Replacement of male mini-puberty

Dimitrios T. Papadimitriou (1) (2), Dionysios Chrysis (3), Georgios Zoupanos (1), Georgia Nyktari (1), Eleni Liakou (1), Anastasios Papadimitriou (2)

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

No disclosures

Background:
• Hormonal replacement in boys with congenital Hypogonadotrophic Hypogonadism remains a challenge.
• Micropenis has been traditionally successfully treated with 3 monthly injections of testosterone enanthate before the age of 2, but when bilateral cryptorchidism coincides, surgery is required.
• But even after a successful surgery, the hypoplastic testes with the deficient proliferation of immature Sertoli cells, 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, are condemned in azoospermia and the boys in infertility.

Objective and hypotheses:
We investigated whether early postnatal daily injections of the commercially available recombinant LH/FSH preparation (Pergoveris®) could mimic the physiological male mini-puberty and successfully resolve bilateral cryptorchidism, repair micropenis, reinstate normal growth velocity and restore the responses of the Leydig and Sertoli cells.

Method:
Five neonates and infants, all with bilateral cryptorchidism in intra-abdominal position and micropenis ≤ 2 cm, (<-2 SDS) 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 were treated for 3 months with daily s.c. injections of the recombinant LH 75 + FSH 150 IU preparation (Pergoveris®). Total dose: LH 6,750 and FSH 13,500 IU with monthly follow-up. For all cases approval for the off-label use of Pergoveris was obtained from the National Organisation for Medicines.

Parents were trained and performed the injections.
• Case 1 had CHARGE syndrome diagnosed before choanal atresia.
• Cases 2 and 4 had non syndromic Kallmann syndrome.
• Case 3 had septo-optic dysplasia and
• Case 5 had aplastic pituitary with panhypopituitarism diagnosed in the neonatal ICU before symptomatic hypoglycemiva and cholestatic jaundice.

Results:
• In all cases testes descended in scrotal position by the end of the 1st in one, 2nd in two and 3rd month in two patients with a volume between 1.5 and 2.5 ml.
• Penile length increased to a median of 4.5 cm.
• During therapy all infants initiated catch-up growth.
• Median LH from undetectable reached high normal 6.5 IU/L and FSH supranormal levels 88 IU/L.
• Inhibin b and AMH from subnormal, reached high normal levels: median 248 pg/ml and 1025 pmol/L respectively.
• Testosterone increased from undetectable to a median of 2.42 ng/ml.
• In 3 cases with a follow-up of 1-5 yrs testes have slightly regressed to 0.5 -1.5 ml but are still in scrotal position.
• In one case with septo-otic dysplasia, one of the testes regressed to low inguinal position 1 year after completion of treatment and was successfully operated.
• Case 5 just completed therapy
• None presented any adverse events or reactions
• Ultrasound examination of the testes at the end of therapy was absolutely normal.

Conclusions:
Treatment with daily s.c. injections with the commercially available preparation of LH 75 / FSH 150 IU
➢ mimics neonatal male mini puberty repairing micropenis and cryptorchidism and inducing 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
➢ A non-invasive strategy that mimics physiology
➢ Costs less than two surgical operations (real cost 6,100 € / patient for the public health insurance), without being able to measure the cost of an unsuccessful surgery
➢ Even if it proves partially unsuccessful in some cases, the work of the surgeon will be much easier

Even if it proves partially unsuccessful in some cases, the work of the surgeon will be much easier for the boys present.