



(CASE REPORT)



## Patient with hypogonadism and infertility successfully treated with clomiphene citrate

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### Abstract

We described 59-year-old men with history of secondary/tertiary hypogonadism, without primary hypothyroidism, elevated prolactin or hemochromatosis with structurally intact hypothalamo- hypophyseal (HT-HP) axis who was diagnosed in 2017. He was treated by different physicians with Testosterone intramuscular injections, hCG intramuscular injections and combination of hCG and FSH intramuscular injections. The patients wanted to have another child and this is why his therapy was changed from testosterone to hCG and later on to hCG and FSH injections three times a week by his urologist. Although his testosterone levels increased his semen analysis showed oligospermia. The patient was not very compliant with his Testosterone, hCG/hCG and FSH injections, because of the discomfort of intramuscular injections. This is why we started the patient from the therapy with hCG and FSH intramuscularly to Clomiphene citrate (CC) 25 mg per mouth every other day in 2021. After eight months therapy with CC the patient semen analysis normalized, Total and Free testosterone levels normalized, LH and FSH increased, his libido, morning erections improved and his erectile dysfunction resolved. Most importantly for the patient his wife become pregnant.

With this case we emphasize the role of Clomiphene citrate in treating male hypogonadism if the patients desire fertility.

**Keywords:** Total testosterone; Free testosterone; Prolactin; Male hypogonadism; Infertility

### 1. Introduction

Hypogonadism is a common medical condition among men. Hypogonadism is a clinical and biochemical testosterone insufficiency syndrome, affecting various organ functions and quality of life, according to the European Association of Urology. Common symptoms of hypogonadism are erectile dysfunction, reduced sexual activity and desire, decreased morning erections, mood changes, and loss of muscle strength among others. The prevalence for symptomatic hypogonadism at age 40–79 years, varies between 2.1% and 13% and increases with age and presence of obesity, cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) type 2, human immunodeficiency virus (HIV), chronic kidney disease, malignancies, obstructive sleep apnea, cirrhosis of the liver, pituitary tumors, hyperprolactinemia, many medications among others. Low testosterone level is also a sign of poor health [1].

The hypogonadism in male patient might be primary in which the cause of decreased testosterone and sperm production is in the testes due to Klinefelter syndrome- number one cause of primary hypogonadism which happens in 1:500 men. Other causes of primary hypogonadism in men are using chemotherapy, radiation therapy, varicocele, tumors of the testes, hemochromatosis among others. In primary hypogonadism the total and free testosterone levels are

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low while the level of FSH and LH are elevated [1]. Also, the patients might be infertile with sperm volume less than 2 cc and sperm count less than 15-20 million per cc, with less than 40 % mobile spermatozooids and less than 4% normal spermatozooids.

In Secondary or tertiary hypogonadism, the cause might be functional without structural changes in hypothalamo-hypophyseal area (HT-HP) area which happens in androgen deficiency in aging men (ADAM) syndrome, Obesity, HIV, Severe obstructive sleep apnea, Genetic syndromes like Kalman syndrome, HT-HP tumors or aneurisms and other diseases of HT-HP area, Diabetes mellitus or severe stress among others. In secondary/tertiary hypogonadism the total and free testosterone levels are low, but FSH, LH are usually low or inappropriately normal for the low levels of testosterone with the infertility and sperm parameters which are abnormal as described above [1].

Testosterone therapy (TTh) is the first-choice treatment for men with hypogonadism [2]. The goal of this treatment is to increase serum testosterone and restore androgen-dependent functions, for example, muscle mass and strength, sexual function, libido, bone density, and general well-being [3].

However, TTh has some notable side effects. The most common side effect in older men is polycythemia and in younger men is acne [6]. Subfertility is one of the most crucial side effects of TTh, especially for men with an active or possible future child wish, because endogenous testosterone is reduced by negative feedback on HT-HP axis [1].

Other side effects are, for example, increase in prostate volume, increase in prostate specific antigen (PSA), elevation of hematocrit. Also, it can increase the serum estrogen concentration and lead to serum lipid alterations as well as worsening of the obstructive sleep. We have described a patient with recurrent TIA's due to testosterone treatment due to testosterone causing polycythemia [4].

Another potential medical treatment for secondary/tertiary hypogonadism and structurally intact HT-HP axis in male patients, especially those desiring fertility and not having primary hypogonadism, is clomiphene citrate. This drug is selective estrogen receptor modulator and antiestrogen.

Although it is not FDA approved yet for treatment of male hypogonadism, because of data describing inconsistent effect several retrospective studies and randomized trials have demonstrated improvement of serum testosterone levels with clomiphene citrate to the degree similar to the Testosterone Gel [2,5,6,7]. Unlike the Testosterone Gel the treatment with Clomiphene citrate improves male fertility [1].

Other potential medical treatment for male patients with secondary/tertiary functional hypogonadism desiring fertility is with the use of hCG intramuscular injections and if needed FSH injections.

Other potential interventions that should be considered to increase testosterone levels include-adequate treatment of diabetes mellitus, obesity, obstructive sleep apnea, dyslipidemia and stress reduction and/or depression due to central biofeedback mechanisms effecting testosterone levels [1].

In our case we describe a male patient with functional secondary/tertiary hypogonadism and infertility treated without significant success in achieving fertility while improving his sexual performance, libido and morning erections with Testosterone cypionate intramuscular injections, intramuscular injections of hCG or hCG and FSH. The patient was not very compliant with intramuscular injection therapy, because of discomfort of the injections.

We switched him to clomiphene citrate (CC) 25 mg per mouth every other day and after 8- months of therapy besides improvement of his gonadal hormonal function his sperm count and motility improved, he become fertile and his wife become pregnant.

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## 2. Case presentation

59-year-old Asian male has been seen by us inconsistently since 2017.

We have been seeing him together with the urologists in town. His records from the urology office have shown that he had secondary/tertiary hypogonadism without structural changes in HT-HP area.

He had normal libido, morning erections and sexual performance before 2017 and fathered one child.

Since 2017 he has not been able to father another child, and he has had decreased morning erections, decreased libido and sexual performance. Detailed examination of his wife done by OBGYN office in town has been normal.

The patient's Total Testosterone (TT) in 2017 was low measured at 8 a.m. twice by LC-MS was 210 and 220 ng/dl (reference ranges- 250-1100), as well as his Free testosterone levels were (FT) – 30 and 31 pg /ml respectively (reference ranges- 35-224) with normal sex hormone binding globulin (SHBG) -31 nmol/l (reference range- 22-77). His LH at the time was 5 mIU/ml (reference range 1.5-12.4) and FSH was 3 mIU/L (reference range- 1.7-8.6). Both LH and FSH were normal. Also, his TSH at the time was normal-2.01 mIU/L (reference range 0.3-4.2) with normal FT3 and FT4 as well as normal Prolactin level of 7 ng/ml (reference range 3-20). He had normal iron level, ferritin level and transferrin saturation in 2017. Other pituitary hormones were normal -IGF-1 and morning ACTH/Cortisol as well. MRI of HT/HP area at the time was normal. His sperm indices were abnormal- sperm volume at the time was 1 cc, with sperm count 10 million per cc, and motility of 30% and only 3% of sperm cells were normal. For reference- normal sperm volume should be 2 cc or more with 15-20 million spermatozooids per 1 cc, motility of the spermatozooids should be 40% or more and at least 4 % of the sperm cells should be normal. The patient had Pre-Diabetes Mellitus type 2 and was overweight. His genital examination was normal. Life style- interventions were introduced and we added Metformin ER 500 mg a day in 2022. He did not have signs of Obstructive sleep apnea- 2- points only on STOP-BANG Questionnaire.

The urologist in 2017- started treating the patient with Testosterone cypionate 100- mg intramuscularly injections every 2- weeks with improvement of patient's morning erections, libido and sexual performance. The patient's morning TT increased to 740 ng/dl and the FT increased to 148 pg/ml, but the patient's continued to be infertile and his sperm volume, count and motility further worsen with the testosterone injection treatment. The sperm analysis showed worsened oligospermic results. The patient stopped his testosterone injections in 2019, because he continued to be infertile and the intramuscular injections were causing some discomfort. He admitted that sometimes he has not been very compliant with his Testosterone intramuscular injections because of this discomfort. Sildenafil was prescribed by the urologist for his erectile dysfunction without significant success.

Later on, the urologist started treating the patient with hCG intramuscular injections- 1000 units- 3- times a week. The patient was still infertile and oligospermic although he admitted not to be very compliant with the treatment with hCG, because of the discomfort using intramuscular injections and later on FSH intramuscular injections were added by the urologist which he used very inconsistently. He was seeing also a fertility specialist who confirmed the continuation of oligospermia in 2021.

When we saw the patient in 2021, we decided that the treatment with hCG with or without FSH was not significantly effective in improving his fertility, because of patient's noncompliance to the intramuscular injections given the patient's discomfort with them.

We decided to start the patient on Clomiphene citrate 25 mg every other day in, 2021 and stop the hCG and FSH intramuscular injections, because injections caused discomfort and the patients was non-compliant with them.

The patient tolerated the per oral medication Clomiphene Citrate 25 mg every other day well and after 8-months of treatment his wife become pregnant.

His sperm volume increased to 2.5 cc, sperm count increase to 40 million per cc, 50% of the sperm cells were motile and 7% were normal. His TT increased to 927 ng/dl, FT-increased to 148 pg/ml and SHBG was normal and LH increased to 20 mIU/L and FSH to 19-mIU/L. There were no complaints from the patient of fatigue or dizziness, no gynecomastia or elevation of the hemoglobin/hematocrit.

The patient continues to be overweight and did not closely follow the life style interventions. He continued to have pre-Diabetes Mellitus type 2 and this is why we started in 2022 Metformin ER -500 mg a day, besides further emphasizing the role of life style interventions, referring him to dietary specialist and giving him some applications for monitoring his calorie intake. We started him also on Atorvastatin 40 mg a day based on his high 10- year cardiovascular risk score.

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### 3. Discussion

Clomiphene citrate is regarded as a useful treatment for men who suffer from secondary hypogonadism with intact HT-HP axis which might have some physiological change who desire fertility although not FDA approved, because of inconsistency of the data [8,9,10].

The drug leads to increase of total Testosterone (TT), the Free Testosterone (FT), LH, FSH, and estradiol also increase. The ratio Testosterone/estradiol increases [11]. These elevations of testosterone and gonadotrophins show that CC is effective in improving endogenous testosterone secretion by stimulating the HT-HP-G-axis in men with hypogonadism by blocking the estrogen inhibitory action in HT for GHRH release. During CC treatment, serum TT achieved the reference value 400-700 ng/dl sufficient for treating hypogonadism, according to the guidelines of the American Urology Association. Different studies comparing CC with testosterone gel concluded the same. Taylor and Levine (2010) ( $n = 103$ ), demonstrated no difference in biochemical outcome of serum TT between CC or usage of testosterone gel [12].

Exogenous testosterone treatment creates negative feedback on the hypothalamic-pituitary axis. This effectively decreases the production of gonadotropin and gonadotropin-releasing hormone. Consequently, the secretion of FSH and LH are also inhibited. These impairments on hormones result in overall decreases in intratesticular testosterone levels (ITT) as well as decreased endogenous testosterone production. Typically, ITT concentrations are roughly fifty to one hundred times higher than the serum levels of TT. Exogenous testosterone treatment can suppress ITT production to such an extent that spermatogenesis can be dramatically compromised [13] ITT is an absolute requirement for normal sperm [14]. However, the rates of success in recovering spermatogenesis after use of exogenous Testosterone are generally quite favorable [1].

In our patient the testosterone injections improved the patient's libido, sexual performance and morning erections, but were detrimental to his fertility. Fortunately, the patient was not very compliant with intramuscular injections of Testosterone, the treatment was less than 2- years, the Testosterone dose was on the lower side and the patient was from Asian origin [1].

All of the above helped the recovery of the sperm parameters after initiation of Clomiphene citrate as described in the literature. We believe the patient was very non-compliant with the treatment with HCG and HCG/FSH intramuscular injections because of discomfort of the injections while still recovering the sperm production from the prior Testosterone injection therapy and this is why this treatment did not significantly improve his sperm parameters.

This case illustrates clearly the role of Clomiphene citrate as a non-expensive, easy to administer, non-invasive with low side effect profile option for treatment of male hypogonadism in male patients desiring fertility [7,15]. This is valid in patients with secondary/tertiary functional hypogonadism. We believe larger randomized studies are needed for further delineation the role of Clomiphene citrate in treatment of male hypogonadism.

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#### **4. Conclusion**

In the case described we wanted to show that the secondary/tertiary non structural male hypogonadism and infertility can be treated by different methods. If fertility is desired definitely not an option is Testosterone treatment, which decreases the sperm production. The intramuscular injections of hCG and FSH three times a week are definitely an option, but frequently discontinued by the patients like in our case, because of the discomfort of the injections- three times a week and because this treatment is very cumbersome- three times a week. We are describing this case to show that cheap and very efficacious alternative is the treatment of male hypogonadism in patients desiring fertility with clomiphene citrate. This type of treatment described buy us might help the clinicians and the society to treat male hypogonadism and infertility in a very efficacious way looking forward!

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#### **Compliance with ethical standards**

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There is no conflict of interest of the authors.

##### *Statement of informed consent*

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