Activation of the Hypothalamic-Pituitary-Gonadal Axis in Infancy: Minipuberty

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Key Words

Minipuberty · Postnatal gonadotrophin surge · Hypothalamic-pituitary-gonadal axis · Infancy · Sex steroid

Abstract

The hypothalamic-pituitary-gonadal (HPG) axis is active in the midgestational foetus but silenced towards term because of the negative feedback effects mediated by the placental hormones. This restraint is removed at birth, leading to reactivation of the axis and an increase in gonadotrophin levels. Gonadotrophin levels are high during the first 3 months of life but decrease towards the age of 6 months except for FSH levels in girls that remain elevated until 3–4 years of age. After this, the HPG axis remains quiescent until puberty. The postnatal gonadotrophin surge results in gonadal activation in both sexes. In boys, testosterone levels rise to a peak at 1–3 months of age and then decline following LH levels. Postnatal HPG axis activation is associated with penile and testicular growth and therefore considered important for the development of male genitalia. In girls, elevated gonadotrophin levels result in the maturation of ovarian follicles and in an increase in oestradiol levels. Biological signifi-

cance and possible long-term consequences of this minipuberty remain elusive, as do the mechanisms that silence the HPG axis until puberty. However, the first months of life provide a 'window of opportunity' for functional studies of the HPG axis prior to pubertal development.

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Introduction

The onset of puberty is preceded by two periods of activity in the hypothalamic-pituitary-gonadal (HPG) axis: the first during the foetal life and the second during the first postnatal months (fig. 1). After the postnatal HPG axis activity, also referred to as minipuberty, the axis is silenced for the childhood years by mechanisms that still remain elusive. The biological significance of foetal HPG axis activation is not completely understood, but in males it has a central role in the development of the genitalia. This is evidenced by the underdevelopment of the penis and maldevelopment of the testes at birth in boys with congenital hypogonadotropic hypogonadism. The role of the second (postnatal) HPG axis activation is even less

Fig. 1. The 3 periods of hypothalamic-pituitary axis activity. During foetal life, the activity peaks at midgestation and decreases towards birth, possibly due to the suppressive effects of placental hormones, especially oestrogens. At birth, gonadotrophin levels are low, but at around 1 week of age the hypothalamic-pituitary

axis becomes active again. This postnatal gonadotrophin surge, or minipuberty, is associated with the activation of gonadal hormone production in both boys and girls. After the peak at 1–3 months of age, hypothalamic-pituitary activity gradually decreases and is then low during childhood until reactivation at puberty.

well understood, especially in females. In this review, we first briefly discuss the foetal activation of the HPG axis, then focus on postnatal HPG axis activation, and finally summarize the current knowledge of the changes in the pituitary and gonadal hormones and associated hormone effects on target tissues in infants.

Foetal HPG Axis Activity

GnRH neurons migrate from the nasal placode to the hypothalamus during early embryogenesis and GnRH is detected in the foetal hypothalamus at around 15 weeks of gestation [1]. Factors involved in the regulation of foetal GnRH neuron activity include kisspeptin and KISS1R [1]. LH and FSH are detected in the anterior pituitary and general circulation by 12–14 weeks of gestation [2, 3]. The exact phase when the pituitary gonadotrophin secretion becomes dependent on the control of the hypothalamic GnRH is not fully elucidated. Vascular connections are already present at the end of the first trimester of pregnancy, but the maturation of the portal vascular system continues after this [for review, see 4]. In anencephalic foetuses that lack the hypothalamus but have an intact pituitary, gonadotrope development is normal up to 17–18 weeks of gestation but thereafter the cells are involuted [5]. After 32 weeks of gestation they are almost absent, suggesting that hypothalamic input is required for the maintenance of the gonadotropes from midgestation onward.

During the first half of pregnancy, female foetuses have a higher pituitary content of gonadotrophins [1, 3] and higher serum LH and FSH levels [2, 3, 6] than male foetuses. This sex difference has been suggested to be due to the negative feedback effects of foetal testicular hor-

mones. At midgestation, LH and FSH levels in female foetuses are very high, resembling the levels of agonadal adults or postmenopausal women [1, 6–9]. In male foetuses, LH levels exceed those of FSH [1, 7–9]. The placenta secretes hCG, the third gonadotrophin, which is structurally similar to LH and has similar biological effects. The foetal levels of hCG rise early in gestation, peak at 8–12 weeks and then decrease towards term but remain at considerable levels until late gestation [2, 9, 10]. LH and FSH levels decrease towards the end of gestation [1, 9] and are low at term in both sexes [7–9]. In contrast, placental oestrogen production increases towards the end of gestation and oestrogen levels are high in both maternal and foetal circulation [11]. These high levels probably suppress the activity of the foetal HPG axis, resulting in low foetal gonadotrophin levels by the end of gestation.

The foetal testis secretes testosterone and anti-müllerian hormone (AMH) at the 8th week of gestation. Testosterone production at this stage is essential for the masculinization of the foetus and testosterone induces the development of the male internal genitalia. Formation of the active metabolite of testosterone, dihydrotestosterone, by the enzyme 5- α reductase 2 (SRD5A2) is required for the development of the prostate, penis and scrotum. AMH causes the regression of the müllerian ducts, preventing the formation of a uterus and fallopian tubes. Testosterone levels are high in male foetuses between 10 and 20 weeks of gestational age, reaching adult values, and decrease thereafter towards term [9, 12].

Initial testicular development is intra-abdominal and the descent of the testes into the scrotum occurs in two phases. The first, transabdominal, phase is completed by 15 weeks of gestation. This phase is independent of an-

drogens but dependent on another Leydig cell product, insulin-like peptide 3 (INSL-3). The second, inguinoscrotal, phase is usually completed by the end of the 35th week of gestation and this phase is androgen dependent [for review, see 13].

Ovaries are not required for the differentiation of female internal or external genitalia. In the absence of AMH, müllerian ducts develop into fallopian tubes, uterus and the upper portion of the vagina. Folliculogenesis is initiated in the foetal ovary around 15 weeks after conception when the first primordial follicles are formed [14]. The first primary follicles develop at around 20 weeks of foetal life and maturation to the antral stage is observed during late pregnancy [14, 15]. The role of pituitary gonadotrophins in ovarian development and function during foetal life is not well understood. In anencephalic female fetuses, normal follicular development up to 34 weeks of gestation is observed but, thereafter, large growing follicles that are common in healthy fetuses are not seen in anencephalic female fetuses [16]. This finding suggests that ovarian development up to the 7th month of pregnancy occurs independently of stimulation by the foetal hypothalamus, but pituitary gonadotrophins later have a role in follicular growth. The ontogenesis of steroid production in foetal human ovaries is not completely understood. Ovarian oestrogen production during foetal life is considered minimal and negligible compared to high placental oestrogen production.

Postnatal Activation of the HPG Axis: Minipuberty Postnatal Pituitary Activation

At birth, gonadotrophin levels are low in both sexes [7, 10, 17]. Placental hormones are cleared from the circulation of the newborn during the first postnatal days [17, 18]. Around 1 week of age, FSH and LH levels start to increase and peak between 1 week and 3 months [17, 19–22]. At this time, FSH levels are higher in girls and LH levels predominate in boys [19, 22–24]. In boys, LH and FSH levels decrease by 6–9 months of age, but in girls, FSH levels remain elevated longer – up to 3–4 years of life [17, 19–21]. LH levels decrease at the same time as in boys [17, 19–21].

Postnatal Testicular Activation

Testosterone levels in boys are low in the cord blood but start to increase after 1 week of age, peak to pubertal levels at 1–3 months and then decline to low prepubertal levels by approximately 6 months of age [19, 20, 22, 25, 26]. These changes in the peripheral blood testosterone levels mirror the changes in the number of Leydig cells

[27] and testosterone concentrations in the testicular tissue [28]. The biological activity of the increased testosterone levels in infancy has been questioned, since the levels of SHBG increase concomitantly, leading to a less significant increase in free rather than total testosterone levels [26]. However, androgen effects such as penile growth [20, 29] and prostatic activity [20] unequivocally demonstrate concomitant androgen actions with the increasing androgen levels. Furthermore, postnatal testosterone levels have been associated with male-type behaviour in 14-month-old infants, suggesting a role for postnatal androgens in neurobehavioral development [30]. The postnatal gonadotrophin surge is also associated with increases in the levels of Leydig cell product INSL-3 [31] and Sertoli cell markers inhibin B [19] and AMH [32].

Testicular size increases during the first months after birth [20, 28, 33], together with an increase in the number of germ cells [34], Leydig cells [27] and Sertoli cells [35]. This increase is followed by a decrease in size towards the 2nd year of life [20]. The androgen receptor is not expressed in the Sertoli cells during infancy and therefore spermatogenesis is not initiated [36–38]. The lack of androgen receptor explains the AMH levels, which remain elevated despite the high testosterone level during the postnatal surge [32, 37–39].

In addition to active testicular androgen production, some weaker androgenic steroids, mainly dehydroepiandrosterone, its sulphate conjugate and androstenedione, are secreted during the first postnatal months from the involuting foetal zone of the adrenal cortex both in girls and boys [25, 40]. These hormones possess little if any androgenic potential, but they can be converted into potent androgens by peripheral target tissues such as the skin. Androgenic skin manifestations, such as sebaceous gland hypertrophy and acne, are common findings during the first postnatal months and are associated with urinary levels of testosterone and DHEAS in both sexes [40].

Postnatal Ovarian Activation

Oestradiol levels are high in the cord blood of both sexes and decrease rapidly during the first postnatal days [18, 41]. At 1 week of age oestradiol levels are low in both sexes, but after this they increase in girls [42] and are then higher than in boys during the following months [42, 43]. This is due to endogenous oestrogen production and is associated with a temporary increase in ovarian follicular development [21, 42]. Large ovarian follicles are seen more often during the 1st than the 2nd year of life [21, 44]. In postmortem ovarian samples, the oestradiol content is higher during the first 6 months of life than in

later infancy [45]. Ovarian granulosa cell products inhibit B [19] and AMH transiently increase at the time of the postnatal gonadotrophin surge [21, 46]. Unlike testosterone levels in boys that show a clear peak at 1–3 months of age and then decrease steadily towards the age of 6 months, oestradiol levels in girls fluctuate (fig. 2) [42], which probably reflects cyclic maturation and atrophy of ovarian follicles. Oestradiol levels decrease during the 2nd year of life [42, 45], but higher oestradiol levels in girls than in boys can also be seen with sensitive assays during the prepubertal years [47].

Placental oestrogen stimulates the oestrogen target tissues in the foetus, and at birth most full-term infants have some breast tissue [48]. Although there is no sex difference in the mammary gland size at birth, later in infancy the mammary gland size is larger in girls than in boys, suggesting biological effects of endogenous oestrogens in girls [42, 43, 48]. Uterine growth is also stimulated prenatally, and after birth, its size rapidly decreases during the first months of life [42, 49]. This reflects the withdrawal of high intrauterine oestrogen levels. Premature girls lack the highest intrauterine oestrogen exposure of late pregnancy, and their mammary glands and uterus are less stimulated than in full-term girls at birth [42]. Consequently, the effects of postnatal endogenous oestrogen levels in premature girls are more visible and postnatal oestradiol levels are associated with simultaneous mammary gland growth and uterine size [42].

Postnatal HPG Axis Activation in Premature Infants

At birth, gonadotrophin levels are higher in premature than in full-term infants [24]. Prematurity appears not to influence the timing of the onset of the postnatal gonadotrophin surge as the gonadotrophin levels begin to increase at the same time after birth as in full-term infants [20, 21]. However, the gonadotrophin surge is augmented in magnitude and also prolonged in premature infants compared to full-term infants, and more clearly in girls than in boys [20, 21, 24, 50]. According to our recent longitudinal data, postnatal pituitary activity declines at approximately the same postmenstrual age in full-term and premature infants, suggesting that the activity of the hypothalamic-pituitary unit in infancy is developmentally regulated [20, 21]. The difference in hypothalamic-pituitary axis activity between full-term and preterm infants during the perinatal period is depicted in figure 3.

Increased HPG axis activity in premature boys is associated with higher postnatal testosterone levels [20, 25, 50] and faster penile and testicular growth after birth compared to full-term boys [20]. In premature girls, go-

Fig. 2. Patterns of postnatal gonadotrophin and sex steroid secretion in boys (a) and girls (b). Gonadotrophin levels start to increase during the 1st week of life, peak at 1–3 months, and then decline towards the age of 6 months. In boys, LH levels are higher than in girls, and in girls, FSH levels predominate and remain elevated until 3–4 years of age. Testosterone levels in boys increase following the LH levels and show a clear peak at 1–3 months of age, but in girls, estradiol levels fluctuate, probably reflecting ovarian follicular growth and atrophy. Estradiol levels in girls decline in the 2nd year of life.

nadotrophin levels are very high after birth [21, 51], but a sharp decrease in FSH levels is seen around term age [21]. This change is associated with maturation of the ovarian follicles and increases in AMH and oestradiol levels, suggesting that the immaturity of the gonadal feedback mechanisms before term-equivalent age could explain the extremely high gonadotrophin levels. The postnatal rise in oestradiol levels is associated with growth of the mammary glands and the uterus in preterm girls [42].

Postnatal HPG Axis Activation in Infants Born Small for Gestational Age

Postnatal FSH levels are increased in small-for-gestational-age (SGA) infants compared to infants born appropriate for gestational age (AGA) [23]. In SGA boys, testosterone levels are higher than in full-term AGA boys

Fig. 3. Differences in postnatal pituitary activity in full-term and preterm infants. Foetal pituitary activity is highest at midgestation and decreases towards term. Cord blood gonadotrophin levels are higher in premature than in full-term infants. After birth and the withdrawal of placental hormones, the hypothalamic-pituitary axis is activated again and gonadotrophin levels begin to increase.

In premature infants, postnatal gonadotrophin levels are higher and remain elevated longer than in full-term infants according to calendar age, which is due to 'time shifting'. The decrease in gonadotrophin levels occurs at approximately the same post-term age in both full-term and preterm infants, indicating that the activity of the HPG axis is developmentally regulated.

[25]. In girls, higher oestradiol levels have been reported in SGA than in AGA girls after a leuprolide (GnRH agonist) test [52], although non-stimulated levels have not been significantly different [23, 52]. The reason for the increased HPG axis activity following intrauterine growth restraint is not known.

Postnatal HPG Axis Activation in Reproductive Disorders

Postnatal HPG axis activation has been studied in several disorders affecting sexual development and these observations provide insight into the potential role of minipuberty in reproductive physiology. Furthermore, the first months of life provide a window of opportunity to examine the function of the HPG axis before puberty.

Infants with complete androgen insensitivity syndrome present lower-than-normal postnatal LH and testosterone levels, whereas in partial androgen insensitivity syndrome, testosterone and LH levels are normal or high [53]. Consequently, androgen signalling appears to have a role in postnatal HPG axis activation. In aromatase deficiency, leading to low oestrogen levels, gonadotrophin levels in infancy are elevated in girls but not in boys [54, 55], suggesting a more important role for oestrogens in the HPG axis negative feedback effects in females than in males.

In Turner syndrome, the pattern of FSH level in infancy is related to karyotype: in infant girls with 45,X, FSH levels are higher than normal and remain elevated up to 6 years of age. In contrast, girls with other karyotypes or mosaicism have close-to-normal FSH levels,

suggesting retained ovarian feedback effects on pituitary FSH secretion [56]. Infant boys with Klinefelter syndrome have also been reported to have normal levels of inhibin B, AMH and INSL-3, suggesting normal Sertoli and Leydig cell function in infancy, although elevated LH [57] and FSH levels [57, 58] have also been reported. Testosterone levels in these boys have been reported to be normal [58] or slightly elevated [57].

Mutations in the NR0B1 gene lead to congenital adrenal hypoplasia, a disorder characterized by adrenal failure, impaired sexual development at puberty (because of hypogonadotrophic hypogonadism) and infertility. However, postnatal HPG axis activation appears to be normal in boys with this disorder [59].

In cryptorchid boys, higher FSH and LH levels, lower inhibin B levels and reduced levels of INSL-3 in relation to LH have been observed at 3 months of age compared to healthy controls [31], while testosterone levels were normal [60].

In congenital hypogonadotrophic hypogonadism, both foetal and postnatal pituitary gonadotrophin secretion is low. During foetal life, placental hCG is able to stimulate the foetal testis, resulting in masculinization of the external genitalia. However, LH is needed for further growth of the penis and testicular descent. Consequently, boys with congenital hypogonadotrophic hypogonadism present a micropenis and often also undescended testes at birth. In boys with hypogonadotrophic hypogonadism, the lack of postnatal HPG axis activation has been associated with involution of the ex-

ternal genitalia after birth [61]. Hormone therapy has been used to induce penile growth and descent of the testes in infant boys with hypogonadotrophic hypogonadism [62].

Conclusions

The hypothalamic-pituitary axis is active in the mid-gestational foetus and the diminishing activity during the latter part of pregnancy results from the suppressive effects of placental hormones on the foetal hypothalamus and pituitary. This restraint is removed at birth, leading to reactivation of hypothalamic-pituitary activity and increased levels of gonadotrophins. As a consequence, gonadal hormone production is activated in both sexes. Go-

nadal steroid levels are increased in a sex-specific manner: testosterone levels peak in boys at 1–3 months of age and decline at 6 months of age, whereas in girls oestradiol levels fluctuate and remain elevated longer. Elevated gonadal steroid levels are able to stimulate the target tissues in both sexes. However, the exact role of this transient activity for further reproductive development still remains uncertain, although in the context of the perinatal programming theory, this period might be important for further reproductive health and disease. In this regard, the possible effects of the altered postnatal HPG axis activity observed in premature or SGA infants in comparison to healthy full-term infants need further attention. Finally, the mechanism that leads to quiescence of the HPG axis after infancy for the rest of the childhood years remains still unknown.

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