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# Off-label Therapy of Hypogonadotropic Hypogonadism in a 35-year-old Male Patient Using Clomiphene Citrate – A Case Study

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## Abstract

*Hypogonadism is either hypergonadotropic (primary) or hypogonadotropic (secondary). When the pituitary gland is secreting an excess of gonadotropins, primary hypogonadism is diagnosed. In secondary hypogonadism, the levels of gonadotropins in the serum remain low. Male patients affected with hypogonadism present numerous symptoms due to a lack of testosterone, e.g., erectile impairment, feminization of the body, and infertility. The deterioration of self-confidence and quality of life underlines the importance of the correct diagnosis and effective treatment. Clomiphene citrate is registered in Europe for the treatment of ovulatory failure in women. It is often used as an off-label drug to treat hypogonadism in men, as it proves efficient in some cases and is relatively safe and easily administered in comparison to other medicaments, e.g., testosterone and gonadotropin analogs. We report on a 35-year-old Caucasian male patient who was admitted to the Department of Endocrinology with symptoms of erectile dysfunction, lowered self-esteem, hypersomnia, and trouble conceiving. A complex diagnostic procedure was performed, which led to the final diagnosis of hypogonadotropic hypogonadism and reactive hyperprolactinemia. The treatment with Clomiphene Citrate was implemented and brought significant improvement – the withdrawal of unwanted symptoms and restored hormonal balance – after two weeks.*

***Key words:*** *pregnancy, vitamins, diet, nutrition, supplementation*

## Introduction

Hypogonadism in men is caused by impaired testosterone production in the testicles. It can be either hypergonadotropic (primary), when the pituitary gland is oversecreting gonadotropins due to the lack of suppression from testicles, or it might be hypogonadotropic (secondary), when the pituitary gland is not secreting gonadotropins or hypothalamus is not secreting the gonadotropin-releasing hormone (GnRH) [1, 2]. Primary hypogonadism is observed in patients with Klinefelter syndrome or those with testicular tissue impairment (due to neoplasm, radiation, chemotherapy, after inflammation

or trauma). Secondary hypogonadism is met in patients affected with Kallmann syndrome, Prader-Willi syndrome, and those with the malfunction of the pituitary or hypothalamus [3]. Patients affected with hypogonadism present various clinical symptoms. The most suggestive ones are reduced libido and lower sexual intercourse count, erectile impairment, infertility, and gynecomastia. Those might be accompanied by nonspecific symptoms such as overall fatigue, lower self-esteem, depressive mood, trouble sleeping, lower muscle strength, and mild anemia [4]. To diagnose patients who present symptoms of hypogonadism, it is crucial to assess testosterone concentration in serum, gonadotropins levels, and spermatogenesis efficiency [5]. It is also advised to perform an ultrasound of the testicles, to evaluate their size and structure [6]. Some cases also require magnetic resonance imaging of the brain to exclude potential tumors [7]. Hypogonadism might be treated with testosterone, dopamine agonists, gonadotropins, clomiphene, tamoxifen, and aromatase inhibitors [1]. No matter what type of hypogonadism the patient is dealing with, it is advised to control the parameters such as body weight, body mass index (BMI), and maintaining a healthy lifestyle – diet, and regular physical exercise [8].

## Material and methods

A literature review regarding Clomiphene citrate and male infertility was performed in March 2023 using the PubMed database with the search terms: hypogonadism, male infertility, and Clomiphene. 17 articles were considered adequate and useful while preparing this article, and are listed in the References section.

## Case report

We report on a 35-year-old male patient who was referred to the Department of Endocrinology with periodic erection dysfunction, troublesome procreation, and hypersomnia. Vitals during admission: body weight of 80 kilograms, height of approx. 179 centimeters, BMI 24.97, blood pressure 112/86, heart

rate 104, body temperature 36.6 degrees Celsius. In laboratory parameters, decreased levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were observed, testosterone was in the lower limit of normal (Table 1).

Semen analysis, ultrasound of testicles, abdomen, and magnetic resonance imaging (MRI) of the pituitary gland were normal. An ultrasound of mammary glands was also performed as the physical examination revealed steatomastia, this examination was, however, also within the normal range. The GnRH stimulation test resulted in no rise in the FSH parameter, however, a significant (over 10 times) rise in the LH level was observed within 30 minutes of the test, which was an adequate response (Table 2).

During the metoclopramide test, the patient reacted with an increase in prolactin (PRL) from 7.54 [ng/ml] (reference rate 2.10–17.70) to 46.12 after one hour and 48.63 after two hours which, prompted the physicians to diagnose reactive hyperprolactinemia. Since the patient suffered from hypersomnia after meals, an oral glucose tolerance test (OGTT) was performed; however, it proved no glucose metabolism disturbances. The patient did not have any chronic illnesses, the family history was also uneventful. The symptoms in a physical examination and laboratory results prompted the physician to set the diagnosis of hypogonadotropic hypogonadism. A decision to start Clomiphene therapy was made. After two weeks of taking 50 milligrams of Clomiphene every second day, the patient came back for a check-up. He reported an improvement in previous physical symptoms and general well-being. The laboratory results after two weeks of therapy are shown in Table 3. The patient presented a significant increase in each examined parameter in comparison to the results on admission. Those results correspond with those stated by Huijben and colleagues. Total testosterone in our patient during admission was 202.50 ng/dL (179.0 ng/dL to 310.3 ng/dL in the referenced meta-analysis). During treatment, total testosterone in our patient increased to 656.72 ng/dL (467.0 ng/dL to 687.9 ng/dL in the referenced meta-analysis).

The LH (2.01 IU/L) and FSH (2.24 IU/L) parameters in our patient during treatment were slightly lower in comparison to the published data (LH = 4.67 IU/L, FSH 4.25 IU/L) [9].

Since the patient presented a significant response to Clomiphene therapy, a decision to decrease the dosage of 50 milligrams from every second day to every three days was made. The patient as of today remains under ambulatory control of the endocrinologist, his wife is also under evaluation for the possible cause of infertility.

## Discussion

When choosing a treatment for a patient affected with hypogonadism, it is crucial to assess whether a patient wants to preserve fertility or not. Testosterone is not available in treatment in patients who have further procreation plans, as it decreases sperm production. Taking this aspect into consideration, as well as other possible side effects of testosterone therapy (increased risk of prostatic cancer, polycythemia, possible heart failure), it was decided not to implement testosterone therapy in this case. Testosterone might be useful in patients dealing with the feminization of the body (gynecomastia, rounded hips, etc.), and low bone mineral density, but with no future paternity plans, and only when testosterone levels in serum are regularly measured [4]. Dopamine agonists – bromocriptine and cabergoline – can help restore fertility in patients who present hyperprolactinemia [10]. Even though this patient reacted with an increase in prolactin during the metoclopramide test, the primary prolactin level was within the normal range, the other exams such as mammary gland ultrasound, MRI of the pituitary gland, and testicles ultrasound were also uneventful, and that prompted the physicians not to introduce dopamine agonists at this point. Gonadotropins such as recombinant/urinary human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), and FSH analogs are highly effective in the induction of spermatogenesis and thus can be used in patients willing to restore fertility [11]. They can also induce puberty in young male patients affected with hypogonadism; however, they are less efficient in this indication [11]. Gonadotropins are administered intramuscularly or subcutaneously. The dosage is determined by serum concentration of testosterone – it should be in the lower norm range to avoid adverse effects such as gynecomastia

and low hematocrit [12]. Those symptoms are caused by excess levels of estradiol which is an end product of testosterone and androstenedione aromatization [13]. In the presented patient therapy, using hCG, which is an LH analog, seems most suitable, as the patient presented a low LH level in serum at admission. However, the financial cost of the therapy with gonadotropins as well as the numerous testosterone level check-ups and injection-type dosages prompted the physicians, in agreement with the patient, not to induce gonadotropins when less involving therapy is available. Selective estrogen receptor modulators (SERMs, e.g., clomiphene citrate, tamoxifen) are used off-label in male patients affected with hypogonadism to restore fertility. European Medicines Agency (EMA) approves Clomiphene in the treatment of ovulatory failure in women. Enclomiphene, which is a trans isomer of Clomiphene, is indicated in the treatment of hypogonadotropic hypogonadism in adult men with a BMI ≥25 kg/m$^2$ wishing to preserve testicular function and spermatogenesis [14]. It is, however, not available in Poland, thus it was not implemented into treatment in this case. SERMs are efficient only when patients have low LH and FSH, as they increase the production of those gonadotropins leading to an improvement of spermatogenesis [15]. Literature states studies where after 50 days of treatment using 50 milligrams of Clomiphene citrate every day, 90% of those examined presented a significant raise (≥11 nmol/L) in mean testosterone concentration. However, three months after discontinuation of Clomiphene citrate administration, 78% of those examined presented a decrease in mean testosterone levels again [16]. That is why a decision to continue therapy with Clomiphene citrate even after the improvement of LH, FSH, and testosterone levels was made. The last group of medications used in the treatment of hypogonadism in men are aromatase inhibitors. This group is represented by Anastrozole and Letrozole which act through inhibition of estradiol production, which leads to an increase in testosterone production. However, recent studies disadvise aromatase inhibitors in this indication, as they lack sufficiency as well as have some major adverse effects – they decrease bone mineral density [17].

## Conclusions

The treatment of hypogonadism is challenging, as not every patient reacts with such a significant improvement after a short period of medication. Despite the fact that Clomiphene citrate is not indicated for treatment of hypogonadism in men, the literature states multiple cases where this drug was used and its efficiency in restoring male fertility was proven. Taking that into consideration, it might be worth expanding indications for therapy with Clomiphene citrate to male patients with hypogonadotropic hypogonadism. In the presented patient, the improvement in hypogonadism symptoms was achieved after two weeks of treatment with Clomiphene. Keeping in mind the relatively low cost of treatment as well as the convenient (oral) administration, it might be worth implementing Clomiphene into treatment in other patients with secondary hypogonadism.

The presented case delivers more clinical data regarding the effectiveness of Clomiphene citrate in the treatment of infertile men and furthers this area of research, which may lead to an extension of indications for Clomiphene therapy in the future.

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