REVIEW

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Clomiphene Citrate for Male Hypogonadism and Infertility: An Updated Review

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Abstract

Clomiphene citrate (CC) is a selective estrogen receptor modulator, originally developed in 1956 and introduced into clinical medicine in 1967 for the treatment of female infertility. CC has also been explored for off-label use for male infertility and male hypogonadal symptoms. This article will review the medical literature on CC and its contribution to the treatment of male hypogonadism. A comprehensive review of the literature pertaining to CC through April 2020 was performed through PubMed. We included 52 articles that were relevant to CC. Abstracts and case reports were not included in this comprehensive review. CC as a monotherapy, as well as CC combined with vitamins and other non-Food and Drug Administration-approved substances, has been shown to have mixed results in improving male factor infertility. A variety of questionnaires have been used to describe changes in hypogonadal symptoms with CC treatment. Articles have reported conflicting outcomes regarding improved hypogonadal symptoms with CC treatment. CC is generally considered a safe drug, and the majority of CC studies do not report any significant side effects. Side effects that have been reported include headache, gynecomastia, visual disturbances, dizziness, and mood instability. CC is regarded as an effective therapy for specific patients who suffer from male factor infertility and complain of hypogonadal symptoms. More studies are needed to further validate CC's efficacy for male infertility and hypogonadism.

Keywords: clomiphene citrate; hypogonadism; testosterone; drug treatment; clomid

Introduction

The prevalence of male hypogonadism is estimated to be between 2% and 13% of the adult male population in the world.¹ Incidence rises with age, with up to 40% of men aged ≥ 45 years diagnosed with hypogonadism through various testosterone assays.² In middle-aged men, total testosterone is approximated to have a 0.8–1.6% yearly decline.³ Decreased libido, depressed mood, lack of energy, diminished mental concentration, erectile dysfunction, and decreased muscle mass are common presenting complaints of hypogonadal men.⁴

The most common treatment for hypogonadism in men is testosterone replacement therapy (TRT), which

has seen a significant increase in recent years. A 2013 study by the Food and Drug Administration (FDA) observed that the number of TRT prescriptions had increased from 1.2 to 2.2 million patients over 2009–2012 (12.4% of these patients were ≤ 39 years).⁵ Side effects of exogenous TRT are significant and include male infertility, testicular atrophy, gynecomastia, secondary polycythemia, and acne.⁶ TRT impairs fertility by suppressing spermatogenesis, as well as endogenous testosterone production. The mechanism of this is suppression of the hypothalamic-pituitary-gonadal (HPG) axis, thereby decreasing production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).⁶ The American

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Urological Association (AUA) 2018 guidelines recommend that men with testosterone deficiency, but who are still interested in fertility, undergo a reproductive evaluation in which they are also made aware of the long-term impact of exogenous testosterone on spermatogenesis and fertility.⁷ Clomiphene citrate (CC) is an off-label treatment for hypogonadism and is among the drugs conditionally supported by AUA guidelines in the treatment of hypogonadal men who desire to preserve fertility.⁷

This communication reviews the published medical literature on CC and its contribution to the treatment of male hypogonadism.

Materials and Methods

We performed a comprehensive literature search using PubMed through April 2020, using keywords such as *clomid*, *CC*, *hypogonadism*, *infertility*, *symptoms*, and *testosterone*. The list of publications was reviewed independently by two authors (B.J.H. and H.M.T.N.) and conflicts regarding inclusion were resolved by examining the full text and discussion among the authors. For the purpose of this review, only full-text publications were included. Case reports and abstracts were excluded from this review. Articles in languages other than English were also excluded. Figure 1 shows the pathway for our literature search and selection of the included studies.

Background

CC is a selective estrogen receptor modulator that was originally developed by Frank Palopoli and his colleagues at the William S. Merrell Company in 1956 as a potential contraceptive. It was then discovered to aid in fertility in women and first introduced into clinical medicine around 1967. The FDA initially approved this drug to promote ovulation in patients with anovulatory conditions, such as polycystic ovarian syndrome, but the drug was also observed to increase the sensitivity of ovarian cells to pituitary hormones.⁸ The innovations in the treatment of female infertility provided a better understanding of CC's effect on the HPG axis, and the drug was later explored for off-label use for male factor infertility.⁹ Since its introduction to the area of male infertility, CC has also contributed to the treatment of symptoms associated with hypogonadism.

Mechanism of Action

The HPG axis in males includes the hypothalamus, the anterior pituitary gland, and the testicles. Gonadotropin-releasing hormone (GnRH) is produced from the hypothalamus, which stimulates the production of LH and FSH in the anterior pituitary gland. LH and FSH released from the anterior pituitary promote the production of testosterone and spermatogenesis. Testosterone is then converted to estradiol by the aromatase enzyme.

FIG. 1. Literature review methodology.

Estradiol in the normal physiological state exhibits part of the negative feedback mechanism on the reproductive axis by binding to the hypothalamus, which inhibits the continuous release of GnRH. CC competes with estradiol at the hypothalamic receptor level, specifically located on the anterior hypothalamus and hypophysis, which blocks the negative feedback mechanism and results in increased GnRH. CC has a half-life of 5 days and is an isomer that consists of two compounds, 38% zuclophene (cis-isomer) and 62% enclomiphene, which are both excreted through the intestines.⁸ Zuclophene is both a partial estrogen agonist and estrogen antagonist, whereas enclomiphene is completely antiestrogenic. Unlike testosterone, both compounds do not suppress the HPG axis, but actually lead to an increase in LH and FSH, which results in an increased production of intratesticular testosterone by the Leydig cells and the promotion of spermatogenesis.^{9,10}

Enclomiphene alone, which is a pure estrogen antagonism unlike the combination in CC, has also been investigated as a therapeutic alternative to treat hypogonadism. Wiehle et al.¹¹ evaluated its effectiveness on spermatogenesis and documented that all of the hypogonadal patients treated with enclomiphene 25 mg daily remained normospermic by the end of treatment. In a randomized controlled trial, Kim et al.¹² documented no significant differences in sperm parameters between enclomiphene and placebo in hypogonadal men over a 5-month treatment period.

CC is also recognized to affect the testosterone-to-estrogen (T:E) ratio. An increase in this ratio is postulated to improve fertility potential by preventing the negative effects of estrogen on the hypothalamus. Increased estrogen and aromatase activity in the testicles theoretically decreases sperm counts and increases the likelihood of embryo loss before and after egg implantation into the uterus.^{13,14} Anastrozole (AZ) is also an effective treatment in lowering estrogen levels for patients by blocking the conversion of T:E facilitated by the aromatase enzyme, which leads to an increased T:E ratio. Sperm concentration and motility have been documented to improve in hypogonadal men who had optimized T:E ratios after 5 months of AZ treatment.^{15,16} A prospective study revealed an increase in the T:E ratios by 60.9% at 12 weeks of 25 mg daily of CC treatment, with a more significant rise in T:E in ≥ 40 -year-old men when compared with those < 40 years old.¹⁷ A retrospective cohort study determined that patients who had a baseline estradiol of ≥ 18.5 pg/mL and a body mass index (BMI) ≥ 29 should

have AZ combined with CC 50 mg every other day to maintain a T:E > 10 and estradiol levels < 50 pg/mL.¹⁸

Use for Infertility

It has been reported in a number of studies that CC restores fertility in hypogonadal patients by exhibiting increases in sperm concentration. Table 1 summarizes the significant studies for the treatment of male infertility with CC. There has been several randomized controlled trials to address this question. Ronnberg,¹⁹ observed, in a randomized double crossover study, an increase in sperm count when patients were prescribed 50 mg CC daily. In a World Health Organization trial including 190 infertile couple treated with daily dose of 25 mg CC, the study observed a statistically significant increase in sperm concentration at 4 months in the CC group, but reported no significant increase in pregnancy rate and no other changes in sperm parameters with CC treatment.²⁰ Wang et al.²¹ and Micic and Dotlic²² also demonstrated an increase in sperm concentration when receiving CC therapy. A retrospective cohort study evaluating sperm concentrations in hypogonadal infertile men with type 2 diabetes mellitus documented a significant increase in sperm concentration after 3 months of treatment with CC 50 mg every other day plus metformin compared with placebo plus metformin.²³ Hussein et al.²⁴ demonstrated that infertile men who are severely oligospermic have a higher likelihood of successful microscopic testicular sperm extraction after 9 months of CC treatment when compared with placebo.

There have also been a number of studies that reported CC having no significant effect on sperm parameters. Sokol et al.²⁵ randomly assigned 23 hypogonadal men to either CC 25 mg daily or placebo, and no significant changes in sperm parameters were observed between the two treatment groups in a 12-month period. A double-blinded randomized controlled trial did not demonstrate a significant increase of sperm parameters in hypogonadal infertile men prescribed CC, although the majority of men included in this study were not oligospermic at baseline, and more than half of the individuals had varicoceles.²⁶ Another retrospective cross-sectional did not demonstrate a significant increase in sperm parameters in 47 hypogonadal men after 3 months of treatment with CC 50 mg every other day.²⁷ In one randomized controlled trial, there were no significant changes in serum anti-Müllerian hormone and inhibin levels in hypogonadal men with metabolic syndrome who were treated with CC 25 mg

Table 1. Summary of Studies for Treatment of Infertility with Clomiphene Citrate

Study	Year	Study design	Number of subjects	Treatment regimen	Study duration	Primary outcome in CC group
Ronnberg ¹⁹	1980	Double-blind crossover study	30	CC 50 mg daily 3 months×2 with 3 months washout in between	9 Months	Higher sperm count in CC group
Micic and Dotlic ²²	1985	RCT	101	CC 50 mg daily	6–9 Months	Improvement in sperm volume, density, and motility
Sokol et al. ²⁵	1988	RCT	23	CC 25 mg daily	3 Months	No difference in sperm volume, density, and motility
World Health Organization ²⁰	1992	RCT	190	CC 25 mg daily	3 Months	No difference in pregnancy rate. No change in sperm parameters
Wang et al. ²¹	1993	RCT	46	CC 25 mg or CC 50 mg daily	6 Months	Increased sperm count in CC group
Hussein et al. ²⁴	2012	Prospective cohort	488	Titrated CC dose until T is 600–800 ng/dL	3 Months	Higher probability of successful sperm extraction with micro-TESE
ElSheikh et al. ³⁰	2015	RCT	90	CC 25 mg daily or vitamin E 400 mg daily	3–6 Months	Significant increase in sperm concentration in CC group over 3-month intervals
Helo et al. ²⁶	2015	RCT	26	CC 25 mg daily	12 Weeks	No difference in sperm concentration
Surbone et al. ²³	2020	Retrospective cohort	18	CC 50 mg every other day	3 Months	Improvement in sperm concentration

CC, clomiphene citrate; micro-TESE, microscopic testicular sperm extraction; RCT, randomized controlled trial; T, testosterone.

daily for 3 months; however, the majority of the men in this study had at least one child in the past, and normal sperm parameters.²⁸

Vitamins and other non-FDA-approved nutritional supplements have also been studied in regard to pregnancy rates and sperm parameters when combined with CC treatment. Reactive oxidative agents have been determined to alter sperm production and sperm quality, and the use of vitamins may have beneficial effects on patients who suffer with infertility.²⁹ ElSheikh et al.³⁰ performed a prospective cohort study evaluating effects of CC and vitamin E on sperm parameters on hypogonadal oligoathenospemic men. The study observed a significant increase in sperm concentration in patients receiving CC, and an even greater increase in sperm concentration when individuals were taking both CC and vitamin E.³⁰ A double-blinded randomized controlled trial of 60 infertile men with an average duration of infertility of 4.5 years demonstrated an increase in pregnancies with the treatment group, which received CC 25 mg daily plus vitamin E 400 mg daily, at a 3- to 6-month follow-up period versus the placebo group (36.7% vs. 13.3%).³¹ In another randomized controlled trial, sperm parameters were evaluated between individuals on a treatment regimen of CC 50 mg daily or 200 mg vitamin C and found no significant difference between the treatment group's rates of pregnancies overall. This study did report an increase in pregnancy rates with individuals taking CC who had a duration of infertility of <18 months before initiating treatment.³² An additional randomized control trial saw investigators document that men who received

CC or L-carnitine experienced an increase in sperm motility compared with the placebo group.³³

CC Use for Men with Hypogonadism

Studies have shown that the use of CC significantly improves hypogonadal symptoms assessed by answer to various questionnaires. Table 2 summarizes the significant studies for the treatment of hypogonadal symptoms with CC. Guay et al.³⁴ used rigidity tests and the international index of erectile function/sexual health inventory for men (SHIM) to assess response to CC therapy. This study did not demonstrate significant changes in sexual function nor rigidity in the entire cohort, but a subset analysis noted that younger men (mean age 53 years), as well as men without diabetes and hypertension, had improved rigidity and sexual function with CC treatment versus placebo.³⁴ The same researcher also demonstrated in one other study that men ≤55 years and younger were 2.3 times more likely to have a positive response to CC treatment compared with men who were >55 years. A positive response was defined as completing intercourse in >50% of attempts.³⁵ In another study, investigators did not observe improvement in SHIM scores after 1 year of treatment with CC. Other outcomes that were observed in hypogonadism included increased BMI and a decline in bone density.³⁶ Also, the use of CC has demonstrated improved bone density and decreased BMI in hypogonadal individuals over a 3-year treatment period.³⁷

The androgen deficiency in aging males (ADAM) questionnaire was utilized in a majority of studies to evaluate CC and its effect on hypogonadal symptoms.

Table 2. Summary of Studies for Treatment of Hypogonadal Symptoms with Clomiphene Citrate

Study	Year	Study design	Number of subjects	Treatment regimen	Study duration	Primary outcome in CC group
Guay et al. ³⁴	1995	Double-blind crossover	17	CC 50 mg every other day × 2 months with 2 weeks washout in between	5 Months	No difference in sexual function or nocturnal tumescence and rigidity
Guay et al. ³⁵	2003	Retrospective cohort	228	CC 50 mg every other day	4 Months	Men <55 years old more likely to successfully complete sexual intercourse
Taylor and Levine ⁴¹	2010	Retrospective cohort	22	Titrate CC dose until T is 550 ng/dL	23–46 Months	Improvement in ADAM score
Moskovic et al. ³⁷	2012	Retrospective cohort	46	CC 25 mg every other day	12–36 Months	Improvement in ADAM score
Katz et al. ⁴²	2012	Retrospective cohort	86	Titrate CC dose until T ~ 550 ng/dL	6 Months	Improvement in ADAM score
Ramasamy et al. ⁴⁷	2014	Cross-sectional	93	CC 25 mg daily or TRT	N/A	Improvement qADAM score seen in CC and TRT
Helo et al. ²⁶	2015	RCT	26	CC 25 mg daily	12 Weeks	No difference in ADAM or IIEF
Chandrapal et al. ³⁶	2016	Retrospective cohort	77	CC 50 mg every other day	12 Months	Improvement in ADAM score, but not SHIM score
Habous et al. ⁴⁶	2017	RCT	95	CC 50 mg daily or 5000 IU hCG twice/week	3 Months	Improvement in qADAM score
Soares et al. ⁴³	2018	RCT	78	CC 50 mg daily	12 Weeks	No improvement in ADAM score

ADAM, androgen deficiency in aging males; hCG, human chorionic gonadotropin; IIEF, International Index of Erectile Function; IU, international units; N/A, not applicable; qADAM, quantitative ADAM; SHIM, sexual health inventory for men; TRT, testosterone replacement therapy.

This questionnaire has a reported sensitivity and specificity of 97% and 30%, respectively, with false positives when hypogonadal patients report depression.^{38–40} Taylor and Levine⁴¹ evaluated changes in hypogonadal symptoms in individuals treated with CC or testosterone gel by utilizing the ADAM score. Both groups achieved testosterone levels ~ 550 ng/dL and reported improvement in libido by exhibiting a decrease in ADAM score.⁴¹ Katz et al.⁴² evaluated a cohort of 86 hypogonadal men prescribed 50 mg CC every other day. This study demonstrated improvement in ADAM score after 6 months of treatment, and found no differences in symptom response to CC treatment in patients with varicoceles versus patients with no varicoceles.⁴² Patients have also demonstrated a significant improvement in ADAM scores after 1 year of receiving CC 50 mg every day or every other day.³⁶ One group of investigators performed a double-blind randomized controlled trial that evaluated changes in hypogonadal symptoms in obese hypogonadal men after 3 months of receiving CC versus placebo. This study did not record a significant difference between ADAM score improvement.⁴³ Another randomized controlled trial evaluating changes in hypogonadal symptoms between CC and AZ treatment did not show significant improvement in ADAM scores after 3 months in either treatment group.²⁶

The quantitative ADAM (qADAM) questionnaire was developed in 2010 to provide numerical values to

the original ADAM questionnaire. A higher numerical score was associated with lower likelihood of hypogonadal symptoms when compared with total testosterone. No specific cutoff values were established to distinguish between positive and negative qADAM scores. The qADAM score also had a positive correlation with total testosterone and with SHIM scores.⁴⁴ Dadhich et al.⁴⁵ evaluated changes in hypogonadal symptoms after 3 months of receiving CC or TRT, and observed a significant improvement in qADAM scores in both the CC and TRT group. Investigators, through a randomized controlled study, also reported that CC and human chorionic gonadotropin therapy both improved qADAM score when these treatment regimens were used separately or as a combination.⁴⁶ Ramasamy et al.⁴⁷ conducted a cross-sectional study that demonstrated an improvement in qADAM score with both CC 25 mg daily and TRT, and did demonstrate a statistically significant difference between the two treatment regimens. Sertoli cell function has also been studied in hypogonadal men treated with CC by measuring serum inhibin and anti-Müllerian hormone. A retrospective cohort study revealed increased serum inhibin levels after treatment with CC 50 mg every other day for 3 months.²³

There is an issue on whether or not the ADAM questionnaire is proven to be a useful tool for monitoring hypogonadal symptoms in the setting of CC treatment, especially when the test was originally used to monitor

hypogonadal systems, when specially using bioavailable testosterone.³⁸ The majority of studies included in the literature that utilized the ADAM questionnaire were based on their definition of testosterone deficiency on total serum testosterone rather than bioavailable serum testosterone. Studies have demonstrated the inability to distinguish between individuals who had a positive or negative ADAM score when measuring total testosterone.^{39,48}

In our practice, we obtain baseline laboratory values before starting the CC. Those include testosterone, estrogen, FSH, and LH. Then we start the lowest dose, which is 25 mg every other day since patients respond differently. We recheck the laboratory values in 6–8 weeks and we titrate based on the response to these laboratory values, gradually going up to a maximum of 50 mg daily depending on the response.

Adverse Effects

CC is generally regarded by investigators to be a tolerable drug in clinical practice.⁶ There have not been many studies investigating the adverse effects of CC in men, especially in comparison with TRT. Most studies reported no major side effects of CC while investigating its efficacy.^{17,21,47,49} Side effects reported with CC treatment include headache, gynecomastia, visual disturbances, dizziness, and mood instability.^{6,20,25,36} When compared with TRT in a multi-institutional retrospective study of 363 patients, Wheeler et al. noted that CC had lower prevalence of secondary polycythemia than TRT (1.7% compared with 11.2%); no men in the CC arm had a hematocrit high enough to necessitate phlebotomy.⁵⁰ In their study of 104 men, Taylor and Levine⁴¹ investigated the long-term safety and efficacy of CC versus testosterone gel and noted that CC did not significantly increase cholesterol, PSA, or hemoglobin. Chandrapal et al.³⁶ reported no effect of CC on PSA and hematocrit in their study of 77 patients on CC. One case reported switching TRT to CC in a patient with secondary polycythemia on TRT. This patient did not subsequently exhibit polycythemia on CC.⁵¹ Recently, Kavoussi et al.⁵² investigated the risk of deep vein thrombosis (DVT) in 1180 hypogonadal men either on TRT or CC and reported that only 1 out of 486 patients on CC developed DVT compared with 9 out of 694 patients on TRT. In a prospective study of 125 hypogonadal men on CC, Da Ros and Averbek⁴⁹ did not find statistically significant differences when comparing pre- and post-treatment high-density lipoprotein-cholesterol, triglycerides, fasting

plasma glucose, and prolactin levels. These studies highlight the safety of CC, especially compared with TRT regarding secondary polycythemia and DVT risks.

Conclusion

CC is regarded as a useful treatment for men who suffer with both infertility and hypogonadal symptoms. CC is generally regarded as safe to prescribe to hypogonadal patients, which is highlighted in the majority of studies. There are mixed results in regard to CC treatment and its effect on sperm parameters throughout the literature. This could be due to the fact that CC is considered an off-label drug for the treatment of infertility and hypogonadism. Since CC is not FDA approved for male hypogonadism, there are no clear guidelines that dictate the correct dosage and frequency of CC treatment. There are also different inclusion and exclusion criteria that qualify subjects to be entered into each study. CC also has mixed results when its used for treating hypogonadal symptoms, which can be attributed to the poor diagnostic accuracy of the ADAM questionnaire. Overall, more studies that consist of criteria that are universally accepted by the male sexual health community would further validate CC's efficacy for infertility and hypogonadism.

Authors' Contributions

Conception and design were by W.J.G.H.; data acquisition and analysis were done by B.J.H. and H.M.T.N.; drafting of article by B.J.H., H.M.T.N., and A.S.; revising the article was by W.J.G.H.; approval by all authors.

Author Disclosure Statement

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Abbreviations Used

ADAM	= androgen deficiency in aging males
AUA	= American Urological Association
AZ	= anastrozole
BMI	= body mass index
CC	= clomiphene citrate
DVT	= deep vein thrombosis
FDA	= Food and Drug Administration
FSH	= follicle-stimulating hormone
GnRH	= gonadotropin-releasing hormone
hCG	= human chorionic gonadotropin
HPG	= hypothalamic-pituitary-gonadal
IIEF	= International Index of Erectile Function
IU	= international units
LH	= luteinizing hormone
micro-TESE	= microscopic testicular sperm extraction
qADAM	= quantitative ADAM
RCT	= randomized controlled trial
SHIM	= sexual health inventory for men
T:E	= testosterone-to-estrogen
TRT	= testosterone replacement therapy

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