ovarian tissue to get pregnant. Of the 36 women treated by cytostatic agents (20 % by cyclophosphamide because of generalized Lupus erythematodes), 11 had died at the time of last follow-up, but 5 experienced spontaneous pregnancies, with none to date having requested reimplantation of their stored ovarian tissue [142].

Is there a lower limit of age? Michaeli et al. [143] consider that ovary cryopreservation can be safely offered even to younger girls since the potential benefits are currently more evident and the risks of anaesthesia appear not to be increased, although they earlier recommended a lower limit of 3 years of age. They believe that there is an ethical obligation of clinicians to offer fertility preservation and to discuss fertility issues with cancer patients or their parents, in order to provide the opportunity for future parenthood.

Postpubertal girls from puberty to the age of 18 may be candidates for mature oocyte cryopreservation following ovarian stimulation.

The exact procedures for these modern techniques of fertility preservation including the benefits and risks of later autotransplantation of ovarian tissue as well as pregnancy outcome in high-risk survivors of cancer are summarized in specialized reviews [107, 108, 129, 132, 135, 138–140, 143].

Non-Oncological Indications

Non-oncological indications for fertility preservation procedures include haematological or autoimmune diseases, as well as certain genetic conditions such as Fragile-X and Turner syndrome, which predispose women to premature ovarian failure. In addition, repeated surgery due to ovarian cysts or ovarian torsion may result in decreased ovarian reserve [108].

Ethical Considerations

There is a need for extreme sensitivity when broaching the topic of fertility preservation. This also may be an option for adolescents who are peripubertal, but still premenarchal. In vitro maturation (IVM) and ovarian tissue conservation (OTC) can also be offered. In prepubertal girls, OTC is currently the only way to cryopreserve gametes. Careful counselling and informed consent is especially recommended. In children, OTC implies the removal of an entire ovary because of its small size. Prepubertal girls who do not have any other options have to be informed about a high risk for POF when significant loss of ovarian follicles in the remaining ovary is anticipated with cancer therapy.

Parents have to be given full information of the invasive process needing a total anaesthesia, the associated risks and the success rates. The patient and her parents should understand the still experimental nature and the potential risks of cancer cell transmission.

Wallace et al. recommend applying the Edinburgh selection criteria to young girls and adolescents. The Edinburgh selection criteria accurately identify the few girls and young women who will develop premature ovarian insufficiency. They have been validated recently for their use for selection of patients for ovarian tissue cryopreservation [144]:

- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years

- A realistic chance of surviving for 5 years
- A high risk of premature ovarian insufficiency (>50 %)
- Informed consent (from parents and, where possible, patient)
- Negative serology results for HIV, syphilis, and hepatitis B
- Not pregnant and no existing children

It has always to be kept in mind that these procedures are in part still experimental and not yet clinical routine. As Wallace and Barr stated recently, it is not likely to be feasible or indeed ethical to perform a randomized study in a well-characterized group of young women to test laparoscopic collection of ovarian cortex versus either dummy laparoscopy or indeed no intervention. In their opinion, and in mine too, it is highly unlikely that IRBs would pass such a study, or indeed that such a randomized study would be able to recruit sufficient patients [145]. Therefore, all treatments for fertility preservation in young girls and adolescents should be done in accredited centres, documented and the data pooled so that a true and accurate description of the success of ovarian cryopreservation for young women at risk of a premature menopause can be provided.

Acquired Delayed Puberty and Reduced Fertility Due to Other Causes

Ovarian Torsion and Gonadectomy

Usually, ovarian torsion and gonadectomy are listed in this category. However, unilateral loss of an ovary by torsion or gonadectomy has no impact on the age of puberty and on later fertility.

The loss of both ovaries implies a timely induction of puberty by the slowly progressive administration of oestradiol and, in a second time, oestradiol combined with a progestatif. Fertility can be reached only by egg or embryo donation if these methods are legal in the country where the patient is living.

Autoimmune Diseases

In young girls and in adolescents, endocrine and non-endocrine autoimmune diseases involving the ovary and provoking a progressive destruction of the ovarian tissue may cause exceptionally a delayed puberty. The more common physiopathology leading to a delayed puberty in presence of an autoimmune disease involves functional hypothalamic hypogonadism (see above).

However, there are reports showing an early progressive destruction of the ovarian tissue by autoimmune processes, mainly in young girls and adolescents suffering from generalized lupus erythematodes [142, 146]. Later infertility can be prevented by applying the same methods of cryopreservation of ovarian tissue recommended for young cancer patients (see above).

Endocrine Disruptors

There have been speculations about a potential responsibility of endocrine disruptors in causing delayed puberty. However, ES have been shown mostly to advance

and less to delay puberty. The potential of EDs to cause precocious puberty has first been noticed in the early 1990s and has been confirmed in numerous animal studies. Subsequently, the use of some of these substances has been prohibited in products used by humans and domestic animals.

In the last years, several environmental endocrine disruptors (EDs) such as phytooestrogens, topical and natural oestrogens, pesticides, industrial chemicals and phthalates have been identified as possible agents affecting pubertal development in humans in different ways [148, 149]. EDs exert their effects through different mechanisms: by binding to the relevant hormone receptors; by direct action on cell signalling pathways or on the central nervous system and the neuroendocrine system, by suppression of hormone synthesis or through their toxic effects on the relevant organs. ES may influence puberty through their oestrogenic, antioestrogenic, androgenic, antiandrogenic effects or through their direct effects on the gonadotropin-releasing hormone (GnRH). EDs may affect puberty by inhibiting the synthesis of endogenous hormones such as testosterone, 17 beta-oestradiol and adrenal steroids via competitive inhibition of P450 steroidogenic enzymes (C17,20-lyase, aromatase). Other environmental chemicals may impair neuroendocrine functions through their effect on the central nervous system and the hypothalamic-hypophyseal-gonadal (HHG) axis. These include pesticides such as thiram, molinate, metam sodium, chlordimeform, amitraz, triazoles, dichloroacetic acid, atrazine, propazine, simazine, methanol and linuron. Depending on their mechanism of action, EDs may lead to precocious puberty, to delayed puberty, or to sexual differentiation disorders.

However, in humans, most known ES exposures lead to early pubarche and menarche in girls.

Delayed puberty has been reported by exposure to imidazole group fungicides, ketoconazole and fadrozole in the peripubertal period in animals. In a study on rats, atrazine caused delayed puberty by suppressing luteinizing hormone (LH) and prolactin levels. Another pesticide, prochloraz, suppresses oestrogen and androgen synthesis via inhibition of aromatase and 17,20-lyase [148].

In humans, Den Hond et al. [150] observed a reduction in testicular volume in boys and a delay in telarche in girls exposed to a substance with dioxin-like activity, but failed to note a change in pubertal development, or a change in the age of pubarche or menarche. Another study confirmed the relation between prenatal PCDD/F exposure and later initiation of breast development [151].

The heavy metal lead, one of the major environmental pollutants, has also been found to affect puberty [149, 152, 153]. Menarche and pubarche were delayed in girls with high serum lead levels. In addition, blood lead concentration was inversely and significantly associated with IQ. In the linear model, each increase of 10 μg per deciliter in the lifetime average blood lead concentration was associated with a 4.6-point decrease in IQ ($P = 0.004$). When estimated in a nonlinear model with the full sample, IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10 μg per deciliter [154].

In conclusion, there are several alarming reports showing that ES and the heavy metal lead influence pubertal development. The only way to stop this inacceptable poisoning of animals and of humans is the strict observance and enforcement of the already existing legal prescriptions and the targeted formulations of new laws protecting the environment against endocrine disruptors.

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