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Efficacy of Clomiphene Citrate in Improving Semen Parameters: A Systematic Overview

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Abstract*—Male infertility accounts for almost 50% of the world's infertility, and idiopathic male infertility and hypogonadism are leading causes. Clomiphene citrate (CC) is a selective estrogen receptor modulator that has found extensive off-label use in men as a means of increasing endogenously produced testosterone and inducing spermatogenesis by stimulating the hypothalamic–pituitary–gonadal (HPG) axis. This systematic review sought to assess the effectiveness, safety, and cost-utility of clomiphene citrate in enhancing semen characteristics and hormonal profiles in infertile men. A wide literature search was performed employing PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, and ResearchGate, including clinical trials, observational studies, and systematic reviews evaluating the effect of Clomiphene citrate on sperm count, motility, morphology, and hormonal alterations. Most of the studies showed Clomiphene citrate profoundly enhancing sperm concentration and motility and having variable effects on morphology and oxidative stress markers. It also raised levels of serum testosterone, LH, and FSH without suppressing spermatogenesis. Enhancements in oxidative stress parameters and decreases in sperm DNA fragmentation further attested to its potential in improving sperm function. Most studies employed daily or alternate-day oral doses ranging between 25–50 mg, demonstrating significant improvements in sperm concentration, motility, and testosterone levels, with variable effects on morphology and oxidative stress markers. The medication was well tolerated with benign and transient effects such as headache, hot flushes, and visual disturbances. With respect to exogenous testosterone therapy, Clomiphene citrate provided an affordable and fertility-sparing alternative in men with idiopathic infertility or hypogonadism. In summary, clomiphene citrate is a potent, safe, and cost-effective therapy for male infertility, yet heterogeneity of dosage, duration, and response underscores the necessity for adequately designed, long-term clinical trials to standardize treatment regimens and measure reproductive outcomes.*

***Keywords*—** *Clomiphene citrate; Male infertility; Semen parameters; Hypogonadism; SERM; Testosterone; Luteinizing hormone; Follicle-stimulating hormone; Spermatogenesis; Oxidative stress; Systematic review.*

I. Introduction

Male infertility accounts for almost 50% of all global cases of infertility and contributes to an estimated 8–12% of reproductive-age couples (69). Of the more common causes, idiopathic oligozoospermia and hypogonadotropic hypogonadism are most prevalent, which are frequently joined by defective spermatogenesis and inadequate hormonal control. Even with improvement in assisted reproductive technology, pharmacological therapy that can correct normal endocrine balance and enhance semen quality is still limited (69).

Clomiphene citrate (CC), a nonsteroidal selective estrogen receptor modulator (SERM), was initially discovered for the treatment of anovulatory infertility in women but has been extensively used off-label in men with hypogonadism and idiopathic infertility (70). Its action is based on competitively binding to estrogen receptors at the hypothalamus and pituitary gland, thus blunting adverse estrogenic feedback, stimulating gonadotropin (LH and FSH) release, and ultimately inducing endogenous testosterone secretion and spermatogenesis (71). In contrast to exogenous TRT, clomiphene citrate preserves intratesticular testosterone and spermatogenesis, providing an efficient oral alternative with fewer negative impacts on fertility (72).

Over the past decade, various clinical trials and meta-analyses have evaluated the effect of clomiphene citrate on semen parameters—sperm concentration, motility, and morphology—on hormonal profiles and on molecular markers of sperm function. The results have been inconsistent because of heterogeneity in study design, duration of treatment, and selection criteria for patients (73). Hence, a systematic review of published literature is needed to synthesize the evidence, evaluate clinical effectiveness, and determine knowledge gaps.

This systematic review is intended to assess the effectiveness of clomiphene citrate in enhancing semen parameters and hormonal profiles among infertile men as well as debating its pharmacological characteristics, relative effectiveness, safety, and therapeutic use in men's reproductive health.

Aim:

To provide a systematic overview of efficacy of clomiphene citrate in improving semen parameters in infertile men.

Objectives:

1. *Primary Objective:*
   - To systematically evaluate the efficacy of clomiphene citrate in improving semen parameters.
2. *Secondary Objectives:*
   - To assess the impact of clomiphene citrate on hormonal profiles (testosterone, LH, FSH, and estradiol levels).
   - To compare the clinical effectiveness of clomiphene citrate with other hormonal and non-hormonal treatment options used in male infertility.
   - To analyze the dose and duration dependent therapeutic outcomes of clomiphene citrate in male reproductive function.

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- To summarize the safety profile, adverse effects, and long-term tolerability of clomiphene citrate in male patients.

Need for the Study:

- ✓ Current pharmacological treatments for male infertility, such as exogenous testosterone therapy, often suppress spermatogenesis and compromise fertility potential.
- ✓ Clomiphene citrate (CC), a selective estrogen receptor modulator, offers an oral, cost-effective alternative that can enhance endogenous testosterone and spermatogenesis without affecting sperm production.
- ✓ Despite its long-standing clinical use, evidence regarding the efficacy of clomiphene citrate in improving semen parameters remains inconsistent across studies.
- ✓ Variability in study designs, dosing regimens, and duration of treatment contributes to uncertainty about its therapeutic outcomes.
- ✓ This study will help to establish evidence-based recommendations for the use of clomiphene citrate and to identify knowledge gaps for future clinical research.

II. METHODOLOGY

Study Design: A Systematic Overview

Search Strategy:

Databases Searched:

PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, and ResearchGate.

Search Terms/Keywords Used: Clomiphene citrate, Male infertility. Semen parameters, Oligospermia, Hypogonadism, Testosterone, Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Spermatogenesis, Hypothalamic–pituitary–gonadal (HPG) axis, Selective estrogen receptor modulator (SERM), Sperm motility.

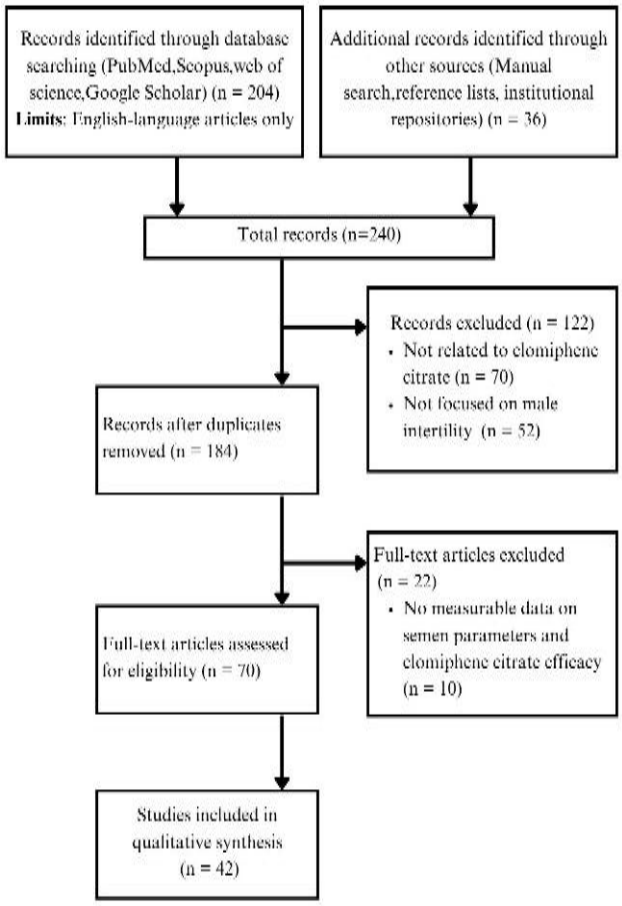
Inclusion Criteria

- Clinical trials, observational studies or systematic reviews assessing the effect of clomiphene citrate on semen parameters or hormonal profiles in men.
- Studies involving infertile or hypogonadal men receiving clomiphene citrate as monotherapy or in combination with other agents.
- Studies reporting quantitative outcomes (e.g., sperm concentration, motility, morphology, testosterone, LH, FSH).

Exclusion Criteria

- Animal or in-vitro studies.
- Case reports, editorials, or conference abstracts lacking quantitative data.
- Studies focusing solely on female infertility or non-reproductive outcomes.
- Articles with incomplete data.

Study Search Diagram:



III. DISCUSSION

Pathophysiology of Hypogonadism and Oligozoospermia

Male hypogonadism is a polyetiologic disorder caused by gene defects, anatomical malformations, infection, trauma, tumors, systemic disease (e.g., diabetes mellitus, cirrhosis, renal failure), or iatrogenic origin such as specific drugs and alcoholism. Pathophysiologically, it expresses dysregulation of the hypothalamic–pituitary–gonadal axis in the form of either primary (testicular dysfunction with low testosterone and high LH/FSH) or secondary (inadequate GnRH/LH/FSH secretion resulting in low testosterone). Testosterone is responsible for sexual function, cognition, mood regulation, muscle strength, bone density, and fat distribution. Deficiency can cause sexual dysfunction, infertility (oligospermia/azoospermia), anemia, sarcopenia, decreased bone mass, central adiposity, depression, and cognitive impairment. Altered androgen signaling also results in erectile dysfunction due to impaired nitric oxide synthase activity and corpora cavernosa structural changes. Therefore, both systemic and local consequences of testosterone deficiency are responsible for the clinical features of hypogonadism(23)

Endogenous Testosterone Stimulation

Bagatell et al. examined the impact of endogenous testosterone (T) and estradiol (E2) on sexual behavior in healthy young men by creating acute hypogonadism through a GnRH antagonist (Nal-Glu) with different androgen

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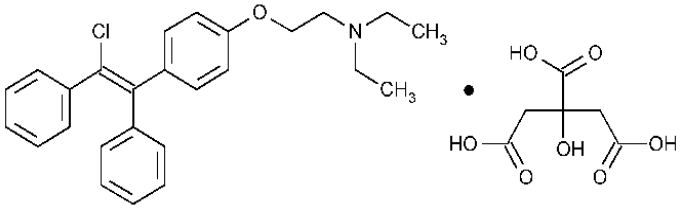
replacement regimens. The findings of the study are Acute hypogonadism induced in normal young men caused significant reductions in sexual desire, fantasies and intercourse following 4-6 weeks, but which were reversed when testosterone levels were restored to normal; partial replacement with testosterone at half the physiological dose was found to preserve sexual function, while selective estradiol depletion had no major effect on sexual or aggressive behaviors, highlighting the crucial role of physiological testosterone for sexual function and the secondary role of peripheral estradiol in normal men(24).

Previous off-label use of Clomiphene in male infertility

Clomiphene citrate (CC), initially approved for female ovulatory dysfunction, has been used off-label in male infertility for many years to augment endogenous testosterone and spermatogenesis by stimulating the hypothalamic–pituitary–gonadal axis. Various clinical trials have investigated its effectiveness. A large retrospective report of 151 men receiving at least 25 mg/day of CC showed significant improvement in sperm concentration and total motile sperm count, indicating a possible therapeutic role in oligospermic men (50). In a meta-analysis and systematic review by Huijben et al. (2023), clomiphene was also found to be used extensively off-label for hypogonadism and male infertility with evidence of improved semen parameters and hormonal profiles in some, but not all, trials (1). Equally, a recent review on empirical drug treatment for male infertility noted that CC improves release of gonadotropins and raises testosterone and spermatogenic activity, although there has been variability in the clinical response (51). However, previous WHO double-blind studies found no significant difference in pregnancy rate or semen parameters compared to placebo, reflecting inconsistent effectiveness (52). In general, although CC is an off-label but commonly used therapy for idiopathic male infertility, its outcome seems to be influenced by baseline hormone status, length of therapy, and intrasubject variability (53).

Structural Relationship Activity of Clomiphene Citrate:



The structure–activity relationship (SAR) of clomiphene citrate reveals how specific chemical features contribute to its selective estrogen receptor modulation. The drug possesses a triphenylethylene backbone, which is essential for mimicking the natural estrogen, estradiol, and for effective binding to estrogen receptors (ERs) through its planar configuration that fits into the receptor's hydrophobic pocket (65). The para-hydroxyl group on one phenyl ring forms critical hydrogen bonds with amino acid residues in the ER ligand-binding domain, a key determinant for receptor recognition and affinity (66). The chloro-substituted phenyl ring enhances lipophilicity and stabilizes receptor binding, favoring anti-estrogenic conformations particularly in hypothalamic tissue, where clomiphene blocks estrogen's negative feedback, thereby stimulating gonadotropin (LH and FSH) release (67).

Additionally, the ethylaminoethoxy side chain influences the compound's agonist/antagonist balance by interacting with the receptor's helix 12 domain, preventing the conformational change needed for coactivator binding and transcriptional activation—hence promoting anti-estrogenic effects at the hypothalamic–pituitary axis (65,68). Clomiphene exists as two geometric isomers: enclomiphene (trans) and zuclomiphene (cis). Enclomiphene exhibits stronger anti-estrogenic activity, primarily responsible for enhancing LH and FSH secretion, while zuclomiphene demonstrates partial estrogenic activity, contributing to prolonged pharmacologic effects (67). The citrate salt form improves oral solubility and bioavailability without altering receptor affinity (66).

Overall, these structural features enable clomiphene citrate to act as a competitive estrogen receptor antagonist in the hypothalamus and a partial agonist in peripheral tissues, making it an effective oral therapy for male hypogonadism and infertility through endogenous stimulation of the hypothalamic–pituitary–gonadal axis (67,68).

Pharmacological Profile of Clomiphene Citrate:

Mechanism of action

Male hypogonadism can be treated with clomiphene citrate, a SERM (Selective Estrogen Receptor Modulator) that was first created for female infertility. Clomiphene blocks estrogen receptors in the hypothalamus arcuate nucleus and competitively inhibits 17β-estradiol. By stimulating the synthesis of gonadotropin and upsetting the negative feedback of estrogen in the pituitary and hypothalamus, this action causes endogenous testosterone release. In contrast to TRT, clomiphene can sustain elevated levels of FSH, LH, and intratesticular testosterone, which enhances spermatogenesis and boosts sperm concentration and motility. Moreover, clomiphene's inexpensive cost, excellent safety profile, and little side effects make it a better option for long-term use than TRT. [1]

Estrogen has a classical negative feedback action at the hypothalamus, in which increasing levels of estradiol inhibit gonadotropin-releasing hormone (GnRH) neuron discharge, resulting in decreased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release. This has been clearly demonstrated in animal and human models, where estradiol suppresses GnRH neuron firing and reduces hypothalamic drive to the pituitary [2,3]. Current neuroendocrine reports validate that estradiol regulates fertility and reproductive function by modulating the hypothalamic–pituitary–gonadal (HPG) axis by means of estrogen receptor-α signaling [4,5].

Men's HPG Axis: The HPG axis coordinates in a cascade manner to govern reproductive activities in both sexes. In males, the hypothalamus, pituitary gland, and testes make up the HPG axis. Gonadotropin-releasing hormone (GnRH) is physiologically secreted by the hypothalamus in a pulsatile rhythm. The pituitary gland receives GnRH, which promotes the production of the gonadotropins FSH and LH. LH promotes the secretion of androgens, such as testosterone, within Leydig cells. Male sex differentiation, physiologic

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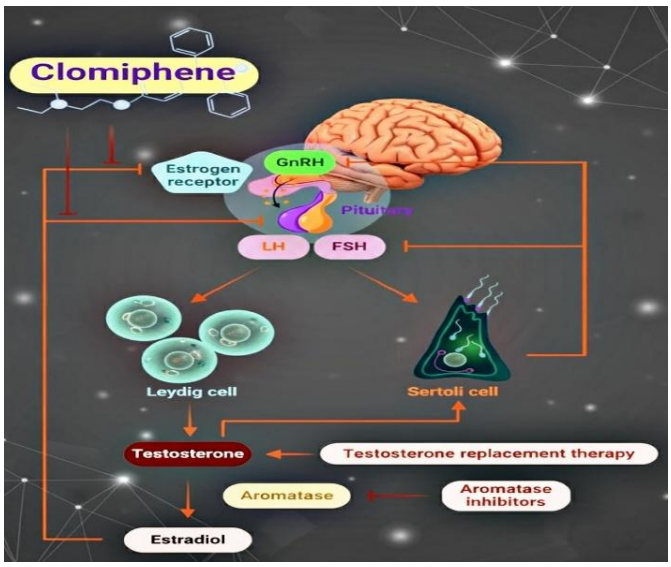
processes, and sexual function are all significantly influenced by testosterone [6]. FSH maintains the milieu for spermatogenesis [8] and works on Sertoli cells, encouraging the creation of aromatase enzymes and androgen-binding proteins [7].



Pharmacokinetics and pharmacodynamics

The selective estrogen receptor modulator (SERM) clomiphene undergoes relatively good oral absorption, high enterohepatic recirculation-with the result of a long half-life of 5 to 7 days, and traces may be found up to 6 weeks with a single dose (9). It is highly bound to plasma proteins (>98%), metabolized primarily by the liver (cytochrome P450), and fecal excretion is the predominant elimination pathway (9,10). Pharmacodynamically, clomiphene is an estrogen antagonist at the pituitary and hypothalamus, which blocks inhibitory estrogen feedback and thus enhances secretion of GnRH, leading to FSH and LH release (9,10). In women, it enhances follicular growth and ovulation, whereas in men it increases testosterone secretion and spermatogenesis (10,11). Its agonist–antagonist activity mixture also accounts for partial estrogenic effects on tissues such as bone and endometrium that are responsible for both therapeutic effects and side effects (9,10).

Comparison with other hormonal and non-hormonal treatments

In comparison to other hormonal agents, clomiphene citrate has an additional advantage of stimulating endogenous testosterone and spermatogenesis. It indirectly stimulates without feedback inhibition of the hypothalamic–pituitary–gonadal (HPG) axis. clomiphene in contrast to exogenous testosterone therapy, which typically enhances serum testosterone at the expense of sperm production through feedback inhibition (11,12). Direct stimulation of Leydig cells to yield testosterone by Human Chorionic Gonadotropin therapy is able to restore fertility but is inconvenient in the form of injections and more expensive (12). Aromatase inhibitors like anastrozole or letrozole decrease estrogen levels and thus enhance gonadotropin release; they are especially helpful in men with obesity or elevated estradiol but can produce side effects of bone loss from low estrogen (13). By comparison, non-hormonal interventions such as antioxidant supplementation (e.g., L-carnitine, vitamin E, coenzyme Q10) attack oxidative stress, a main player in the pathogenesis of sperm dysfunction, and have reported modest gains in semen parameters though evidence is still heterogeneous (14). Surgical interventions like varicocelectomy treat anatomical causes of infertility. It may improve semen quality in carefully selected men but are invasive and patient-specific (15). As a whole, clomiphene citrate shows—oral, cheap, and capable of enhancing both hormonal equilibrium and spermatogenesis—and is thus better than exogenous testosterone in males wishing for fertility, although individualized therapy must still be followed.

Clinical Evidence on Semen Parameters:

1) Impact on sperm concentration/oligospermia- Clomiphene citrate has shown a consistent beneficial effect on sperm concentration, especially in patients with oligospermia. Through stimulation of FSH and LH release, it causes increased spermatogenesis and testosterone secretion with consequent increases in sperm counts. Various clinical trials record an increase in sperm concentration by 2–3 times following 3–6 months of treatment, and hence it is particularly useful in men with low initial counts (16).
2) Impact on sperm motility- Sperm motility has also been found to improve with clomiphene treatment due to increased Sertoli cell function and better intratesticular hormonal equilibrium. Improvement varies, but in some men is quite evident, in others little change occurs, implying patient-variable response (17).
3) Impact on sperm morphology- The effect of clomiphene citrate on sperm morphology is less certain. Some series have shown modest gains in normal forms of sperm, whereas others have noted no difference from baseline. This lack of consistency suggests that morphology is perhaps less responsive to hormonal treatment compared with concentration or motility and that further supportive therapies might be needed (12).
4) Impact on Sperm DNA Fragmentation & Oxidative Stress Markers- In addition to traditional semen parameters, clomiphene citrate has exhibited beneficial impacts on molecular sperm quality markers. Clinical trials have proven decreases in DNA fragmentation index (DFI) and enhancement of seminal antioxidant function, including superoxide dismutase and catalase activity increase, with oxidative stress markers decrease such as malondialdehyde. These effects indicate that clomiphene not only enhances sperm number and motility, but also increases sperm function at the molecular level, which can contribute to improved fertilization and pregnancy rates (20).
5) Dose and duration dependency of effects- Clomiphene citrate's effects on semen parameters and on hormonal equilibrium are dose-dependent. Doses ranging from 25–50 mg daily or every second day are commonly employed in most studies and are sufficiently effective in

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raising LH, FSH, and testosterone without serious adverse effects (17,21). Increased dosing (≥100 mg/day) has been linked to paradoxical gonadotropin suppression because of receptor desensitization, and augmented risk for side effects like visual disturbances and mood changes (21). Hence, low-to-moderate dosing is optimal to result in sperm concentration and motility improvements and yet ensure safety. The beneficial therapeutic effects of clomiphene are also time-dependent because they mirror the long spermatogenesis cycle (circa 74 days). Clinical trials indicate that at least 3 months of treatment is required to notice significant changes in sperm concentration and motility, with optimal effects typically occurring after 6 months of sustained therapy . Prolonged courses lasting longer than 6–9 months might sustain enhanced semen quality but do not always provide added benefit, and treatment is typically re-evaluated at this point to see if ongoing need exists . Significantly, antioxidant gains (e.g., decreased DNA fragmentation and oxidative stress) also become apparent following several months of treatment, consistent with cycles of sperm generation (19).

Impact on Hormonal Profile:

1) Effect on Testosterone Levels- Clomiphene citrate elevates total and free testosterone levels substantially by inducing secretion of endogenous LH, which in turn stimulates Leydig cells. It has no effect on suppressing spermatogenesis, unlike exogenous testosterone therapy, and is thus an ideal choice in hypogonadal men who wish to preserve fertility. All clinical trials have confirmed testosterone elevations in the mid-normal or even high-normal range of physiology following dosing with 25–50 mg/day, accompanied by symptomatic improvement in libido and energy (17).
2) Alterations in LH, FSH, and Estradiol- Pharmacologically, clomiphene competes with estrogen receptors in the hypothalamus and pituitary, decreasing inhibitory estrogen feedback. This results in an increase in GnRH, which induces pituitary release of LH and FSH. LH mainly elevates intratesticular testosterone, whereas FSH maintains Sertoli cell function and spermatogenesis (21). Estradiol levels might even increase slightly from heightened peripheral aromatization of the increased testosterone, but these tend to fall within normal ranges of physiology.
3) T/E2 Ratio and Its Significance- One of the crucial clinical benefits of clomiphene treatment is an improvement in the ratio of testosterone to estradiol (T/E2). An impaired T/E2 ratio has been related to abnormal spermatogenesis, erectile dysfunction, and risk factors for metabolism. Clomiphene increases testosterone to a greater extent than estradiol and results in an enhanced T/E2 ratio. This balance is especially true in obese or infertile men, where heightened aromatase activity increases estradiol while inhibiting gonadotropins. Reconstituting a favorable T/E2 ratio improves not only reproductive potential but also general metabolic and sexual health (22).

Safety and Adverse Effects:

In clinical practice, clomiphene is generally thought to be a reasonably acceptable drug. However, it is linked to a number of negative effects because it functions as both an estrogen agonist and an antagonist. Side effects such headaches, hot flushes, and visual abnormalities can result from clomiphene's anti-estrogenic qualities [25,26]. Dizziness, gynecomastia, breast and nipple soreness, mood swings, and testicular enlargement are further side effects that have been described [27]. 400 patients who had clomiphene medication over an 8-year period were assessed in a retrospective analysis [37], with an emphasis on long-term results, especially those involving treatment durations longer than three years. According to that study, 77% of patients who took clomiphene for more than three years saw improvements in their hypogonadal symptoms, and 88% of them saw an increase in eugonadal testosterone levels.

With just 8% of patients reporting side effects, none of which were severe or resulted in long-term adverse events, clomiphene had a good safety profile in that long-term cohort. Mood swings, impaired vision, and breast soreness were the most often reported adverse effects, and these are in line with the known clomiphene side effects seen in shorter-term studies. However, two case investigations have documented significant hypertriglyceridemia caused by clomiphene [28,29]. We looked into how clomiphene therapy affected lipid markers in light of these results. Men with hypogonadism who were taking 25 mg of clomiphene daily had reduced levels of total cholesterol, according to Da Ros et al. [30].

Other studies, however, found no discernible decrease in total cholesterol levels [12,39]. Body mass index (BMI) before and during clomiphene medication has been studied in earlier research. Only one of these trials revealed a substantial drop in BMI following three years of clomiphene medication [38], whereas the others [98,99,31] showed no discernible changes in BMI before and during treatment. Polycythemia may result from elevated testosterone levels. Major adverse cardiovascular events, venous thromboembolic events, and stroke are more common in men with polycythemia [32,33]. TRT has been demonstrated to dramatically increase hematocrit and hemoglobin counts, especially in individuals undergoing intramuscular injections [32,34,35].

As a result, the FDA advises against using TRT because of secondary polycythemia, one of its principal side effects [41]. There is no evidence on the risk of secondary polycythemia in men undergoing clomiphene therapy, despite the fact that increased serum testosterone levels can also be seen during this treatment [38]. According to Wheeler et al. [42], men using clomiphene treatment have a substantially lower prevalence of polycythemia than men doing TRT (1.7% vs. 11.2%). A case report showed that patients receiving clomiphene medication experienced azoospermia, the opposite result. Following clomiphene medication, Pasqualotto et al. [36] also discovered azoospermia in oligospermia patients. To confirm the negative effects of clomiphene treatment on reproductive function, more research is necessary.

Comparative Efficacy:

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Clinical investigations comparing the efficacy of clomiphene citrate (CC) versus placebo, gonadotropins, aromatase inhibitors, and combination therapy have yielded positive but inconsistent findings. Clomiphene significantly improved hormonal and reproductive outcomes in studies with placebo control. Compared to a placebo, clomiphene increased sperm concentration and quality in males, while CC treatment increased mid-luteal progesterone and conception rates in infertile individuals (43,44). However, clomiphene citrate improved ovulation and clinical pregnancy rates, but its effect on live birth rates was uneven, according to a comprehensive Cochrane study (45). This suggests that the effectiveness of clomiphene citrate may vary based on the hormonal and the reproductive profiles of individual patients. Clomiphene exhibited comparable rates of ovulation and pregnancy to gonadotropins and aromatase inhibitors such as anastrozole; nevertheless, it was associated with higher levels of estradiol, which increased the risk of hyperstimulation.

In a randomized trial, women who received clomiphene plus FSH had more mature follicles than did those who received anastrozole, though conception rates were similar (46). Both clomiphene and anastrozole elevated testosterone in hypogonadal men, but clomiphene yielded a more desirable testosterone-to-estradiol ratio, signifying enhanced endocrine balance (12). Enclomiphene, a pure trans-isomer of clomiphene, has been as effective as testosterone-boosting with fewer anti-estrogenic disturbances, a more refined alternative to traditional CC therapy.

Combination therapy has also been found to have additional benefits in some patients. Treatment of men with clomiphene and anastrozole resulted in better total motile sperm count and a normalization of the testosterone-to-estradiol ratio than with either drug alone (47,48). In anovulatory and polycystic ovary syndrome (PCOS) women, the combination of metformin with clomiphene enhanced ovulation and pregnancy rates compared with clomiphene alone, particularly in women with insulin resistance (49). As a whole, clomiphene is still a mainstay in the treatment of infertility but reaches its highest therapeutic potential when tailored and, in certain cases, combined with agents that affect estrogen or insulin sensitivity.

Clinical Trial Evidences:

Recent clinical trials have routinely confirmed the therapeutic efficacy of clomiphene citrate (CC) in enhancing hormonal and reproductive parameters in hypogonadal and subfertile men. In a randomized controlled study, Busch et al. proved that CC significantly boosted circulating levels of LH, FSH, and total testosterone without affecting sperm production, suggesting effective HPG-axis stimulation (61). Likewise, Wheeler et al. summarized several clinical experiences and concluded that CC is effective and safe oral substitute to TRT that can restore eugonadal levels of testosterone with preserving fertility (62).

Combination regimens have proved to have even more promise—Schlegel et al. found that co-administration with anastrozole enhanced total motile sperm count and maximized the testosterone-to-estradiol ratio over monotherapy, indicating synergistic effects by estrogen modulation (63). Similarly, Habous et al. discovered that short-term administration of CC or hCG were both effective in raising serum testosterone in men with hypogonadism, with similar efficacy and good tolerability (64). Together, these results support clomiphene citrate as a cost-effective, fertility-sparing, and hormonally advantageous treatment for male hypogonadism and infertility management.

IV. Conclusion

This systematic review concludes that clomiphene citrate (CC) is a useful, cost-effective, and fertility-sparing treatment in men with idiopathic infertility and hypogonadism. Through its action as a selective estrogen receptor modulator, CC increases endogenous release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), increasing intratesticular testosterone levels and inducing spermatogenesis. Many clinical studies show marked improvement in sperm concentration and motility, with inconsistent improvement in morphology and markers of oxidative stress.

The drug's beneficial hormonal regulation, oral administration, and low side effects make it a reasonable option to exogenous testosterone treatment, especially in patients wanting to preserve fertility. Yet interstudy variation in dosage, duration of treatment, and outcome parameters emphasizes the necessity for large, well-controlled, long-term clinical trials to define standardized treatment regimens and affirm its impact on pregnancy and live-birth rates.

Overall, clomiphene citrate is a promising empirical treatment in the management of male infertility that possesses a good balance of efficacy, safety, and cost-effectiveness, and that preserves natural reproductive function by restoring physiologic hormones.

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