

## ORIGINAL RESEARCH

## A Randomized Prospective Double-Blind Comparison Trial of Clomiphene Citrate and Anastrozole in Raising Testosterone in Hypogonadal Infertile Men

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### ABSTRACT

**Aim.** Clomiphene citrate (CC) and anastrozole (AZ) have been used off label to increase testosterone (T) in hypogonadal infertile men (HIM). Both medications have been shown to increase T with different effects on estradiol (E2) and T-to-E2 ratios. There are no reported randomized trials comparing CC and AZ to improve T levels in HIM. We aimed to establish equivalence of CC vs. AZ with respect to improvement in T levels in HIM.

**Methods.** We randomized 26 HIM (T less than 350 ng/dL and normal luteinizing hormone [LH]). Patients were randomized to CC (25 mg/day) or AZ (1 mg/day) for 12 weeks. Hormones assayed were total T, free T, E2, LH, follicle stimulating hormone (FSH), and sex hormone binding globulin (SHBG). Patient-reported outcomes were the International Index of Erectile Function, Erection Hardness Scale, and the Androgen Deficiency in the Aging Male questionnaires. Blood tests and questionnaires were recorded at baseline, 6 and 12 weeks. Semen analyses were performed at baseline and 12 weeks.

**Results.** T increased significantly from baseline in both groups at 6 and 12 weeks. There was a significantly larger increase in T and mean increase from baseline in CC vs. AZ (571 vs. 408 ng/dL, respectively). Whereas E-2 levels increased in the CC group, they decreased in the AZ group. Though both groups demonstrated an increase in T-to-E-2 ratio from baseline, statistic significance at 6 and 12 weeks was only achieved with AZ. Neither group demonstrated significant changes in seminal parameters or patient-reported outcomes.

**Conclusions.** We failed to demonstrate equivalence of CC vs. AZ. CC resulted in significantly higher T levels than AZ. AZ resulted in a significantly larger increase in T/E-2 ratio than CC. No significant differences between CC and AZ on seminal parameters or patient-reported outcomes were demonstrated. **Helo S, Ellen J, Mechlin C, Feustel P, Grossman M, Ditkoff E, and McCullough A. A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men. J Sex Med 2015;12:1761–1769.**

**Key Words.** Hypogonadism; Testosterone; Anastrozole; Clomiphene Citrate; Infertility

### Introduction

Hypogonadism affects a significant number of men over the age of 30. In a US population-based observational study of over 1,400 men, the prevalence of symptomatic androgen deficiency in

men age 30–79 years was reported at 5.6% [1]. Although a 1997 retrospective study reported that endocrine malfunctions as the primary cause of male infertility were rare [2], the prevalence of low testosterone (T) (<300 ng/dL) in infertile men has been reported to be as high as 41% and does not

always correlate with impaired seminal parameters or classic hypogonadal symptoms [3]. T is important in normal spermatogenesis [4] and its deficiency can have significant adverse effects on glucose metabolism, cardiovascular health, bone density, muscle deposition, and erectile function long after a pregnancy is achieved [5,6]. While symptomatic hypogonadism in adults is most often treated by T replacement, T replacement can have deleterious effects on spermatogenesis.

Spermatogenesis is dependent on the maintenance of high levels of intratesticular T as well as Sertoli cell stimulation via the hypothalamic–pituitary axis [7,8]. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary result in Sertoli cell stimulation and Leydig cell T secretion, respectively [9]. Aromatase is a cytochrome P-450 enzyme that converts T to estradiol, which subsequently exerts a potent negative feedback effect on both T production and spermatogenesis at both the pituitary and hypothalamic level by inhibiting LH and FSH release [9,10].

Medical therapy for male infertility is frequently aimed at inhibiting the negative feedback of estrogens on the hypothalamic–pituitary axis to promote T production and increase LH and FSH levels. The selective estrogen receptor modulator (SERM) clomiphene citrate (CC), and the aromatase inhibitor (AI) anastrozole (AZ) are two of these therapies used, off label, in the hypogonadal infertile male (HIM). CC functions by blocking the negative feedback of E2 on the hypothalamus and pituitary [11], whereas AZ limits E2 production by reducing testicular and peripheral conversion of T to E2. Because of these mechanisms, each has a different effect on T-to-E2 ratios while stimulating gonadotropin and T secretion.

CC has been used since the 1960s to treat female infertility with good success. Its use, largely in the management of idiopathic male infertility, since the 1970s has produced mixed results [12–16]. In observational studies, AI's have been used predominantly in HIM and have been shown to improve sperm quality with increases in T [17–19]. Low T-to-E2 ratios have been proposed as a marker for severe male factor infertility in the HIM population. A study by Pavlovich et al. characterized the T-to-E2 ratios in men with severe male factor infertility as compared with age-matched controls. They found improved semen analysis associated with T-to-E2 ratio above ten after administering the AI testolactone [17]. They concluded that normalizing T and increasing

T-to-E2 ratios are important in improving male fertility in HIM.

Although previous studies have shown that CC and AZ are effective at increasing T as compared with placebo [14–19], a randomized double-blind study comparing the effects of CC and AZ hormonal production in the HIM has never been performed. In this study we aimed to show equivalence of CC and AZ in increasing the serum T in HIM.

## Methods

### Patient Selection

We designed a prospective double-blind randomized equivalence trial, of 26 men who presented to the Urological Institute of Northeastern New York between 2013 and 2014 with male infertility, defined as the inability to conceive after 1 year, and hypogonadism, defined as serum T less than 350 ng/dL and LH (between 1.2 and 8.6 mIU/mL). This study was approved by the Albany Medical Center Institutional Review Board. Eligible subjects included men between the ages of 18 and 50 with a baseline morning total T between 150 and 350 ng/dL, as determined by the average of two consecutive morning measurements 1 week apart. Men were excluded for a sperm count less than 1 million, a body mass index greater than 40, hematocrit less than 36% or greater than 52%, history of prostate specific antigen greater than 4.0 ng/dL, history of chronic opioid use, intravenous or inhaled steroid use within the previous 3 months, or use of drugs known to affect steroid hormone or sex hormone binding globulin (SHBG) levels. Additional exclusion criteria included known testicular or pituitary disease, history of prostate cancer or severe benign prostatic hypertrophy. All patients with varicoceles were offered repair but declined in favor of inclusion in the study. All CONSORT guidelines for a randomized trial were followed.

### Treatment

Men were randomized by a computer-generated assignment in a blinded 1:1 ratio to receive either AZ 1 mg daily or CC 25 mg daily for a total of 12 weeks. The capsules were blinded to the patients and investigators by placing them in inert capsules by the Albany Medical Center pharmacy. Medical staff was also blinded to the treatment patients received. Subjects were seen in clinic at baseline, and then at 6 and 12 weeks of treatment. All

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