CASE REPORT

Clomiphene Citrate Treatment in Male Hypogonadism: A Case Report and Review

Na Shen, MD and Amy Chow, MD

Abstract

Male hypogonadism is characterized by testosterone deficiency and associated with a constellation of symptoms including fatigue, low libido, depressed mood, low concentration, and erectile dysfunction. Testosterone replacement therapy is the main treatment, however, has many limitations including multiple side effects, unclear cardiovascular risks, inability to preserve fertility, and no oral bioavailability. There are many alternative therapies to treat male hypogonadism. We present a case of a young man with hypogonadism treated effectively with clomiphene citrate.

Introduction

Male hypogonadism is one of the most common endocrine disorders in the world, affecting approximately 5 million men in the US alone.[1] Although hypogonadism typically presents in older men due to a gradual yearly decline of 1-2% in testosterone, this can affect young men causing infertility and sexual dysfunction.[1] Testosterone is the primary treatment and given via intramuscular injections, subcutaneous implants, and transdermal applications. (No oral testosterone replacement is available in the US.)

Side effects can include acne, gynecomastia, polycythemia, reduced fertility, and testicular atrophy. There is also controversy regarding the cardiac safety of testosterone replacement. Clomiphene citrate (CC) is a selective estrogen receptor modular (SERM) that has an antagonistic effect on the estrogen receptor at the level of the hypothalamus.[2] This results in increased gonadotropin-releasing hormones that stimulate the pituitary to increase luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion, which causes increased testosterone production in the testes.[2] CC is an oral agent that is FDA indicated for ovulation induction in female infertility, but multiple studies have demonstrated it as safe and effective to treat male hypogonadism.[1] We report a case of a young man with hypogonadism successfully treated with CC.

Case Report

Patient is a 27-year-old male who initially presented with low libido, fatigue and headaches. Patient was otherwise healthy and did not take any prescription medications including steroids or pain medications. Morning labs showed a total testosterone of 106 ng/dL (250-1100 ng/dL), free testosterone of 24.5 pg/mL (35-155 pg/mL), LH 9.7 mIU/mL (2-12mIU/mL), FSH 4.4 mIU/mL (1.6-9 mIU/ml), prolactin 8.4 ng/mL (3.8-18.9), and TSH 1.13 mIU/mL (0.4-4.5 mIU/mL). Patient completed a PHQ-9 screening with a score of eight that is consistent with mild depression. Pituitary MRI was negative for a supra-seller mass. Patient was interested in preserving his fertility and started on CC 25mg daily. He was also evaluated by his psychiatrist who placed him on anxiety medications. Repeat morning labs 3 months later showed total testosterone level of 639 ng/dL, free testosterone 99.8 pg/mL, LH 12 mIU/mL, and FSH 4.8 IU/mL. CC was reduced from daily to five days a week. He did not report any side effects and during this time interval, he was able to conceive a child with his wife. Morning labs 3 months later showed a total testosterone level of 643 ng/dL so patient was then placed on a protocol to wean off CC. His spouse was 6 months pregnant at the time. Unfortunately, the patient was lost to follow-up so there is no follow-up data.

Discussion

Male hypogonadism is becoming a health epidemic affecting almost 40% of men over the age of 45 as well as numerous younger men.[2] Although testosterone replacement is the most common treatment, it can be associated with multiple undesirable side effects, controversial cardiac risks, high costs and inconvenience in administration due to lack of oral bioavailability. CC is an oral pill that acts as a SERM to raise endogenous testosterone levels in men by inhibiting the negative feedback of estradiol to the hypothalamic-pituitary-gonadal axis. CC is currently being used off-label to treat male hypogonadism given several studies demonstrating its safety and efficacy.

CC effectively raises FSH, LH and testosterone levels in both older and younger men. Santen et al[3] evaluated 283 male patients (mean age 54.3 years) with hypogonadotropic hypogonadism treated with CC 50mg three times weekly for 4 months. Testosterone and LH levels improved in all the patients while erectile dysfunction improved in 75.1% of the subjects.[3] Another study by Katz et al[4] examined 86 men (mean age 29 years) with hypogonadism with infertility being the most common reason to seek treatment. 70% of the subjects were being treated with CC 25mg every other day while the remainder were using 50mg every other day for 19 months.[4] Mean testosterone and gonadotropin levels increased in all patients during treatment.[4] Subjective response to treatment using the androgen deficiency in aging males (ADAM)

questionnaire also showed more than half the patients had improvement in at least three symptoms.[4] Data also suggests a role for long term management of male hypogonadism with CC. Moskovic et al [5] assessed 46 men with hypogonadism (mean age 44 years) on CC treated for 12 months with follow up data up to 3 years. This study not only showed an improvement in testosterone levels and ADAM scores with long term follow up but also improvement in bone density scores.[5]

More importantly, multiple studies have shown that CC is not only effective but also safe and cost-effective. No major side effects were reported in any of the studies listed above. Minor side effects described may include nausea, dizziness, weight gain and fluid retention.[2] Although CC raises estradiol levels as demonstrated by several studies, neither gynecomastia nor breast tenderness have been reported.[1,4,5] Taylor and Levine[6] performed a comparative study assessing the biochemical, clinical efficacy and cost between CC and testosterone gel in 104 patients with secondary hypogonadism. The study found that the average costs of the daily testosterone gel averaged $265-270 monthly while CC given at 50mg every other day averaged $83 monthly.[6]

In conclusion, we report a young man with hypogonadism treated successfully with CC. Because the patient wished to preserve his fertility, testosterone therapy was not the ideal agent for him. The patient achieved significantly increased testosterone and LH levels after just 3 months of a standard CC regimen with no major side effects reported. He was even able to conceive with his spouse during this time interval. Although CC is currently being administered off-label to treat male hypogonadism, this medication should be considered in select patients with informed consent given its efficacy, safety and cost effectiveness profile.

REFERENCES

1. **Aydogdu A, Swerdloff RS.** Emerging medication for the treatment of male hypogonadism. *Expert Opin Emerg Drugs.* 2016 Sep;21(3):255-66. doi:10.1080/14728214.2016.1226799. Review. PubMed PMID: 27552127.
2 **Ramasamy R, Scovell JM, Kovac JR, Lipshultz LI.** Testosterone supplementation versus clomiphene citrate for hypogonadism: an age matched comparison of satisfaction and efficacy. *J Urol.* 2014 Sep;192(3):875-9. doi: 10.1016/j.juro.2014.03.089. Epub 2014 Mar 21. PubMed PMID: 24657837.
3. **Santen RJ, Leonard JM, Sherins RJ, Gandy HM, Paulsen CA.** Short- and long-term effects of clomiphene citrate on the pituitary-testicular axis. *J Clin Endocrinol Metab.* 1971 Dec;33(6):970-9. PubMed PMID: 5135636.
4. **Katz DJ, Nabulsi O, Tal R, Mulhall JP.** Outcomes of clomiphene citrate treatment in young hypogonadal men. *BJU Int.* 2012 Aug;110(4):573-8. doi: 10.1111/j.1464-410X.2011.10702.x. Epub 2011 Nov 1. PubMed PMID: 22044663.
5. **Moskovic DJ, Katz DJ, Akhavan A, Park K, Mulhall JP.** Clomiphene citrate is safe and effective for long-term management of hypogonadism. *BJU Int.* 2012 Nov;110(10):1524-8. doi: 10.1111/j.1464-410X.2012.10968.x. Epub 2012 Mar 28. PubMed PMID: 22458540.
6. **Taylor F, Levine L.** Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. *J Sex Med.* 2010 Jan;7(1 Pt 1):269-76. doi: 10.1111/j.1743-6109.2009.01454.x. Epub 2009 Aug 17. PubMed PMID: 19694928.

Submitted September 5, 2017