Replacement of male mini-puberty in neonates and children with microopenis and cryptorchidism due to hypopitadogenic hypogonadism. Results of the "REMAP" study IRCTN13007297

Dimitrios T. Papadimitriou (1), Dionissia Chrysa (2), Georgia Nkytari (1), George Zoupanos (1), Eleftherios Laskos (1), Anastasios Papadimitriou (2) and George Mastorakeas (4)

(1) Atekes Medical Center, Athens, Greece
(2) University Hospital of Patras, Patras, Greece
(3) Atekes University Hospital, Athens, Greece
(4) Atekes Hospital, University of Athens, Athens, Greece

info@pcisendocr.gr

Successful surgery but then what?

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 hypogonadic, anospermia and infertility.

Work of references:

Two neonates: P1 with hypospadias and P2 with HH (microopenis + microtestes): received LH and FSH with Confirmation: Substitution. Injection with an intracutaneous pump.
P1: from the age of 6 weeks to 4 months 26.KU IU 0.035 IU/kg/day
P2: from the age of 20 weeks to 4 months 520.KU IU 0.13 IU/kg/day
Total doses: P1 LH 3000IU+FSH 22.656 IU+P2 LH 6724IU+FSH 8340 IU

[Clin Endocrinol Metab. 2008 Jan;90(1):22-25-5]

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% of the cost of the injections (-40,000€)

Results (1)

- All testes descended to scrotal position reaching 1.5-2.5 cm by the end of the 3rd, 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 normal 4.4 IU/l, and FSH supranormal levels 86 IU/l,
- Inhibin B and AMH from subnormal, reached normal levels: 240 pg/ml and 1805 pg/ml,
- Testosterone increased from undetectable to a median of 2.2 ng/ml

Conclusions (1)

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

- Microopenis neonatal male mini-puberty requiring microopenis and cryptorchidism
- Induces high-normal activation of Leydig and Sertoli cells
- May be as well beneficial to the brain as to the testes
- Seems to stimulate initiation of catch-up growth

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. Prader-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 the 1st in the fetal life (32-24 wk) was missed - in the male gender development as well in normal growth should be further investigated and seriously taken into account

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 themselves
- Costs much less than two surgical operations (-4000€/patient)
- Not being able to measure the cost of an unsuccessful surgery or future infertility
- Even if additional testicular stabilization may be needed in some cases, the work of the surgeon will be much easier

Poster presented at:

American Urological Association, May 2014