Clomiphene for hypogonadism complicated by polycythemia

Roshirl Francisco, BA^a , Sarah Jaroudi, BS^a , Mariam Murtaza Ali, MD^b, Jill Frost, PharmD^c, Rama Chemitiganti, MD^b, and Alan N. Peiris, MD, PhD^{a,d}

^aTexas Tech University Health Sciences Center School of Medicine, Lubbock, Texas; ^bDepartment of Internal Medicine, Texas Tech University Health Sciences Center School of Medicine at Permian Basin, Texas; ^cDepartment of Pharmacy Practice, Texas Tech University Health Sciences Center School of Pharmacy, Amarillo, Texas; ^dDepartment of Internal Medicine, Texas Tech University Health Sciences Center Clinical Research Institute, Lubbock, Texas; ^eDepartment of Internal Medicine, Texas Tech University Health Sciences Center School of Medicine, Lubbock, Texas

ABSTRACT

Male hypogonadism is associated with poor sexual function. Testosterone therapy via the intramuscular route is the preferred treatment but is associated with secondary polycythemia. We report a patient in whom clomiphene citrate improved hypogonadal symptoms and restored normal free testosterone levels. Clomiphene is inexpensive and can be given orally in secondary hypogonadism. Clomiphene citrate is a promising alternative in patients who develop secondary polycythemia with testosterone.

KEYWORDS Clomiphene; male hypogonadism; secondary polycythemia; testosterone replacement

Screening for male hypogonadism is prevalent. Treatment with testosterone replacement is associated with better bone mass, improved sexual function, and improved quality of life.¹ However, testosterone administration may induce secondary polycythemia.² We report a patient in whom clomiphene use was a successful alternative to testosterone.

CASE DESCRIPTION

A 45-year-old Caucasian man presented with decreased libido and erectile dysfunction. His past medical history included urethritis, depression, obesity, obstructive sleep apnea treated with a continuous positive airway pressure device, gastroesophageal reflux disease, hyperlipidemia, and hypertension. His medications were phentermine (37.5 mg) and lisdexamfetamine (40 mg) for weight loss, azilsartan (40 mg) for hypertension, methocarbamol (1500 mg) for muscle pain, sildenafil (100 mg) for erectile dysfunction, and testosterone (200 mg/mL intramuscularly) every 2 weeks for secondary hypogonadism. He reported polycythemia with a

previous higher dose of testosterone and one venesection. The patient had an intact sense of smell. He denied any substance abuse, illicit drug use, or over-the-counter testosterone supplements. His body mass index was 39.27 kg/m². He had lipomastia but no gynecomastia along with normal secondary sexual characteristics.

At the first visit, the patient's hemoglobin was 18.5 g/dL; hematocrit, 55% (normal range 38.8%–50%); and serum creatinine, 1.4 mg/dL (normal range 0.6–1.2 mg/dL). The testosterone was discontinued due to secondary polycythemia. Six weeks after discontinuing testosterone therapy, his hemoglobin was 16.1 g/dL and hematocrit was 49.5%. His follicle-stimulating hormone level was 8.6 mIU/mL; luteinizing hormone, 7.7 mIU/mL; prolactin, 10.5 ng/mL; and prostate-specific antigen, 1.3 ng/mL. He had a low total testosterone of 219 pg/mL (2.29 nmol/L) and a low free testosterone of 23.5 pg/mL (0.14 nmol/L).

Two months later, the patient was doing well off testosterone but still continued to have some sexual dysfunction. Magnetic resonance imaging with contrast of the head revealed no pituitary lesions. His hemoglobin was 15.8 g/dL

Corresponding author: Roshirl Francisco, BA, Department of Internal Medicine, Texas Tech University Health Sciences Center School of Medicine, 3601 4th Street, Lubbock, TX 79430 (e-mail: roshirl.francisco@ttuhsc.edu)

This report includes an off-label use of clomiphene.

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and hematocrit was 46.7%. The patient was started on clomiphene 25 mg daily, increasing after a few weeks to 50 mg daily based on suggested treatment guidelines. On clomiphene, his serum total testosterone level was 388 ng/dL (13.46 nmol/L) and free testosterone was 41.5 pg/mL (0.25 nmol/L) with an improvement in his libido and erectile dysfunction associated with hypogonadism.

DISCUSSION

Our patient had an increase in testosterone level with clomiphene and resolution of symptoms related to hypogonadism. There was no evidence of polycythemia with ongoing use of clomiphene. Prior testosterone therapy had resulted in development of polycythemia in our patient requiring venesection on at least one occasion. Discontinuing testosterone replacement therapy led to the resolution of the polycythemia. Our patient did not wish to consider testosterone administration again and was commenced on clomiphene citrate.

Clomiphene citrate is a selective estrogen receptor modulator. It has been primarily used for infertility treatment in both genders for over 50 years. In the context of male hypogonadism, it works to inhibit negative feedback to promote gonadotropin-dependent testosterone secretion by the testes.³ It selectively blocks estrogen receptors in the hypothalamus and pituitary, thereby increasing gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone release. This boosts endogenous testosterone levels. It also can raise estrogen levels, leading to side effects such as gynecomastia and hypertriglyceridemia. Clomiphene has been successful in raising testosterone levels in a variety of hypogonadal states, including hemodialysis.⁴ However, there is evidence that clomiphene may be unsuccessful in raising testosterone levels in conventionally treated nonfunctioning pituitary adenomas.⁵ Given its mechanism of action, clomiphene is not likely to be efficacious for primary hypogonadism.

Ramasamy et al reported that clomiphene achieved testosterone levels comparable to those of testosterone gels.⁶ Testosterone levels with clomiphene were lower than those obtained after intramuscular injections. These investigators also reported greater libido in men receiving intramuscular testosterone compared to clomiphene and gel testosterone. However, overall symptomatic relief was similar between clomiphene and testosterone replacement. In contrast, other investigators reported that the magnitude of the testosterone increase with clomiphene was comparable to that of testosterone administered through gels.⁷ Clomiphene was reported to raise sperm count more effectively than the gel formulation of testosterone, considering that testosterone decreases spermatogenesis.

There is a limited amount of research concerning long-term clomiphene citrate use in male hypogonadism, considering that it is an off-label use. Katz et al, in a prospective study of clomiphene over 19 months, reported safety and efficacy in treating hypogonadism in young men.⁸ Chandrapral et al

found that the drug significantly increased testosterone levels without changing prostate-specific antigen or hematocrit values.⁹ Wheeler et al came to a similar conclusion when they compared rates of polycythemia after use of either testosterone or clomiphene.¹⁰ Moskovic et al reported improved bone mineral density after clomiphene treatment.¹¹ Clomiphene is a less expensive alternative to testosterone replacement with the added benefit on fertility. Clomiphene analogs such as enclomiphene and zuclomiphene may emerge as having a role but are not yet approved by the Food and Drug Administration.

The patient's symptoms of hypogonadism improved and he did not experience polycythemia on clomiphene. Patient satisfaction may be increased in those taking clomiphene compared to those taking testosterone replacement therapy. In patients who develop polycythemia with testosterone replacement, offering clomiphene should be considered over venesection. We do recommend that testosterone values be monitored on clomiphene.

Clomiphene is a cost-effective treatment for secondary hypogonadism once a pituitary tumor has been excluded by magnetic resonance imaging. Long-term studies of clomiphene treatment for male hypogonadism are needed. It remains a viable option in patients who develop secondary polycythemia on testosterone replacement. We believe that it is a better option than serial venesections to deal with secondary polycythemia associated with testosterone replacement.

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ORCID

Roshiri Francisco <http://orcid.org/0000-0002-5710-2011>

Sarah Jaroudi <http://orcid.org/0000-0003-2737-4128>

Alan N. Peiris <http://orcid.org/0000-0001-9323-7557>

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Avocations

“San Antonio” by Jay Hoppenstein, MD. Dr. Hoppenstein (e-mail: navigato@aol.com) is a surgeon who was on the medical staff at Baylor University Medical Center at Dallas from 1971 until his retirement in 2005. He also served as chairman of the Department of Surgery at Presbyterian Hospital of Dallas.