RESEARCH

Gonadotropin administration to mimic mini-puberty in hypogonadotropic males: pump or injections?

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Abstract

Objective: Newborns with congenital hypogonadotropic hypogonadism (CHH) have an impaired postnatal activation of the gonadotropic axis. Substitutive therapy with recombinant gonadotropins can be proposed to mimic physiological male mini-puberty during the first months of life. The aim of this study was to compare the clinical and biological efficacy of two treatment modalities of gonadotropins administration during mini-puberty in CHH neonates.
Design: Multicenter retrospective analytical epidemiological study comparing two treatments, pump vs injection, between 2004 and 2019.
Methods: Clinical (penile size, testis size, testicular descent) and biological parameters (serum concentrations of testosterone, anti-Müllerian hormone (AMH) and Inhibin B) were compared between the two groups by multivariate analyses.
Results: Thirty-five patients were included. A significantly higher increase in penile length and testosterone level was observed in the injection group compared to the pump group (+0.16 ± 0.02 mm vs +0.10 ± 0.02 mm per day, $P = 0.002$; and +0.04 ± 0.007 ng/mL vs +0.01 ± 0.008 ng/mL per day, $P = 0.001$). In both groups, significant increases in penile length and width, testosterone, AMH, and Inhibin B levels were observed, as well as improved testicular descent (odds ratio of not being in a scrotal position at the end of treatment = 0.97 (0.96; 0.99)).
Conclusions: Early postnatal administration of recombinant gonadotropins in CHH boys is effective in stimulating penile growth, Sertoli cell proliferation, and testicular descent, with both treatment modalities.

Key Words

- recombinant gonadotropins
- mini-puberty
- boys
- hypogonadotropic hypogonadism
- pump
- injections

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Introduction

Congenital hypogonadotropic hypogonadism (CHH), a rare genetic condition of unknown prevalence (approximately 1/5000), can be diagnosed shortly after birth in boys who present with micropenis and/or unilateral or bilateral cryptorchidism (1). It can be isolated or part of a combined pituitary hormone deficiency (CPHD) (2) and is usually in relation to a dysfunction in gonadotropin-releasing hormone (GnRH) secretion or action. The major clinical consequences of CHH are pubertal failure and infertility.

Mini-puberty is a period of neonatal life which corresponds to an early and transient activation of the gonadotropic axis. Several studies have shown that this period is crucial for the early proliferation of Leydig and Sertoli cells, and perhaps, by extension, for future fertility (3, 4, 5, 6). Anti-Müllerian hormone (AMH) and Inhibin B are reliable biomarkers reflecting Sertoli cells function, while testosterone is an index of Leydig cell activation. Boys with CHH usually have low testosterone, AMH, Inhibin B, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels during mini-puberty (7).

Since the 2000s, a few studies reported the efficacy of gonadotropin treatments in boys with CHH on small number of patients (8, 9, 10, 11, 12). The parameters studied were penile length, testicular volume and testosterone, AMH, and Inhibin B levels.

In addition, to date, there is no consensus regarding the dose and type of recombinant hormone used as well as for the modality of administration of gonadotropins.

The aim of the study was to compare the clinical (penile size, testis size, and descent) and biological efficacy (testosterone, AMH, Inhibin B, and FSH serum levels) of two different modalities of gonadotropins administration in two groups of CHH boys, treated during the mini-pubertal period. Multi-weekly injections of recombinant human chorionic gonadotrophin (hCG) and FSH for 3 months was the first modality (injection group). Continuous administration of gonadotropins (recombinant LH and FSH) for 6 months was the other modality, through a pump connected to a subcutaneous catheter (pump group).

Materials and methods

Patients

CHH patients treated with gonadotropins between 2004 and 2019 were recorded from two Pediatric Endocrinology departments of the Assistance Publique-Hôpitaux de Paris.

Patients were identified as males treated with gonadotropins during mini-puberty with a clinical and biological diagnosis of CHH (defined by a micropenis length < –2.5 S.D. (13), and/or unilateral or bilateral cryptorchidism, as well as low testosterone, LH, FSH, AMH, and Inhibin B levels during the first weeks of life). All patients presented with typical morphologic changes in cerebral magnetic resonance imaging (MRI), and genetic analysis was performed for all the cases.

Paper or digital files (Orbis software) were collected retrospectively. The closest clinical visit was used for the data collection. The clinical data collected were age at the start of treatment, height, penile length and width, testis length and width, and testis position. The biological data collected were plasma concentrations of testosterone, AMH, Inhibin B, FSH, and LH/hCG prior to and throughout the treatment: at d0 (day of treatment onset), d8, d15, d30, d60, d90, d120, d150, d180, or d210 (or the closest clinical visit), depending on the duration of treatment. Other data collected were testicular volume measured by ultrasound at the beginning and end of treatment, cerebral MRI, genetic test results performed in the context of a clinical laboratory, presence or absence of combined hormone deficiencies, duration of rhFSH treatment, duration of rhLH (recombinant human luteinizing hormone) or rhCG (recombinant human chorionic gonadotrophin) treatment, and previous intramuscular testosterone administration. Testicular volume based on ultrasound was calculated by the ellipsoid formula = width × height^2 × $\pi/6$.

Parental consent for the treatment had been obtained for all patients.

Treatment modalities

Pump group: Recombinant gonadotropins were administered continuously using a Paradigm insulin pump (Minimed, Northridge, CA, USA) along with a subcutaneous catheter (quick set 6 mm, 60 cm length). Treatment consisted of rhLH (Luveris 75 IU, Merck) and rhFSH (Gonal-F 450 IU/0.75 mL, Merck). The reservoir and catheter were changed every 3 days. The pump flow rate was set at 2.4 IU/h in order to deliver 75 IU of Gonal-F per day and 75 IU of Luveris per day. Treatment was administered for 6 months.

Injection group: The treatment consisted of two subcutaneous injections per week of 260 IU rhCG (Ovitrelle 250 µg/0.50 mL Merck) and three subcutaneous injections per week of 25 IU rhFSH (Gonal-F 450 IU/0.75 mL, Merck). The injections were performed with

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BD-micro-fine 4 mm needles in the arm or upper thighs. The injections were in the majority of cases performed by a nurse at home or by the parents after demonstration by the hospital nurse. Treatment lasted 3 months.

Hormonal assays

Pump group: Plasma concentrations of Inhibin B were measured by enzyme immunometric assays (Oxford Bio-Innovation reagents, Serotec, Oxford, UK). The lower limit of detection was 10 pg/mL. Inhibin B coefficient of variation (CV) intra- and inter-assays were, respectively, 6.8 and 21.5% for 52 pg/mL and 4.2 and 10.2% for 215 pg/mL.

FSH and LH were measured using a sensitive chemiluminescent immunometric assay (Centaur, Siemens). The intra- and inter-assays CV were, respectively, 2.9 and 2.7% for FSH (6.9 IU/L expressed relative to 2nd IRP WHO 94/632) and 2.3 and 1.5% for LH (4.2 IU/L, 2nd IRP WHO 80/552). The detection limits were 0.3 IU/L for FSH and 0.07 IU/L for LH. Plasma concentrations of AMH were measured by enzyme immunometric assays (Immunotech reagents, Beckman Coulter Company, Marseille, France). The lower limit of detection was 1 pmol/L. AMH intra- and inter-assays CV were, respectively, lower than 12.3 and 14.2%. Total plasma testosterone concentration (TT) was measured by a direct radioimmunoassay method using Orion Diagnostica (Spectria, Espoo, Finland). The intra- and inter-assays CV were 3.8 and 4.8%, respectively (3.2 and 2.6 ng/mL, 11.1 and 9 nmol/L). The detection limits were 0.02 ng/mL (0.06 nmol/L).

Injection group: Plasma Inhibin B concentration was measured by ELISA from Beckman Coulter (Beckman Coulter-DSL, Webster, TX, USA). The lower detectable concentration is 7 pg/mL. The inter-assay CV provided by the manufacturer is 7.6% at 50.1 pg/mL, 6.3% at 188.4 pg/mL, and 6.2% at 355 pg/mL; intra-assay CV is 3.5% at 69 pg/mL, 4.6% at 274 pg/mL, and 5.6% at 472 pg/mL. LH, FSH, and AMH were measured using a sensitive chemiluminescent immunometric assay (DXi600 Beckman Coulter). The intra- and inter-assays CV were, respectively, 4.6 and 5.2% for FSH and 3.5 and 6.4% for LH. The detection limits were 0.2 IU/L for FSH and 0.2 IU/L for LH. The lower limit of detection of AMH was 0.02 pmol/L. AMH CV intra and inter assays were respectively lower than 3.8 and 8%. TT was measured by liquid chromatography-mass spectrometry. The intra- and inter-assays CV were 5.5 and 6.7%, respectively. The detection limit was 0.01 ng/mL (0.03 nmol/L).

Genetics

Genetic analyses on DNA (deoxyribonucleic acid) extracted from serum samples were performed for all patients in the genetic department of the respective hospitals and analyzed by CGH array (comparative genomic hybridization array) and on a CHH gene next-generation sequencing) panel. The selection of the genes investigated was based on the PubMed and Orphanet bibliography (ORPHA432 and ORPHA478) and on the OMIM database. The genes investigated in the IHH were *GNRHR, GNRH1, KISS1R, KISS1, TACR3, TAC3, ANOS1, FGFR1, FGF8, PROKR2, PROK2, WDR11, CHD7, SEMA3A, NSMF, HS6ST1, FSHB, LHB, SOX3, FGF17, IL17RD, DUSP6, SPRY4, FLRT3, FEZF1, IGSF10,* and *TSHZ1*. The genes investigated in the CPHD were *PROP1, NR0B1, PCSK1, LHX4, HESX1, OTX2, RNF216, OTUD4, SOX2, POU1F1, SOX10, PNPLA6, STUB1, POLR3A, POLR3B, GLI3, GLI2, DCAF17, RAB3GAP1, RAB3GAP2, TBC1D20,* and *PTCH1*.

Statistical analyses

Initial clinical and biological values were compared between the 'Injection' and 'Pump' groups using Student's *t* tests for continuous and chi-square tests for categorical variables.

Eleven hierarchical linear (models 1–3 and 5–11) and non-linear logistic models (model 4) were used in order to account for repeated measurements in a single patient and thus non-independent data. A random effect on the intercept was introduced for each individual. The model coefficients were compared to 0 using Student tests. The predicted variable for linear models 1–3 was respectively height, penile length, and penile width. Model 4 was a logistic model assessing the factors associated with cryptorchidism. Linear models 5–11 were dedicated to the quantitative value of testis length, testis width, testis volume, testosterone, AMH, Inhibin B, and FSH. Univariate analyses were first performed in order to detect potential confusing factors, which were then incorporated into the multivariate analysis. The variables 'LH', 'LH peak', and 'FSH peak' could not be added to the multivariate model due to the lack of available data. An interaction parameter between the treatment groups and the time ('Pump × Time') was introduced in the multivariate models in order to detect a difference in slope. Predictions were finally measured using these models at T = 0, T = 3 months, and T = 6 months.

The threshold for statistical significance was defined as $P < 0.05$. Assumptions of normality and

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homoscedasticity of errors were tested. The statistical analyses were performed on R 3.6.2 (https://www.r-project.org/) using the nlme (https://cran.r-project.org/package=nlme) and ggplot (14) packages.

Given that duration and doses of treatment were also different between the two groups, analyses were performed by comparison of the highest values obtained (and the slope of progression) for testosterone, AMH and Inhibin B concentrations, and for penile length and testicular volume, with the objective to be the closest to the normal range for age as possible, or by comparison of the time to objective (in order to evaluate if there was an impact of a longer duration of treatment).

Ethics

This retrospective observational study was approved by the Ethics Review Committee for Biomedical Research Project of Paris-Saclay University (No 169) and the French data protection authority (CNIL MR04), in accordance with the Declaration of Helsinki.

Results

Patient characteristics

At treatment initiation, there was no significant clinical difference in the two groups concerning the following assessment: patient age (5.1 ± 3.5 months in the pump group vs 13 ± 17.7 months in the injection group, $P=0.074$), mean patient height, penile length and width, testis position, testis length and width, and mean volume of the testis (Table 1). Regarding biological assessment, mean serum testosterone and AMH levels were significantly higher at treatment initiation in the injection group; however, there was no significant difference between the other biological assessment (Table 2). Finally, there was no significant difference between the two groups regarding the number of patients with IHH (11 patients in the pump group vs 8 patients in the injection group, $P=0.406$), or between MRI (Table 3). Concerning genetics (Supplementary Table 1, see section on supplementary materials given at the end of this article), four mutations of *ANOS1* (22%) in the pump group and one mutation in the injection group (6%) were identified. *FGFR1* was found to be pathogenic in two patients in the pump group (11%). *CHD7* mutation was found in two patients in the pump group and two patients in the injection group (11% and 12%, respectively). *GLI2* was mutated in one patient in the pump group and one patient in the injection group (6% for each group), and a mutation of *SOX2* was found in one patient in the pump group. Finally, a 6q24 deletion, a mutation of *FEZF1* and *GNRHR* were found, respectively, in one patient (6%) of the injection group. No molecular diagnosis was found in eight patients of the pump group (44%) and in ten patients of the injection group (59%). The complete description of the population is available in the additional table.

Clinical data during treatment

A significant ($P < 0.001$) increase in mean penile length during treatment was observed, greater in the injection group than in the pump group (+0.16 ± 0.02 mm per day in the injection group vs +0.1 ± 0.02 mm per day in the pump

Table 1 Clinical assessment at treatment initiation.

		Pump	Injection	
		n = 18 (51.4%)	*n* = 17 (48.6%)	*P*
Age (months)				
	Mean ± S.D.	5.15 ± 3.46	13.03 ± 17.75	0.074
	Median	5.00	3.00	
	Range	0.75–11.50	1.00–57.00	
	IQR	5.25	20.00	
T0 mean height (cm) ± S.D.		61.05 ± 5.50	64.97 ± 18.39	0.408
T0 mean penis length (mm) ± S.D.		19.83 ± 6.45	21.35 ± 7.91	0.537
T0 mean penis width (mm) ± S.D.		7.65 ± 2.97	8.80 ± 2.57	0.342
T0 testis position				0.642
	Cryptorchid	16/36 (44%)	17/34 (50%)	
	Intrascrotal	20/36 (56%)	17/34 (50%)	
T0 mean testis length (mm) ± S.D.		9.45 ± 2.21	10.50 ± 2.67	0.403
T0 mean testis width (mm) ± S.D.		7.49 ± 2.41	7.39 ± 1.74	0.930
T0 mean US testis volume (mL) ± S.D.		0.12 ± 0.04	0.19 ± 0.09	0.149

IQR, interquartile range; US, ultrasound.

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Table 2 Biological assessment at treatment initiation.

	Pump	Injection	*P*
	n = 18 (51.4%)	*n* = 17 (48.6%)	
T0 mean testosterone (ng/mL)	0.05 ± 0.09	0.12 ± 0.07	**0.016**
T0 mean AMH (pmol/L)	463 ± 191	247 ± 164	**0.001**
T0 mean inhibin B (pg/mL)	68.31 ± 50.90	61.60 ± 54.70	0.726
T0 mean FSH (UI/L)	0.35 ± 0.37	0.58 ± 0.80	0.271
T0 mean LH (UI/L)	0.08 ± 0.07	0.16 ± 0.17	0.076
T0 mean FSH peak (UI/L)	3.08 ± 3.25	2.93 ± 3.81	0.939
T0 mean LH peak (UI/L)	1.52 ± 0.99	0.16 ± 1.08	0.298

AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
Bold indicates statistical significance.

group, $P = 0.002$) (Supplementary Table 2, Fig. 1A and B). There was a significant increase ($P < 0.001$) in the mean width of the penis under treatment with no significant difference between the two groups (+0.05 ± 0.01 mm per day in the injection group vs +0.03 ± 0.01 mm per day in the pump group, $P = 0.169$) (Supplementary Table 3, Fig. 1C and D). The risk of cryptorchidism decreased significantly over time during treatment (OR = 0.97 (0.96; 0.99) per day, $P < 0.001$), after stratification on other potential confounding factors, particularly age at the start of treatment, with similar results between both groups (OR vs time = 1 (0.99; 1.02), $P = 0.640$) (Fig. 1E). In the injection group, in the 11 patients with cryptorchidism (unilateral or bilateral) at treatment initiation, testis descended to the scrotal position at the end of treatment in 5 patients. In the pump group, in the nine patients with cryptorchidism (unilateral or bilateral) at treatment initiation, the testis descended to the scrotal position at the end of treatment in five patients. There was no significant change in testicular length and testicular width during treatment and between the two groups (Supplementary Fig. 1, Supplementary Tables 4 and 5). In the pump group (insufficient data for injection group), the testicular volume increased during treatment (+0.005 mL per day, $P < 0.001$) (Supplementary Table 6).

Table 3 Characteristics of the population at diagnosis.

		Pump	Injection	*P*
		n = 18 (51.4%)	*n* = 17 (48.6%)	
IHH		11 (61%)	8 (47%)	0.406
MRI				0.251
	EPP	8 (44%)	8 (47%)	
	BOBA	4 (22%)	2 (12%)	
	UOBA	1 (6%)	1 (6%)	
	Other	1 (6%)	1 (6%)	
	Normal	0 (0%)	5 (29%)	

BOBA, bilateral olfactory bulb agenesis; EPP, ectopic posterior pituitary gland; IHH, isolated hypogonadotropic hypogonadism; MRI, magnetic resonance imaging; UOBA, unilateral olfactory bulb agenesis.

Biological results during treatment

Mean testosteroneT level increased significantly in both groups during treatment, with a significant greater increase in the injection group compared to the pump group (+0.04 ng/mL per day in the injection group vs +0.01 ng/mL per day in the pump group, $P = 0.001$) (Supplementary Table 7, Fig. 2A and B). Serum AMH increased during treatment with no significant difference between the two groups (+3.6 pmol/L per day in the injection group vs + 2.9 pmol/L per day in the pump group, $P = 0.546$) (Supplementary Table 8, Fig. 2C and D). Serum Inhibin B levels increased significantly during treatment similarly between the two groups (+2.8 pg/mL per day in the injection group vs +1.6 pg/mL per day in the pump group, $P = 0.066$) (Supplementary Table 9, Fig. 2E and F). Finally, the peak values were higher in the pump group than in the injection group for AMH, Inhibin B, and FSH ($P < 0.001$) (Table 4).

Discussion

In CHH, hypothalamic secretion of GnRH may be disrupted prenatally, neonatally, and postnatally. FSH drives the development of the Sertoli cells and spermatogonia (seminiferous tubules), and LH stimulates the Leydig cells to produce testosterone. Gonadotropin treatment could be a good replacement therapy to restore mini-puberty, even though the role of mini-puberty in the initiation and maintenance of a normal reproductive axis later in life in humans remains to be confirmed. The main objective of gonadotropin treatment during mini-puberty is its impact on Sertoli cells, spermatogonia and testicular descent, as testosterone treatment alone can also increase penile size in CHH neonates.

Our study presents the largest cohort of CHH boys reported to date and is the first to compare two modalities of gonadotropin administration. Several authors have described the impact of gonadotropin administration in smaller cohorts of CHH neonates (7, 8, 9, 10, 11, 15, 16) and demonstrated that neonatal treatment results in increased penile size, testicular volume, and restoration of mini puberty levels of testosterone, AMH and Inhibin B during treatment. Table 5 reports the key findings of these studies.

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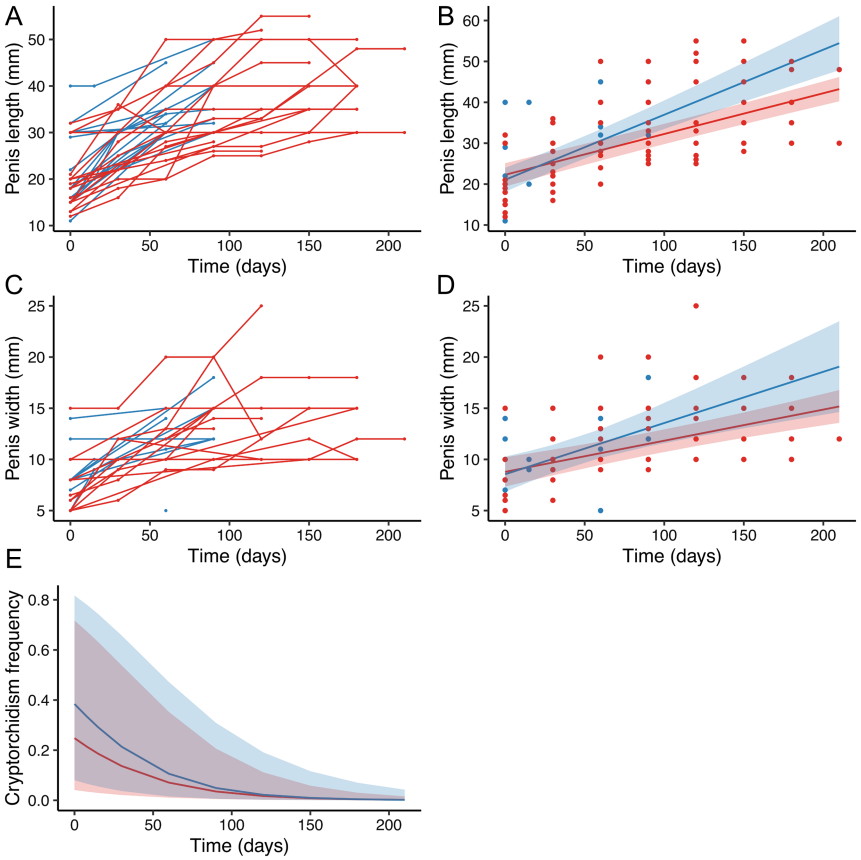

Figure 1
Individual (A) and predicted (B) penile length, individual (C) and predicted (D) penile width values as a function of time after the beginning of treatment (in days), with confidence interval. Predicted cryptorchidism frequency as a function of time after the beginning of treatment (in days), with confidence interval (E). Red = 'Pump'; blue = 'Injection'. The shading depicts the confidence interval in the legend.

In our study, penile growth was more efficient in the injection group related to a greater increase in testosterone levels under hCG. As samples were not collected at a unique time point (12 h after hCG injection for instance), testosterone levels may have been overestimated. Nevertheless, higher testosterone levels may be explained by a longer half-life of hCG compared to recombinant LH (17). However, the mean length and width of the penis were not impacted by the duration of rhLH/rhCG treatment. Indeed, a plateau was observed after about 100 days of treatment, which confirms that a 3-month treatment with rhLH/rhCG seems to be sufficient to obtain a normal penile length and width. As observed by Bin-Abbas B *et al.* and Main *et al.*, an increase in the length and width of the penis was observed in patients who had been pre-treated with testosterone (13, 18).

Prior to our study, only Lambert and Bougnères had studied testicular descent during treatment. They showed that subcutaneous gonadotropin infusion was able to induce testicular descent in a large proportion of infants with CHH. In our study, testicular descent was also improved during gonadotropin treatment, with similar results between the two groups. Our study confirms that gonadotropin treatment permits testis descent into the intra-scrotal position. Gonadotropins could therefore offer an alternative to orchidopexy surgery in this population (15).

Although different assays were employed over time for the measurement of Inhibin B, LH, FSH, and AMH between the two groups, which may affect the comparison between treatment modalities. However, Inhibin B and AMH levels were increased under both treatments and reached levels that are in the normal range or above, whatever the assay used in correlation with testicular size. The effect on testicular volume may be critical for future sperm production capacity and adult fertility (5, 19). According to previous work, gonadotropins have a beneficial effect on the proliferation of Sertoli cells, which constitute with the spermatogonia the major part of the testicular volume (20, 21).

Finally, we would like to continue to follow our patients in a prospective study starting at puberty to prove the late beneficial effects of gonadotropin treatment during the mini-pubertal period (faster pubertal induction, better fertility outcomes, etc.). To date, only 14 CHH boys aged 9.9–17.7 years, treated for 2 months to 2.8 years with rhFSH prior pubertal initiation by gonadotropins, have been reported in the literature, with

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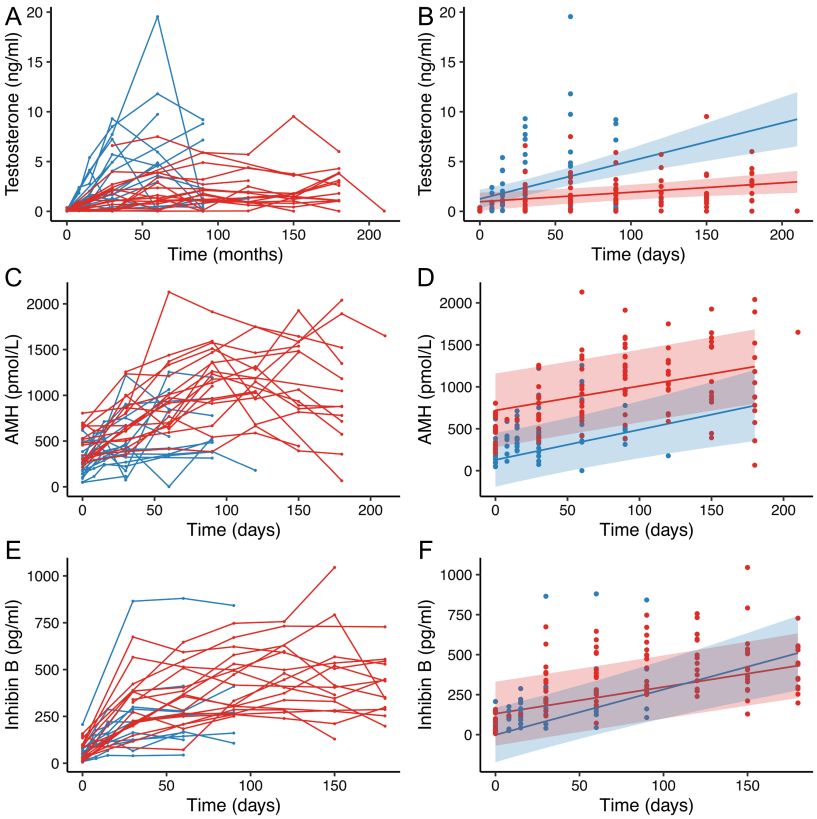

Figure 2
Individual (A) and predicted (B) testosterone values, individual (C) and predicted (D) AMH values, and individual (E) and predicted (F) Inhibin B values as a function of time after the onset of treatment (in days), with confidence interval. Red = 'Pump'; blue = 'Injection'. The shading depicts the confidence interval in the legend.

Table 4 Basal and peak individual data for hormone levels. The *P*-values correspond to the results of a two-way simple ANOVA. A *P*-value of less than 0.05 indicates a significant difference in mean value between the two groups.

Modalities	**Testosterone** (ng/mL)	**AMH** (pmol/L)	**Inhibin B** (pg/mL)	**FSH** (IU/L)	**LH** (IU/L)
Basal values					
Injection					
Mean ± S.D.	0.12 ± 0.07	246.6 ± 163.6	61.60 ± 54.70	0.58 ± 0.80	0.16 ± 0.17
Median	0.10	215.00	52.00	0.30	0.10
Minimum	0.05	47.80	9.00	0.20	0.10
Maximum	0.38	616.70	207.00	3.50	0.70
Pump					
Mean ± S.D.	0.05 ± 0.09	463.4 ± 190.6	68.31 ± 50.90	0.35 ± 0.37	0.08 ± 0.07
Median	0.02	469.00	66.50	0.30	0.07
Minimum	0.02	213.00	6.00	0.03	0.01
Maximum	0.37	805.00	158.00	1.20	0.30
P-values	**0.016**	**0.001**	0.726	0.271	0.076
Peak values					
Injection					
Mean ± S.D.	6.05 ± 4.84	679.6 ± 330.9	259.7 ± 204.0	5.56 ± 4.36	
Median	4.87	536	216.50	4.60	
Minimum	0.60	115	44.00	1.30	
Maximum	19.55	1255	880.00	15.00	
Pump					
Mean ± S.D.	3.25 ± 2.28	1375 ± 395.2	522.9 ± 204.9	33.94 ± 15.41	
Median	2.63	1340	514.00	31.00	
Minimum	1.12	665.00	274.00	9.72	
Maximum	9.52	2129	1045	66.90	
P-values	**0.034**	**<0.001**	**<0.001**	**<0.001**	

Bold indicates statistical significance.

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Table 5 Previous studies on gonadotropin treatment in the neonatal period.

Reference	Year	*n*	Age at treatment initiation	Treatment	Pump	Clinical effect	Biological effect
Main *et al.* (8)	2002	1	7.9 months	rhFSH + rhLH	No	↑ Testicular volume ↑ Penile length	↑ Inhibin B ↑ Estradiol
Bougnères *et al.* (9)	2008	2	2 and 5 months	rhFSH + rhLH	Yes	↑ Testicular volume ↑ Penile length	↑ Testosterone ↑ Inhibin B ↑ AMH
Sarfati *et al.* (6)	2015	1	1 month	rhFSH + rhLH	Yes	↑ Testicular volume ↑ Penile length	
Lambert et Bougnères (14)	2016	8	0.25–11 months	rhFSH + rhLH	Yes	↑ Testicular volume ↑ Penile length ↑ Testis descent	↑ Testosterone ↑ Inhibin B ↑ AMH
Stoupa *et al.* (10)	2017	5	3–5.5 months	rhFSH + rhLH	Yes	↑ Penile length	↑ Testosterone ↑ Inhibin B ↑ AMH
Kohva *et al.* (7)	2019	5	0.7–4.2 months	rhFSH + testosterone	No	↑ Penile length	↑ Inhibin B (transitory)
Papadimitriou *et al.* (15)	2019	10	2.3–9.4 months	rhFSH + rhLH	No	↑ Testicular volume ↑ Penile length	↑ Testosterone ↑ Inhibin B ↑ AMH

n, number of patients.

a significant increase in testicular volume and Inhibin B ($P < 0.001$) (22). Seven boys provided semen samples: one had azoospermia, while the others had sperm counts of 2.9–92 million/mL, suggesting a beneficial effect of rhFSH initiation prior the onset of puberty on testicular function later in life. However, whether a combination of FSH and hCG/LH treatment during mini-puberty could improve these results remains to be evaluated.

There was no difference in growth during treatment between patients at the two centers. No difference on any of the parameters studied was found between IHH and CPHD patients. Gonadotropin treatment can thus be as efficient in a patient with isolated hypogonadotropic hypogonadism as in a patient with CPHD.

As neonatal gonadotropin therapy remains an experimental treatment, it is imperative that it remains offered only in a specialized center with active monitoring.

Conclusion

In CHH, treatment with recombinant gonadotropins by injection or pump route during the mini-pubertal period has been shown to be effective. There was no difference between the two administration modalities, with the exception of penile length and plasma testosterone levels. Treatment with recombinant gonadotropins mimics the natural activation of the reproductive axis in mini-puberty, resulting in penile growth and increased plasma testosterone, AMH, and inhibin B levels. In addition, our study confirmed the effect of gonadotropins on testicular descent. Thus, early postnatal administration of recombinant gonadotropins could become an essential treatment to stimulate gonadal development, inducing Sertoli cell proliferation, testicular growth and descent, and thus improving future fertility in patients with CHH. Finally, this is only the second study to evaluate testis descent with gonadotropin therapy during mini-puberty.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0252.

Declaration of interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research.

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Author contribution statement

TA: conceptualization, methodology, writing; QH: methodology, statistics; LM and CB: methodology, supervision; all authors participated in the review of the article.

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