



Overview of Clomiphene Citrate Use in Male Hypogonadism and Infertility

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The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Clomiphene Citrate (CC) has been widely used in medicine since the 1970s, primarily as a Selective Estrogen Receptor Modulator (SERM) for female ovulation induction. However, its off-label use in men has gained traction, particularly for the treatment of hypogonadotropic hypogonadism and idiopathic infertility. CC's mechanism of action, which increases gonadotropin-releasing hormone (GnRH) secretion and subsequently elevates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, offers a unique advantage by preserving the hypothalamic-pituitary-gonadal axis and maintaining fertility.

This article presents evidence supporting CC's efficacy and safety in these contexts, summarizing data from systematic reviews, meta-analyses, and retrospective studies. In hypogonadotropic men, CC has been shown to significantly improve total and free testosterone levels, gonadotropin concentrations, and hypogonadism symptoms, while avoiding common complications of testosterone replacement therapy (TRT), such as secondary polycythemia. CC also demonstrated favorable outcomes in seminal parameters, including sperm concentration and motility, as well as improved pregnancy rates in idiopathic infertility cases.

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Adverse effects reported with CC use include reduced energy, mood instability, and occasional visual disturbances, most of which are mild and reversible. Long-term safety data are reassuring, with rare severe adverse events such as thrombotic complications. Studies comparing CC to TRT indicate a lower risk of hematological and prostate-related complications, underscoring its safety profile.

While the evidence supports CC as a viable alternative or adjunct to TRT in specific patient populations, further research is needed to refine treatment protocols, assess long-term outcomes, and explore biofunctional sperm parameters. Overall, CC represents a promising, cost-effective therapeutic option for addressing male hypogonadism and infertility, with its integration into clinical practice guided by careful patient selection and ongoing monitoring.

Keywords: *Clomiphene citrate; hypogonadism; male infertility; testosterone replacement therapy; gonadotropins; polycythemia.*

1. INTRODUCTION

Clomiphene Citrate (CC), which has been used in medicine since the 1970s, is a Selective Estrogen Receptor Modulator (SERM) derived from a racemic mixture of the trans isomer enclomiphene (62%) and the cis isomer zuclophene (38%) (National Library of Medicine. (n.d.)). Its pharmacological action occurs through an antagonistic mechanism, competing with estrogen at estrogen receptors in the hypothalamus and pituitary gland, leading to increased secretion of GnRH (gonadotropin-releasing hormone) as well as elevated levels of LH (luteinizing hormone) and FSH (follicle-stimulating hormone) (National Library of Medicine. (n.d.)).

Thus, in addition to its classic indications for female ovulation induction, it has also been used, in an off label use in most countries, as an adjunct treatment for male hypogonadism, particularly the hypogonadotropic type, whether or not associated with impaired sperm parameters or infertility (National Library of Medicine. (n.d.); ClinicalTrials.gov. (n.d.)).

Although its use is predominantly off-label, several controlled studies, ranging from phase 1 to phase 3, using CC or enclomiphene for hypogonadism and fertility, in different clinical scenarios (eg. Diabetes Mellitus, Obesity,

Chronic pain), showing clinical safety and efficacy, have been previously registered and published in clinical trial registries such as ClinicalTrials.gov (n.d.) (Table 1).

In this context, several authors (Ide et al., 2020; Lo et al., 2018) have proposed Clomiphene Citrate (CC) as a potential alternative to testosterone therapy, particularly due to its advantage of not suppressing the hypothalamic-pituitary-gonadal axis, thereby preserving fertility and testicular morphology while simultaneously increasing testosterone levels in individuals with hypogonadotropic hypogonadism. Another noteworthy factor observed is the reduced impact on hematocrit elevation, which is a common side effect of testosterone therapy, especially with injectable formulations, along with a comparatively lower treatment cost (Ide et al., 2020; Lo et al., 2018).

Given that central hypogonadism, particularly the functional type often resulting from obesity, late-onset hypogonadism (age-related), drug- or medication-induced conditions (opioids, glucocorticoids, and/or anabolic androgenic steroids), hyperprolactinemia, and Cushing's syndrome, is increasingly prevalent among patients who could potentially respond well to Clomiphene Citrate (CC) therapy, the clinical discussion of CC as a therapeutic option has gained importance (Ide et al., 2020; Lo et al., 2018).

Table 1. Study phase, clinical trials.gov registration number (NCT), study status

Study Phase	NCT	Status
Phase 1	NCT01923857, NCT02274181, NCT01923870	Completed
Phase 2	NCT01155518, NCT03933618, NCT01270841, NCT01904734, NCT00697814, NCT02380755, NCT02651688, NCT03245827, NCT01191320, NCT01386606	Completed
Phase 3	NCT01739582, NCT01534208, NCT01619683, NCT00962637, NCT01067365, NCT01993225, NCT01993212	Completed

Thus, the central aim of this article, is to provide a summary offering an overview of the efficacy and safety of CC as a therapeutic proposal in medical practice. Although this article does not follow the methodology of a traditional review, a structured search was conducted to gather relevant information, preferably high-quality evidence. This search focused on studies published on the topic, deemed significant for the proposed objective, and was carried out using the PubMed database, as detailed below: ("Clomiphene"[Mesh] OR (Clomifene) OR Chloramiphene OR (Clomifen) OR (Clomiphene Citrate) OR (Citrate, Clomiphene) OR (Clomiphene Hydrochloride) OR (Hydrochloride, Clomiphene) OR (Serophene) OR (Gravosan) OR (Klostilbegit) OR (Clostilbegit) OR (Clomid) OR (Clomide) OR (Dyneric) AND ("Hypogonadism"[Mesh] OR (Hypogonadism, Isolated Hypogonadotropic) OR (Hypogonadotropic Hypogonadism) OR (Hypogonadism, Hypogonadotropic))). Based on the results obtained, relevant and pertinent studies were selected to support the development of the presented text.

Hypogonadism: The systematic review and meta-analysis by Tienforti et al. (2023) aimed to evaluate the efficacy and safety of Selective Estrogen Receptor Modulators (SERMs) in obese men with functional androgen deficiency. The analysis included 292 men treated with clomiphene (12.5–50 mg daily) or enclomiphene (12.5–25 mg daily) over periods ranging from 1.5 to 4 months. The results indicated a significant increase in testosterone levels, both with clomiphene (mean difference of 11.56 nmol/L) and enclomiphene (mean difference of 7.50 nmol/L). Furthermore, no unexpected findings related to the clinical safety of these treatments were observed, as assessed by the presence of major side effects or adverse events.

According to the authors, the review provided a robust quantitative analysis of testosterone levels (quality analysis performed through risk of bias assessment, with most studies classified as moderate or high quality), demonstrating that SERMs could serve as an effective and safe alternative to testosterone replacement therapy in men with functional androgen deficiency related to obesity Tienforti et al. (2023).

Huijben et al. (2022) conducted another recent synthesis of scientific evidence aimed at evaluating the efficacy and safety of Clomiphene Citrate (CC) for men with hypogonadism. To achieve this, a comprehensive systematic review

and meta-analysis was performed, including 19 studies (four randomized clinical trials and 15 observational studies), comprising a total of 1,642 patients.

The inclusion criteria encompassed men aged 18 years or older diagnosed with hypogonadism. CC doses ranged from 25 mg to 50 mg daily or every other day, with treatment and follow-up durations varying from 1.5 months to 52 months.

The results showed that CC significantly increased total testosterone levels (from 179.0–310.3 ng/dL pre-treatment to 467.0–687.9 ng/dL post-treatment) and free testosterone levels (Standard Mean Difference - SMD: 1.78; 95% CI: 0.65, 2.91; $p = 0.002$), as well as LH and FSH levels (Mean Difference - MD: 4.67 IU/L; 95% CI: 3.67, 5.68; $p < 0.00001$, and MD: 4.25 IU/L; 95% CI: 2.70, 5.81; $p < 0.00001$, respectively) and estradiol (MD: 17.69 pg/mL; 95% CI: 12.46, 22.92; $p < 0.00001$). Additionally, CC improved clinical symptoms of hypogonadism, as measured by the ADAM scale (MD: -3.13; 95% CI: -4.16, -2.10; $p < 0.00001$). Side effects were reported in less than 10% of patients, with no severe adverse events, indicating that CC is a clinically safe and effective therapeutic option Huijben et al. (2022).

The results discussed in this section are summarized in the table below (Table 2).

Infertility: The systematic review and meta-analysis by Bridges et al. (2015) aimed to evaluate the efficacy of Clomiphene Citrate (CC) in improving seminal parameters in men with oligospermia. Through a structured systematic search of randomized controlled and prospective studies, the authors included data from a total of 197 men with a mean age of 32.8 years. Of these, 115 were treated with a minimum dose of 25 mg of CC every other day for at least three months, while 82 men received a placebo or no treatment.

The analysis results indicated a significant increase of 7.7 million sperm per ml in the group treated with CC compared to the control group, with no significant heterogeneity observed between studies. This finding aligns with other published studies that reported significant improvements in sperm concentration with CC use, although variations exist across different research studies (sample characteristics, patient age, presence of comorbidities, treatment duration, and administered dose) (Bridges et al., 2015).

Table 2. Summary of studies on the use of Clomiphene Citrate (CC) and hypogonadism

Study	Objective	Population	Key Results
Tienforti et al. (2023)	Evaluate efficacy and safety of SERMs in obese men with functional androgen deficiency.	292 men treated with clomiphene (12.5–50 mg daily) or enclomiphene (12.5–25 mg daily), 1.5–4 months.	Significant testosterone increase: Clomiphene (11.56 nmol/L), Enclomiphene (7.50 nmol/L). No major side effects observed.
Huijben et al. (2022)	Evaluate efficacy and safety of Clomiphene Citrate (CC) for men with hypogonadism.	1,642 men aged ≥18 years diagnosed with hypogonadism, treated with CC (25–50 mg daily or every other day), 1.5–52 months.	Significant increase in testosterone, LH, FSH, and estradiol. Improved ADAM scale scores. Side effects <10%, no severe events.

The few side effects reported by the authors included gastrointestinal disturbances (gastritis, abdominal discomfort), gynecomastia, and occasionally visual disturbances, which were tolerable and generally reversible shortly after discontinuation of the medication. The authors concluded that CC could be clinically relevant for assisted reproduction techniques, such as artificial insemination, given its observed efficacy and adequate clinical safety (Bridges et al., 2015).

However, according to the authors, the current criteria for identifying patients more likely to benefit from CC treatment include a diagnosis of idiopathic infertility, sperm concentrations below 20 million but above 10 million per ml, low levels of FSH and LH, and normal or slightly below normal motility and morphology. Additionally, no significant benefit was observed with a 50 mg daily dose compared to a 25 mg daily dose (Bridges et al., 2015).

Another systematic review and meta-analysis conducted by Cannarella et al. (2019) investigated the effects of Selective Estrogen Receptor Modulators (SERMs) in the treatment of idiopathic male infertility (Cannarella et al. 2019). The study included 16 controlled and uncontrolled studies that evaluated conventional sperm parameters, serum levels of gonadotropins and testosterone, and pregnancy rates in normogonadotropic patients with oligozoospermia.

The results demonstrated that the administration of SERMs, specifically Clomiphene Citrate (CC), significantly increased sperm concentration, total sperm count, and serum levels of LH, FSH, and total testosterone compared to baseline values. Additionally, there was an improvement in total sperm motility, although no significant improvement was observed in progressive

motility or sperm morphology when compared to the control group (Cannarella et al. 2019).

Pregnancy rates were significantly higher in patients treated with CC, suggesting a positive effect of this medication on male fertility and encouraging its clinical use. However, the review also highlights the need for future studies to more thoroughly and robustly assess the effects of CC on both conventional and biofunctional sperm parameters (e.g., sperm DNA fragmentation) as well as objective measurements of pregnancy rates (Cannarella et al. 2019).

An additional highly relevant study by Huijben et al. (2023) systematically reviewed and conducted a meta-analysis on the efficacy of Clomiphene Citrate (CC) in the treatment of male infertility (Huijben et al. 2023). The analysis included 18 studies for qualitative review and 15 studies for meta-analysis, encompassing a population of 731 infertile men. The researchers aimed to evaluate the effects of CC on semen parameters such as concentration, motility, and morphology, as well as hormonal levels and pregnancy rates.

The results showed that treatment with CC significantly increased sperm concentration and motility without causing severe adverse effects. However, no significant differences were observed in sperm morphology (Huijben et al. 2023).

Additionally, the pregnancy rate during treatment averaged 17% in the CC group compared to approximately 8% in the control group (rate of infertile couples attempting conception in the second year). Finally, while minor side effects were reported in some studies, no severe adverse events were observed by the researchers (Huijben et al. 2023).

Table 3. Summary of studies on the use of clomiphene citrate (CC) and infertility

Study	Objective	Population	Key Results
Bridges et al. (2015)	Evaluate the efficacy of CC in improving seminal parameters in men with oligospermia.	197 men (32.8 years on average), 115 treated with CC (25 mg every other day for ≥3 months), 82 controls.	Significant increase of 7.7 million sperm/ml in CC group. No significant heterogeneity. Few mild side effects.
Cannarella et al. (2019)	Investigate the effects of SERMs, specifically CC, on idiopathic male infertility.	Normogonadotropic patients with oligozoospermia from 16 studies (controlled and uncontrolled).	Increased sperm concentration, count, LH, FSH, testosterone. No significant improvement in morphology. Higher pregnancy rates.
Huijben et al. (2023)	Evaluate the efficacy of CC on semen parameters, hormonal levels, and pregnancy rates in infertile men.	731 infertile men, 18 studies (15 included in meta-analysis).	Increased sperm concentration and motility. No significant differences in morphology. Pregnancy rate: 17% (CC group) vs 8% (control).

The results discussed in this section are summarized in the table (Table 3).

Adverse effects: The study by Gundewar T et al., (2021) presents a systematic review aimed at identifying the adverse effects of CC on semen parameters in men (Gundewar T et al., 2021). This review included 384 men aged 20 to 50 years, encompassing both healthy volunteers and subfertile patients with idiopathic subfertility or idiopathic oligospermia. The inclusion criteria focused on studies reporting adverse effects of CC on semen parameters, excluding men with identifiable causes of male infertility. Clomiphene Citrate doses ranged from 25 to 400 mg/day, with treatment durations varying from 2 to 15 months and follow-ups of up to 6 months (Gundewar T et al., 2021)].

The results indicated that 19% of men treated with CC experienced a reduction in sperm count, 21% in sperm concentration, 17% in sperm motility, and 24% in total motile sperm count. In 17% of patients, the deterioration in semen parameters did not recover after discontinuing therapy (Gundewar T et al., 2021). It was presented in the article discussion some potential mechanisms for this deterioration, which include technical variations in analysis, direct effects of CC on testicular histology, and increased estrogen concentrations resulting from CC therapy.

Additionally, intra-individual variability in semen parameters may influence the results, and abnormal germ cell production could directly

result from CC's effects in individuals with specific sensitivities or genetic polymorphisms. In this regard, the authors highlighted the following four points of concern regarding the conclusions: 1) High biological variability (homeostatic regulation); 2) Significant intra-individual variability (10.3% to 26.8%); 3) In 10.4% of cases with abnormal findings in the first test, results normalized in the second test; and 4) The possibility of natural variation (regression to the mean phenomenon) (Gundewar T et al., 2021).

In conclusion, the authors stated that CC therapy may potentially (with the above caveats) be associated with reductions in sperm count, concentration, motility, morphology, and total motile sperm count in up to 20% of patients (individual sensitivity or genetic polymorphism). Therefore, the benefits of CC therapy and its potential negative impacts on fertility should always be carefully monitored through close follow-up with periodic evaluations (Gundewar T et al., 2021).

The retrospective study conducted by Chandrapal et al. (2016) aimed to determine the safety profile of CC in men treated for hypogonadism or infertility (Chandrapal et al., 2016). The sample included 77 patients, with a mean age of 34 years, who were treated with 50 mg of CC daily or on alternate days. The primary objective of the researchers was to evaluate the effects of CC on PSA levels, hematocrit (Hct), and testosterone levels over a mean follow-up period of 358 days.

The results showed a significant increase in total and bioavailable testosterone levels, with mean increases of 200 ng/dL and 126 ng/dL, respectively. This increase led to clinically significant improvements in hypogonadism symptoms, as measured by the ADAM questionnaire. Another key finding was that PSA and Hct levels remained within normal ranges, with no significant changes during the treatment period, suggesting that CC use did not increase the risks of major prostate-related issues or elevated red blood cell concentrations (Chandrapal et al., 2016).

On the other hand, 31% of patients reported side effects, the most common being reduced energy (19%), libido (6%), mood instability (5%), sleep disturbances (4%), and visual disturbances (3%). These side effects led to dose adjustments in some cases and discontinuation of treatment, primarily due to inadequate responses or persistent adverse effects. However, despite 31% of patients reporting side effects, only 5% found them bothersome enough to discontinue treatment. In this regard, among the patients who discontinued treatment (with a mean time from

initiation to discontinuation of 127 days), 10% had an inadequate response, 9% no longer desired fertility, 4% experienced a paradoxical response, and 3% developed hyperestrogenemia. Ten percent of patients had their doses adjusted (reduced) due to elevated estradiol and testosterone levels, which were corrected after personalized dosing. The mean time to the onset of side effects was 77 days, with a wide variation ranging from 18 to 709 days (Chandrapal et al., 2016).

Despite potential methodological limitations of a retrospective approach, the study provides valuable insights into the safety and efficacy of CC in men with hypogonadism or infertility, suggesting that routine monitoring of PSA and hematocrit levels may not be necessary in all cases. Instead, regular evaluation of testosterone, SHBG, and estradiol levels is recommended to monitor the treatment response. The authors concluded that CC is a safe and effective option for increasing testosterone levels and improving hypogonadism symptoms in men without increasing the risks of polycythemia or prostate-related events (Chandrapal et al., 2016).

Table 4. Summary of studies on the use of clomiphene citrate (CC) and adverse effects

Study	Objective	Population	Key Results	Side Effects
Gundewar T et al. (2021)	Identify adverse effects of CC on semen parameters.	384 men (20–50 years), CC doses 25–400 mg/day for 2–15 months.	Up to 20% experienced reductions in semen parameters. 17% did not recover after discontinuation.	Deterioration in semen parameters, potentially linked to technical, hormonal, or genetic factors.
Chandrapal et al. (2016)	Determine the safety profile of CC in men treated for hypogonadism or infertility.	77 men (mean age 34 years), treated with 50 mg of CC daily/alternate days.	31% reported side effects; 5% discontinued due to bothersome effects. PSA and Hct levels remained normal.	Reduced energy, libido, mood instability, sleep/visual disturbances. Minor side effects led to dose adjustments.
Wheeler et al. (2017)	Compare prevalence of secondary polycythemia in men treated with CC versus TRT.	188 men on CC (mean age 38) vs. 175 men on TRT (mean age 51.5).	Polycythemia: 11.2% (TRT) vs. 1.7% (CC). Similar testosterone increases in both groups.	Higher polycythemia risk with TRT; minimal risk with CC.
Kavoussi et al. (2019)	Assess the risk of deep vein thrombosis (DVT) in hypogonadal men treated with CC or TRT.	1,180 men (mean follow-up 25 months), treated with CC or TRT.	DVT incidence: 0.8% overall. Most cases (9/10) on TRT, none linked to polycythemia.	DVT risk primarily associated with TRT, often linked to other identifiable causes.

A retrospective and multi-institutional study by Wheeler et al. (2017) compared the prevalence of secondary polycythemia (elevated hematocrit) in hypogonadal men treated with CC versus Testosterone Replacement Therapy (TRT) (Wheeler et al. 2017). The sample included 188 men treated with CC and 175 men treated with TRT, with mean ages of 38 and 51.5 years, respectively. Patients on TRT exhibited a prevalence of polycythemia of 11.2%, compared to only 1.7% in the CC group. This significant difference persisted after adjustments for age, treatment site, smoking history, and pre-treatment hematocrit levels. Serum testosterone levels increased similarly in both groups, with no clinical difference and mean changes of 333.1 ng/dL in the TRT group and 367.6 ng/dL in the CC group (Wheeler et al. 2017).

The results indicate that TRT is associated with a significantly higher risk of developing secondary polycythemia compared to CC. Therefore, regular monitoring of hemoglobin and hematocrit is recommended for patients on TRT but may not be necessary for those on CC. This study is pioneering in evaluating the rate of polycythemia between these two treatment modalities, providing valuable insights for clinical practice.

Lastly, a major concern, albeit derived from data on CC use in women, is the potential increased risk of thrombotic events, which was investigated by Kavoussi et al. (2019). This retrospective study analyzed 1,180 hypogonadal men treated with either TRT or CC to assess the risk of deep vein thrombosis (DVT). Patients were followed for a mean interval of 25 months, and 10 men (0.8%) were diagnosed with DVT during treatment. Of these, 9 were on TRT and 1 on CC. Most DVT cases (70%) had other identifiable etiologies, such as Klinefelter syndrome, Factor V Leiden deficiency, trauma-related events, or prolonged immobilization. None of the patients diagnosed with DVT had polycythemia at the time of diagnosis (Kavoussi et al., 2019).

The results discussed in this section are summarized in the table (Table 4).

Cost-Effectiveness: An insightful study aimed to compare the biochemical and clinical efficacy, as well as the cost, of Clomiphene Citrate (CC) versus Testosterone Gel Replacement Therapy (TGRT) in men with hypogonadism, was conducted by Taylor F & Levine L. (2010).

This retrospective research included 104 men divided into two groups: those treated with CC (65 men) and those treated with TGRT (39 men), with mean ages of 42 and 57 years, respectively. Participants received CC 50 mg on alternate days or TGRT 5 g daily, with an average follow-up duration of 23 months for the CC group and 46 months for the TGRT group.

According to the authors, the results showed a significant increase in testosterone levels in both groups: 573 ng/dL for CC and 553 ng/dL for TGRT, with a statistically significant difference ($P < 0.001$) between pre- and post-treatment levels but no significant difference between the two groups. Additionally, the CC group showed a significant reduction in ADAM questionnaire scores, from 4.9 to 2.1 ($P < 0.05$), indicating subjective improvement in hypogonadism symptoms, particularly in sexual function.

The researchers emphasized that CC is a viable treatment option for hypogonadism, demonstrating comparable clinical and biochemical efficacy to TGRT but at a much lower cost. The monthly cost of CC was \$83 USD, compared to \$270 USD for Testim® and \$265 USD for Androgel®. No major adverse effects were reported in the CC group, while one patient in the TGRT group discontinued due to local skin irritation.

2. CONCLUSION

Clomiphene Citrate (CC) has demonstrated significant efficacy and safety as a therapeutic option for men with hypogonadism and infertility. Its ability to increase testosterone levels while preserving the hypothalamic-pituitary-gonadal axis and maintaining fertility represents a distinct advantage over testosterone replacement therapy (TRT). Additionally, CC has shown favorable effects on seminal parameters and clinical symptoms, with a lower risk of secondary polycythemia and other TRT-associated complications.

The presented studies in this article consistently support CC's role as an effective and well-tolerated treatment. While adverse effects such as decreased energy, libido, and occasional mood disturbances have been reported, they were generally manageable with dose adjustments or resolved upon discontinuation. Importantly, CC has a reassuring safety profile, with rare incidences of severe events such as thrombotic complications or sustained declines in

semen quality. Nonetheless, individualized treatment approaches and close monitoring of hormonal and seminal parameters remain critical to optimizing outcomes and addressing potential side effects.

Considering the growing evidence, CC offers a compelling alternative or adjunct to conventional therapies, particularly for patients with hypogonadotropic hypogonadism or idiopathic infertility. However, there is still a need for further well-designed, long-term studies to refine patient selection, evaluate biofunctional sperm outcomes, and better understand CC's long-term impact on fertility and overall health. These efforts will be essential in ensuring the continued integration of CC into evidence-based clinical practice.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The authors declare that generative AI was used only at the final stage of manuscript preparation (after writing) and exclusively for linguistic refinement in English Language (Name: ChatGPT; Version: GPT-4; Model: OpenAI's Large Language Model; Source: OpenAI - <https://openai.com>). No original text was generated or substantively edited by the AI.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

Bridges, N., Trofimenko, V., Fields, S., Carrell, D., Aston, K., & Hotaling, J. (2015). Male factor infertility and clomiphene citrate: A meta-analysis—The effect of clomiphene citrate on oligospermia. *Urology Practice*, 2(4), 199–205. doi:10.1016/j.urpr.2014.10.007

Cannarella, R., Condorelli, R. A., Mongioì, L. M., Barbagallo, F., Calogero, A. E., & La Vignera, S. (2019). Effects of selective estrogen receptor modulators for the treatment of male infertility: A systematic review and meta-analysis. *Expert Opinion on Pharmacotherapy*, 20(12), 1517–1525. doi:10.1080/14656566.2019.1615057

Chandrapal, J. C., Nielson, S., Patel, D. P., Zhang, C., Presson, A. P., Brant, W. O., et al. (2016). Characterising the safety of clomiphene citrate in male patients through prostate-specific antigen, haematocrit, and testosterone levels. *BJU International*, 118(6), 994–1000. doi:10.1111/bju.13546

ClinicalTrials.gov. (n.d.). *Clomiphene citrate*. Retrieved from <https://clinicaltrials.gov/search?intr=clomiphene>

Gundewar, T., Kuchakulla, M., & Ramasamy, R. (2021). A paradoxical decline in semen parameters in men treated with clomiphene citrate: A systematic review. *Andrologia*, 53(1), e13848. doi:10.1111/and.13848

Huijben, M., Huijsmans, R. L. N., Lock, M. T. W. T., de Kemp, V. F., & de Kort, L. M. O. (2023). Clomiphene citrate for male infertility: A systematic review and meta-analysis. *Andrology*, 11(6), 987–996. doi:10.1111/andr.13388

Huijben, M., Lock, M. T. W. T., de Kemp, V. F., & de Kort, L. M. O. (2022). Clomiphene citrate for men with hypogonadism: A systematic review and meta-analysis. *Andrology*, 10(3), 451–469. doi:10.1111/andr.13146

Ide, V., Vanderschueren, D., & Antonio, L. (2020). Treatment of men with central hypogonadism: Alternatives for testosterone replacement therapy. *International Journal of Molecular Sciences*, 22(1), 21. doi:10.3390/ijms22010021

Kavoussi, P. K., Machen, G. L., Wenzel, J. L., Ellis, A. M., Kavoussi, M., Kavoussi, K. M., et al. (2019). Medical treatments for hypogonadism do not significantly increase the risk of deep vein thrombosis over general population risk. *Urology*, 124, 127–130. doi:10.1016/j.urology.2018.11.009

Lo, E. M., Rodriguez, K. M., Pastuszak, A. W., & Khera, M. (2018). Alternatives to testosterone therapy: A review. *Sexual Medicine Reviews*, 6(1), 106–113. doi:10.1016/j.sxmr.2017.09.004

National Library of Medicine. (n.d.). *Clomiphene citrate*. Retrieved from <https://pubchem.ncbi.nlm.nih.gov/compound/Clomiphene-Citrate>

Taylor, F., & Levine, L. (2010). Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: Efficacy and treatment cost. *Journal of Sexual*

- Medicine*, 7(1 Pt 1), 269–276. doi:10.1111/j.1743-6109.2009.01454.x
- Tienforti, D., Castellini, C., Di Giulio, F., Totaro, M., Dalmazio, G., Spagnolo, L., et al. (2023). Selective modulation of estrogen receptor in obese men with androgen deficiency: A systematic review and meta-analysis. *Andrology*, 11(6), 1067–1076. doi:10.1111/andr.13373
- Wheeler, K. M., Smith, R. P., Kumar, R. A., Setia, S., Costabile, R. A., & Kavoussi, P. K. (2017). A comparison of secondary polycythemia in hypogonadal men treated with clomiphene citrate versus testosterone replacement: A multi-institutional study. *Journal of Urology*, 197(4), 1127–1131. doi:10.1016/j.juro.2016.10.068

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