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Case Report

Primary Combined Therapy in Azoospermia Treatment Due to Hypogonadotrophic Hypogonadism

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ABSTRACT

A 34-year-old male with previous use of testosterone for 14 years went to our office in the State of São Paulo (SUS) due to infertility. After diagnosing hypogonadotropic hypogonadism, the patient received combined drug therapy with spermatogenesis recovery in less than 30 days.

INTRODUCTION

Boehm et al. [1] define Hypogonadotropic Hypogonadism (HH) as a disorder characterized by a hypothalamic defect or failure of the pituitary gland to produce enough gonadotropins to stimulate and maintain testicular function. It may be congenital in origin, as in Kallman syndrome, or acquired by direct injury to the hypothalamus or pituitary gland [2]. In men, HH can present decreased libido, gynecomastia, eunuchoidism, osteoporosis, and infertility due to azoospermia [2]. The treatment of azoospermia arising from HH with the intention of sperm recovery can be performed using gonadotropins, gonadotropin-releasing hormone (GnRH), and antiandrogens [3]. Initially, therapy is performed alone (monotherapy) for at least 90 days. In approximately 44% of patients, monotherapy is unsuccessful, requiring combined treatment (two drugs) with increased time and financial cost [4].

CASE DESCRIPTION

A 34-year-old male, married, went to the Unified Health System (SUS) in São Paulo, Brazil, complaining of primary marital infertility for the past 7 years. He underwent short-term treatment of HH with testosterone for 12 years and suspended the medication for 30 days. The patient had a 29-year-old wife, nulliparous, with regular menstrual cycles, BMI of 29.7Kg / m^2, and no changes on ultrasound and hysterosalpingography. On physical examination, a grade I varicocele was identified on the left. The complementary etiological investigation included laboratory (Table 1) and radiological tests.GnRH receptor mutation (negative molecular test) and Kalmann Syndrome (Magnetic Resonance - Figure 1) were investigated and not confirmed. The patient had three previous spermogram showed azoospermia after total centrifugation. The testicles ultrasound described testicles with a volume of 12 ml. With HH diagnosis, the patient was treated with human chorionic gonadotropin (hCG) 5000UI weekly, divided into 3 weekly doses in association with clomiphene citrate

50mg/day. The first spermogram collected, performed 23 days after starting the combination drug therapy, showed rare immobile sperm and 1 non-progressive mobile sperm (Figure 2). After four months of partner's combined drug therapy, his partner underwent controlled ovarian stimulation (COE) with recombinant FSH modified by a mini-dose of hCG when five follicles ≥ 14mm, forming embryos, of which 2 were transferred at stage D3, from which a topical pregnancy of a single, live-born female fetus. Figure 3 shows obstetric ultrasound (10 weeks pregnancy) .

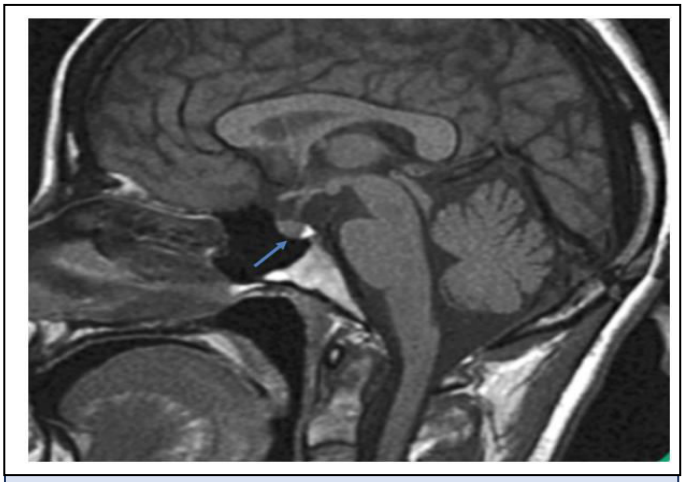

Figure 1: Pituitary MRI without anatomical changes (Blue arrow shows pituitary gland).

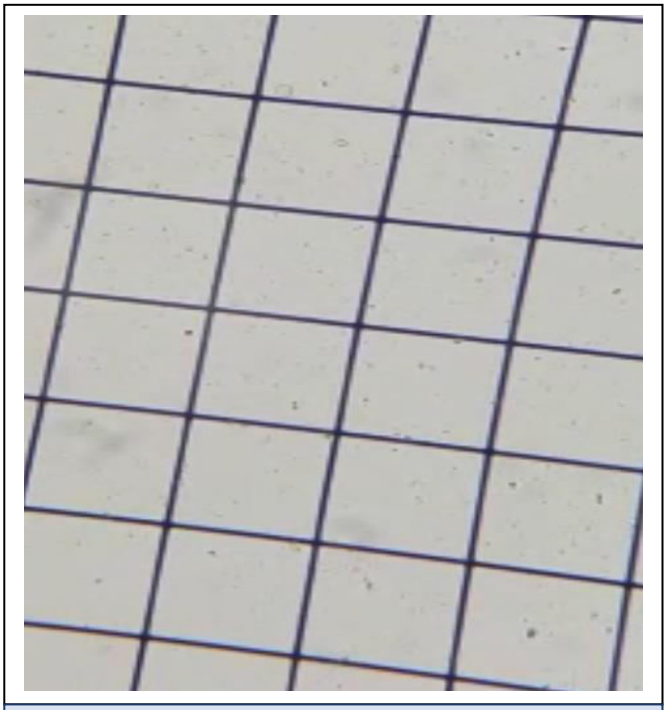

Figure 2: Makler chamber with rare sperm.

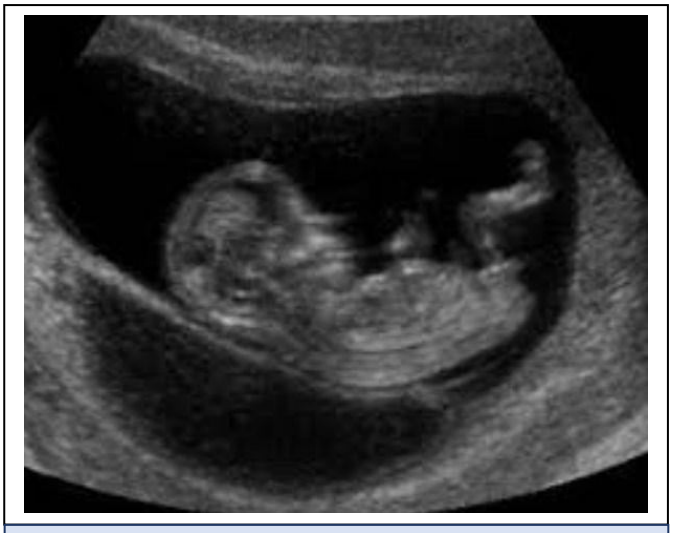

Figure 3: Obstetric ultrasound - 10 weeks of pregnancy.

Table 1: Laboratory tests (30 days without testosterone).

Male Exams	Dosage	Reference Value
FSH	6,5mIU/mL	1,5 a 9,8
LH	1,4mIU/mL	1,1 a 25,0
Estradiol	70pg/mL	até 87
Prolactin	153ng/mL	54 a 340
TSH	2,8uIU/mL	0,3 a 4,5
T4 total	12,4ng/dL	8,9 a 17,2
Testosterone total	**70ng/dL**	220 a 1050
Karyotype	46XY.	46XY.

DISCUSSION

Pulsatile secretion of Gonadotropin-Releasing Hormone (GnRH) by the hypothalamus is a prerequisite for initiating, developing, and maintaining the human reproductive axis [5]. Failure of GnRH secretion results in the clinical syndrome of HH characterized by failure of gonadal function. Secondary to deficient secretion of gonadotropins[6]. Biochemically, low steroid levels are found in the presence of low or inappropriately normal levels of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) [2]. The gonadotropins FSH and LH are released by gonadotrophic cells of the anterior pituitary. In men, the primary target cells for LH are Leydig cells, which subsequently secrete testosterone. FSH stimulates Sertoli cells adjacent to germ cells in the seminiferous tubules. Both LH-stimulated intratesticular testosterone and FSH stimulation of Sertoli cells are essential for the induction of spermatogenesis [7].

For induction of pubertal development, sex steroid therapy is required. After inducing the development of secondary sexual

characteristics, testosterone replacement therapy is required to maintain normal sexual function, muscle mass, and prevent osteoporosis [2]. Exogenous testosterone therapy significantly decreases intratesticular testosterone, impairing spermatogenesis [8]. For this reason, the American Endocrinology Society does not recommend testosterone therapy in men planning fertility in the near future [9]. If traditional treatments for HH with monotherapy fail, the association with other gonadotropins should be used, preferably with FSH. The duration of treatment so that it is possible to find sperm in the ejaculate is influenced by the drug used and by the association or not with other gonadotropins [6]. Men treated with hCG and hMG usually produce sperm in approximately 6 to 10 months, with pregnancy up to 49 months [10].

Since 2009, Lyu et al. have documented that the median time to first sperm was 7.1 months (95% CI 6.3-10.1) in a study of 75 men with HH treated with hCG. In this same sample, the authors report that the mean time of conception in the 38 men who became fathers was 28.2 months (95% CI 21.6-38.5) [11]. Among the possibilities of treatment is the use of Clomiphene Citrate (CC), as monotherapy or in association with hCG [12]. Habous et al. evaluated the increase in serum testosterone in 282 adult patients with HH randomized into three treatment groups: (i) CC 50 mg/day, (ii) hCG 5,000 IU/day, and (iii) CC + hCG. There was no statistically significant difference in the increase in testosterone between the groups [12]. Unfortunately, some studies omit that the spouse receives non-harmless ovulatory hormonal stimuli during male therapy.

In another study, Warne et al. analyzed combination treatment for HH, with an 84% response rate for obtaining sperm in patients who failed hCG monotherapy [13]. Even though we know the controversial and antagonistic results in the literature, we decided on dual therapy from the beginning to generate less female morbidity, shorter hormone treatment time, and lower final cost. Although human spermatogenesis has a complete cycle in 78 days, sperm recovery in 23 days after starting combined drug therapy (clomiphene and hCG) is a safe, economical, and unprecedented option.

CONCLUSION

We described a case of successful treatment of HH in a patient with long-term hormone therapy replacement. Faced with so many possibilities for treating male HH, we believe there is a need for more randomized studies to define the best therapy given the governmental costs and physical harm associated with female stimulation.

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