

## Opinion Article

### Prescription Strategies of Clomiphene Citrate in Male Hypogonadism and Fertility

**Comment [WU1]:** The topic can be more appealing, see suggestions in the reviewer's comments

#### Abstract:

**Comment [WU2]:** 1. Can the modalities reviewed be clearly stated at the beginning of the abstract for example.. This article seeks to appraise three practical approaches to CC prescription which includes the pulse protocol, low dose protocol and its combination with other agents.  
2. Kindly keep the abstract under 200 words (currently about 270 words)

Clomiphene Citrate (CC), a selective estrogen receptor modulator, represents a valuable therapeutic option for addressing male hypogonadism and infertility. This article reviews practical approaches to CC prescription, emphasizing its use both as monotherapy and in combination with other treatments. Clinical evidence consistently demonstrates that relatively low doses of CC, ranging from 12.5 to 50 mg daily or on alternate days, are sufficient to elevate testosterone levels, relieve symptoms of androgen deficiency, and improve fertility markers such as sperm concentration and total motile sperm count (TMSC). Importantly, higher doses, while reported in some studies, appear to offer no additional benefit and may increase the risk of adverse effects.

For more complex clinical scenarios, such as elevated estradiol levels or an unfavorable testosterone-to-estradiol ratio, combination therapies provide a targeted solution. The addition of Anastrozole (AZ) can help mitigate estradiol elevations, optimizing the hormonal balance while maintaining the therapeutic effects of CC. Similarly, combining CC with human chorionic gonadotropin (hCG) has shown promise in enhancing testosterone levels while preserving spermatogenesis. However, adherence challenges associated with frequent injections and cost must be considered when prescribing combination therapies. Notably, improved TMSC observed in these combination approaches suggests potential advantages for men pursuing assisted reproductive techniques.

Overall, CC stands out as an effective, safe, and affordable alternative to traditional testosterone replacement therapy, particularly for hypogonadal men seeking to maintain fertility. Its versatility and favorable safety profile makes it a practical choice, especially in younger populations. While current evidence supports its clinical utility, further well-designed studies are essential to refine treatment protocols,

**Comment [WU3]:** Kindly summarize and further compress this paragraph

**Comment [WU4]:** This should read "makes"

assess long-term outcomes, and better identify patient subgroups that would derive the greatest benefit from this approach.

**Keywords:**

Clomiphene Citrate, hypogonadism, male infertility, testosterone replacement therapy, gonadotropins, polycythemia

**Comment [WU5]:** Kindly expunge this word as it does not feature in the entire article. Elevated hematocrit as one of the side effects under CC-AZ combined protocol in the body of the review does not necessarily translate to polycythemia

**Introduction:**

Clomiphene Citrate (CC), a compound utilized in medical practice since the 1970s, belongs to the class of Selective Estrogen Receptor Modulators (SERMs). It is composed of a racemic mixture of the trans isomer **enclomiphene** and the cis isomer **zuclomiphene** [1]. The pharmacological effect of CC is primarily mediated through its antagonistic action on estrogen receptors located in the hypothalamus and pituitary gland. By competitively inhibiting estrogen binding at these sites, CC promotes an increase in the secretion of gonadotropin-releasing hormone (GnRH), which in turn stimulates the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [1].

Although its use in male patients remains largely off-label, Clinical trials registry databases (Clinicaltrials.gov) present multiple controlled studies, including phase 1 (NCT01923857, NCT02274181, NCT01923870), phase 2 (NCT01155518, NCT03933618, NCT01270841, NCT01904734, NCT00697814, NCT02380755, NCT02651688, NCT03245827, NCT01191320, NCT01386606), and phase 3 (NCT01739582, NCT01534208, NCT01619683, NCT00962637, NCT01067365, NCT01993225, NCT01993212), that have evaluated the safety and efficacy of CC or its isomer enclomiphene in the treatment of hypogonadism and infertility [2]. These studies have been conducted across diverse clinical contexts of hypogonadism and infertility, including conditions such as diabetes mellitus, obesity, and chronic pain [2].

Indeed, recent systematic reviews and meta-analyses have been published, reporting positive outcomes with the use of CC for male hypogonadism and infertility [3-7]. The prescription of CC should be individualized, preferably with periodic monitoring of clinical signs, symptoms, and laboratory tests, with the therapeutic goal of achieving hormone and sperm levels within the physiological range [3-7].

Furthermore, as there is no universally accepted ideal protocol or evidence-based recommendation endorsed by different medical societies, primarily due to its off-label use, the central objective of this article is to provide an overview of therapeutic prescription possibilities, based on previously published studies, including doses and combinations, that have been tested and have demonstrated positive clinical and laboratorial results.

**- Pulsed use:**

The study by Marconi et al. (2016) [8] investigated the effects of discontinuing CC treatment in patients with hypogonadism, defined as symptoms of testosterone deficiency associated with two consecutive total testosterone (TT) measurements below 11 nmol/L, indicative of late-onset hypogonadism (LOH). Twenty-seven patients, with a mean age of 50.1 years, were recruited and treated with 50 mg of CC daily for 50 days. The study monitored serial measurements of TT levels before treatment and three months (90 days) after discontinuation.

As a result, the researchers observed that treatment with CC significantly increased TT levels from  $8.5 \pm 1.8$  nmol/L to  $22.7 \pm 8.1$  nmol/L. However, three months after discontinuation, the mean TT levels dropped to  $10.2 \pm 3.9$  nmol/L, with 78% of patients presenting TT levels below 11 nmol/L. Only 22% maintained normal TT levels, but these also declined to below 11 nmol/L six months after discontinuation [8].

The authors concluded that LOH does not appear to be reversible in the short term after CC treatment. However, CC therapy is effective in the short term for increasing TT levels, although most patients will require continuous treatment to maintain these levels [8].

As a critical analysis of the findings by Marconi et al. (2016), it can be suggested that measuring TT levels at shorter intervals (e.g., 30 days) following CC discontinuation ("wash-out") might yield different potential outcomes. From this perspective, if serum TT levels could be maintained at appropriate levels for longer periods, it may be feasible to implement a one-month treatment break or alternate treatment cycles, such as one month on, one month off.

### **a) Low dose use:**

The study by Turek et al. (2003) [9] was a prospective cohort investigation evaluating the efficacy of CC in men with acquired hypogonadotropic hypogonadism. Seven male patients were included in the analysis: three with infertility and four with sexual dysfunction, all diagnosed with partial hypogonadotropic hypogonadism. The administered dose was 12.5 mg of CC daily, adjusted as necessary to optimize testosterone levels and alleviate symptoms [9].

Over the course of the three-year study, significant improvements were observed. Baseline total testosterone levels ranged between 130 ng/dL and 180 ng/dL, with a mean of 153.4 ng/dL, while post-treatment levels increased to a range of 580 ng/dL to 620 ng/dL, averaging 601.4 ng/dL. This represents a mean increase of approximately 448 ng/dL. Luteinizing hormone (LH) levels also improved, rising from pre-treatment values between 1.1 mIU/mL and 1.6 mIU/mL (mean: 1.33 mIU/mL) to post-treatment values ranging from 4.2 mIU/mL to 5.1 mIU/mL (mean: 4.77 mIU/mL). Similarly, follicle-stimulating hormone (FSH) levels showed a consistent rise, increasing from baseline values of 1.6 mIU/mL to 2.1 mIU/mL (mean: 1.84 mIU/mL) to post-treatment levels ranging between 4.5 mIU/mL and 5.2 mIU/mL (mean: 4.81 mIU/mL) [9].

Clinically, the results demonstrated significant improvements in semen quality among the infertile patients, with one case achieving natural conception. Additionally, all patients experiencing sexual dysfunction reported normalization of erectile function and libido. Importantly, no adverse effects were observed throughout the study, supporting the conclusion that CC, even at low doses of 12.5 mg once daily, is a safe and effective therapeutic option for managing hypogonadotropic hypogonadism [9].

### **b) Combined Therapy use:**

#### **1) Clomiphene Citrate and Anastrozole**

A retrospective study conducted by Alder et al. (2018) [10] aimed to evaluate the efficacy and safety of combined therapy with CC and Anastrozole (AZ) in subfertile

men with hypoandrogenism. The study included 51 men with a mean age of 35.4 years and an average BMI of 35 kg/m<sup>2</sup>, treated between 2014 and 2017.

Initially, patients were treated with CC alone, at doses ranging from 25 to 100 mg daily or on alternate days, with adjustments made based on treatment response. Anastrozole was added if estradiol levels exceeded 50 pg/mL or if the testosterone-to-estradiol ratio fell below 10. The initial dose of AZ was 1 mg, administered two to three times per week and adjusted as needed [10].

The results showed significant increases in both total testosterone and bioavailable testosterone levels following treatment with CC alone. Specifically, total testosterone increased from a baseline mean of 257.6 ng/dL to 667.2 ng/dL after approximately three months of CC treatment ( $p < 0.001$ ), while bioavailable testosterone rose from 147.3 ng/dL to 386.8 ng/dL during the same period ( $p < 0.001$ ). However, this rise was accompanied by a substantial increase in estradiol levels, which climbed from 21.0 pg/mL at baseline to 65.6 pg/mL ( $p < 0.001$ ).

Following the introduction of AZ, estradiol levels normalized significantly, declining to a mean of 33.9 pg/mL ( $p < 0.001$ ), and the testosterone-to-estradiol ratio improved considerably, rising from a pre-treatment ratio of 13.2 to 25.9 ( $p < 0.001$ ). Meanwhile, total testosterone and bioavailable testosterone levels remained stable within the therapeutic range, averaging 689.8 ng/dL and 402.0 ng/dL, respectively, after approximately 9 weeks of combined therapy. These values were sustained over the long term, with total testosterone at 630.2 ng/dL and bioavailable testosterone at 354.9 ng/dL after 32 weeks of treatment [10].

In terms of safety, 11 patients reported adverse effects, the most common being anxiety or irritability (9.8%), decreased libido (7.8%), and elevated hematocrit (3.9%). Four patients discontinued treatment due to adverse effects. PSA levels remained within age-appropriate normal limits throughout the study period, and no cases of prostate cancer were diagnosed.

Semen analysis showed a significant improvement in sperm concentration, increasing from a baseline median of 8.6 million/mL to 12.9 million/mL ( $p = 0.03$ ). However, there were no statistically significant changes in sperm motility or total motile sperm count.

The authors of the study concluded that combined therapy with CC and AZ is an effective and safe approach for managing hypoandrogenic and subfertile men, particularly those with elevated estradiol levels or a low testosterone-to-estradiol ratio [10].

A recent multicenter retrospective study conducted by Osadchiy et al. (2024) [11], investigated the effects of combined therapy with CC and AZ compared to AZ monotherapy in 90 young men with idiopathic infertility. The study included a median patient age of 36 years, with a median therapeutic follow-up duration of 91 days (range: 64–117 days). The median dose of AZ was 3 mg per week (range: 3–7 mg), while CC was administered at standard doses of 25 mg daily or 50 mg on alternate days [11].

The results demonstrated that 43% of men in the combined therapy group achieved normozoospermia compared to 25% in the monotherapy group. Additionally, the combined therapy group exhibited a significant improvement in total motile sperm count (TMSC), increasing to a median of 11.3 million (range: 0.4–43.0 million), compared to 2.1 million (range: 0.0–9.9 million) in the monotherapy group ( $p = 0.03$ ). Although not statistically significant, there was a trend toward higher sperm concentration in the combination group, with values rising to a median of 6.9 million/mL (range: 0.9–39.0 million/mL), compared to 3.2 million/mL (range: 0.0–12.4 million/mL) in the monotherapy group ( $p = 0.06$ ) [11].

Baseline hormonal parameters revealed that men in the combined therapy group had significantly lower LH levels (5.0 IU/L, range: 3.2–6.8 IU/L) compared to the monotherapy group (7.3 IU/L, range: 4.0–12.1 IU/L;  $p = 0.03$ ). Furthermore, the testosterone-to-LH ratio was significantly higher in the combined therapy group (79.3, range: 26.5–138.2) than in the monotherapy group (35.3, range: 21.2–66.0;  $p = 0.046$ ). Post-treatment, testosterone levels increased in both groups, with the combined therapy group reaching an average of 529 ng/dL and the monotherapy group achieving 453 ng/dL [11].

Adverse effects were minimal, with no severe adverse events reported during the study period. Improvements in TMSC, although observed in both groups, were significantly more pronounced in the combination group. The authors highlighted that a TMSC of  $\geq 9$  million has been associated with higher success rates in assisted

reproduction, suggesting that men in the combined therapy group, with a median TMSC of 11.3 million, may experience better clinical outcomes compared to the monotherapy group.

## 2) Clomiphene Citrate and Human Chorionic Gonadotrophin

**Comment [WU6]:** A comment on the TMSC in the other review will be further beneficial as regards comparison which seem to be unavailable here as clearly stated in the CC-AZ review. If unavailable it could be stated as such

Habous et al. (2018) [12] conducted a randomized, prospective, multicenter clinical trial comparing the efficacy of different treatments for hypogonadism in adult men seeking to preserve fertility. A total of 282 hypogonadal men were included and divided into three treatment groups: one group received 50 mg of CC daily, the second group was treated with a combination of 5000 IU of human chorionic gonadotropin (hCG) twice per week and 50 mg of CC daily, while the third group received 5000 IU of hCG twice per week alone [12].

The results demonstrated a significant increase in testosterone levels across all groups at 1 month and 3 months of treatment. Mean serum testosterone levels increased to 5.48 nmol/L in the CC group, 5.31 nmol/L in the combined hCG + CC group, and 4.67 nmol/L in the hCG-only group after 3 months. The relative percentage increase in testosterone was highest in the combination group (235%) and slightly lower in the CC group (225%) and the hCG-only group (210%). Improvements in the ADAM questionnaire scores, which assess the severity of androgen deficiency symptoms, were observed across all groups. Specifically, scores improved from baseline to a mean of 12.73 in the CC group, 15.13 in the hCG + CC group, and 11.82 in the hCG-only group after 3 months. The combination group exhibited a marginally superior improvement compared to the other two groups [12].

Treatment adherence varied among groups. The CC group demonstrated the lowest dropout rate, with only 5.3% of patients (5 out of 95) discontinuing treatment. In contrast, the dropout rate in the combined hCG + CC group was significantly higher at 19.2% (18 out of 94), while the hCG-only group experienced a dropout rate of 17.1% (16 out of 94). The primary reasons for discontinuation in the hCG and combination therapy groups were intolerance to frequent injections and the higher treatment costs, which patients were required to cover themselves [12].

## Discussion:

The use of CC in treating male hypogonadism and infertility has been consistently shown to be both effective and safe [3-7], whether as a standalone therapy or in combination with other agents such as Anastrozole (AZ) or Human Chorionic Gonadotropin (hCG) [10-12]. The results of multiple studies reinforce the notion that lower doses of CC, typically ranging between 25 mg and 50 mg daily or on alternate days, are sufficient to achieve meaningful clinical and hormonal improvements.

Evidence suggests that higher doses, such as 400 mg/day as seen in the study by Gundewar T, et al. (2021) [13], are not necessary, as therapeutic effects are already observed with more modest doses. For instance, the study by Turek et al. (2003) demonstrated significant increases in testosterone levels and improved symptoms of hypogonadism and infertility with just 12.5 mg of CC daily, further underscoring that lower doses are effective in clinical practice [9].

Combination therapy has emerged as an additional strategy for specific clinical needs. In cases where elevated estradiol levels are present or testosterone-to-estradiol ratios are unfavorable, the addition of AZ has proven beneficial. Alder et al. (2018) demonstrated that CC, when combined with AZ, not only stabilized testosterone levels but also effectively reduced estradiol levels and improved hormonal balance [10]. Similarly, Habous et al. (2018) showed that combining hCG with CC produced comparable increases in testosterone while preserving fertility, although adherence was slightly lower due to injection frequency and associated costs [12].

When it comes to fertility outcomes, combination therapy appears to offer an edge. Osadchiy et al. (2024) reported a significant improvement in total motile sperm count (TMSC) in men receiving CC and AZ, a parameter closely linked to success in assisted reproductive techniques. Achieving a TMSC above 9 million, as seen in this study, can be clinically significant for couples seeking conception [11].

Overall, the findings across these studies highlight the versatility of CC as a therapeutic option. Whether used alone or in combination, CC consistently improves testosterone levels, semen parameters, and associated symptoms, all while

maintaining an excellent safety profile. Starting with low doses remains a practical and effective approach, minimizing side effects while achieving desirable outcomes. Tailored treatment strategies, such as adding AZ or hCG, can further enhance results for specific patient profiles. However, further long-term studies are warranted to optimize protocols and confirm these findings in broader populations.

### Conclusion:

Clomiphene Citrate (CC) stands out as a clinically safe, effective, and adaptable therapeutic option for addressing male hypogonadism and infertility. Its ability to improve testosterone levels, reduce symptoms of androgen deficiency, and enhance fertility parameters, such as total motile sperm count, makes it a valuable alternative, particularly for patients aiming to preserve fertility. Importantly, meaningful results have been achieved with relatively low doses, typically between 12.5 and 50 mg daily or on alternate days, avoiding the risks and unnecessary burden associated with higher doses.

For more complex cases, such as those involving elevated estradiol or unfavorable testosterone-to-estradiol ratios, combining CC with agents like anastrozole or human chorionic gonadotropin (hCG) has demonstrated additional benefits. These combined approaches offer flexibility, allowing treatment to be tailored to individual patient profiles and specific clinical needs.

In summary, CC provides an accessible and cost-effective treatment option, balancing efficacy, safety, and patient convenience. Its versatility—whether used alone or in combination—reinforces its clinical relevance for hypogonadal men, especially those seeking to maintain fertility. Moving forward, further studies will help refine these treatment protocols and expand our understanding of its long-term outcomes across broader patient populations.

### References:

1- Clomiphene Citrate, in National Library of Medicine – available at <https://pubchem.ncbi.nlm.nih.gov/compound/Clomiphene-Citrate>

#### Comment [WU7]:

The references cited are not diverse enough as over 75% of the references are from Epub only.

For this magnitude of review and to make valid assertions, 13 references seem sub-optimal, though they are recent references, additional references are advised

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3 - Tienforti D, Castellini C, Di Giulio F, Totaro M, Dalmazio G, Spagnolo L, et al. Selective modulation of estrogen receptor in obese men with androgen deficiency: A systematic review and meta-analysis. *Andrology*. 2023 Sep;11(6):1067-1076. doi: 10.1111/andr.13373. Epub 2023 Jan 18. PMID: 36604313.

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11 - Osadchiy V, Munoz-Lopez C, Jiang T, Naelitz BD, Parekh N, Vij SC, Mills JN, Lundy SD, Eleswarapu SV. Combination clomiphene citrate and anastrozole duotherapy improves semen parameters in a multi-institutional, retrospective cohort of infertile men. *Transl Androl Urol*. 2024 Feb 29;13(2):245-251. doi: 10.21037/tau-23-454. Epub 2024 Feb 22. PMID: 38481873.

12 - Habous M, Giona S, Tealab A, Aziz M, Williamson B, Nassar M, et al. Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study. *BJU Int.* 2018 Nov;122(5):889-897. doi: 10.1111/bju.14401. Epub 2018 Jun 14. PMID: 29772111.

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