

The efficacy of recombinant human follicle-stimulating hormone in the treatment of various types of male factor infertility at a single university hospital

OZAN EFESYOY, SELAHİTTİN ÇAYAN,* AND ERDEM AKBAY

Department of Urology,
University of Mersin School of Medicine, Mersin, Turkey

RUNNING TITLE: rhFSH in the treatment of male infertility

A part of this paper was presented at the 24th Annual Meeting of the European Society of Human Reproduction and Embryology, July 6-9, 2008, Barcelona, Spain.

Correspondence address*:

Selahittin Çayan, MD
Associate Professor of Urology
University of Mersin School of Medicine
Department of Urology
33079-Mersin, TURKEY
Fax: 90-324-337-4311
E-mail: selcayan@mersin.edu.tr

ABSTRACT

The aim of the study was to prospectively investigate the efficacy of recombinant human follicle-stimulating hormone (rhFSH) in the treatment of various types of male factor infertility at a single university hospital. The study included 61 infertile men receiving rhFSH due to various type of male infertility. Treatment included 100-150 IU of rhFSH for 2-3 times/week. All men were divided into 4 groups as hypogonadotropic hypogonadism (n=21), isolated FSH deficiency (n=13), idiopathic oligoasthenospermia (n=16) and maturation arrest on testicular biopsy (n=11). Total motile sperm count (TMSC), serum FSH level and testicular volume were compared before and after the treatment in all groups. In the hypogonadotropic hypogonadism group, spermatozoa appeared in the ejaculate, with a mean of 6.67 ± 1.57 million TMSC, in 15 of 21 patients (71.4%) who were totally azoospermic before the treatment. In the isolated FSH deficiency group, TMSC significantly increased from 6.64 ± 3.27 to 32.4 ± 9.09 million after the treatment ($p=0.003$). TMSC did not significantly increase in the idiopathic oligoasthenospermia group. Two of the men with maturation arrest (18.1%) had spermatozoa in the ejaculate after the treatment. rhFSH therapy may be effectively used to improve sperm parameters in infertile men with hypogonadotropic hypogonadism and isolated FSH deficiency. In addition, rhFSH may have some improvement by either providing sperm in ejaculate or increasing ICSI success in infertile men with maturation arrest.

Key words: Male infertility, treatment, recombinant human FSH, sperm

INTRODUCTION

Male infertility may occur due to varicocele, hypogonadism, gonadotoxin exposure, testicular atrophy after mumps orchitis and obstruction of the genital tract (McLachlan et al, 2007; Çayan et al, 2002; Kadioğlu et al, 2001; Meacham et al, 2007; Nachtigall et al, 1997). Evaluation of male infertility plays important role in approximately 50% of the couples (Mosher, 1985; De Kretser, 1997). The aim of the evaluation of men for infertility is to diagnose correctable pathologies, to detect genetic disease and also to diagnose life threatening disease. It is sometimes not possible to treat men with idiopathic oligospermia or azoospermia, and these men are referred for intrauterine insemination (IUI), in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) based on impaired semen quality. However, infertility has been reported to be on the rise worldwide, and use of assisted reproductive techniques (ART) is an economic burden. Therefore, the aims of patho-physiologic specific treatment of male infertility are to achieve spontaneous pregnancy, to obviate the need for ART, to downstage the level of ART needed to bypass male factor infertility, and also to increase pregnancy rates with ART in cases who achieved unassisted reproduction.

Hypogonadotropic hypogonadism includes idiopathic, excessive exercise, trauma, stress, Kalmann syndrome, late puberty and hyperprolactinemia (Nachtigall et al, 1997). Treatment of male hypogonadotropic hypogonadism includes human chorionic gonadotropin (hCG) for 2-3 months initially, and then plus recombinant human follicle-stimulating hormone (rhFSH) for up to 12-18 months (Boulox et al, 2002, 2003). Spontaneous pregnancies can be achieved with the treatment of hypogonadotropic hypogonadism, however, in cases who fail therapy, treatment may increase pregnancy rates with ART (Bakircioglu et al, 2007).

Follicle-stimulating hormone plays an important role for the initiation and maintenance of spermatogenesis in males (Nieschlag et al, 1999). rhFSH has been used in the treatment of male infertility, and studies have reported successful results in separate patient groups with limited number of patients, including hypogonadotropic hypogonadism, idiopathic infertility and maturation arrest (Boulox et al, 2002, 2003; Bakircioglu et al, 2007; Kamischke et al, 1998; Caroppo et al, 2003; Selman et al, 2004, 2006; Foresta et al, 2002). However, no study has investigated the effect of rhFSH in the treatment of various types of male factor infertility in the same population. Therefore, the aim of this study was to investigate the efficacy of rhFSH in the treatment of various types of male factor infertility at a single university hospital.

MATERIAL AND METHODS

This prospective study included 61 infertile men receiving rhFSH due to various types of male factor infertility. The study was approved by the ethical committee at the University of Mersin School of Medicine. An informed consent was taken from all patients. All men were evaluated by a single physician (S.Ç.) at one hospital (University of Mersin School of Medicine). All men underwent a detailed history, physical examination, measurement of serum hormone levels and semen analysis.

Testicular volumes were measured with an ellipsoid orchidometer (Prader orchidometer, ASSI, NY) at baseline and after the end of treatment. Mean value of bilateral testicular volume was included for the comparison before and after the treatment. Blood samples for hormonal evaluation were taken in the early morning between 8:00-10:00 AM. For each patient, hormonal evaluation included measurement of plasma serum follicle stimulating hormone (FSH), lutenizing hormone (LH), prolactin and testosterone. In patients with isolated FSH deficiency in the presence of normal LH and testosterone level, if serum FSH level was low in the first measurement, the measurement was repeated to confirm FSH deficiency. Semen samples were collected by masturbation after 2-4 days of sexual abstinence and processed within 1 hour of ejaculation. At baseline, a minimum of 3 specimens were collected, separated by a 2-4 week interval. All semen analyses were performed in the same andrology laboratory according to World Health Organization criteria (normal sperm concentration: > 20 million/ml, and normal sperm motility: >50%)

(World Health Organization, 1998). Pre-treatment and post-treatment total motile sperm counts (ejaculate volume x concentration x motile fraction, TMSC) were calculated on all semen analyses. For each patient, the greatest TMSC value was used and compared from pre-treatment to post-treatment.

Hypogonadotropic hypogonadism was considered in the presence of undetectable or low level of serum testosterone (Normal range: 3.3-9 ng/ml), FSH (Normal range: 2.8-8 mIU/ml) and LH (Normal range 3-9 mIU/ml). Isolated FSH deficiency was defined as the presence of <2 mIU/ml of serum FSH level. Maturation arrest at the spermatocyte or spermatid level was diagnosed on testicular biopsy or cytology. Idiopathic infertility was considered in the presence of normal testicular volume and gonadotropin level with abnormal semen analysis. All men (n=61) were treated with 100-150 IU of rhFSH (Puregon, Schering Plough, USA) for 2-3 times/week. The men with hypogonadotropic hypogonadism initially and additionally received human chorionic gonadotropin (hCG) for 1500 IU (Pregnyl®, Schering Plough, USA) x 2-3/week to achieve sufficient serum testosterone level. When achieved serum testosterone level in normal range with approximately 3 months of hCG treatment, rhFSH was added.

All men were divided into 4 groups as hypogonadotropic hypogonadism (n=21), isolated FSH deficiency (n=13), idiopathic oligoasthenospermia (n=16) and maturation arrest on testicular biopsy or cytology (n=11). Of the men with maturation arrest, 4 were at the spermatocyte level, and 7 were at the spermatid level. TMSC, serum hormone levels and testicular volumes were compared before and after the treatment in all groups.

All female partners underwent a basic diagnostic infertility evaluation including a history, physical examination and pelvic ultrasound. Couples in whom the female partners had a history of gynecologic surgery or ovulatory abnormalities were excluded from the study.

STATISTICAL ANALYSIS

Statistical analysis was performed using paired t tests to compare pre-treatment to post-treatment TMSC, serum hormone levels and testicular volumes in individual patients. All data are given as mean ± standard deviation (SD). Probability values of <0.05 were considered significant.

RESULTS

The mean age was 23.19±7.79 years in the hypogonadotropic hypogonadism group, 30.23±7.01 years in the isolated FSH deficiency group, 31.43±7.01 years in the idiopathic oligoasthenospermia group and 31.09±4.52 years in the maturation arrest group. The mean treatment duration was 13.66±4.77 months in the hypogonadotropic hypogonadism group, 12.11±4.7 months in the isolated FSH deficiency group, 9.56±3.22 months in the idiopathic oligoasthenospermia group and 7.45±4.5 months in the maturation arrest group.

In all patients, no side effects were observed with the treatment. As shown in table 1, mean FSH level significantly increased in all groups from pre-treatment to post-treatment ($p=0.001$ for the hypogonadotropic hypogonadism group, $p=0.004$ for the isolated FSH deficiency group, $p=0.001$ for the idiopathic oligoasthenospermia group, $p=0.004$ for the maturation arrest group). In patients with isolated FSH deficiency, pre-treatment LH level was 4.37 ± 0.6 mIU/ml, and post-treatment LH level was 4.23 ± 0.42 , revealing no significant difference ($p=0.744$). Pre-treatment serum testosterone level was 5.89 ± 0.51 ng/ml, and post-treatment testosterone level was 6.08 ± 0.81 ng/ml, revealing no statistical significance ($p=0.582$).

Mean testicular volume significantly increased in the hypogonadotropic hypogonadism group ($p=0.001$), isolated FSH deficiency group ($p=0.011$) and maturation arrest group ($p=0.038$), however mean testicular volume did not change in the idiopathic oligoasthenospermia group ($p=0.544$).

In the hypogonadotropic hypogonadism group, TMSC increased from 0 to 4.77 ± 1.3 million, revealing a significant difference ($p=0.002$). Spermatozoa appeared in the ejaculate, with a mean of 6.67 ± 1.57 million TMSC, in 15 of 21 patients (71.4%) who were totally azoospermic before the treatment, although 6 patients (28.6%) still remained azoospermic. Sperm appeared in the ejaculate with a median of 7 months of the treatment. Of the patients who were still azoospermic on the treatment, 2 had sperm with testicular sperm extraction (TESE) procedure. In the isolated FSH deficiency group, TMSC significantly increased from 6.64 ± 3.27 to 32.4 ± 9.09 million after the treatment, revealing significant difference ($p=0.003$). In the idiopathic oligoasthenospermia group, pre-treatment TMSC was 2.18 ± 0.74 million, and post-treatment TMSC was 2.51 ± 0.85 million, revealing no statistical significance ($p=0.095$). In the maturation arrest group, post-treatment TMSC was 0.02 ± 0.02 million, while all were azoospermic before the treatment, revealing no statistical significance after the treatment ($p=0.323$). However, of the men with maturation arrest, 2 (18.1%) had spermatozoa in the ejaculate and 2 (18.1%) had spermatozoa on TESE, while all were azoospermic before the treatment.

DISCUSSION

Efficacy and safety of rhFSH has been well documented in the treatment of hypogonadotropic hypogonadism in men and women. This study is important to include treatment of various types of male factor infertility with rhFSH. In addition to the men with hypogonadotropic hypogonadism, treatment with rhFSH has provided significant improvement in men with isolated FSH deficiency and maturation arrest. Gonadotropins are required for fully normal spermatogenesis. FSH is absolutely necessary to initiate spermatogenesis. FSH may stimulate early events in spermatogenesis including spermatogonial proliferation and meiosis (Sofitikis et al, 2008). In addition, the administration of FSH had a positive role

in sperm cytostructural parameters (Baccetti et al, 1997). FSH in connection with LH/testosterone is also fundamental for the maintenance of quantitatively normal spermatogenesis (Nieschlag et al, 1999).

The induction of spermatogenesis in men with hypogonadotropic hypogonadism can be successfully achieved using gonadotropins or gonadotropin releasing hormone (GnRH) (Bouloux et al, 2002, 2003; Bakircioglu et al, 2007; Aydos et al, 2003; Miyagawa et al, 2005; Delemarre-van de Waal, 2004). Gonadotropins include human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), and urinary and recombinant FSH preparations. Full spermatogenesis and pregnancy may not be achieved in all cases despite prolonged treatment. Fahmy et al reported outcomes of ICSI using testicular sperm in male hypogonadotropic hypogonadism unresponsive to gonadotropin therapy (Fahmy et al, 2004). In 11 out of 15 patients (73%) after the treatment of 75 IU hMG thrice weekly and 5000 IU hCG once or twice weekly for more than 6 months, sperm could be retrieved from testicular tissue and were used for ICSI. Treatment of male hypogonadotropic hypogonadism includes human chorionic gonadotropin (hCG) 1500 IU 3 times/week for 2-3 months initially to supply the necessary LH bioactivity to stimulate the Leydig cells, and then plus human recombinant FSH (hrFSH) 100-150 IU 3 times/week for 12-18 months to stimulate the Sertoli cells (Bouloux et al, 2002, 2003; Bakircioglu et al, 2007). Initial testicular volume before treatment may provide a developmental perspective of the severity of these syndromes. Long term administration of hCG/hMG therapy in men with hypogonadotropic hypogonadism successfully increased and maintained serum testosterone level and testicular volume values, and improved sexual dysfunction as well as anejaculation. The small testis subset responded poorly in terms of serum testosterone levels and did not achieve sufficient testicular volume, only 36% of the patients in this subset showed sperm production. In contrast, 71% of the large testis subset showed sperm production (Miyagawa et al, 2005). Bakircioglu et al (2007) reported results of gonadotropin therapy in combination with ICSI in 25 men with hypogonadotropic hypogonadism. All men were treated with hCG twice weekly for one month plus 100 IU of rhFSH 3 times a week the following month, until spermatozoa appeared in the ejaculate. Spontaneous pregnancies were achieved in four couples, and 12 pregnancies were achieved with ICSI using ejaculated or testicular spermatozoa. RhFSH has been shown to be both well tolerated and effective for the stimulation of spermatogenesis in infertile men. Bouloux et al (2002) reported that after the treatment of rhFSH 150-225 IU 3 times weekly for up to 18 months, spermatogenesis was achieved in 15 of 19 azoospermic patients with a 9 months of median time to initiation of spermatogenesis, 12 achieving a sperm concentration of ≥ 1.5 million. Treatment was well tolerated, and serum antibodies to FSH were not detected (Bouloux et al, 2003). In the present study, in the hypogonadotropic hypogonadism group, mean serum FSH value and mean testicular volume significantly increased after the treatment. TMSC significantly increased from 0 to 4.77 ± 1.3 million. Spermatozoa appeared in the ejaculate, with a mean of 6.67 ± 1.57 million TMSC, in 15 of 21 patients

(71.4%) who were totally azoospermic before the treatment, although 6 patients (28.6%) remained still azoospermic. rhFSH treatment was well tolerated in our study population, and no side effect was observed with the treatment.

Isolated FSH deficiency has been reported in infertile men (Berger et al, 2005; Mantovani et al, 2003), and successful results have been obtained with treatment. After 6 months of hMG treatment, spermatogenesis was successfully induced in an azoospermic man with isolated FSH deficiency (Muraio et al, 2008). In the present study, TMSC significantly increased from 6.64 ± 3.27 to 32.4 ± 9.09 million after the treatment with rhFSH. In addition, mean serum FSH level and mean testicular volume significantly increased after the treatment. To our knowledge, this is the first study to report outcomes of treatment with rhFSH in infertile men with isolated FSH deficiency.

Use of rhFSH has been reported in the treatment of men with idiopathic infertility. Foresta et al (1998) suggested that rhFSH treatment may be appropriate for oligospermic men who have normal FSH plasma levels and a testicular evaluation characterized by hypospermatogenesis without maturational disturbances. In their recent controlled study, Foresta et al (2002) evaluated 3 months of treatment with rhFSH or no treatment. Treatment with rhFSH at a dose of 50 IU induced no increase in sperm concentration, while treatment with rhFSH at a dose of 100 IU induced significant increase in sperm concentration in 11 of 15 patients with hypospermatogenesis on testicular aspiration cytology. Caroppo et al (2003) reported 33 infertile men with idiopathic oligoasthenoteratozoospermia who failed to conceive after previous ICSI attempts. After the treatment with 150 IU of recFSH 3 times a week for 3 months, the mean fertilization and pregnancy rates were higher in the treatment group (62.3% and 30.4%, respectively) than in the control group (47.2% and 0, respectively), although no significant difference in the increase of sperm parameters between the two groups. Kamischke et al (1998) reported outcomes of treatment with rhFSH for male idiopathic infertility in a randomized, double-blind, placebo-controlled, clinical trial. rhFSH did not lead to an improvement of conventional or EM sperm parameters nor to an increase in pregnancy rates, however the increased testicular volume and sperm DNA condensation was seen in the treated group compared with the control group. In the present study, in contrast to the study by Kamischke et al (1998), mean testicular volume did not change, although mean FSH level significantly increased after the treatment in the idiopathic oligoasthenospermia group. TMSC did not significantly increase in the idiopathic oligoasthenospermia group in agreement with the controlled studies published (Kamischke et al, 1998; Foresta et al, 2002). Sperm structure may affect ICSI outcomes, and low fertilization rates may be due to acrosomal dysfunction or disturbed axonemal or DNA integrity, and therefore, treatment with rhFSH may promote increased sperm DNA condensation (Kamischke et al, Sakkas et al, 1998). However, more clinical trials are needed for men with idiopathic infertility to predict subgroups who would have response to rhFSH treatment.

Rescue of spermatogenesis arrest has been reported in azoospermic men after long-term gonadotropin treatment. Selman et al reported a total of 49 infertile men who failed to produce any mature sperm for IVF/ICSI cycle, showing maturation arrest at the spermatocytes or spermatids level on testicular biopsy (Selman et al, 2006). All men underwent long-term gonadotropin therapy with 75 IU of rhFSH on alternate days for the first 2 months, and then 150 IU on alternate days plus 2000 IU of hCG twice weekly for the four months. After six months of the gonadotropin therapy, testicular sperm were found in 11 of 49 patients (22.4%). In the present study, 4 (36.3%) of the 11 men with maturation arrest had spermatozoa either in the ejaculate or on the testicular tissue samples, while all were azoospermic before the rhFSH treatment. An azoospermic patient with a Y chromosome microdeletion was treated with recFSH for 6 months, and successful twin pregnancy was obtained with ICSI using ejaculated sperm after the treatment, while the patient had no sperm in the ejaculate and maturation arrest on testicular biopsy before the treatment (Selman et al, 2004). These findings suggest that rhFSH treatment may improve spermatogenesis in some azoospermic men with maturation arrest, leading to successful sperm retrieval from either ejaculate or testicular tissue samples for ICSI cycles. Treatment with FSH may also improve the success of testicular sperm retrieval in non-obstructive azoospermic men with normal FSH levels. In the present study, in the maturation arrest group, TMSC increased from 0 to 0.02 ± 0.02 million, revealing no statistical significance, although mean serum FSH level and mean testicular volume significantly increased after the treatment. However, of the men with maturation arrest, 2 (18.1%) had spermatozoa in the ejaculate and 2 (18.1%) had spermatozoa on TESE, while all were azoospermic before the treatment. Aydos et al (2003) reported that pure FSH treatment for 3 months increased the quantity of retrieved spermatozoa compared to control values (64% versus 33%). These findings suggest that rhFSH may increase chances of ejaculated sperm and testicular sperm retrieval rate for ICSI in infertile men with maturation arrest. However, further studies including control group are needed to emphasize the findings.

Conclusions:

rhFSH therapy may be effectively used to improve sperm parameters in infertile men with hypogonadotropic hypogonadism and isolated FSH deficiency. In addition, rhFSH may have some improvement by either providing sperm in ejaculate or increasing ICSI success in infertile men with maturation arrest.

REFERENCES

- Aydos K, Unlu C, Demirel LC, Evirgen O, Tolunay O. The effect of pure FSH administration in non-obstructive azoospermic men on testicular sperm retrieval. *Eur J Obstet Gynecol Reprod Biol.* 2003;108:54-58.
- Baccetti B, Strehler E, Capitani S, Colloodel G, De Santo M, Moretti E, et al. The effect of follicle stimulating hormone therapy on human sperm structure (Notulae seminologicae II). *Hum Reprod.* 1997;12:1955-1968.
- Bakircioglu E, Erden HF, Çiray HN, Bayazit N, Bahçeci M. Gonadotrophin therapy in combination with ICSI in men with hypogonadotrophic hypogonadism. *Reprod Biomed Online.* 2007;15:156-160.
- Berger K, Souza H, Brito VN, d'Alva CB, Mendonca BB, Latronico AC. Clinical and hormonal features of selective follicle-stimulating hormone (FSH) deficiency due to FSH beta-subunit gene mutations in both sexes. *Fertil Steril.* 2005;83:466-470.
- Bouloux P, Warne DW, Loumaye E for the FSH Study Group in Male Infertility. Efficacy and safety of recombinant human follicle-stimulating hormone in men with isolated hypogonadotropic hypogonadism. *Fertil Steril.* 2002;77:270-273.
- Bouloux P, Nieschlag E, Burger HG, Skakkebaek NE, Wu FCW, Handelsman D, Baker G, et al. Induction of spermatogenesis by recombinant human follicle-stimulating hormone (Puregon) in hypogonadotropic azoospermic men who failed to respond to human chorionic gonadotropin alone. *J Androl.* 2003;24:604-611.
- Caroppo E, Niederberger C, Vizziello GM, D'Amato G. Recombinant human follicle-stimulating hormone as a pretreatment for idiopathic oligoasthenoteratozoospermic patients undergoing intracytoplasmic sperm injection. *Fertil Steril.* 2003;80:1398-1403.
- Çayan S, Erdemir F, Özbey İ, Turek PJ, Kadioğlu A, Tellaloğlu S. Can varicocelelectomy significantly change the way couples use assisted reproductive Technologies? *J Urol.* 2002;167:1749-1752.
- Delemarre-van de Waal HA. Application of gonadotropin releasing hormone in hypogonadotropic hypogonadism-diagnostic and therapeutic aspects. *Eur J Endocrin.* 2004;151:U89-U94.
- De Kretser DM. Male infertility. *Lancet.* 1997;349:787-790.
- Fahmy I, Kamal A, Shamloul R, Mansour R, Serour G, Aboulghar M. ICSI using testicular sperm in male hypogonadotrophic hypogonadism unresponsive to gonadotrophin therapy. *Hum Reprod.* 2004;19:1558-1561.
- Foresta C, Bettella A, Ferlin A, Garolla A, Rossato M. Evidence for a stimulatory role of follicle-stimulating hormone on the spermatogonial population in adult males. *Fertil Steril.* 1998;69:636-642.
- Foresta C, Bettella A, Merico M, Garolla A, Ferlin A, Rossato M. Use of recombinant human follicle-stimulating hormone in the treatment of male factor infertility. *Fertil Steril.* 2002;77:238-244.
- Kadioğlu A, Çayan S, Tefekli A, Orhan İ, Engin G, Turek PJI. Does response to treatment of ejaculatory duct obstruction in infertile men vary with pathology? *Fertil Steril.* 2001;76:138-142.
- Kamischke A, Behre HM, Bergmann M, Simoni M, Schafer T, Nieschlag E. Recombinant human follicle stimulating hormone for treatment of male idiopathic infertility: a randomized, double-blind, placebo-controlled, clinical trial. *Hum Reprod.* 1998;13(3):596-603.
- Mantovani G, Borgato S, Beck-Peccoz P, Romoli R, Borretta G, Persani L. Isolated follicle-stimulating hormone (FSH) deficiency in a young man with normal virilization who did not have mutations in the FSHbeta gene. *Fertil Steril.* 2003;79:434-436.

- McLachlan RI, Rajpert-De Meyts E, Hoei-Hansen CE, de Kretser DM, Skakkebaek NE. Histological evaluation of the human testis-approaches to optimizing the clinical value of the assessment: Mini review. *Hum Reprod.* 2007;1:2-16
- Meacham RB, Joyce GF, Wise M, Kparker A, Niederberger C; Urologic Diseases in America Project. Male infertility. *J Urol.* 2007;177:2058-2066.
- Miyagawa Y, Tsujimura A, Matsumiya K, Takao T, Tohda A, Koga M, et al. Outcome of gonadotropin therapy for male hypogonadotropic hypogonadism at university affiliated male infertility centers: a 30-year retrospective study. *J Urol.* 2005;173:2072-2075.
- Mosher WD. Reproductive impairments in the United States, 1965-1982. *Demography.* 1985;22:415-30.
- Murao K, Imachi H, Muraoka T, Fujiwara M, Kushida Y, Haba R, Ishida T. Isolated follicle-stimulating hormone (FSH) deficiency without mutation of the FSHbeta gene and successful treatment with human menopausal gonadotropin. *Fertil Steril.* 2008;90:2012e17-e19.
- Nachtigall LB, Boepple PA, Pralong FP, Crowley WF Jr. Adult-onset idiopathic hypogonadotropic hypogonadism-a treatable form of male infertility. *N Engl J Med.* 1997;336(6):410-415.
- Nieschlag E, Simoni M, Gromoll J, Weinbauer GF. Role of FSH in the regulation of spermatogenesis: clinical aspects. *Clin Endocrinol.* 1999;51:139-146.
- Sakkas D, Urner F, Bizzarro D, Manicardi G, Bianchi PG, Shoukil Y, et al. Sperm nuclear DNA damage and altered chromatin structure: effect on fertilization and embryo development. *Hum Reprod.* 1998;13:11-19.
- Selman HA, Cipollone G, Stuppia L, De Santo M, Sterzik K, El-Danasouri I. Gonadotropin treatment of an azoospermic patient with a Y-chromosome microdeletion. *Fertil Steril.* 2004;82:218-219.
- Selman H, De Santo M, Sterzik K, Cipollone G, Aragona C, El-Danasouri I. Rescue of spermatogenesis arrest in azoospermic men after long-term gonadotropin treatment. *Fertil Steril.* 2006;86:466-468.
- Sofitakis N, Giotitsas N, Tsounapi P, Baltogiannis D, Giannakis D, Pardalidis N. Hormonal regulation of spermatogenesis and spermiogenesis. *J Ster Biochem Mol Biol.* 2008;109:323-330.
- WHO laboratory manual for the examination of human semen and semen-cervical mucus interaction, 5th edition: World Health Organization, New York, Cambridge University Press, 1998.

Table 1: Mean age at baseline, mean treatment duration, pre-treatment and post-treatment serum FSH levels, testicular volume and TMSC of the groups.

Groups	n	Age (year)	Treatment duration (month)	Serum FSH level (mIU/ml)			Testicular volume (ml)			Total motile sperm count (million)		
				Pre-treatment	Post-treatment	P value	Pre-treatment	Post-treatment	P value	Pre-treatment	Post-treatment	P value
Hypogonadotropic hypogonadism	21	23.19±7.79	13.66±4.77	0.71±0.15	3.77±0.39	0.001	4.08±0.57	12.38±1.42	0.001	0.00±0.00	4.77±1.3	0.002
Isolated FSH deficiency	13	30.23±7.01	12.11±4.7	1.59±0.21	4.81±0.83	0.004	16.46±1.11	17.38±1.11	0.011	6.64±3.27	32.4±9.09	0.003
Idiopathic oligoasthenospermia	16	31.43±7.01	9.56±3.22	7.18±0.63	10.16±0.86	0.001	17.13±0.84	17.25±0.86	0.544	2.18±0.74	2.51±0.85	0.095
Maturation arrest	11	31.09±4.52	7.45±4.5	5.66±1.43	8.41±1.86	0.004	15.09±1.07	15.45±1.03	0.038	0.00±0.00	0.02±0.02	0.323