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Replacement of Male Mini-Puberty

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Context: Clinical management of congenital hypogonadotropic hypogonadism (CHH) remains a challenge in pediatric endocrinology.

Objective: To investigate whether daily subcutaneous injections of the recombinant human LH/FSH preparation could mimic the physiological male mini-puberty.

Design and Setting: The REMAP (REplacement of MAle mini-Puberty) study with up to 10 years of follow-up.

Patients and Intervention: Ten neonates or infants, all with bilateral cryptorchidism in intra-abdominal/inguinal position and micropenis with the absence of neonatal male mini-puberty, received daily subcutaneous injections of Pergoveris® (LH/FSH 75/150 IU) for 3 months.

Main Outcome Measures: Restoration of bilateral cryptorchidism/micropenis and the Leydig/Sertoli cells function.

Results: At the end of treatment, median LH and FSH, both undetectable before treatment, reached high normal levels of 4.45 IU/L and supranormal levels 83 IU/L, respectively; median inhibin-b and anti-Mullerian hormone levels increased from subnormal (27.8 and 1.54 ng/mL, respectively) to normal levels (365 and 150 ng/mL, respectively); median testosterone increased from just detectable (0.02 ng/mL) to normal levels (3.3 ng/mL). Stretched penile length increased from a median of 2 to 3.8 cm. During therapy, all testes descended to the scrotal position (by the end of the first month in three patients, the second month in four patients, and the third month in three patients), measuring 1.5 mL and appearing normal in ultrasonography. Three infants received additional treatment with testosterone enanthate. In two infants, one of two testes regressed in the low inguinal area; both infants were successfully treated surgically. After 1 to 10 years of follow-up, all testes are still in scrotal position and have slightly regressed in size.

Conclusions: The proposed regimen mimics neonatal male mini-puberty and successfully treats infants with micropenis and cryptorchidism in CHH.

Freeform/Key Words: micropenis, cryptorchidism, hypogonadotropic hypogonadism, recombinant LH, recombinant FSH, pergoveris

Abbreviations: AMH, anti-Mullerian hormone; CHH, congenital hypogonadotropic hypogonadism; nIHH, normosmic idiopathic hypogonadotropic hypogonadism; REMAP, REplacement of MAle mini Puberty; rh, recombinant human; SC, subcutaneous.

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Clinical management of congenital hypogonadotropic hypogonadism (CHH), a rare disorder caused by the deficient production, secretion, or action of GnRH [1], remains a challenge in pediatric endocrinology [2, 3]. A higher presence of congenital male tract anomalies (*i.e.*, micropenis and monolateral or bilateral cryptorchidism) is found in isolated hypogonadotropic hypogonadism [4], which is a rare, highly heterogeneous disorder characterized by abnormal pubertal development and/or infertility (the number of familial cases is probably underestimated [5]). Isolated hypogonadotropic hypogonadism refers to a wide spectrum of reproductive phenotypes, including GnRH deficiency with anosmia (Kallmann syndrome) and normosmic idiopathic hypogonadotropic hypogonadism (nIHH) [6], with the prevalence of cryptorchidism being nearly three times greater in Kallmann syndrome than in nIHH despite comparable testicular volumes [7]. This phenotypic heterogeneity is accompanied by a considerable genetic heterogeneity, with more than 35 genes implicated but with the genetic basis being uncovered in about half the patients [6, 8, 9]. Micropenis has been traditionally successfully treated, usually with three monthly injections of testosterone enanthate, ideally in the postneonatal period or in early infancy [10]. However, when bilateral cryptorchidism coincides with micropenis, two surgical operations are usually required. Even after successful surgery, the hypoplastic testes with the deficient proliferation of immature Sertoli cells before and during puberty, due mainly to the lack of the male mini-puberty in the neonatal period as well as the subsequent midinfancy surge in pulsatile gonadotropin secretion, result in azoospermia and infertility in adulthood [11]. Mini-puberty consists of activation of the hypothalamic–pituitary–gonadal axis during the neonatal period, resulting in high gonadotropin and sex steroid levels and allowing penile and testicular growth and the proliferation of gonadic cells [12]. During this phase, serum T and gonadotropin levels rise rapidly and peak at the age of 3 months, approaching adult male levels, before the mid-childhood quiescence by about 6 months of age [13], providing a 6-month window of opportunity of making early diagnoses in patients with suspected sexual reproductive disorders [12] who would demonstrate abnormally low FSH, LH, and testosterone levels [13]. Thus, precise and early diagnosis in CHH offers the advantage of a definitive prepubertal diagnosis [13], enabling the prompt initiation of preplanned pubertal-induction at a median age of pubertal onset, preventing negative physical and psychological sequelae, preserving normal peak bone mass, and hopefully restoring fertility in affected patients [3].

The aim of the REMAP (REplacement of MAle mini Puberty) study in neonates and infants with micropenis and/or cryptorchidism due to hypogonadotropic hypogonadism, ISRCTN13007297, was to investigate whether daily subcutaneous (SC) injections of the commercially available recombinant LH plus FSH preparation (Pergoveris®) for 3 months could mimic physiological male mini-puberty by resolving bilateral cryptorchidism, repairing micropenis and restoring the Leydig and Sertoli cell function.

1. Materials and Methods

A. Patients

Ten neonates and infants were included, all with bilateral cryptorchidism in the intra-abdominal or inguinal position and micropenis ≤2 cm (≤2 SDS) [14]. The absence of neonatal male mini-puberty was confirmed with at least three repeated measurements at 8 hours of undetectable LH, FSH, and testosterone from 15 days of life up to 3 months of age [15]. Penile length was measured by the method of Schonfeld with the penis being stretched to resistance. Five patients had Kallmann syndrome [8] diagnosed at the neonatal period before bilateral cryptorchidism (abdominal in two cases and inguinal position in three cases) and micropenis; one patient had syndromic features and neurodevelopmental delay [16], one had normosmic idiopathic hypogonadotropic hypogonadism [17] (nIHH) (testes in inguinal position), one had CHARGE syndrome [18] (coloboma, heart defects, atresia of the choanae, retarded growth and development, genital-urinary anomalies, and ear defects) diagnosed at birth before choanal atresia (testes in abdominal position), two had septo-optic dysplasia [19] (testes in abdominal

position) diagnosed in the Neonatal Intensive Care Unit (one because of symptomatic hypoglycemia and cholestatic jaundice and one due to severe diabetes insipidus with a sodium of 174 mmol/L at 12 hours of life), and one had congenital panhypopituitarism diagnosed before hypogonadism and cholestatic jaundice (one testicle in the abdominal position and one in the inguinal position). Brain-pituitary MRI showed unilateral hypoplasia/absence of the olfactory tract in three cases and unilateral/complete absence of the olfactory bulbs in the other two cases of Kallmann syndrome but was normal in the patient with nIHH. Hypoplastic pituitary and optic nerve atrophy was noted in the septo-optic dysplasia cases, aplastic pituitary [20] in the panhypopituitarism case, and cerebellar hypoplasia in the CHARGE syndrome case.

All subjects started treatment at the median age of 0.35 years (0.19 to 0.78) for 3 months with daily subcutaneous injections of Pergoveris® (recombinant human LH 75 IU and FSH 150 IU), receiving a total dose of 6750 IU of LH and 13,500 IU of FSH, and were monitored clinically monthly. Parents were trained and performed the injections at home.

B. Hormone Assays

LH and FSH were measured with an Elecsys immunoassay analyzer (Roche) [21, 22]. Testosterone was measured by liquid chromatography/tandem mass spectrometry. Serum anti-Mullerian hormone (AMH) was measured using the AMH/Mullerian-inhibiting substance ELISA kit (Immunotech-Beckman, Marseilles, France) [23]. Serum inhibin-b was measured using specific Generation II ELISA (Demeditec Diagnostics GmbH, Kiel, Germany) [24].

C. Statistical Analysis

Data are reported as median and range.

D. Ethical Approval and Permissions

The study was approved by the institutional Scientific Board and Ethics Committee. Written informed consent was obtained from both parent because this comprised an off-label treatment. The Greek National Organization for Medicines issued permission for the off-label use of Pergoveris for each of the cases, and the primary health insurance covered 100% the cost of the injections [90 injections with a total cost ~6000€ (~$6731 US)].

2. Results

During therapy, all infants increased their height velocity. None of the infants had local or systemic adverse events or reactions. At the end of therapy, 24 hours after the last injection, median LH increased from undetectable before treatment to high normal (4.45, 4 to 7.22 IU/L), median FSH increased from undetectable before treatment and reached supranormal levels (83, 60.3 to 132 IU/L), inhibin-b increased from subnormal before treatment (27.8, 9 to 42 pg/mL) and reached normal levels (365, 252 to 650 pg/mL), and AMH increased from subnormal (1.5, 0.9 to 2.2 ng/mL; 11, 6.65 to 15.4 pmol/L) and reached 150 (112.4 to 249.3) ng/mL (1071.4, 802.8 to 1780.7 pmol/L). Median testosterone increased from just detectable (0.02, 0 to 0.14 ng/mL; 0.07, 0 to 0.48 nmol/L) to completely normal levels (3.3, 1.8 to 4.3 ng/mL; 11.4, 6.2 to 14.90 nmol/L) [25]. Stretched penile length increased from a median of 2 cm (1.5 to 2.5 cm) to 3.8 cm (3.2 to 4.5 cm). Although penile length normalized in all patients, we decided to "optimize" penile length (meaning to reach the 50th percentile for age) in three patients with additional treatment with IM injections of testosterone enanthate at the dose of 50 mg/mo for 3 months around the age of 2 years (i.e., at the end of the first physiologic phase of penile growth). During therapy all testes descended to the scrotal position by the end of the first month in three patients, the second month in four patients, and the third month in three patients. Testes measured 1.5 mL (1.0 to 2.5 mL) with a Pradder orchidometer and had a completely normal ultrasonography by an experienced pediatric radiologist. In two patients, one with septo-optic dysplasia and one with aplastic pituitary, one of the two testes regressed

in the low inguinal area; both patients were successfully treated surgically by an experienced pediatric urologist before 1 year of age. After 3 to 10 years of annual follow-up (two patients reached 10 years post treatment, one patient reached 9 years, two patients reached 6 years, one patient reached 5 years, two patients reached 4 years, and two patients reached 3 years), in all cases testes are still in the scrotal position; the testes slightly regressed in size at 1.0 mL (0.5 to 2.0 mL, reports from the last annual visit) but are still measurable with a Pradder orchidometer. No patient has reached the presumed age of entering puberty according to their growth pattern, and none has presented signs of spontaneous pubertal maturation.

3. Discussion

Daily subcutaneous injections for 3 months of the commercially available recombinant human LH (75 IU) plus FSH (150 IU) preparation mimics neonatal male mini-puberty, successfully repairing micropenis as well as bilateral cryptorchidism either in the inguinal or the intra-abdominal position. We acknowledge the limited number of patients in the REMAP study. Nonetheless, given the estimated prevalence of CHH at 1:5000 births [26] with the genetic basis still being uncovered in about half the cases studied [8], our prospective interventional 10-year single-center study has included the highest number of patients published so far, at least to our knowledge [27]. Although we did not perform genetic analysis for the specific candidate genes in our cohort, there was confirmation of CHH with at least three repeated measurements at 8 hours of undetectable LH, FSH, and testosterone from 15 days of life up to 3 months of age [15], proving the lack of the physiological male mini-puberty. Moreover, all patients included had micropenis and bilateral cryptorchidism.

This noninvasive strategy is safe because there are no side effects and because the possibility of an unsuccessful surgery or postsurgical testicular atrophy is spared. This strategy also costs far less than the estimated $18,000 for 6 months of treatment with rLH and rFSH using an insulin pump [27] and even less than two surgical operations, calculated to be at least $5000 each [28]. Furthermore, up to 50% of testicles in the intra-abdominal position may require a laparoscopic two-stage operation [29], requiring three or four operations in bilateral cryptorchidism. Moreover, this treatment strategy has a short duration, it can be administered at home by the parents using a commercially available LH/FSH preparation, and it likely preserves fertility. It may be as important to the brain as to the testes because fetal Leydig cells produce the high levels of androgen (testosterone or androstenedione, depending upon the species) required for differentiation of male genitalia and masculinization of the brain [30], influencing human neurobehavioral development [31]. In CHH with the fetal gonadotropic surge being missed, replacement of mini-puberty may be of crucial importance to the masculinization of the brain. In fact, emerging evidence suggests that the early postnatal period is important as well [31]. Regarding somatic growth, boys show greater linear growth velocities through their first 6 months of life than girls, with the greatest difference observed at the time of peak testosterone production [32], implying that replacement of mini-puberty in CHH may play an important role in infants' growth.

The first attempt to repair micropenis and cryptorchidism involved recombinant human (rh)LH and FSH in doses of 20 and 21.3 IU SC, respectively, twice weekly for 5 months in an 8-month-old boy diagnosed with CHH. Whereas serum testosterone remained undetectable, penile length and testicular volume increased significantly [33].

The work of reference came from Bougnères *et al.* [11] in St Vinvent de Paul Hospital in Paris: two neonates, one with hypotuitarism (patient 1) and one with CHH (patient 2), both with micropenis and microorchidism, received LH and FSH with continuous subcutaneous injection with an insulin pump: patient 1 from the age of 8 weeks for 4 months at a mean infusion rate of 56 IU rhLH and 67 IU of rhFSH per day (for a total dose of 6720 IU of LH and 8040 IU of FSH) and patient 2 from the age of 20 weeks for 6 months at a mean infusion rate of 50 IU rhLH and 125 IU rhFSH per day (for a total dose of 9000 IU of LH and 22,500 IU of FSH). The results led to serum testosterone (which was previously undetectable) levels that are normal for mini-puberty, normal LH, and high FSH levels, with normalization of AMH

and inhibin-b levels. Micro-orchidism and micropenis were successfully resolved. Another more recent publication from the same group reported eight patients aged 6.03 ± 3.75 months (range, 0.25 to 11 months) receiving recombinant LH at a total dose of 7000 IU and recombinant FSH up to 21,000 IU with a subcutaneous pump for 6 ± 0.58 months at a total cost of $18,000 [27]. The investigators increased the FSH daily dose to 150 IU to force Sertoli cells to produce AMH and inhibin B at a more physiological level, based on their previous experience [11]. The authors speculated that, in patients with CHH born with cryptorchidism, there may be some resistance of Sertoli cells to FSH, possibly because of the prolonged lack of exposure to pituitary FSH during prenatal life. Regarding the deleterious effect that high circulating gonadotropins might have on germ cells in cryptorchid testes, Lambert and Bougneres [27] argue that such deleterious effects have only been reported in boys with idiopathic cryptorchidism (with or without primary testicular insufficiency) treated with hCG, not in the CHH population or in response to rhLH or rhFSH.

In our series, the total dose administered to each patient was 6750 IU of LH and 13,500 IU of FSH, analogous to that of Bougnères *et al.* [11]. Our results in testosterone, LH, FSH, AMH, and inhibine-b levels, as well as in penile length and testicular volume, were in accordance with their results, aiming to normalize AMH and inhibin-b secretion from Sertoli cells. However, in our series, all patients had bilateral crypto-orchidism rather than micro-orchidism, with both testes in the intra-abdominal and/or inguinal position. Furthermore, the duration of our study was limited to 12 weeks, and the treatment was performed at home by the parents, simplifying the procedure as much as possible. The supranormal FSH levels had no obvious side effects to the patients and their testicular architecture, at least to the extent that a high-quality ultrasound could disclose. These FSH levels may be of benefit because in CHH there is complete absence of the subtle normal gonadotropin levels that are normally observed during childhood, the absence of which results in a reduction in testicular volume after completion of therapy but with testes remaining in the scrotal position up to 10 years after the initial intervention. Although two patients required unilateral orchidopexy because two testes regressed to the low inguinal area a few months later, the surgical procedure was fast and easy and was successfully performed by experienced hands in a day clinic.

Regarding the latest guidelines for the management of undescended testes from the European Association of Urology/European Society for Pediatric Urology [34] and the American Urological Association [35], no consensus exists on the various forms of hormonal treatment, which are to be assessed on an individual basis only. Providers should not use hormonal therapy to induce testicular descent because evidence shows low response rates and a lack of evidence of long-term efficacy. Hence, an appropriate specialist (*i.e.*, a pediatric endocrinologist) should be consulted for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development. Although there are no reports on long-term fertility outcomes of isolated hormonal therapy, the latter may optimize germ cell maturation and/or sperm production because LHRH or hCG administration prior to orchidopexy has been shown to improve the fertility index on biopsies obtained at the time of orchidopexy [35]. The finding that neoadjuvant gonadotropin-releasing hormone therapy before surgery may improve the fertility index in undescended testes was proven by a prospective randomized trial [36], in which a total of 42 boys at median age of 33.5 months with unilateral (21 patients; median age, 34 months) or bilateral cryptorchidism (21 patients; median age, 34 months) received intranasal gonadorelin (1.2 mg/d) for 4 weeks before orchidopexy (30 testes; median patient age, 32 months) vs surgery alone (33 testes; median patient age, 47 months). In this trial, statistical significance in the fertility index was only observed in boys treated before the age of 2 years ($P = 0.03$), whereas in bilateral cryptorchidism the mean fertility index was significantly higher after hormonal treatment: 0.96 (SD ± 0.47; range, 0.5 to 2) vs 0.56 (SD ± 0.38; range, 0 to 1.12) without hormonal stimulation. Although a decrease in total Leydig cell population was noted in all cases, in older boys preoperative GnRH therapy was equally beneficial, although normal testis histology was not restored. On the other hand, the outcome of the operated testes is well described in the literature: ~4% of the nonpalpable testes failed the operation, and another 2% presented

atrophy after orchidopexy [35]. In a subset of bilateral hypoplastic testes in intra-abdominal position due to CHH, the failure percentage is expected to be even higher.

To study the future fertility in male CHH, Bouvattier *et al.* [37] comprehensively reported that standard treatments, usually started after the onset of puberty, often only partially corrected the genital abnormalities and spermatogenesis. In children, interventions and particular hormone replacement therapy protocols have been historically directed at virilizing the patient [38], maximizing height potential, and minimizing psychosocial morbidity, although issues of future fertility have decreased [39]. Therefore, treatment with gonadotropins during the neonatal period not only corrects genital hypotrophy and restores testicular endocrine function but might also improve the response to future treatments intended to restore fertility [37]. Early intervention, such as neonatal gonadotropin therapy mimicking mini-puberty, may improve testicular function and genital development [40]. Furthermore, because of the weak expression of the androgen receptor in infant Sertoli cells, administration of hCG/LH instead of an hCG/LH+FSH combination would not result in sufficient Sertoli cell maturation beneficial to future spermatogenesis [11, 37, 41]. The importance of the physiological gonadotropin surge in the fetal life (8 to 24 weeks) and early postnatally (15 days to 3 months) in the male sex development and the masculinization of the brain should be taken into account [42].

With the current availability of rhLH and rhFSH, as well as their combination, in pens, analogous to that of insulin delivery devices, puberty induction protocols may be planned and implemented with daily subcutaneous administration of rhLH/FSH, establishing the optimal LH/FSH ratio, dosage, and frequency of administration. Another interesting alternative [43] would be the use of a commercial preparation of recombinant human chorionic gonadotrophin (Ovitrelle) [44] combined with the long-acting FSH agonist corifollitropin alfa (Elonva) [45] injected once a week in gradually increasing doses. A more physiological approach like this might further improve future fertility than more complex protocols with rhCG, rhFSH, and long-acting testosterone [40]; may be safer to the testicles than high doses of hCG [46]; and may have better outcomes in terms of pubertal maturation and adult height attainment than by supplying directly testosterone as the end product, even though long-acting testosterone undecanoate IM injections offer advantages in terms of smoother pharmacokinetics and adherence can be optimized by combining monitoring and dose administration into a single visit [47]. In our experience, the latter approach in pubertal induction is easy to implement with excellent adherence in hypogonadal boys but leaves the problem of future fertility unsolved.

Further studies are needed to evaluate our strategy and to test its effectiveness in other hypogonadic pathologies, such as idiopathic bilateral cryptorchidism and Pradder-Willi syndrome.

In summary, timely replacement of the neonatal male mini-puberty by daily SC injections of the commercially available rhLH (75 IU)/rhFSH (150 IU) for 3 months repairs even intra-abdominal cryptorchidism safely and cost-effectively, inducing high/normal activation of Sertoli and Leydig cells. This strategy corrects genital hypotrophy, restores testicular endocrine function, and may improve the response to future treatments intended to induce fertility.

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