REplacement of MAle mini-Puberty in neonates and children with micropenis and cryptorchidism due to hypogonadotropic hypogonadism. Results of the "REMAP" study ISRCTN13007297

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Successful surgery but then what ?

Standard treatments, started after puberty, only partially correct genital abnormalities and spermatogenesis.

Nature Reviews Endocrinology 8, 172-182 (March 2012)

In congenital HH, even after a successful surgery,
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,
are considered responsible for hypoplastic testes, azoospermia and infertility

Work of reference:

Two neonates: P1 with hypopituitarism and P2 with HH (micropenis + microorchidism)
received LH and FSH with Continuous Subcutaneous Injection with an insulin pump,
P1 from the age of 8 wk for 4 months 56 IU LH + 67 IU FSH/day
P2 from the age of 20 wk for 6 months 50IU LH + 125 IU FSH/day
Total dose: P1 LH 9000+FSH 22,500-P2 LH 6720+FSH 8,040 IU

J Clin Endocrinol Metab. 2008 Jun;93(6):2202-5

Hormonal replacement in boys with congenital HH remains a challenge in pediatric endocrinology

Congenital HH presents clinically with: micropenis + bilateral crypto/microorchidism

Micropenis has been traditionally successfully treated with 3 monthly injections of 25/50 mg of testosterone enanthate in the post-neonatal period or in early infancy, or at the onset of puberty

Arch Fr Pediatr. 1984 Aug-Sep;41(7):467-71

But when bilateral cryptorchidism coincides, surgical intervention - needed twice - is required
Current recommendations for the treatment of bilateral cryptorchidism

(American Urological Association, May 2014)

Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy (*B*).

Non-palpable testes: 4% unsuccessful operation and 2% atrophy

Neoadjuvant gonadotropin-releasing hormone therapy before surgery may improve the fertility index in undescended testes in boys younger than < 2 yrs of age.

J Urol. 2005 Mar;173(3):974-7

We investigate whether daily injections for 3 months of the commercially available preparation of rh LH 75 + FSH 150 IU could mimic the physiological male mini puberty

8 neonates and infants aged 3 m – 3 yrs with

- **bilateral cryptorchidism,**
- **non-palpable testes in intra-abdominal position and**
- **micropenis (≤ 2 cm) with absence of neonatal male mini-puberty:**

LH < 0.44, FSH < 0.73 IU/L and undetectable basal Testosterone measured repeatedly from age 15 days up to 3-6 months.

- **1 had CHARGE syndrome**
- **3 had non-syndromic Kallmann syndrome** and
- **1 had syndromic Kallmann syndrome**
- **2 had septo-optic dysplasia**
- **1 aplastic pituitary**

Replacement protocol of male mini-puberty

- **All received for 3 months daily s.c. injections of Pergoveris® (LH 75 + FSH 150 IU)**
- **Total dose: LH 6,750 and FSH 13,500 IU** - monthly follow-up
- **Parents were trained and performed the injections**
- **The Greek National Organization for Medicines (EOF) issued permission** for the off-label use of Pergoveris and **the primary health insurance covered 100% the cost of the injections** (≈6,000 €)

Results (1)

- All **testes descended in scrotal position** reaching 1.5-2.5 ml by the end of the 1st in 2, 2nd in 3 and 3rd month in 3
- **Penile length** increased to a median of **4.3 cm**
- During therapy **all infants initiated catch-up growth**
- **Median LH** from undetectable reached **high normal 6.4 IU/L and FSH supranormal levels 86 IU/L**
- **Inhibine b** and **AMH** from subnormal, reached **high normal levels: 248 pg/ml** and **1025 pmol/L**
- **Testosterone** increased from undetectable to a **median of 2.2 ng/ml**

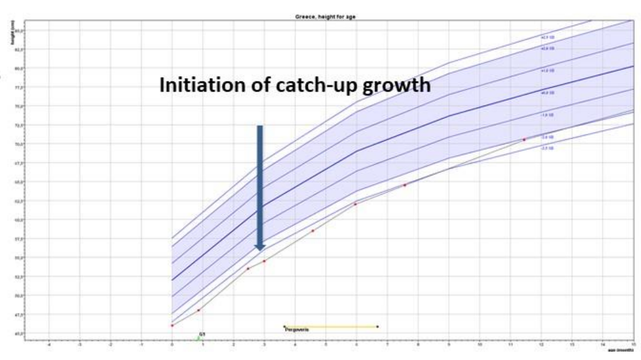
Results (2)

- **After a follow-up of 1-8 years testes** have slightly regressed to 0.5 -1.5 ml but **are still in scrotal position**
- In one case with septo-optic dysplasia **one** of the two **testes needed surgical stabilization as 6 months after completion of treatment it regressed in low inguinal position**.
- **The same boy needed a supplementary treatment with 3 monthly I.M. injections of 50 mg testosterone enanthate increase penile length from 3.5 to 5 cm (50th percentile for age).**
- **None presented any local or systemic adverse events or reactions**
- **Ultrasound** examination of the testes at the end of therapy **was normal**

Conclusions (1)

Treatment for 3 months with daily s.c. injections of the commercially available preparation of LH 75 / FSH 150 IU

- **mimics neonatal male mini puberty repairing micropenis and cryptorchidism**
- **induces high-normal activation of Leydig and Sertoli cells**
- **may be as well as beneficial to the brain as to the testes**
- **seems to stimulate initiation of catch-up growth**



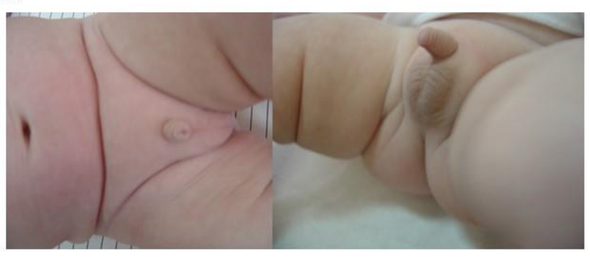
Conclusions (2)

Treatment for 3 months with daily s.c. injections of the commercially available preparation of LH 75 / FSH 150 IU

- **This treatment is a non-invasive strategy that mimics physiology**
- **corrects genital hypotrophy and restores testicular endocrine function**
- **The potential for future fertility is likely to be preserved**
- **And may also improve the response to future treatments intended to induce fertility**
- **Can be easily performed at home by the parents them-selves**
- **Costs much less than two surgical operations (≈6000€/patient)**
- **Not being able to measure the cost of an unsuccessful surgery or future infertility**
- **Even if it additional testicular stabilization may be needed in some cases, the work of the surgeon will be much easier**

Future implications

- **Further studies are needed to optimize this strategy (maybe a 1:1 or 2:1 preparation should be tested)**
- **Can be tried in idiopathic or even secondary bilateral cryptorchidism (i.e. Pradder-Willi syndrome)**
- **Puberty induction protocols with the combination of LH/FSH in gradually increasing doses may be developed**
- **The importance and the benefits of the postnatal physiological gonadotropin surge** - given that that the 1st in the fetal life (8-24 wks) was missed - **in the male gender development as well in normal growth** should be further investigated and seriously taken into account



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Pituitary, neuroendocrinology and puberty

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