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REVIEWS

Opinion

Hypogonadism in Pediatric Health: Adult Medicine Concepts Fail

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The classical definition of hypogonadism, used in adult medicine, as gonadal failure resulting in deficient steroid and gamete production, and its classification into hypergonadotropic and hypogonadotropic refer to primary gonadal and hypothalamic–pituitary disorders respectively and may lead to under- or misdiagnosis in pediatrics. Indeed, in children with primary gonadal failure, gonadotropin levels may be within the reference range for age. Conversely, since gonadotropins and steroids are normally low during childhood, it may prove impossible to show the existence of a hypogonadotropic state before pubertal age. Anti-Müllerian hormone (AMH) and inhibin B arise as more adequate biomarkers to assess gonadal function and increase the possibility of making an earlier diagnosis of hypogonadism in children, which may positively impact on timely management.

Most Concepts Used in Biomedical Sciences Were Coined for Adult Biology

In the long history of medicine, pediatrics is a relatively recent branch in healthcare, approximately 200 years old. It is, therefore, not surprising that medical studies have traditionally addressed mostly the anatomy, histology, physiology, and pathology of adults (Box 1).

The Usual Definition of Hypogonadism Was Coined for Adult Medicine

Hypogonadism has classically been defined as gonadal failure resulting in steroid deficiency and impaired gamete production. The most recent guidelines recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and consistently low serum testosterone concentrations [2]. Furthermore, hypogonadism is usually classified as hypergonadotropic when the testes [3] or the ovaries [4] are primarily affected, or hypogonadotropic when the hypothalamic–pituitary axis carries the initial disturbance. These definitions, irreproachably applicable in adult medicine, are difficult to support in children of prepubertal age, as we discuss below (see Outstanding Questions).

The major clinical syndromes were characterized in adults during the second half of the 19th century and first part of the 20th century thanks to the descriptions made by meticulous observers who became the pioneers of contemporary medicine. The most conspicuous forms of primary (or hypergonadotropic) and central (or hypogonadotropic) hypogonadism, Klinefelter [5] and Kallmann [6] syndrome, respectively, were characterized in adults even though they are now both well recognized congenital conditions: Klinefelter syndrome as a consequence of X-chromosome polysomy [7], and Kallmann syndrome – initially described by Maestre de San Juan in 1856 [8] – due to mutations in one or more genes involved in gonadotropin-releasing hormone (GnRH) neuron differentiation and/or migration [9].

The Ontogeny of the Hypothalamic–Pituitary–Gonadal (HPG) Axis

Fetal Period

Initial differentiation of GnRH neurons, gonadotropes, and gonads occurs more or less simultaneously by the 6th gestational week in humans. Counterintuitively, the fetal gonads become functional first, the gonadotropes follow, and the GnRH neurons are last [9,10]. Indeed, the fetal testes are completely differentiated and secrete testosterone and AMH by week 8. These hormones drive internal and external genitalia through the male differentiation pathway before hypothalamic–pituitary regulation of the gonads is established [10]. In this period, it is human chorionic gonadotropin (hCG), secreted by the placenta, that provides the stimulus for Leydig cell androgen

Highlights

Like many other definitions of clinical conditions, that of hypogonadism has been coined for adults. The disregard of a broader definition applicable to all developmental stages may result in underdiagnosis, especially in pediatric patients.

Fetal hypogonadism in males results in ambiguous or female genitalia if established in the first trimester, and in small male genitalia and cryptorchidism if established in the second or third trimester, whereas in females it is clinically unremarkable.

While gonadotropins and sex steroids are informative for the diagnosis of hypogonadism in infancy, pubertal age, and adulthood, Sertoli and granulosa cell biomarkers – AMH and inhibin B – are the only useful biomarkers during childhood.

In childhood, primary hypogonadism is not always hypergonadotropic and the diagnosis can be missed in up to ~70% of the cases if based on serum gonadotropin measurement.

With the currently available clinical and biochemical assessments, the diagnosis of central (hypogonadotropic) hypogonadism is virtually impossible to prove during childhood.

Chronic hormone replacement of hypogonadism is usually not necessary during childhood, but could prove beneficial during infancy.

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Box 1. History of the Focus of the Medical Field on Adult Physiology

Even though the knowledge of the diseases of childhood appears from the *Ebers papyrus* in 1552 BC, it was not until the end of the 18th century that the need for specific care of the diseases of children became apparent [1]. Hence, the first children's hospitals were created first in Europe, with the pioneering Hôpital des Enfants-Malades in Paris in 1802.

Interestingly, it was also the adult's body that attracted the attention of the learned along the history of art: Leonardo da Vinci in his anatomical drawings and Vitruvial Man (15th century), Rembrandt in The Anatomy Lesson of Dr Nicolaes Tulp (17th century), and Thomas Eakins in the Agnew Clinic (19th century) drew or portrayed the bodies of adult men or women.

The most popular textbooks of anatomy, histology, physiology, and pathology used in medical education are almost entirely devoted to the study of the adult. Embryology, developmental biology, and pediatrics are specific subjects that represent an extremely minor part in the curricula of university studies in medicine, dentistry, and biology. Indeed, when a student or a doctor talks of the adrenal gland it is instinctive to think of the adult gland, unless it is specifically made clear that the adrenal of the fetus or the developing child is intended.

production needed for virilization of the Wolffian ducts, urogenital sinus, and external genitalia. The fetal ovaries are also functionally differentiated independently of gonadotropin regulation, but play no role in the differentiation of female genitalia in fetal life. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are released into the circulation only by fetal week 12. The gonadotropes can differentiate in the absence of the hypothalamus, as seen in the anencephalic fetus; however, GnRH is essential for maintenance of gonadotropin secretion beyond the 18th week. Another curious feature is that, unlike most hypothalamic neurons, the GnRH neurons originate outside the central nervous system, in the nasal placode, and migrate to the arcuate nucleus and the preoptic area of the hypothalamus following the vomeronasal nerves. GnRH can be detected in the hypothalamus by fetal week 15. In summary, genital sex differentiation, driven by the presence or the absence of testicular hormone action, occurs independently of pituitary gonadotropins during the first trimester of fetal development (Figure 1).

In the second and third trimesters, pituitary gonadotropins progressively take over the regulation of gonadal hormone production [9]. In males, LH maintains Leydig cell function, revealed by secretion of testosterone and insulin-like factor (INSL)3. Androgens are involved in enlargement of the penis and scrotum and, together with INSL3 [11], in the descent of the testes from the abdominal cavity into the scrotum (Figure 1). FSH promotes Sertoli cell proliferation, the main determinant of testicular size in this period, and secretion of AMH and inhibin B [12]. The fetal ovary is much less active than the testis [13]. Folliculogenesis is initiated independently of FSH, and antral follicles >6 mm, indicating FSH-dependent growth, are present only by week 34 [14].

Infancy and Childhood

Infancy, encompassing the first 2 years of postnatal life, is typically characterized by maternal lactation, followed by childhood, when dependence for food intake and protection progressively disappears. With a clear sex dimorphism [15,16], the HPG axis remains active during infancy (Figure 2). This mini-puberty, as many authors call it, differs from overt puberty, since no progression to complete gametogenesis occurs [17].

In the human male (Figure 2), gonadotropin levels remain high during the 3–6 first months after birth [16,18]. FSH induces further increase in testicular volume and AMH and inhibin B secretion [19]. LH-induced testosterone secretion results in further penile size increase [19,20]. Curiously, although gonadotropin and androgen levels in fetal and neonatal periods are similar to those observed in adults, the testes do not show maturational changes: Sertoli cells retain an immature phenotype and spermatogenesis does not develop beyond spermatogonial proliferation [21,22]. This is due to the lack of androgen receptor expression in Sertoli cells, which renders the seminiferous tubules physiologically insensitive to testosterone during the first year of life [23,24]. Subsequently,

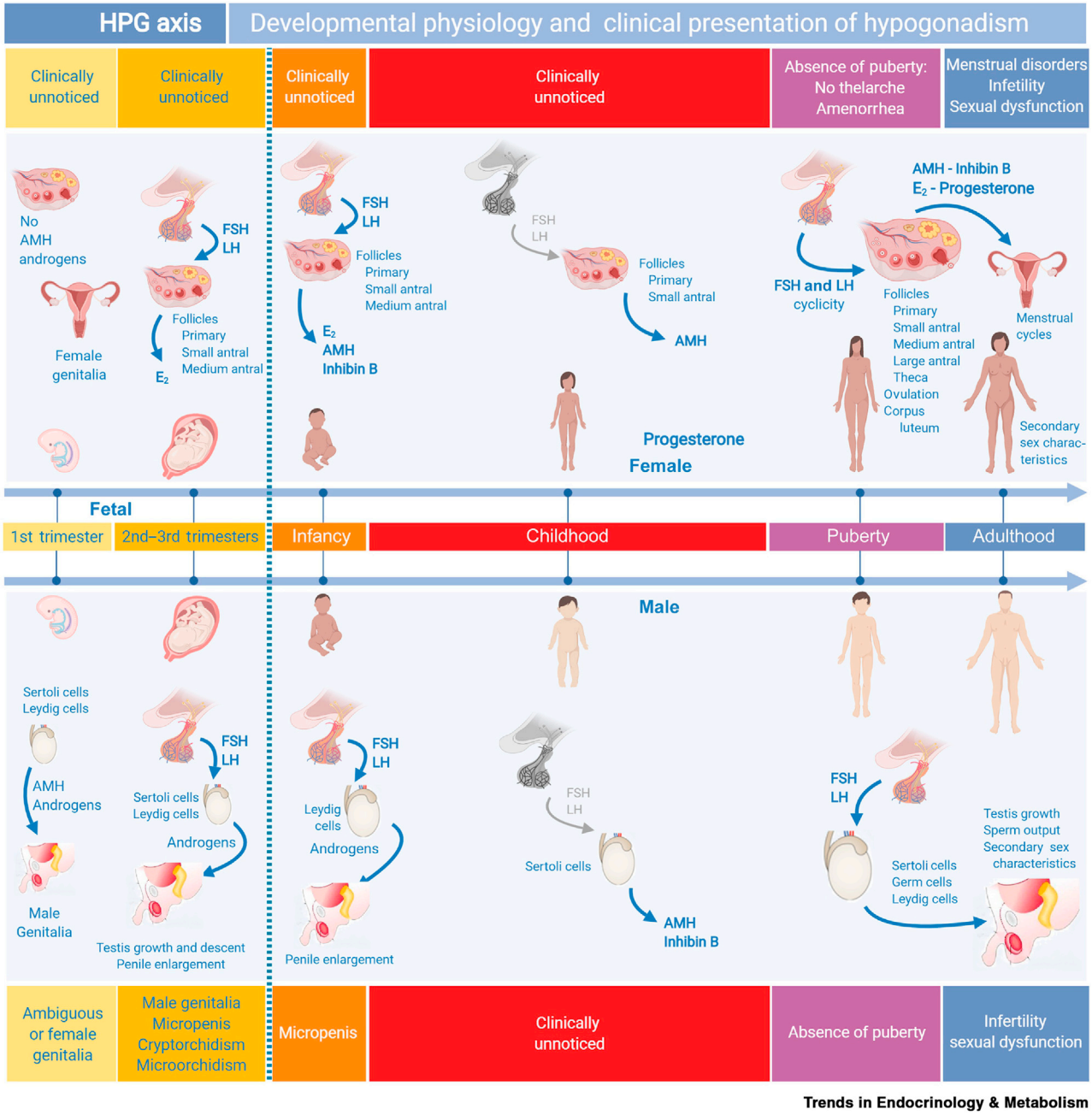

Figure 1. Ontogeny of the Hypothalamic–Pituitary–Gonadal (HPG) Axis in Women (Top) and Men (Bottom), and Its Impact on Clinical Presentation of Hypogonadism.

The gonads differentiate in the first trimester of fetal life, independently of pituitary gonadotropins. Testicular androgens and anti-Müllerian hormone (AMH) provoke male differentiation of the genitalia, whereas their absence lead to female differentiation. Hypogonadal states in this period lead to ambiguous or female genitalia in XY individuals, whereas it goes unnoticed in XX newborns. In the second and third trimesters, the testis increase in size and androgens provoke testicular descent and penile enlargement. Primary and central hypogonadisms result in micropenis, micro-orchidism, and/or cryptorchidism in a newborn with male genitalia. In infancy, gonadotropin and steroid secretion is active in both sexes; hypogonadism precludes penile enlargement in boys but goes clinically unnoticed in girls. During infancy gonadotropins and steroids are normally low or even undetectable; hypogonadism established in this period does not result in clinically evident signs and may only be detected if AMH or inhibin B levels are assessed. During puberty, the HPG axis is

(Figure legend continued at the bottom of the next page.)

gonadotropins and testosterone decline to low levels. This quiescent period of the HPG axis is nonetheless characterized by a notorious activity of Sertoli cells, which secrete high amounts of AMH and moderate amounts of inhibin B [12].

In girls (Figure 2), FSH is higher than LH, it peaks by months 2–3 of life and persists high until the second year of life [18,25,26]. This postnatal activation is reflected in small to medium antral follicle development in the ovaries and a concomitant elevation in estrogen [14] and AMH levels [14,15]. Within the periphery of small antral follicles, theca cells develop and respond to LH with androgen production, serving as a source for aromatization to estrogens in the neighboring granulosa cells [27,28]. Follicular granulosa cells also secrete inhibin B. Follicle development does not progress beyond the small (1–6 mm) to medium (7–11 mm) antral stages [14] and oocytes remain arrested at the dictyotene stage of the first meiotic division [28]. After the second year of life, the quiescent period is characterized by low serum gonadotropin and undetectable estrogen concentrations, with stable AMH levels [29].

Puberty

The reawakening of the GnRH pulse generator results in the occurrence of gonadotropin pulses, leading to gonadal maturation and completion of puberty. Within the testes, androgens provoke Sertoli cell maturation and lead to the development of adult spermatogenesis, characterized by a dramatic increase in testicular volume and sperm production [12,17]. Serum testosterone and inhibin B levels exert a negative feedback on LH and FSH secretion, respectively (Figure 2) [30,31].

In the ovaries, the concerted action of gonadotropins and local factors leads to the activation of terminal follicular growth [13,27,32]. Meiosis resumes, and cyclic follicle recruitment occurs leading to the development of antral (Graafian) follicles through the large (12–17 mm) and preovulatory (18–23 mm) stages. Production of androgens by theca cells and estrogens by granulosa cells increases significantly [28]. Large follicles secrete inhibin B and corpus luteum secretes inhibin A, involved in negative feedback on pituitary FSH production [4]. Initially, menstrual cycles are irregular in normal adolescents [33]: most cycles range from 21 to 45 days in the first year after menarche [34]. The prevalence of ovulatory cycles, as defined by serum progesterone levels resulting from corpus luteum secretion, increases progressively from only 15% in the first postmenarchal year to 41% in the third year and 75% in the sixth year [35].

Approaching Pediatric Hypogonadism to Avoid Flaws

Primary Endpoints for Assessment of the HPG Axis Are Different

Low androgen levels and impaired sperm production are the hallmarks of male hypogonadism in adult patients [2]. As discussed above, in pediatric ages androgens are secreted by the testes at high levels only during a limited period of infancy and from mid-puberty onwards, and sperm production only starts in mid-puberty [36]. Thus, androgen levels and sperm output have limited clinical application for the diagnosis of hypogonadism in boys. Conversely, Sertoli cells are the most active cell population of the testis during childhood, and serum AMH and inhibin B stand out as the most useful biomarkers for the evaluation of gonadal function (Figure 2) [12]. Testicular volume is another clinical endpoint: small gonadal size reflects low germ cell numbers in the adult but reduced Sertoli cell numbers in childhood [17,37].

In adult women, serum estradiol and progesterone are the hallmarks of ovarian function in the follicular and luteal phases, respectively (Figure 2). Frequency and duration of menses are major clinical markers of HPG function. Also, ultrasonography is used to monitor cyclic antral follicle progression

reactivated and results in the typical development of secondary sex characteristics; hypogonadism may result in absent or incomplete pubertal development, or later in menstrual cycle disorders (females), infertility and/or sexual dysfunction. This figure was created using BioRender (https://biorender.com/). Abbreviations: E_2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

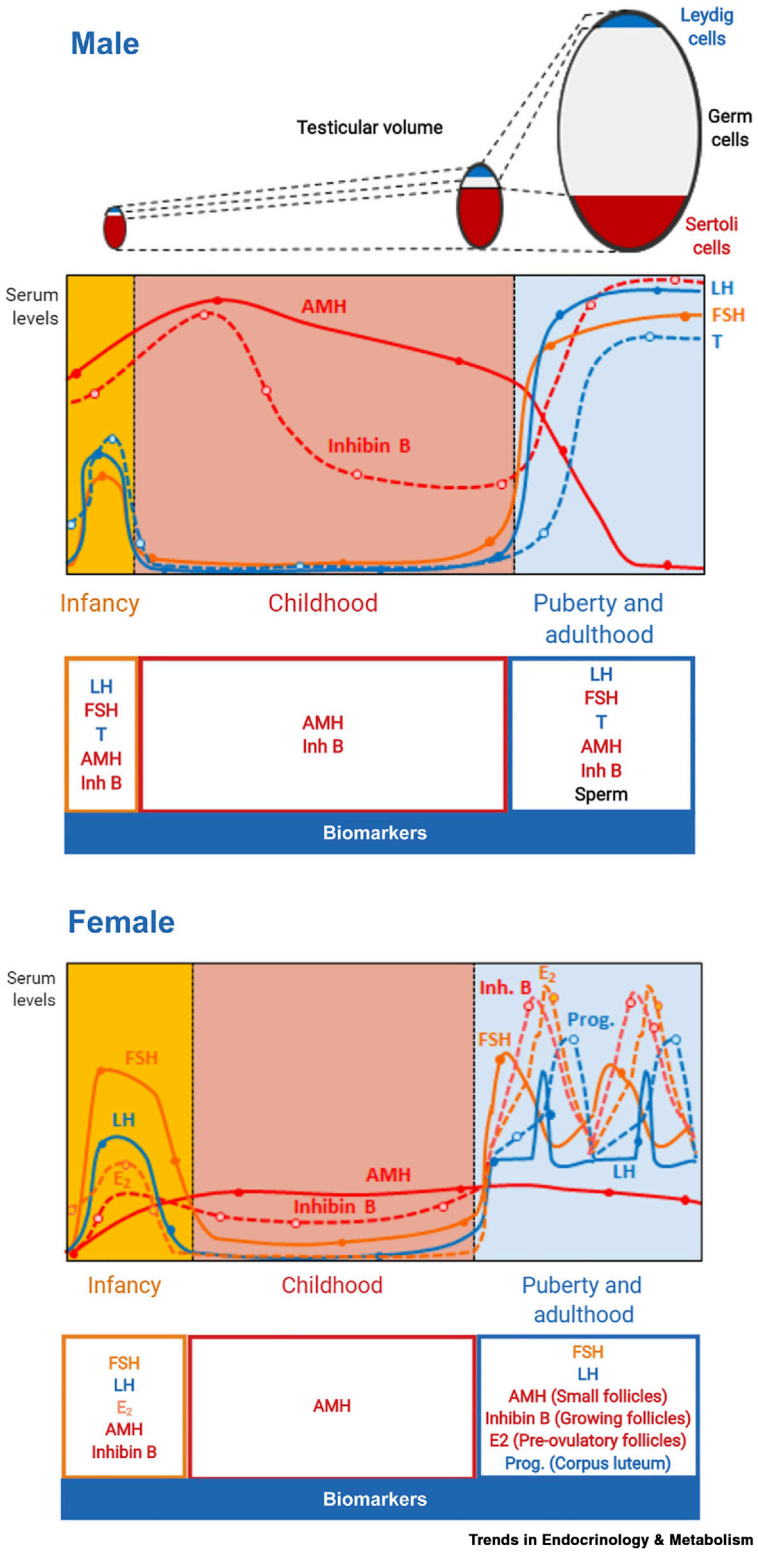

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Table 1. Serum Levels of Pituitary–Gonadal Axis Hormones in Normal Individuals and Patients with Central Hypogonadism at Different Stages of Postnatal Development[a]

		Postnatal activation (mini-puberty)		Childhood		Adulthood	
		Normal	Central hypogonadism	Normal	Central hypogonadism	Normal	Central hypogonadism
Females	FSH (IU/L)	0.48–24.0	0.10–0.25	0.15–5.60	N.A.[b]	2.40–7.90	<0.10–5.10
	LH (IU/L)	0.05–1.00	0.05–0.40	0.05–0.98	N.A.	2.20–8.20	<0.10–5.30
	Estradiol (pg/mL)	10–26	<10	10–22	N.A.	13–97	2–28
	AMH (pmol/L)	5–30	N.A.	6–57	N.A.	20–80	7–60
	Inhibin B (pg/mL)	18–226	N.A.	20–55	N.A.	23–130	7–50
Males	FSH (IU/L)	0.90–2.93	<0.10–0.80	0.30–1.70	<0.10–1.60	2.20–7.40	<0.10–2.90
	LH (IU/L)	0.90–2.64	<0.10–0.70	0.10–0.35	<0.10–0.30	1.60–5.60	<0.10–2.60
	Testosterone (ng/dL)	53–188	<10–13	<10–15	<10	340–740	20–130
	INSL3 (ng/mL)	0.05–0.60	N.A.	0.05–0.10	N.A.	380–938	17–103
	AMH (pmol/L)	421–1470	94–665	684–1831	68–660	25–137	157–550
	Inhibin B (pg/mL)	204–427	20–149	18–258	10–209	105–360	26–74

[a]Data from [18,19,29,43,54,64–66,71,73,83–88]
[b]N.A., not available

and ovulation, and follicle count and serum AMH are biomarkers of small follicle reserve [38,39]. Of all this battery, only follicle size and serum AMH can be used throughout childhood to assess the status of the female gonads [40].

To increase the confusion, several terms are used to indicate primary hypogonadism in females [41]. Premature ovarian failure (POF) and primary ovarian insufficiency (POI) are usually considered as synonyms to describe the condition defined by the coexistence of amenorrhea for at least 4 months, sex steroid deficiency, and two recordings of serum concentrations of FSH >40 IU/L at least 1 month apart, in a female aged <40 years [4,41]. The use of POF and POI, terms clearly created for adult medicine, has also been extended to pediatrics, against all rationale: amenorrhea and low sex steroids are the physiological state in prepuberty and, as we discuss in the next section, FSH remains frequently below 40 IU/L in girls with primary hypogonadism.

Primary Hypogonadism Is Not Always Hypergonadotropic during Childhood

The classical approach in the diagnosis of hypogonadism in adult patients prompts the classification into hypergonadotropic or hypogonadotropic to drive the attention to a primary gonadal failure in the first case and to a hypothalamic–pituitary deficiency in the second (Table 1). This approach is also applicable to most cases during the activation stage of the infantile period of life [42–46] and during pubertal ages [9,44–46].

However, as in normal children, gonadotropin levels decline and can fall within the normal range for age in patients with primary hypogonadism during childhood. The most patent evidence proceeds

Figure 2. Serum Levels of Gonadotropins [Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)], Sex Steroids (Estradiol, Progesterone, and Testosterone) and Gonadal Peptides [Anti-Müllerian Hormone (AMH) and Inhibin B], and Their Usefulness as Biomarkers in Different Periods of Postnatal Development.

Top figure, modified with permission from [3]. This figure was created using BioRender (https://biorender.com/). Abbreviations: E_2, estradiol; HPG, hypothalamic–pituitary–gonadal; Inh. B, inhibin B; Prog. progesterone; T, testosterone.

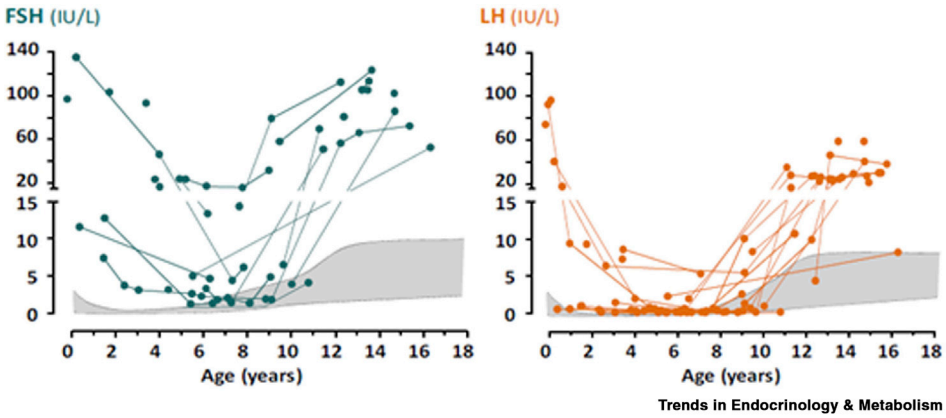

Figure 3. Serum Levels of Gonadotropins May Not Be Elevated in Agonadal Children.
Boys with anorchidism may have normal follicle-stimulating hormone (FSH) (top) and luteinizing hormone (LH) (bottom) levels in childhood. Shaded area represents the normal ranges of gonadotropins for age. Reproduced with permission from [46].

from the findings in agonadal children (Figure 3). Already in 1975, Conte and colleagues [44] showed the existence of a diphasic pattern of gonadotropin secretion in girls with Turner syndrome, characterized by the existence of normal FSH and LH levels between 4 and 10 years of age. A similar pattern could be observed in boys with anorchidism [47,48]. In a series of 35 anorchid boys with longitudinal follow-up [46], we found that while both gonadotropins were elevated in 90–100% of the boys during the first 3 years after birth and from the age of 13 years onwards, significantly lower levels were observed in between, reaching normal values in many cases (Figure 3). Indeed, the sensitivity of elevated FSH for anorchidism fell to 68% in boys aged 6–10.9 years. For LH, the situation was even more remarkable: the sensitivity of elevated serum LH was as low as 27% at 9–10.9 years. These results indicate that at least 32%, and up to 73%, of the patients would have been underdiagnosed – because they were not hypergonadotropic – if the typical classification used for adult hypogonadism had been applied.

It becomes obvious that misled diagnoses can reach higher proportions during childhood in patients with present but dysfunctional gonads, unless the adequate endpoint variables are assessed. Cryptorchidism is a relatively frequent cause of referral to the pediatric surgeon, urologist, or endocrinologist, but impaired testicular function is often underdiagnosed. Basal gonadotropin and testosterone levels are most frequently uninformative, and even testosterone measured after hCG stimulation may be misleading [49]. Conversely, the assessment of serum AMH [49–53] or inhibin B [50,52,53] may uncover a hypogonadal state. In a recent study of 310 boys with cryptorchidism [51], we found that a hypogonadal state, as reflected by low serum AMH, was present in approximately 7% of boys with unilateral cryptorchidism and 18–36% of patients with bilateral cryptorchidism aged 6 moths to 8.9 years. However, FSH elevation was observed in only 1–3% of patients with unilateral cryptorchidism and <6% of those with bilateral cryptorchidism, clearly showing a low sensitivity of elevated FSH for the diagnosis of primary hypogonadism in childhood.

In girls with Turner syndrome due to miscellaneous karyotypes (non 45,X single-lineage), low serum AMH [29] or inhibin B [54] indicates the presence of some functional ovarian tissue, with a decreased follicle reserve, that is, primary hypogonadism. Nonetheless, serum gonadotropins fall within the normal range in most cases between 4 and 9 years of age [44,54]. Furthermore, in that age interval gonadotropin pulse periodicity is similar to that of normal girls [55]. Another congenital condition characterized by primary ovarian insufficiency is galactosemia [56]. Ovarian function is severely affected in 95% of galactosemic girls aged <10 years, as revealed by undetectable serum AMH, whereas FSH is elevated in only 33 % of the cases [57].

Acquired primary ovarian dysfunction may result from cancer therapy in girls. Decreased levels of serum AMH or inhibin B reflect gonadotoxicity due to chemotherapy; however, FSH levels do not increase over the normal range in most of the girls aged <12 years [58–61].

Is It Possible to Diagnose Hypogonadotropic Hypogonadism in Childhood?

As discussed previously, once the postnatal activation period of the HPG axis has vanished, gonadotropins and sex steroid decrease to low levels, or even undetectable values for LH, testosterone, and estradiol, in normal girls and boys (Figure 1). While early infancy is a propitious period for establishing the diagnosis of central (hypogonadotropic) hypogonadism [42,43,62], it becomes evident how impossible it is to find lower than normal levels of basal LH and sex steroids in childhood (Table 1). Stimulation tests with GnRH or a GnRH agonist, which may be helpful in patients of pubertal age [63], have not been validated for the diagnosis of central hypogonadism in children below the age of 10 years. Here again, in boys, direct Sertoli cell biomarkers like AMH and inhibin B could be informative when they are low [19,43,64,65], but their diagnostic efficiency needs to be assessed in large series. In girls, no reliable biomarker exists. Similarly, multigene panels for the molecular diagnosis of central hypogonadism have progressively increased their diagnostic efficiency, and approximately half of the cases may be diagnosed even during childhood, provided the condition is suspected [9].

Impact on Management of Hypogonadism in Childhood

If the HPG axis is quiescent during childhood and gonadal dysfunction does not result in clinically evident symptoms during childhood (Figure 1), do hypogonadal children need to be treated with hormone replacement? Intuitively, the answer would be no. Furthermore, chronic treatment with estradiol or testosterone could even be deleterious to the child's health, as it would result in precocious advancement of bone age and development of secondary sex characteristics. Nonetheless, based on the physiology of the early postnatal activation period (mini-puberty), recent work has underscored the potential benefits of early replacement with gonadotropins in patients with congenital central hypogonadism [19,66,67]. While short courses of testosterone are the accepted treatment for micropenis in hypogonadal infants or children, FSH administration for a sufficient period mimics physiological Sertoli cell proliferation, resulting in testis volume increase, and functional hormone secretion when the treatment is initiated either during early infancy [19,65,66,68–70], or later during childhood [71,72], or at the age of puberty [64,73–76].

Although steroid levels are below the detection limit of usual immunoassays in the quiescent period of the HPG axis, low levels are detected with sensitive mass spectrometry [77], which has raised the question whether the administration of low doses of steroids during childhood would be beneficial for the child's health [78–81].

A Broader Definition and Classification of Hypogonadism, Based on Developmental Physiology

Contrasting with the classical definition, a more comprehensive definition of hypogonadism based on developmental physiology refers to decreased gonadal function, as compared to what is expected for age, involving an impaired hormone secretion (androgens, INSL3, estrogens, AMH, and/or inhibins) and/or a disorder of gametogenesis.

Since hypogonadism may have different clinical presentations and health consequences, according to the level of the HPG axis primarily affected, the gonadal cell population initially impaired, and the period of life when hypogonadism is established, we advocate for the use of an exhaustive classification of hypogonadism [82], as summarized in Table 2.

Concluding Remarks

The correct appraisal of hypogonadal states in different periods of life requires ample knowledge of the normal functional ontogeny of the HPG axis in males and females. The choice of

Table 2. Classification of Hypogonadism, with Illustrative Examples

	Primary hypogonadism	Central hypogonadism	Dual hypogonadism
Fetal-onset			
Whole gonadal dysfunction	Gonadal dysgenesis (46,XY, 46,XX, 45,X, other karyotypes) Gonadal torsion Galactosemia Vanishing testes	Congenital multiple pituitary hormone deficiency Isolated central hypogonadism (Kallmann syndrome, normosmic, etc.)	Prader–Willi syndrome X-linked adrenal hypoplasia congenita (*DAX1* mutation)
Dissociated gonadal dysfunction	LH receptor mutation (Leydig cells and theca) Steroidogenic enzyme defects (Leydig cells and theca) FSH receptor mutation (Sertoli and granulosa cells) AMH mutation (Sertoli and granulosa cells) Aromatase deficiency (granulosa cells) *USP9Y* mutations, *AZF* and *Yq* deletions (germ cells) *BMP15* mutation, *FMR1* premutation, *Xq* deletion (germ cells)	*LHX4* mutation (LH, Leydig cells, and theca) *TAC3* or *TACR3* mutation (LH, Leydig cells, and theca) *LHβ* mutation (LH, Leydig cells, and theca) *FSHβ* mutation (FSH, Sertoli, and granulosa cells)	
Postnatal-onset			
Whole gonadal dysfunction	Orchitis/oophoritis Gonadal torsion Amyloidosis, granulomatous diseases	CNS tumors, histiocytosis, trauma, radiotherapy Hypothyroidism, hyperprolactinemia, acromegaly Alcohol or drug abuse Chronic illness	Chemotherapy + cranial radiotherapy Lead intoxication Marijuana consumption Total body irradiation
Dissociated gonadal dysfunction	Chemotherapy (germ cells) Pelvic radiotherapy (germ cells) Ketoconazole or spironolactone (Leydig cells and theca) Aromatase inhibitors (granulosa cells)		

biomarkers for the assessment of the HPG axis differs according to the sex and age of the patient. Definitions and classifications coined for adult medicine should be specifically adapted for the use in pediatrics, based on developmental physiology and pathology. Terms like hypergonadotropic and hypogonadotropic hypogonadism may lead to missed diagnoses in children of prepubertal age and would better be replaced by gonadal or primary and central or secondary hypogonadism. The definition of POI or POF should be redefined for pediatric patients according to adequate biomarkers of ovarian function at that age, and these terms should be replaced – for the sake of homogeneity – by primary hypogonadism. Finally, the definition of hypogonadism itself should be broadened to consider the pathophysiology expected for the developmental period of life that is being analyzed, and its classification should consider the level of the HPG axis primarily affected, the cell population of the gonads that are initially affected, and the period of life when the gonadal function begins to fail. The recent advancements in medical technology, including the development of biomarkers and genomic studies, have increased the possibilities of making an earlier diagnosis of hypogonadism in children, thus prompting immediate medical actions. The impact on adult reproductive health resulting from a timely management during infancy and childhood will only be established after sufficient follow-up.

Author Contributions

R.A.R. conceptualized the outline. R.P.G., A.V.F., and R.A.R. discussed the content, drafted the manuscript, and approved the final version.

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Outstanding Questions

Should we rethink medical terminology according to the developmental stage of our patients rather than forcingly adapting definitions coined for adult medicine?

Will the new biomarkers prove efficacious for an accurate diagnosis of primary or central hypogonadism during childhood?

Will early management of hypogonadism in infancy or childhood result in improved reproductive health in puberty and adulthood?

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