Hormone Therapy During Infancy or Early Childhood for Patients with Hypogonadotropic Hypogonadism, Klinefelter or Turner Syndrome: Has the Time Come?

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KEYWORDS

• Minipuberty • Androgens • Estrogens • Gonadotropins
• Hypogonadotropic hypogonadism • Klinefelter syndrome • Turner syndrome

KEY POINTS

- Mimicking minipuberty in CHH with gonadotropins.
- Low dose androgens during infancy in Klinefelter syndrome.
- Low dose oestrogens during infancy in Turner syndrome
- Managing patients unable to produce sex steroids using gonadotropins to mimic minipuberty in hypogonadotropic hypogonadism, or sex steroids in patients with Klinefelter or Turner syndrome, is promising.
- There is a need to pursue research in this area, with large prospective cohorts and long-term data before these treatments can be routinely considered.

INTRODUCTION

Understanding the physiologic secretion of gonadotropins and sex steroids throughout development[1,2] has led to a new area of potential therapeutic windows.[3]

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During fetal development, activation of gonadal secretion is initially under the control of human chorionic gonadotropin (hCG). During the first trimester, anti-Müllerian hormone (AMH), synthesized by Sertoli cells, and sex steroids, principally testosterone, biosynthesized by Leydig cells, drive the differentiation of internal and external genitalia. The hypothalamic–pituitary secretions of gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) start around the 16th week of gestation in humans.[4] From the second trimester and on, gonadal secretions will be controlled by hypothalamic–pituitary stimulation. The gonadotropic axis follows a triphasic pattern of activation (**Fig. 1**, for the gonadotropic axis throughout development in males). The first activation occurs during the fetal period. A second activation phase is observed during the neonatal period, called minipuberty,[1,2] which lasts from 2 postnatal weeks in full-term newborns (delayed in preterm infants) until a few months after birth (for a shorter period in males compared to females). The third phase starts at puberty. Each of these activation phases is important for gonadal development and hormone secretion, development of genital organs and secondary sexual characteristics, as well as to prepare future fertility. Sex steroid secretion during minipuberty and infancy has also been related to neurodevelopment, metabolic, and bone health. Several studies have evaluated the impact of gonadotropins or sex steroid supplementation in different conditions affecting sex steroid production prior to puberty. We will review herein the relevance of gonadotropin treatment in hypogonadotropic hypogonadism in male patients and sex steroid treatment in patients with Klinefelter syndrome (KS) or Turner syndrome (TS) during infancy and early childhood.

Male Patients with Congenital Hypogonadotropic Hypogonadism

Congenital hypogonadotropic hypogonadism (CHH) is a group of rare diseases characterized by inadequate secretion of gonadotropins during physiologic activation periods of the gonadotropic axis. Clinically, CHH in males may be associated with neonatal clinical signs (micropenis, cryptorchidism in boys in about half of the cases).[5] The minipuberty provides a brief window of opportunity to diagnose CHH. Typically, low testosterone, LH, and FSH levels are reported.[5] AMH levels, however, may be

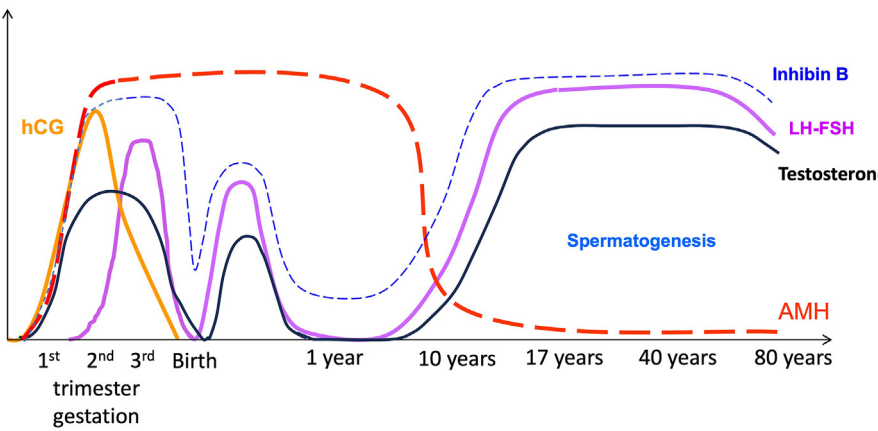

Fig. 1. Gonadotropic axis secretions throughout development and infancy in males. AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

low or partially maintained.[6] The diagnosis is sometimes only evoked in case of pubertal delay or pubertal maturation arrest in the adolescent.

Different therapeutic options for pubertal induction have been described for CHH patients, but we lack the necessary larger randomized trials to define the best approaches. Since there is no report of decreased follicular reserve[7] and fertility induction and pregnancy rates are high in women with CHH, there is currently no evidence of a beneficial impact of gonadotropins to induce puberty rather than the use of sex steroid in this population.[5,7]

Studies have demonstrated that physiologic gonadal activation by gonadotropins during male puberty is associated with a better outcome for spermatogenesis[8,9] and may offer important psychological reassurance in adolescents and enhance self-confidence.[8]

Pretreatment with FSH alone in case of severe GnRH deficiency has proved to increase inhibin B levels—a marker of Sertoli cell function—and testicular volume, consistent with proliferation of Sertoli cells.[10,11]

Based on these results and the fact that testicular volume and inhibin B levels prior to pubertal induction correlate positively with a better spermatogenic outcome,[12,13] some teams suggested that treatment by gonadotropins during the neonatal period to mimic minipuberty could improve pubertal induction of spermatogenesis and fertility outcome in adulthood.

Treatment with gonadotropins during the neonatal period

To date, hormonal therapy during the neonatal period has only been offered to CHH male patients exhibiting micropenis and/or cryptorchidism. The main goal is to increase penile length and when possible, stimulate testicular volume.

For penile enlargement and enhancement of scrotal development, the usual practice consists of the administration of 2 to 4 doses of intramuscular testosterone enanthate injection, 25 to 50 mg every 2 to 4 weeks.[14] Few case series have been published, as summarized by Mason and colleagues.[14]

However, androgen therapy does not stimulate testicular volume and has no impact on cryptorchidism. During this period in life, serum gonadotropin and testicular hormone levels (testosterone, inhibin B, and AMH) increase, and penile length and testicular volume grow.[15] Testicular volume is a reflection of the increase in the number of immature Sertoli cells[6] in response to FSH. Since these cells only weakly express the androgen receptor in infants, LH-induced endogenous testosterone does not mature the Sertoli cells or activate spermatogenesis.[16] Given that the number of Sertoli cells correlates with sperm-producing capacity later in life, the minipuberty may prepare for future reproductive ability.[11,17] This gives an argument to discuss replacement therapy with gonadotropins in CHH boys.[6]

In addition, hCG therapy alone or in combination with nasal spray of GnRH has been shown to treat cryptorchidism in neonates and prepubertal boys.[18] As cryptorchidism is a factor of poor prognosis for adult fertility and testicular malignancy,[19] gonadotropins may represent an alternative to surgery.

Main and colleagues reported the clinical and biological effects of subcutaneous injections of recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) during the first year of life in a CHH boy with micropenis. The treatment led to an increase in penile size from 1.6 to 2.4 cm as well as a 170% increase in testicular volume and inhibin B levels.[20] Bougnères and colleagues reported the use of gonadotropin infusion by pump for 6 months in 2 neonates (1 with isolated CHH and 1 with combined pituitary hormone deficiency). The treatment allowed penile length to increase as well as testicular growth and an increase in testosterone, AMH, and inhibin

Table 1
Studies reporting the use of gonadotropins to mimic minipuberty in congenital hypogonadotropic hypogonadism boys

Reference	*n*	Age at Treatment Initiation	Treatment	Pump	Clinical Effect	Biological Effect
Main et al,[20] 2002	1	7.9 mo	*rhFSH 20 IU sc twice weekly* *rhLH 21.3 IU sc twice weekly*	No	↑ Testicular volume by 170% ↑ Penile length 1.6–2.4 cm	↑ Inhibin B ↑ Estradiol Testosterone undetectable
Bougnères et al,[21] 2008	2	2 and 5 mo	*rhFSH 67–125 IU/d* *rhLH 50–56 IU/d*	Yes	↑ Testicular volume 0.5–2.1 mL ↑ Penile length 8–21 mm and 12–48 mm	↑ Inhibin B ↑ AMH ↑ Testosterone
Sarfati et al,[27] 2015	1	1 mo	*rhFSH 75 IU/d* *rhLH 75 IU/d*	Yes	↑ Testicular volume 0.33–2.3 mL ↑ Penile length 15–38 mm	
Lambert & Bougnères,[24] 2016	8	0.25–11 mo	*rhFSH 75–150 IU/d* *rhLH 50 IU/d*	Yes	↑ Testicular volume to 1.27 mL ↑ Testis descent 70% at the end ↑ Penile length mean + 18.9 mm	↑ Inhibin B ↑ AMH ↑ Testosterone
Stoupa et al,[23] 2017	5	3–5.5 mo	*rhFSH 75 IU/d* *rhLH 75 IU/d*	Yes	↑ Penile length from 13.8 ± 4.5–42.6 ± 5 mm	↑ Testosterone to 3.5 ± 4.06 ng/mL ↑ Inhibin B from 94.8 ± 74.9–469.4 ± 282.5 pg/mL ↑ AMH from 49.6 ± 30.6–142 ± 76.5 ng/mL

Kohva et al,[26] 2019	5	0.7–4.2 mo	*rhFSH 3.4–7.5 UI/kg/week in 2–3 sc* *Testosterone 25 mg/month 3 mo*	No	↑ Penile length mean 17.2–28.8 mm	↑ Inhibin B (transient)
Papadimitriou et al,[25] 2019	10	2.3–9.4 mo	*rhFSH 150 UI/d* *rhLH 75 UI/d*	No	↑ Testicular volume to 1.5 mL ↑ Testis descent 100% at the end ↑ Penile length from 2 to 3.8 cm	↑ Inhibin B 27.8–365 ng/mL ↑ AMH 1.54–150 ng/mL ↑ Testosterone 0.02–3.3 ng/mL
Avril et al,[22] 2022	35	5.1 ± 3.5 mo	*rhFSH 75 UI/d* *rhLH 75 UI/d (n = 18)*	Yes	↑ Testicular volume ↑ Testis descent ↑ Penile length	↑↑ AMH 463.4 ± 190.6–1375 ± 395.2 pmol/L ↑↑ Inhibin B 68.31 ± 50.90–522.9 ± 204.9 ng/mL ↑ Testosterone 0.05 ± 0.09–3.25 ± 2.28 ng/mL
		13 ± 17.7 mo	*rhFSH 25 UI × 3/week* *rhCG 260 UI × 2/week (n = 17)*	No	↑ Testicular volume ↑ Testis descent 50% at the end ↑ Penile length	↑ AMH 246.6 ± 163.6–679.6 ± 330.9 pmol/L ↑ Inhibin B 61.60 ± 54.70–259.7 ± 204.0 ↑↑ Testosterone 0.12 ± 0.07–6.05 ± 4.84 ng/mL

Abbreviation: rhFSH, recombinant human follicle stimulating hormone; rhLH, recombinant human luteinizing hormone.

B levels.[21] Six other clinical case series have since been reported, demonstrating similar results (**Table 1**).[20–27] Recently, Avril and colleagues analyzed retrospectively the clinical and biological efficacy of 2 gonadotropin treatment regimens during minipuberty. The authors compared the administration of gonadotropins during the first months of life using either subcutaneous injections 5 times per week (recombiant human chorionic gonadotropin [rhCG] and rFSH), or subcutaneous continuous infusion by pump (rLH and rFSH).[22] Thirty-five patients were included, which represent the largest cohort to date of CHH boys treated during minipuberty with gonadotropins. In both groups, results showed a significant increase in penile length and width, testosterone, AMH, and inhibin B levels, as well as improved testicular descent. Recombinant hCG injections induced higher testosterone levels than continuous LH infusion but frequently above the upper limit of normal. The low-dose rFSH regimen (equivalent to 10 IU/day) permitted AMH and inhibin B levels to reach the normal range for minipuberty. Finally, no additional benefit was seen with the 6 month regimen compared to the 3 month regimen. Thus, the current best treatment option for gonadotropins would be to use recombinant LH and FSH by pump for a 3-month period. However, this will need to be evaluated prospectively.

In addition, only results on the short term have been published. Although the results from these studies are promising by showing that gonadotropins allow testicular descent, increase testicular volume, and probably stimulate Sertoli cell proliferation, there are currently no long-term follow-up data on these markers, on future pubertal induction, and ability to produce sperm. Thus, these studies should be considered preliminary, and more data are warranted before these treatments can be offered aside from specialized centers and clinical trials.

In the future, discussion might also arise on the purpose of minipuberty in girls, and whether mimicking minipuberty or pubertal induction by gonadotropins could have a rationale.

Klinefelter Syndrome

KS is the most common sex chromosomal aneuploidy, with an estimated prevalence of 1:650 male births. Affected males are characterized by hypergonadotropic hypogonadism and infertility but can also have associated comorbidities including neurocognitive deficits, low bone mass, hypotonia, and an adverse cardiometabolic profile. Androgen therapy is the cornerstone of treatment in adolescents and adults.[28]

Most studies regarding secretion of testosterone in KS boys during minipuberty have found on average lower levels.[29] Clinical characteristics such as micropenis and cryptorchidism are also suggestive of testosterone deficiency in early life.[30] As the development of noninvasive prenatal screening allows earlier diagnosis of boys with KS, there is a great interest to understand whether androgen administration in early life and childhood could result in improvements of the various manifestations of KS.

Neurodevelopment profile

The neurodevelopmental profile of males with KS includes weaknesses in executive functioning, language-based learning disabilities; neuromotor dysfunction, and muscle hypotonia.[31,32] Full-Scale Intelligence Quotient is 10 to 20 points lower in KS boys than controls.[33] MRI of boys with KS shows that they have a thinner frontal cortex (important for executive functioning)[34] and a reduced hippocampus volume (role in spatial memory).[35]

Some studies underline a relationship between testosterone and brain morphology in the hippocampus and temporal and prefrontal cortex.[36,37] Studies in aging men and men with hypogonadotropic hypogonadism showed that low testosterone is

associated with a decline in memory and visual performance, and the initiation of substitutive androgen treatment mitigates these problems.[38] It was thus hypothesized that androgen treatment in early life could improve neurodevelopmental issues in boys with KS.

In several retrospective studies, injections of testosterone enanthate in early infancy and childhood (<6 years) were associated with improvement in various cognitive domains including auditory comprehension, expressive ability, and verbal intelligence,[39–41] as well as in motor skills.[42] In a cross-sectional retrospective analysis of 111 boys with KS, injections of testosterone enanthate administered before 5 years of age, or between 5 and 10 years of age, were associated with better performances in working memory.[43] In a 2 year double-blind clinical trial in which prepubertal patients were randomized to treatment with oxandrolone or to placebo, hippocampal volume was found to be bigger in the oxandrolone group relative to the placebo group, associated with a better performance in spatial memory tasks.[44] However, Ross and colleagues in a randomized, double-blind, placebo-controlled clinical trial of 84 boys with KS aged between 4 and 12 year old, treated with oxandrolone 0.06 mg/kg/d or placebo for 2 years, and evaluated at 12 and 24 months, found no significant difference between the 2 groups concerning cognitive function and language tests, as well as for working memory and attention tests. On the other hand, a significant improvement in anxiety, depression, and social problems scales was seen, without significant differences in hyperactive or aggressive behaviors.[45] Improvement in behavioral functioning was also confirmed in several other studies.[46,47]

Cardiometabolic profile

Men with KS have an unfavorable body composition, with increased adiposity and decreased muscle mass. Up to half of men with KS have metabolic syndrome.[48] Morbidity and mortality related to cardiometabolic diseases are increased.[49] It was recently recognized that even young boys with KS have a high prevalence of metabolic syndrome, as well as increased adiposity.[50] Testosterone deficiency is known to cause increased adiposity and decreased insulin sensitivity, which are improved with androgens.[51] In a cross-sectional study of prepubertal boys with KS, it was found that testicular function is inversely associated with features of metabolic syndrome.[52]

In a randomized clinical trial of 2 years of oral oxandrolone versus placebo in 93 prepubertal children with KS, oxandrolone modestly improved body composition, with lowered percentage of body fat and improved triglyceride levels. Oxandrolone treatment was relatively well tolerated, although it did result in bone age advancement and lowered high-density lipoprotein (HDL) cholesterol levels.[50] In a prospective, randomized trial, 20 infants with KS between 6 and 15 weeks of age received testosterone cypionate 25 mg intramuscularly monthly for 3 doses versus no treatment. The increase in percent fat mass Z-scores was greater in the untreated group than in the treated group. On the other hand, fat-free mass, length Z-score, stretched penile length, and growth velocity were greater in the treated group.

Bone health

Between 25% and 43% of adults with KS have low bone mass.[53] An increased risk of vertebral fractures was recently described. A recent meta-analysis of 1141 KS men observed an improvement in bone mass with testosterone replacement.[54] Androgens mediate their effects on the skeleton via aromatization to estradiol, by a direct effect via the androgen receptor, and by increased muscle mass.[55] In vitro, oxandrolone stimulates osteoblast differentiation.[56] As childhood and adolescence are known critical time windows for building optimal peak bone mass, androgen treatment in early

childhood could decrease lifelong rates of osteoporosis and fractures. In a randomized, double-blind, placebo-controlled clinical trial of oxandrolone (0.06 mg/kg daily; $n = 38$) versus placebo ($n = 40$) for 2 years in boys with KS (ages 4–12 years), the bone health index was higher in the oxandrolone group at 2 years.[57] This result is expected to be independent of estrogen action, as oxandrolone is a non-aromatizable testosterone derivative.

Almost all studies described earlier show positive effect of androgen treatment in childhood in boys with KS on neurodevelopmental issues, cardiovascular profile, and bone health. However, many of them are retrospective studies including few numbers of patients. The timing of treatment is different from one study to another and between patients. Results in studies about the neurodevelopmental profile were generally not adjusted for parental ages, education, and occupation, or for timing of diagnosis. Laboratory tests were not performed in most of these studies, making it difficult to evaluate the relationship between androgen levels and symptoms. Moreover, no data are available on the long-term effects of androgen treatment in early life and outcomes (fertility, adult height, etc.). One study reported a higher risk of pubarche and puberty at an early age following oxandrolone treatment in prepubertal boys.[58]

Therefore, these studies should be considered preliminary, and these findings need further validation with longer term studies. There is also a need for additional research to decipher underlying mechanisms leading to clinical symptoms in KS patients in order to develop targeted treatment.

Turner Syndrome

TS is a condition characterized by complete or partial absence of one X chromosome, affecting approximately 1 in 2000 to 2500 live-born girls. Aside from short stature and gonadal failure, patients may have several congenital or acquired associated conditions and a particular neurocognitive profile.

In healthy girls, estradiol is already secreted by ovaries in the prepubertal period.[59] Studies in girls with TS show that there is an impaired secretion of estradiol in infancy and early childhood.[60] It has been suggested that this prolonged estrogen deficiency may have negative effects across many body systems. Several studies have evaluated benefits of low-dose estrogen replacement during early childhood in this population.

Growth

A double-blind, placebo-controlled trial showed a trend toward a synergistic growth benefit from childhood low-dose estrogen (from a starting dose of 25 ng/kilogram/day) treatment combined with GH treatment, with a modest (2.1 cm) enhancement of adult height.[61] Similarly, an increment in adult height of approximately 3 cm was shown with a combination of low doses of oxandrolone and estrogen (40 ng/kg/day) when treatment was started before puberty but after the age of 8 years.[62] This effect seems due to increased local responsiveness of the skeletal growth plate to insulin-like growth factor 1 (IGF1) and/or GH.

Pubertal development

A randomized, double-blind, placebo-controlled clinical trial of growth hormone (GH) and low-dose ethinyl estradiol (EE) initiated during childhood, from 5 years of age, in a large cohort of girls with TS ($n = 149$) showed that girls who received EE therapy had significantly earlier thelarche and a correspondingly slower tempo of puberty (3.3 vs 2.2 years), without advancement in bone maturation.[63] The near normalization of puberty tempo may have positive psychosocial effects as there is a reported association

between breast development and positive body image/social adjustment in girls with TS.[64]

Lipid profile

Lipid profile was evaluated in 14 TS girls treated with low-dose estrogen replacement (17β-estradiol, 62.5 μg daily) before age 12 years (mean age 10.5 years) followed by a pubertal induction regimen after age 12 years and compared to 14 TS girls treated with conventional estrogen replacement started after age 12 years (mean age 14 years). After 3 years of treatment, a healthier lipid profile was found in girls treated with low-dose estrogen replacement therapy, with lower total and low-density lipoprotein (LDL) cholesterol, compared with girls treated with the conventional estrogen replacement regimen.[65]

Bone mineral density

Hasegawa and colleagues described bone mineral density in a group of 17 TS patients who started their EE therapy with an ultra-low dosage (1–5 ng/kg/day) from 9.8 to 13.7 years. Bone mineral density (BMD) was significantly lower in these patients compared to BMD of TS patients with spontaneous puberty; but there was no significant difference compared to BMD in TS patients who started conjugated estrogens at the age of 12.2 to 18.7 years, with a minimal initial dose of 0.3125 mg/day, once a week.[66] These results may indicate that ultra-low dosage of estrogens in girls with TS should be started earlier in life.

Cognitive profile

The TS phenotype is characterized by a specific neurocognitive profile of impaired visual-spatial and/or visual-perceptual abilities and difficulty with motor function. In a randomized double-blind study, nonverbal processing speed, motor performance, and verbal and nonverbal memory were significantly better in estrogen-treated girls from 5.0 to 12.0 years of age than in placebo recipients of the same age.[67] Whether these findings will influence the psychoeducational outcome or quality of life of women with TS is not yet known.

Thus, the addition of low doses of estrogen in early childhood in patients with TS could potentially be beneficial. However, these studies have several limitations, mostly the fact that they have been evaluated in small groups of participants, that the dosing and administration of childhood estrogens have not been optimized, and that long-term safety has not been assessed. In the TS Clinical Practice Guidelines published in 2016, the authors suggest not routinely adding very low-dose estrogen supplementation in the prepubertal years to further promote growth.[68] Further studies should be performed.

SUMMARY

New insights into the physiology of gonadotropic axis activation, the role of minipuberty, and of sex steroids during infancy have undoubtedly produced new areas of research and proposed new therapeutic options. Many studies have been conducted to date demonstrating promising results, but most still lack the long-term data needed to assess their full effects and safety. In addition, all these treatments remain off-label. Thus, clinical trials with long-term follow-up are warranted.

In the meantime, families must be informed of the possibility of these treatments and if considered, then patients should be directed to specialized tertiary centers where treatments may be proposed as part of approved clinical trials.

CLINICS CARE POINTS

- Mimicking minipuberty in hypogonadotropic hypogonadism using gonadotropins may avoid surgical management of cryptorchidism and improve fertility outcome.
- Treatment with low-dose androgens during infancy in Klinefelter syndrome may improve neurodevelopment and metabolic issues.
- Treatment with low-dose estrogens during infancy in Turner syndrome may improve growth, neurodevelopment, and metabolic issues.
- The long-term effects of these treatments are not yet known.
- These treatments must be further evaluated in large prospective studies before generalized treatment to all patients must be considered.

DISCLOSURE

The authors declare no conflict of interest regarding the content of this article.

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