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Mini-puberty and true puberty: Differences in testicular function

Mini-puberté et vraie puberté : différences au niveau de la fonction testiculaire

Rodolfo A. Rey [a,b,*]

[a] *Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE), CONICET-FEI-División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, Gallo 1330, C1425EFD Buenos Aires, Argentina*

[b] *Departamento de Histología, Biología Celular, Embriología y Genética, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, C1121ABG Buenos Aires, Argentina*

Abstract

The ontogeny of the hypothalamic-pituitary-gonadal axis is particularly characterised by incomplete functional maturation in utero and during early postnatal life, followed by functional regression and partial quiescence during childhood, and subsequently by final complete maturation during puberty. This review addresses the distinctive features of testis developmental physiology – especially in the seminiferous tubule compartment – which explain the differences observed in testicular function and its disorders between the early postnatal activation period – which many authors call "mini-puberty" – and canonical puberty.

Keywords: AMH; Cryptorchidism; Hypogonadism; Gonadotrophins; Testosterone

Résumé

L'ontogenèse de l'axe hypothalamo-hypophyso-gonadique est caractérisée par un développement fonctionnel incomplet pendant la vie fœtale et les premiers mois de la vie postnatale, suivi par une régression fonctionnelle et une quiescence partielle pendant l'enfance, et finalement par une maturation complète au cours de la puberté. Cette revue analyse les caractéristiques distinctives de la physiologie du développement testiculaire – et spécialement celles des tubes séminifères – qui peut expliquer les différences observées au niveau de la fonction testiculaire et ses anomalies entre la période d'activation postnatale – appelée « mini-puberté » par certains auteurs – et la vraie puberté.

Mots clés : AMH ; Cryptorchidie ; Hypogonadisme ; Gonadotrophines ; Testostérone

The ontogeny of the gonads is very different from that of most of the organs. While differentiation in early foetal life followed by a progressive maturation process is the rule in most tissues and systems, incomplete functional maturation in utero and during early postnatal life, followed by functional regression and partial quiescence during childhood and subsequently by final complete maturation during puberty characterises the development of the gonads. Although this ontogeny seems to reflect the fluctuations

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* Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE), CONICET-FEI-División de Endocrinología, Hospital de Niños Ricardo Gutiérrez, Gallo 1330, C1425EFD Buenos Aires, Argentina.

E-mail address: rodolforey@cedie.org.ar.

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in the activity of the hypothalamic-gonadotroph axis, a careful look into gonadal developmental physiology uncovers distinctive features in the development of the gonads, which explain for instance the differences observed in testicular function and its disorders between the early postnatal activation period – which many authors call "mini-puberty" – and canonical puberty. The differences observed between these two periods – especially in the seminiferous tubule compartment – will be addressed in this review.

1. Early testis development in the human embryo

1.1. Pituitary-independent testicular differentiation

The testis differentiates from the gonadal ridge, independently of gonadotrophins, in the 7th embryonic week. Somatic cells of the gonadal anlage give rise to Sertoli, peritubular, Leydig, and mesenchymal cells, whereas germ cells are of extra-testicular origin and migrate into the developing gonads (reviewed in ref. [1]). Sertoli and germ cells aggregate, surrounded by peritubular cells, to form the seminiferous cords. Mesenchymal cells and differentiating Leydig cells remain in the interstitial tissue. Sertoli cells secrete anti-Müllerian hormone (AMH), responsible for the regression of the Müllerian ducts, i.e. the anlagen of the uterus, Fallopian tubes and upper vagina. Basal AMH expression is independent of gonadotrophin stimulation; however, during the second half of gestation and after birth, FSH increases testicular AMH secretion by stimulating Sertoli cell multiplication and upregulating AMH expression in each Sertoli cell [2,3]. FSH also induces inhibin B secretion by Sertoli cells; inhibin B exerts a negative feedback on FSH. Germ cells proliferate by mitosis but do not enter meiosis during foetal life.

Leydig cells secrete androgens, which are responsible for the differentiation of Wolffian ducts into the epididymis, vas deferens and seminal vesicle, and for the virilisation of the hitherto undifferentiated urogenital sinus and external genitalia. Gonadotrophin activity is essential for the maintenance of Leydig cell differentiation and steroidogenic activity. In the first trimester, chorionic gonadotrophin (hCG in the human) is the main regulator of Leydig cell function. Thereafter, pituitary LH progressively takes over. Testosterone exerts a negative feedback on LH.

2. The hypothalamic-pituitary-testicular axis from foetal life to puberty

2.1. Pituitary-dependent testicular activity in foetal life and "mini-puberty"

The hypothalamus regulates the reproductive axis through its secretion of GnRH, which acts on the pituitary gonadotroph inducing the release of LH and FSH from the 17th–18th foetal weeks (reviewed in ref. [4]). LH levels are higher than FSH levels in the male foetus. Gonadotrophins decrease in circulation towards the end of gestation [5], probably due to the negative feedback exerted by placental oestrogens. Testosterone levels are high, reaching adult levels, between 10–20 weeks of foetal life, and decrease thereafter (reviewed in ref. [4]).

At birth, gonadotrophins and testicular hormones are low [6–8]. Gonadotrophin levels increase from the first week [8], followed by AMH and testosterone [7]. Peak levels of gonadotrophins and testosterone are reached at 3 months [8–10]; thereafter, they decrease and are very low or undetectable from approximately 6 months of age until the onset of puberty (Fig. 1). Similar changes are observed in the number of Leydig cells [11] and in testosterone concentration [10] within the testis.

During the gestational and early infantile periods, the marked hypothalamic-pituitary-Leydig cell axis activity has only a minor effect on the seminiferous cords: Sertoli cells and germ cells (spermatogonia) proliferate but remain at an immature stage of their development. Nonetheless, these minor effects seem to be critical for the normal spermatogenic process taking place at puberty [12].

The physiological changes occurring during "mini-puberty" are reflected clinically: Sertoli cell proliferation results in a moderate increase in testicular volume, which cannot be detected by palpation [8,13–15], and Leydig cell steroidogenic activity induces a trophic effect on the genitalia [8].

2.2. Quiescent gonadotroph but partially active testis in childhood

The reduced activity of the hypothalamic-gonadotroph axis after the 6th month of postnatal life is reflected in the disappearance of typical Leydig cells from the testis and the decrease of serum testosterone. Conversely, Sertoli cells remain active, as shown by their capacity to secrete high levels of AMH, a typical marker of the immature, i.e. prepubertal, testis. Therefore, serum AMH is the preferred marker to study testicular function during the so-called prepubertal "pause" of the reproductive axis [16]. The prepubertal testis also produces inhibin B, which does not seem to play any role in the decline of FSH during childhood, since the latter occurs also in anorchid boys [17].

2.3. Puberty: Sertoli cell maturation and complete spermatogenesis

The word "puberty" may have different meanings: while the neuroscientist uses it to refer the re-activation of the hypothalamic-gonadotroph axis and the experimental reproductive biologist to the moment when the gonads start producing the gametes (i.e. usually when the animal model becomes fertile), clinicians use it to describe the period – rather than a moment – of life characterised by the development of secondary sexual characteristics and the progressive acquisition of the reproductive capacity. Undoubtedly, the pubertal process is much longer in humans than in most experimental laboratory models, not only from an absolute standpoint (years versus weeks), but also from a relative point of view. In

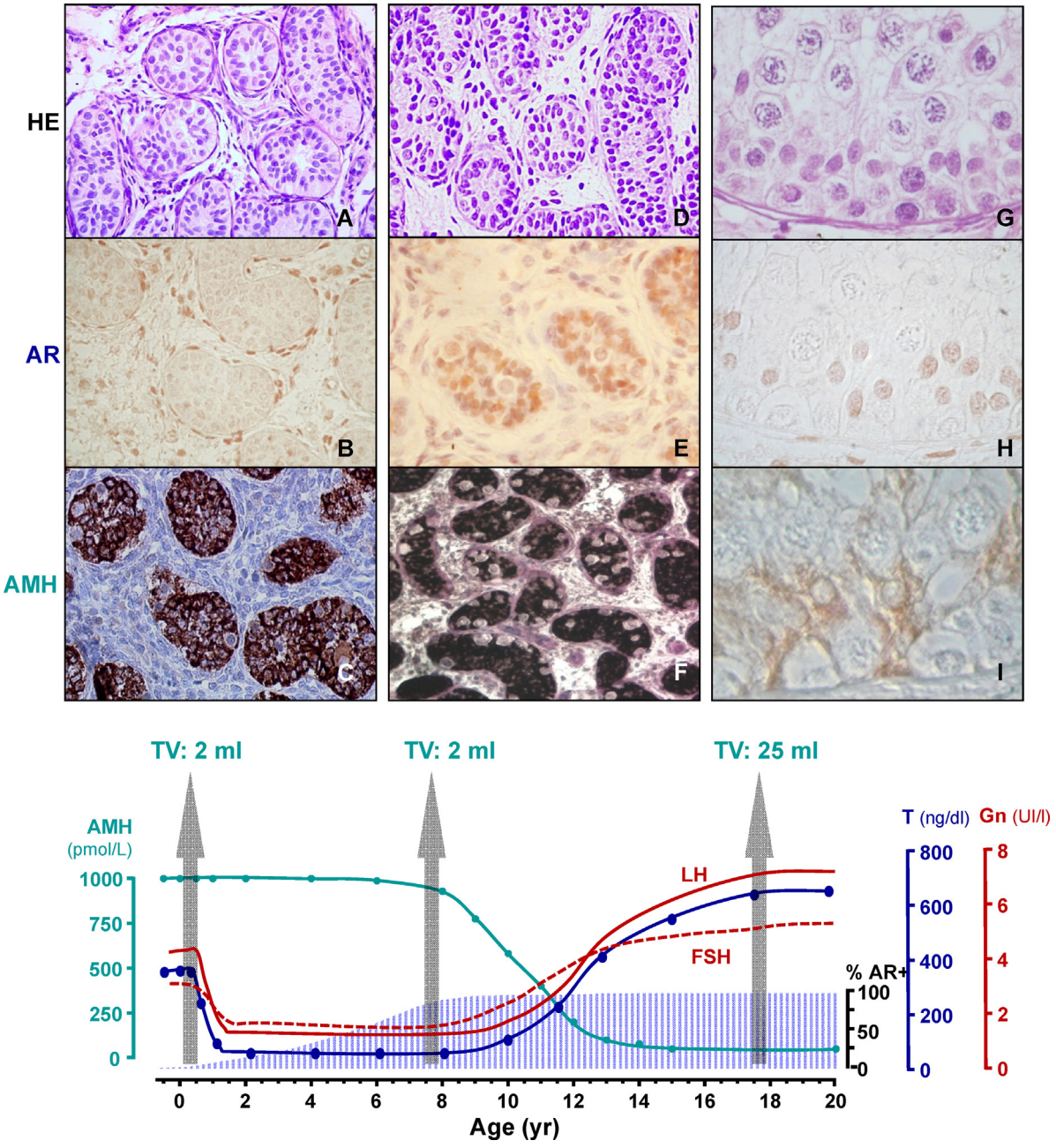

Fig. 1. Schematic representation of the activity of the pituitary-testicular axis in humans. Relationship between gonadotrophin (Gn), testosterone and AMH levels, and androgen receptor (AR) expression in the human testis from foetal life to puberty. At 3 months (A–C), Leydig cells of the interstitial tissue secrete testosterone, but AR is not expressed in Sertoli cells (% of AR positive cells is null); consequently, AMH production is not inhibited by testosterone, and spermatogenesis does not progress into meiosis. At 8 years (D–F), most Sertoli cells express the AR, but the interstitial tissue does not have mature Leydig cells and testosterone is low; therefore, Sertoli cells remain immature, AMH is high, and no meiosis occurs. At late puberty (G–I), testosterone increases and acts on Sertoli cells – which express the AR – to provoke their maturation, reflected in the inhibition of AMH expression and also in the development of full spermatogenesis. Magnification: A–F: 3200; G–I: 3500. Reprinted, with modifications, from Chemes HE, Rey RA, Nistal M et al. Physiologic androgen insensitivity of the fetal, neonatal, and early infantile testis is explained by the ontogeny of the androgen receptor expression in Sertoli cells. *J Clin Endocrinol Metab* 2008;93:4408–12, Copyright 2008, The Endocrine Society, and Rey RA, Musse M, Venara M, Chemes HE. Ontogeny of the androgen receptor expression in the fetal and postnatal testis: its relevance on Sertoli cell maturation and the onset of adult spermatogenesis. *Microsc Res Tech* 2009;72:787–95, copyright 2009 Wiley-Liss, Inc.

fact, the duration of spermatogenesis is approximately 60 days in human [18] and rodents [19,20]; however, pubertal spermatogenesis is efficient in rodents, which become fertile with the completion of the first spermatogenic wave, but very inefficient in humans in whom spermarche only takes place about 1–2 years after the initial signs of pubertal development [21].

Clinically, in the boy pubertal onset is defined by the attainment of a testicular volume of 4 mL. However, physiologically puberty has begun earlier, with a progressive increase in

gonadotrophin pulse amplitude and frequency (reviewed in ref. [22]). FSH increases and re-boosts immature Sertoli cell proliferation, probably the main responsible for the initial increase of testicular volume from 2 to 4 mL. In fact, the progression of testis volume from 2 to 3 mL is an early predictor of pubertal onset [23]. LH induces the differentiation of mature Leydig cells; androgen concentration increases within the testis long before it does in serum [24,25] and provokes Sertoli cell maturation, characterised by the loss of mitotic capacity, the development of the blood-testis barrier and the down-regulation of AMH production (reviewed in ref. [26]). Germ cells enter meiosis, and go through the complete spermatogenic process giving rise to sperm production (Fig. 1). Spermatogenic development is the main responsible for testis volume increase during puberty, from 4 to 25 mL (reviewed in ref. [27]). FSH and germ cells induce an increase in inhibin B, the major negative feedback regulator of pituitary FSH secretion.

3. Why "mini-puberty" is not overt puberty? Androgen receptors in Sertoli cells

As discussed above, the hypothalamus, the gonadotrophs and Leydig cells are as active during foetal life and the 6 months that follow birth as during puberty. Intriguingly though, the characteristic features of testicular puberty do not occur in utero or in early infancy. In fact, why do Sertoli cells not mature – i.e. stop diving by mitosis, decrease their AMH production and develop the blood-testis barrier – and germ cells not go through spermatogenesis beyond meiosis despite the long-lasting exposure to high intratesticular androgen levels between the 8th foetal week and the 6th postnatal month?

A transient state of physiological androgen insensitivity of the Sertoli cell population seems to be the answer. Studies of the ontogeny of the androgen receptor expression in Sertoli cells in rodents [28,29], monkeys [30] and humans [31–33] clearly show that the androgen receptor, although present from early foetal life in the nuclei of most peritubular and Leydig cells, is absent from foetal and infantile Sertoli cells (Fig. 1).

In the mouse, intratesticular androgen levels do not decline perinatally. When the androgen receptor begins to be expressed in Sertoli cells – at postnatal days 4 to 7 – AMH expression is down-regulated and spermatogenesis develops beyond meiosis [29]. The negative correlation between Sertoli cell androgen receptor and AMH expressions has also been described in the monkey [34]. In the human, androgen receptor expression appears faintly in a low proportion of Sertoli cell nuclei by the end of the first year of life [32]. A progressive increase is observed between ages 2–8 years. However, intratesticular testosterone is normally very low and cannot induce any androgen-dependent changes. By the age of pubertal onset (9–14 years), all Sertoli cell nuclei are AR-positive and respond to the increase of local androgen concentration with cytological signs of maturation, AMH down-regulation and massive entry of germ cells into meiosis (Fig. 1) [32].

4. Clinical relevance

4.1. Neonatal activation of the hypothalamic-pituitary-gonadal axis and future fertility

"Mini-puberty" represents a window of opportunity for both the diagnosis and early treatment of congenital central hypogonadism in males [35]. The existence of micropenis, cryptorchidism and/or microorchidism in a newborn alert of the possibility of an isolated pituitary deficiency of gonadotrophins, or even more importantly of a multiple congenital pituitary hormone deficiency. Standard treatments for central hypogonadism, usually started after the age of puberty, often achieve an only partial success to correct the genital abnormalities and spermatogenesis. Additional benefits of gonadotrophin therapy during early infancy have been suggested [36].

Fertility prognosis is related to the number of germ cells present in the seminiferous tubules at the moment of orchidopexy in boys with cryptorchidism. Early orchidopexy in the first year of life has been encouraged to avoid germ cell loss. However, 35% of boys submitted to orchidopexy before the age of 6 months will be infertile. This may be explained by the insufficient testosterone surge observed during the early infantile period [12].

4.2. Activation of the hypothalamic-pituitary-gonadal axis in boys born preterm or small for gestational age

Preterm birth is associated with higher gonadotrophin and testosterone levels in males. Prematurity does not influence the timing of the onset of the postnatal gonadotrophin surge, which starts at the same time after birth as in full-term infants; however, the surge is prolonged, and gonadotrophin and testosterone levels decline at the expected corrected age [8,37]. The higher and prolonged androgen secretion is associated with faster penile and testicular growth after birth [8].

Full-term boys born small for gestational age have higher FSH and testosterone levels than those born appropriate for gestational age, but the underlying pathophysiology and clinical relevance remain unknown [38].

4.3. Impaired activation of the hypothalamic-pituitary-gonadal axis in patients with androgen insensitivity

The gonadotrophin and testosterone surge is blunted in infants with complete androgen insensitivity, but not in those with partial androgen insensitivity [39], which suggests that androgen effect at the hypothalamic-pituitary level may play a role in the axis activation during "mini-puberty".

4.4. Physiological androgen insensitivity of Sertoli cells in infancy may explain oligo-symptomatology in very early-onset precocious puberty

Precocious puberty is rarely diagnosed in males before the age of 3–4 years, even in cases where the underlying

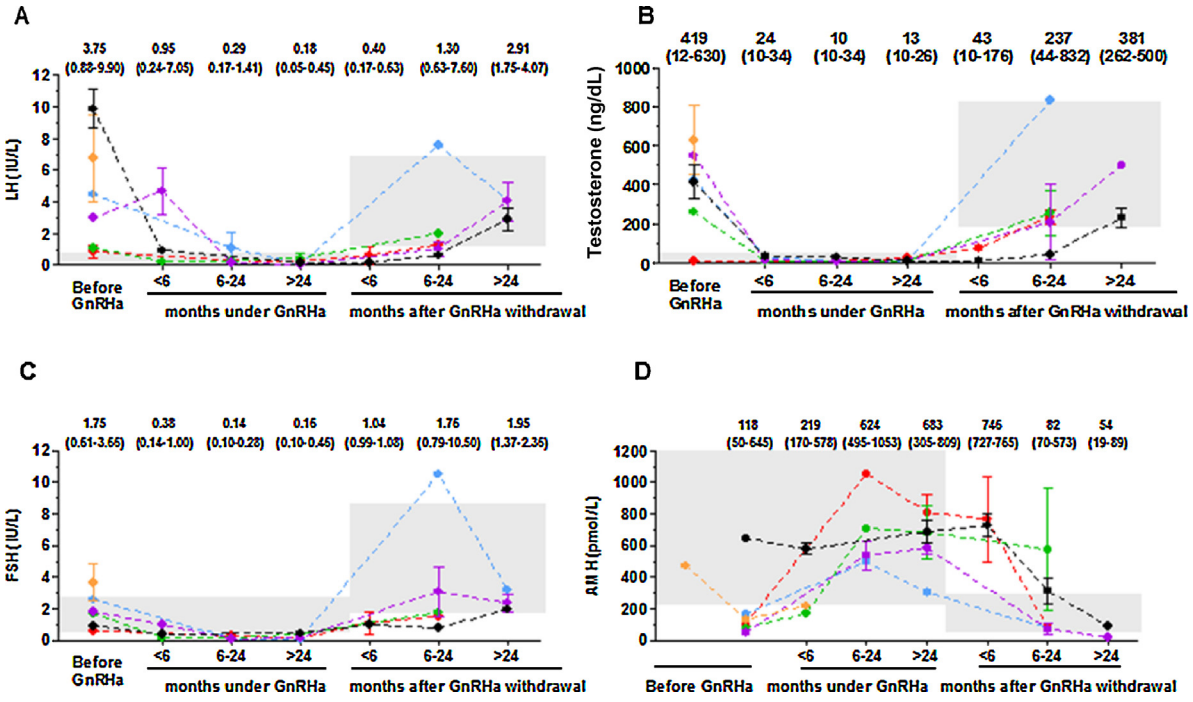

Fig. 2. Hormone levels of boys with central precocious puberty before, during, and after withdrawal of GnRH analogue treatment. Medians and ranges are shown on the top of each figure for each time point. Gray areas indicate normal ranges for age. Note that the 2 patients who had prepubertal AMH levels were aged 10 and 13 months at the moment of the diagnosis (Sertoli cells do not express the androgen receptor at those ages); the others were older than 2 years. One of the two patients could not be treated until the age of 2.2 years (an age when the androgen receptor becomes expressed in Sertoli cells) and AMH was inhibited. Reprinted, with modifications, from Grinspon RP, Andreone L, Bedecarrás P et al. Male central precocious puberty: serum profile of anti-Müllerian hormone and inhibin B before, during, and after treatment with GnRH analogue. *Int J Endocrinol* 2013; Article ID 823064, 6 pages; doi:110.1155/2013/823064, copyright 2013 R.P. Grinspon et al.

aetiology is congenital. We recently reported two patients in whom central precocious puberty was suspected at the ages of 10 and 13 months because of increased penile size; however testis volume was < 4 mL and AMH levels were not down-regulated despite high testosterone levels (Fig. 2) [40]. Clearly, the abnormally high androgen secretion was capable of triggering peripheral signs of pubertal development but was unable to induce Sertoli cell maturation in both patients. Due to social difficulties in one of them, GnRH analogue treatment could not be started until the age of 2.2 years, an age at which Sertoli cells already start expressing the androgen receptor [32]; at that moment, testicular volume had reached 4 mL and serum AMH had decreased to pubertal values, reflecting intratesticular androgen effect [40]. In vitro studies using a prepubertal mouse Sertoli cell line devoid of androgen receptor expression confirmed the lack of androgen-induced AMH inhibition expression despite high local androgen concentration in the culture medium until the Sertoli cell line was transfected with an androgen receptor expression vector [33].

5. Concluding remarks

The hypothalamic-pituitary-gonadal axis is active in foetal life, in early infancy and from puberty through adulthood. However, the increased gonadotrophin activity on the testis are not capable of inducing pubertal changes in the seminiferous tubules before the age of 2–3 years owing to the insufficient androgen receptor expression in Sertoli cells. This difference seems to underlie the major disparities observed in testicular physiology between the so-called "mini-puberty", an incomplete version of puberty, and the complete pubertal onset, occurring normally after the age of 9 years but also before – though apparently never before the age of 2 years – in boys with precocious development.

Disclosure of interest

The author has received honoraria from CONICET (Argentina) for technology services using the AMH assay.

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