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Research Article

Clomiphene Citrate a First Step to Improve Idiopathic Male Infertility: A Retrospective Analysis

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Background. Infertility in men is a common and worldwide problem with limited registered treatment options and licensed therapies. Clomiphene citrate (CC) is an empirical off-label therapy. CC is a selective estrogen receptor modulator that may improve testicular function, including sperm quality, by stimulating steroidogenesis and spermatogenesis. However, there is a lack of evidence regarding the efficacy of CC as therapy for male infertility. *Objectives*. To assess the improvement of CC on sperm parameters, pregnancy, hypogonadism, and measurement of safety. *Methods*. In this retrospective study, 52 men treated with CC for idiopathic nonobstructive infertility were analyzed. Data of sperm parameters, pregnancy rate, hormonal values, side effects, improvement in hypogonadal symptoms, and potential predictors of treatment response were collected. *Results*. A total of 52 infertile men underwent CC treatment. An increase in sperm concentration was observed in 19 patients (37%). An upgrade in sperm concentration classification according to the WHO criteria was noted in 21% of the patients receiving CC therapy. Additionally, 15% of initially ineligible patients for intrauterine insemination became eligible during CC. In total, 33% of couples achieved pregnancy, either spontaneously or with assisted reproductive techniques (ART). Low-normal follicle-stimulating hormone and larger testis volume before CC treatment were predictors for better semen concentration during treatment. The retrieval rate was 75% for azoospermic patients who underwent testicular sperm extraction or percutaneous epididymal sperm aspiration, enough for intracytoplasmic sperm injection. With CC, testosterone levels increased and hypogonadal symptoms improved. Mild side effects were reported by 8% of patients. *Conclusion*. The results of this study contribute to the existing evidence that CC is a safe and noninvasive therapy for idiopathic infertile males. It could be considered as a step-up therapy before initiating more invasive ART procedures.

1. Introduction

Worldwide, infertility affects 10%–15% of couples [1]. According to the International Glossary on Infertility and Fertility Care, infertility is defined as the inability to achieve a clinical pregnancy after 1 year of regular unprotected sexual activity [2]. It is estimated that male infertility is solely responsible for infertility in 20%–40% of the cases [1]. Assisted reproductive techniques (ART) are commonly used to facilitate conception in infertile couples [3]. However, these techniques primarily focus on optimizing the use of low-quality semen rather than improving semen parameters. Moreover, ART is expensive and can be a burdensome process for the female partner [4].

As a prior step or to avoid ART, antiestrogens and antioxidants have been explored as less invasive and more affordable empirical therapies for male infertility. These agents are sometimes used as inducers or stimulators of spermatogenesis [3]. Clomiphene citrate (CC), an antiestrogen, has been utilized in the treatment of male hypogonadism [5, 6]. CC acts as a modulator of estrogen receptors in the hypothalamus and pituitary, leading to the stimulation of gonadotropic releasing hormone, luteinizing hormone (LH), and follicle stimulating hormone (FSH). Consequently, testosterone synthesis and spermatogenesis are promoted [7]. Despite encouraging findings from earlier studies regarding CC's ability to stimulate testosterone production and spermatogenesis [5], the US Food and Drug Administration (FDA) maintains its off-label status due to insufficient

evidence supporting its efficacy and safety in male infertility. The FDA recommends further research to establish the effectiveness of CC in male infertility [8].

Therefore, the objective of this retrospective cohort study is to contribute additional evidence on the efficacy of CC in idiopathic male infertility, as reflected by sperm parameters and pregnancy rates. Furthermore, the study aims to assess safety outcomes, hormonal values, and identify potential predictors of response to CC therapy.

2. Materials and Methods

A retrospective analysis was conducted on idiopathic, non-obstructive infertile males who received CC treatment between 2012 and 2021 at the University Medical Center (UMC) Utrecht, Netherlands. Patients were provided with counseling regarding the off-label use of CC. The study obtained ethical approval from the local Research Ethics Committee at UMC Utrecht, Netherlands (WAG/mb/20/500309).

2.1. Patient Population. The inclusion criteria for this study were as follows: age > 18 years, at least two pretreatment semen analyses conforming the diagnosis of infertility with a male factor, and documented semen analyses and hormonal evaluation before and during CC treatment. Patients with total testosterone (TT) levels <12.1 nmol/L were classified as hypogonadal. Patients with FSH levels >10.3 IU/L were classified as having elevated FSH [9, 10]. Exclusion criteria included CC in combination with testosterone replacement therapy, human chorionic gonadotrophin (hCG), aromatase inhibitors, or the use of these medications within 12 months prior to initiating CC.

2.2. Study Design. At the start of CC treatment, men received a dosage of 25 mg every other day or 25–50 mg daily if their body weight exceeded 100 kg. This was based on clinical experience and consensus at that time. The dosage was adjusted to 50 mg daily if there was an inadequate response in TT levels after 1–3 months (TT levels last under 12.1 nmol/L). Semen analyses were primarily conducted at the UMC Utrecht laboratory using the Medical Electronic System SQA-V Gold (Medical Electronic System, Los Angeles, CA). Some semen analyses were performed at other hospital laboratories, all following the World Health Organization 2010 standards. Data on therapy duration, patient characteristics (age, body mass index (BMI), obesity (BMI > 25 kg/m^2), smoking status, ultrasound determined testicular volume, and medical history (HIV, testicular surgery, DM, cardiovascular disease, Klinefelter syndrome diagnosis, malignancies, and polycythemia) were manually collected from patient files.

2.3. Primary Outcomes. The primary outcomes of this study were semen parameters at baseline and during treatment, assessed at least 3 months after treatment, and analyzed in the fertility laboratory of the UMC Utrecht or affiliated laboratories/hospitals. Semen parameters included sperm concentration ($\times10^6$/mL), sperm morphology (% normal), progressive sperm motility (%), total motility (%), semen volume (mL), VCM (volume × concentration × % motility),

total motile sperm count (TMSC) (volume × sperm concentration × total motility)/100%, sperm pH, abstinence time (days), and classification of patients based on concentration of mild oligospermia (concentration 5–15 × 10^6/mL), severe oligospermia (concentration 0–5 × 10^6/mL), or azoospermia (concentration of 0 × 10^6/mL) [11].

2.4. Secondary Outcomes. Secondary outcomes included:

(1) Pregnancy outcomes (pregnancy rate, time to pregnancy, spontaneous pregnancy, use of ART, successful pregnancy, and number of pregnancies).

(2) Hormonal assessment measured with immunoassay (Atellica®, Siemens, Erlangen, Germany), including TT, free testosterone (FT) from early morning blood draws (<11 am), LH, FSH, estradiol, sex-hormone binding globulin (SHBG), and albumin before and during follow-up (FU).

(3) Assessment of hypogonadal symptoms, scored by an experienced physician at baseline, with subjective symptom improvement evaluated during FU.

(4) Self-reported side effects during FU.

(5) Hematocrit (Ht), hemoglobin (Hb), thrombocytes, alanine aminotransferase, aspartate aminotransaminase, alkalic phosphatases, gamma-glutamyl transferase, and total prostate-specific antigen (PSA) before and during FU.

(6) Usage and type of ART during CC treatmen and results of ART.

2.5. Data Analysis. Data were recorded and tabulated using Microsoft Excel® software. Descriptive statistics were reported as number (%), mean (standard deviation (SD)), or median (interquartile range (IQR) first, third quartiles) for non-normally distributed data. Normality of continuous variables was assessed using the Shapiro–Wilk test, histograms, and normality-quantile plots. Paired sample *t*-test or Wilcoxon-signed rank tests were used to compare before and during treatment outcomes, depending on the normality assumption. Bivariate correlation was assessed using the Pearson test or Spearman test if the normality assumption was not met. Statistical significance was set at *p*-value ≤ 0.05. The data analysis was performed using SPSS (IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp.).

3. Results

3.1. Study Population. Initially, a total of 96 male patients using CC were screened for inclusion, out of which 52 patients met the inclusion criteria. The reasons for excluding 44 patients were no semen analysis was conducted during treatment (*n* = 31), CC was used in combination with hCG or tamoxifen (*n* = 3), no wash-out period longer than 12 months existed between testosterone replacement therapy and the start of CC therapy (*n* = 1), and loss to follow-up occurred before any hormonal evaluation or semen analysis (*n* = 9). Patient characteristics, comorbidities, and dosages at the start of treatment are provided in Table 1. The dosage was

Table 1: Patient characteristics at baseline.

Characteristics	Total 52 patients	
Age, mean $\pm$ SD (range), years	35.4 $\pm$ 6.6 (23–59)	($n = 52$)
Overweight (BMI > 25 kg/m^2), n (%)	25 (63)	($n = 40$)
BMI, median (IQR)	26.9 (24.1–29.6)	($n = 40$)
Current smoker, n (%)	7 (14)	($n = 50$)
Testis volume, mL		
Left testis, median (range)	13.5 (3.0–23.0)	($n = 44$)
Right testis, median (range)	14.4 (23.0–30.0)	($n = 46$)
Medical history, n (%)		
Orchiectomy	6 (12)	
Orchidopexy	8 (15)	
Diabetes mellitus	1 (2)	
Testicular tumor	5 (10)	($n = 52$)
Usage of TTh in past >1 year	6 (12)	
Elevated FSH*	23 (46)	
Hypogonadal hypogonadism**	48 (92)	
Dosage of CC therapy at start, n (%)		
25 mg/2 day	46 (88)	
25 mg/day	1 (2)	($n = 52$)
50 mg/2 day	4 (8)	
50 mg/day	2 (4)	

n, number of patients; BMI, body mass index; FU, follow-up; SD, standard deviation; IQR, interquartile range; TTh, testosterone replacement therapy. *Elevated follicle stimulating hormone > 10.3 IU/L. **Hypogonadal hypogonadism = total testosterone < 12.1 nmol/L.

increased in nine patients (17%) due to minimal TT response. The median duration of follow-up was 4 months (range, 2–15). Prior to treatment, 32 patients were azoospermic (62%), nine of them were cryptospermic (their semen analysis varied between azoospermia and cryptospermia), 17 had severe oligozoospermia (33%), and three had mild oligozoospermia (5%).

3.2. Semen Analyses. The effect of CC on semen parameters is presented in Table 2, categorized by sperm concentration classification before treatment. Ejaculate volume, percentage of normal morphology, pH, and abstention days remained similar before and during treatment. There was no change in sperm motility or morphology. However, sperm concentration increased during CC treatment. Specifically, there was an increase in sperm concentration in 19 out of 52 patients (37%). The median duration till change in sperm concentration was 4 months (range, 2–15). Eleven out of 52 patients (21%) had an upgrade in their sperm concentration classification. Four patients transitioned from azoospermia to severe oligozoospermia (including one cryptospermic patient), one patient shifted from severe to mild oligozoospermia, five patients progressed from azoospermia to normospermia, and one patient improved from severe oligozoospermia to normospermia. In the subgroup analysis based on infertility classification (Table 2), only the azoospermic group showed significant improvement in concentration. When using the cut-off of 5 million TMSC for intrauterine insemination (IUI), nine out of 49 patients (18%) who were initially ineligible became eligible for IUI. Patients with higher FSH before

CC had lower sperm concentration during CC treatment compared to patients with normal FSH before CC, with mean concentrations of 4.8×10^6/mL $\pm$ 22.2 and 9.4×10^6/mL $\pm$ 17.6, respectively (Figure 1). Patients with FSH >4 IU/L and <7 IU/L before treatment had the best response in sperm concentration.

3.3. Assisted Reproductive Techniques. During CC therapy, 25 patients (48%) underwent a form of ART. Among the nine patients who were eligible for IUI, only three patients underwent IUI. Six before treatment azoospermic patients achieved enough improvement of semen (to severe oligospermia) with CC for intracytoplasmic sperm injection (ICSI) without sperm retrieval procedures. The remaining 16 patients underwent testicular sperm extraction (TESE) ($n = 13$) or percutaneous epididymal sperm aspiration (PESA) ($n = 3$). Out of these 16 patients, 12 (75%) had usable sperm for ICSI.

3.4. Pregnancy. During treatment, 20 couples (38%) achieved pregnancy, either with or without ART, resulting in a total of 25 successful pregnancies. Eight couples experienced spontaneous pregnancy (15%), with four of them being azoospermic before CC treatment (50%). The median time until the first pregnancy was 12 months (range, 1–24). Among the six couples who underwent solely ICSI, three couples (50%) reached a total of four pregnancies. Among the 16 couples who underwent TESE or PESA, six (38%) achieved a total of nine pregnancies. All three couples (100%) who underwent IUI, successfully achieved pregnancy, resulting in a total of four pregnancies.

3.5. Hormonal Evaluation. Hormonal parameters are presented in Table 3. The initial measurement was taken at a median of 1.3 months (range, 1–6). Forty-eight patients (92%) had biochemical hypogonadism before treatment. With CC, 43 patients (83%) achieved TT levels above the biochemical hypogonadism threshold of 12.1 nmol/L. During the first measurement of treatment, the mean TT increased from 8 to 18 nmol/L, representing a biochemical increase in 49 patients (94%). The mean FSH level before treatment was 13.4 IU/L, which increased to 20.3 IU/L during the first measurement of treatment. Mean levels of TT, FT, LH, FSH, and SHBG showed significant increases during the first measurement ($p \leq 0.05$).

3.6. Hypogonadal Symptoms. Seventeen patients, in addition to fertility issues, had biochemical hypogonadism. Among them, 14 patients (82%) experienced symptomatic manifestations, such as erectile dysfunction ($n = 6$), decreased libido ($n = 9$), and fatigue ($n = 11$). Three patients were asymptomatic but had TT levels below 12.1 nmol/L (18%) as reason for treatment. Fifteen patients (88%), including one patient who was symptomatic in hindsight, reported subjective improvement in symptoms and continued CC therapy for the indication of hypogonadism. The median duration until symptom improvement was 3 months (range, 1–12). The reported improvements in symptoms included erectile dysfunction ($n = 6$), libido ($n = 7$), and fatigue ($n = 13$).

3.7. Safety Aspects and Side Effects. None of the patients exhibited elevated levels of Hb, Ht, or PSA above the normal

TABLE 2: Semen parameters before and during CC treatment.

	Median (IQR) before CC	Median (IQR) after CC	p-Value
All patients (n = 52)			
Volume (mL)	2.9 (2.0–3.5)	2.8 (1.8–3.9)	0.633
Concentration (10^6/mL)	0.0 (0.00–0.3)	0.01 (0.0–1.7)	**0.042***
Progressive motility (A)	0 (0.0–1.0)	2 (0–22)	**0.001***
Total motility (A + B)	0 (0.0–11.0)	0 (0–32)	**0.001***
Morphology (% normal)	0.0 (0.0–0.0)	0.1 (0.1–2.1)	0.106
TMSC (10^6/mL)	0.0 (0.0–6.5)	0.0 (0–158)	**0.003***
pH	8.3 (8.1–8.7)	8.3 (8.1–8.7)	0.547
Abstention days	4 (3–5)	4.0 (3.0–4.8)	0.137
Mild oligozoospermic (n = 3)			
Volume (mL)	2.3 (2.2–4.3)	2.2 (1.8–3.3)	0.199
Concentration (10^6/mL)	9.8 (5.9–9.9)	12.1 (5.0–13.4)	0.285
Progressive motility	5.0 (1–14)	20 (6–35)	0.109
Total motility	11.0 (9–29)	25.0 (19–48)	0.109
Morphology (% normal)	1.0 (0–1)	4.0 (0–7)	0.285
TMSC (10^6/mL)	3.8 (1.4–6.5)	11.1 (1.7–12.8)	0.109
pH	n.a.	n.a.	n.a.
Abstention days	4.0 (3–4)	2.0 (2–4)	0.180
Severe oligozoospermic (n = 17)			
Volume (mL)	2.3 (0.2–4.3)	2.3 (0.5–4.9)	0.825
Concentration (10^6/mL)	0.3 (0.1–3.5)	0.7 (0.0–41)	0.962
Progressive motility	3.0 (0–35)	7.0 (0.0–51)	0.263
Total motility	13 (0–46)	25 (0–55)	0.132
Morphology (% normal)	1.0 (0–7)	1.0 (0–5)	0.550
TMSC (10^6/mL)	0.1 (0–3.7)	0.3 (0–10.7)	0.532
pH	8.3 (6.5–9.2)	8.4 (7.9–8.5)	0.102
Abstention days	5.0 (1–10)	4.0 (1–7)	0.058
Azoospermic (n = 32)			
Volume (mL)	2.9 (2.1–3.7)	3.0 (2.2–4.0)	0.736
Concentration (10^6/mL)	0.0 (0.0–0.0)	0.0 (0.0–0.2)	**0.004***
Progressive motility	0.0 (0.0–0.0)	0.0 (0.0–7.8)	**0.003***
Total motility	0.0 (0.0–0.0)	0.0 (0.0–20.5)	**0.005***
Morphology (% normal)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	**0.017***
TMSC (10^6/mL)	0.0 (0–0)	0.0 (0.0–158)	**0.005***
pH	8.5 (8.1–8.7)	8.3 (8.1–8.6)	0.210
Abstention days	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.968

CC, clomiphene citrate; SD, standard deviation; IQR, interquartile range; n, number of patients; n.a., not available; n.s., not significant; TMSC, total motile sperm count. *$p \leq 0.05$. Mild oligospermia = sperm concentration of $5–15 \times 10^6$/mL. Severe oligospermia = sperm concentration of $0–5 \times 10^6$/mL. Azoospermia = sperm concentration of 0×10^6/mL. Bold values signify significant outcomes.

range (Table 3). Side effects were reported in four patients (8%). One patient experienced severe perspiration, and three patients complained of agitation, although these side effects were not severe enough to warrant discontinuation of CC therapy. During treatment, two azoospermic patients experienced a decrease in testosterone levels, from 6.1 to 3.7 nmol/L and from 6.4 to 1.4 nmol/L, respectively, at the first measurement after starting treatment. These patients discontinued therapy due to this reverse effect.

3.8. Correlations. See Table 4 for correlations. FSH and LH in the lower range of normal before treatment showed a significant association with higher sperm concentration during treatment ($p = 0.000$, $r = -0.487$ and $p = 0.045$, $r = -0.282$,

respectively). If corrected for orchiectomy a larger testis volume right and left before treatment was associated with higher sperm concentration during treatment ($p = 0.031$, $r = 0.330$, and $p = 0.025$, $r = 0.346$, respectively), with a testis volume >18 mL having the best response. A lower BMI before treatment was found to be correlated with a higher pregnancy rate during treatment ($p = 0.014$, $r = -0.384$) and higher TT levels ($p = 0.009$, $r = -0.410$).

4. Discussion

In the present study, a total of 52 infertile male patients underwent CC therapy to assess its effectiveness in improving sperm parameters in men with infertility. The study
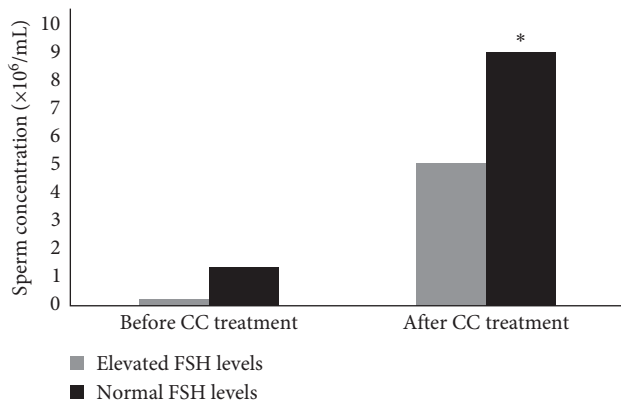
FIGURE 1: Before and after treatment sperm concentration for pre-treatment normal vs. elevated FSH infertile male patients. CC, clomiphene citrate. *Significant difference between the two subgroups ($p = 0.015$).

findings reveal that during CC treatment, 37% of the patients experienced an increase in sperm concentration, and 88% of the infertile patients with hypogonadal symptoms reported symptom improvement. FSH levels >4 and <7 IU/L and a testis volume >18 mL before CC treatment appeared to be predictive factors for treatment response and in 75% of azoospermic patients CC led to a retrieval rate enough for ICSI after TESE or PESA. Along with analyzing semen and hormonal parameters and assessing side effects, this study focused on the pregnancy rate and predictive factors of treatment response.

The mean sperm concentration increased from $0.9 \pm 2.2 \times 10^6$/mL before treatment to $7.3 \pm 19.8 \times 10^6$/mL during treatment. This increase appears to be consistent with a meta-analysis on CC therapy for infertility, which reported a mean difference in sperm concentration before and during treatment of 8.38×10^6/mL in 15 studies [12]. Among 19 patients (37%), there was an increase in sperm concentration to some degree. The response rates observed in this study are similar to those found in two other recent retrospective cohort studies ($n = 140$–151) [13, 14] but lower than those reported in the smaller study by Surbone et al. [15] ($n = 18$). The divergence in response rates could be attributed to variations in the definition of response rates and inclusion criteria. Additionally, in 11 out of 52 patients (21%), there was improvement in the classification of sperm concentration, thereby avoiding the need for more invasive and expensive forms of ART.

When applying a cut-off of >5 million TMSC as the minimum requirement for IUI, nine out of 49 patients (18%) became eligible for IUI who were not eligible before treatment [1]. This percentage was lower compared to the studies conducted by Lundy et al. [13] and Sharma et al. [14], which reported percentages of 25% and 37%, respectively. A possible explanation for this difference could be the inclusion of a higher proportion of azoospermic men in our study (62%), compared to the study by Lundy et al. [13] (13%) and Sharma et al. [14] (15%). However, we did not observe an increase in sperm motility. The literature presents conflicting findings

regarding changes in sperm motility, with studies reporting contradictory outcomes [13, 14, 16, 17]. The underlying cause for these differences remains unclear.

No patients had a downgrade of sperm concentration classification. The patients who varied before treatment between cryptospermia not enough for ICSI and azoospermia had azoospermia in the last measurement before TESE. Two case studies have reported lower sperm count and motility following CC treatment, but this potential reverse effect could not be confirmed in a large systematic review and meta-analysis involving 17 studies and a total of 537 participants [12]. Natural variation could explain the decrease in sperm concentration [18, 19].

In our study, 20 couples achieved pregnancy (38%) either with or without ART, resulting in a total of 25 successful pregnancies. Among them, eight couples experienced spontaneous pregnancy (15%), with a median time to conception of 12 months. These findings are consistent with the results of a systematic review that included 10 studies reporting pregnancy rates. The median pregnancy rate in that study was 12%, ranging from 0% to 40% [12]. Out of the 16 patients who underwent TESE or PESA, 12 had viable sperm for ICSI (75%). This retrieval rate is higher than the 50% reported in a previous systematic review and meta-analysis of Corona et al. [20]. Patients with lower baseline FSH and LH levels prior to treatment had higher posttreatment sperm concentrations, which aligns with the findings of Lundy et al.'s [13] study.

However, our study is the first defining a FSH level range that seems predictive of better sperm concentration outcomes. Additionally, we observed that a higher pretreatment BMI was associated with a lower pregnancy rate and a lower TT level during treatment. Furthermore, a larger testis volume (corrected for orchiectomy) before treatment was associated with higher sperm concentration during treatment, with the best response at a testis volume of >18 mL. Notably, a previous study of Sharma [14] did not find any predictors for sperm improvement, including BMI and FSH levels. We have no clear explanation for this difference in outcome. However, a possible explanation for a larger testis volume is that there is more testis volume that can be stimulated by CC for spermatogenesis.

The mean TT levels increased from 8 to 18 nmol/L, with a biochemical increase observed in 49 patients (94%). This finding is consistent with a systematic review and meta-analysis conducted on male hypogonadism [5]. Two patients had elevated FSH levels and a decrease in TT levels during CC treatment. As soon as this reversed effect on TT was detected, these patients immediately discontinued CC therapy. Previous studies have reported a reversed effect in less than 1% of cases [6, 13]. In our opinion, it is necessary to monitor this potential reversed effect closely to ensure timely discontinuation of treatment. Out of the 17 patients treated for clinical hypogonadism, 15 (88%) reported subjective improvement of symptoms. This improvement rate is even higher compared to previous studies, which reported improvement in approximately 75% of patients [6, 13]. Only 8% of patients described side effects, such as severe sweating and agitation. These levels of side effect are similar

TABLE 3: Hormonal evaluation and serum parameters before and during CC treatment.

Hormones	Before CC treatment	First measurement of CC treatment	One month with CC treatment	Three months with CC treatment	Six months with CC treatment	One year with CC treatment
TT (nmol/L)	8.3 ± 3.1 (n = 52)	17.6 ± 7.1* (n = 52)	17.0 ± 7.0* (n = 27)	17.5 ± 7.1* (n = 38)	19.1 ± 7.3* (n = 18)	21.0 ± 9.9* (n = 2)
FT (pmol/L)	177.5 ± 57.9 (n = 52)	379.3 ± 154.1* (n = 52)	353.2 ± 145.4* (n = 28)	390.7 ± 166.8* (n = 37)	397.4 ± 169.5* (n = 16)	365.0 ± 77.8* (n = 2)
LH (IU/L)	4.7 (3.2–6.1) (n = 51)	7.1 (5.7–11.5)* (n = 49)	7.0 (5.6–12.0)* (n = 27)	7.3 (5.0–9.3)* (n = 30)	7.9 (5.1–13.8)* (n = 16)	11.0* (n = 1)
FSH (IU/L)	13.4 ± 9.5 (n = 52)	20.3 ± 14.9* (n = 49)	19.8 ± 13.6* (n = 27)	11.0 (8.0–29.8) (n = 30)	23.0 ± 17.8* (n = 16)	22.0* (n = 1)
Estradiol (pmol/L)	109 (91–126) (n = 5)	102 (85–237) (n = 7)	237 (79–237)* (n = 3)	93 (79–327) (n = 4)	114 (71–144) (n = 2)	n.a.
SHBG (nmol/L)	24 (19–45) (n = 52)	33 (22–53)* (n = 51)	33 (19–45) * (n = 28)	28 (22–58) (n = 33)	33 (26–54)* (n = 18)	57 (34–57)* (n = 2)
Albumin (g/L)	44.4 ± 2.4 (n = 52)	43.9 ± 2.5 (n = 51)	43.8 ± 2.7 (n = 28)	43.7 ± 2.0 (n = 33)	43.2 ± 2.6 (n = 16)	41.5 ± 1.3 (n = 2)
Serum parameters						
Hematocrit (L/L)	0.44 ± 0.03 (n = 17)	0.44 ± 0.03 (n = 21)	0.44 ± 0.04 (n = 9)	0.46 ± 0.04 (n = 8)	0.46 ± 0.03 (n = 8)	n.a.
Hemoglobin (mmol/L)	9.2 ± 0.7 (n = 18)	9.4 ± 0.6 (n = 23)	9.3 ± 0.7 (n = 10)	9.3 ± 0.7 (n = 9)	9.7 ± 0.6 (n = 8)	n.a.
Thrombocytes (×10^9/L)	248 ± 59 (n = 17)	228 ± 57 (n = 21)	249 ± 62 (n = 8)	228 ± 46 (n = 7)	224 ± 57 (n = 10)	n.a.
ALAT (U/L)	22 (17–36) (n = 17)	21 (19–33) (n = 19)	19 (16–48) (n = 6)	22 ± 3 (n = 7)	24 ± 6 (n = 8)	n.a.
ASAT (U/L)	23 (20–27) (n = 16)	25 (21–28) (n = 18)	25 ± 5 (n = 6)	22 ± 4 (n = 5)	23 ± 5 (n = 8)	n.a.
AF (U/L)	80 ± 21 (n = 16)	70 ± 15 (n = 16)	77 ± 9 (n = 6)	71 ± 14 (n = 6)	67 ± 17 (n = 6)	n.a.
gGT (U/L)	24 (19–36) (n = 17)	24 (20–37) (n = 19)	32 ± 12 (n = 6)	26 ± 11 (n = 5)	29 ± 15 (n = 6)	n.a.
PSA (µg/L)	0.7 ± 0.3 (n = 43)	0.7 (0.5–0.8) (n = 21)	0.6 ± 0.1 (n = 5)	0.8 (0.5–0.9) (n = 9)	0.8 ± 0.4 (n = 8)	n.a.

Data are tabulated as mean ± SD or median (IQR). TT, total testosterone; FT, free testosterone; LH, luteinizing hormone; FSH, follicle stimulating hormone; SHBG, sex hormone binding globulin; n, number of patients; CC, clomiphene citrate; SD, standard deviation; ALAT, alanine aminotransferase; ASAT, aspartate transaminase; AF, alkalic phosphatases; gGT, gamma-glutamyl transferase; PSA, prostate-specific antigen; n.a., not available. *$p \leq 0.05$.

TABLE 4: Correlations between patient characteristics and outcomes during CC treatment.

	Sperm concentration		Total testosterone level		Pregnancy	
Age ($n = 52$)	$r = -0.041$	$p = 0.771$	$r = -0.041$	$p = 0.771$	$r = -0.13$	$p = 0.928$
BMI pretreatment ($n = 40$)	$r = -0.132$	$p = 0.415$	$r = -0.410$	$p = 0.009$	$r = -0.384$	$p = 0.014$
Smoker ($n = 50$)	$r = -0.175$	$p = 0.225$	$r = -0.054$	$p = 0.709$	$r = -0.138$	$p = 0.338$
Orchidopexy ($n = 52$)	$r = -0.093$	$p = 0.512$	$r = 0.057$	$p = 0.689$	$r = 0.081$	$p = 0.566$
Orchiectomy ($n = 52$)	$r = -0.084$	$p = 0.554$	$r = 0.076$	$p = 0.591$	$r = 0.169$	$p = 0.232$
Testis volume* left ($n = 44$)	$r = 0.346$	$p = 0.025$	$r = 0.278$	$p = 0.075$	$r = -0.037$	$p = 0.814$
Testis volume* right ($n = 46$)	$r = 0.330$	$p = 0.031$	$r = 0.287$	$p = 0.062$	$r = 0.015$	$p = 0.925$
FSH pretreatment ($n = 52$)	$r = -0.487$	$p = 0.000$	$r = -0.148$	$p = 0.294$	$r = -0.119$	$p = 0.401$
LH pretreatment ($n = 52$)	$r = -0.282$	$p = 0.045$	$r = -0.190$	$p = 0.183$	$r = -0.155$	$p = 0.277$

BMI, body mass index; CC, clomiphene citrate; FSH, follicle stimulating hormone; LH, luteinizing hormone; n, number of patients. *Testis volumes were corrected for orchiectomy in correlation analysis. Bold = significant difference ($p < 0.05$).

to those reported in previous studies, where side effects ranged from 4% to 11% [5, 6, 12]. We did not find any case of testicular cancer development. The FDA's 2012 report stated that gynecomastia and testicular cancer could occur during CC therapy. The report was based on a previous cohort study by Nilsson and Nilsson [21], which described two cases of testicular tumors in a cohort of 650 patients, one after the usage of CC therapy and one during CC therapy. However, this incidence seems comparable to the normal rate of testicular tumor development in this age group, which according to the American Cancer Society [22] is one in 250 men. Other previous studies on CC therapy in hypogonadal and/or infertile males also did not provide evidence of testicular tumor development [5, 12]. No elevations in Hb, Ht, and PSA levels above the normal range were observed in our study. Similarly, previous studies did not describe any effects on Hb, Ht, and PSA either [6, 23].

Despite the valuable insights gained from this study, several limitations need to be acknowledged. First, the retrospective design prevented the control of confounding factors, potentially introducing bias to the results. Second, the study included male patients with different etiologies of infertility, including normo- and hypergonadotropic individuals, leading to heterogeneity and limiting the generalizability of the findings to all infertility etiologies. Third, the systematic recording of side effects was lacking, which likely resulted in an underestimation of adverse events. Fourth, there was limited information available regarding the fertility of the female partners of the patients. Lastly, the study included only a small number of patients, so it is difficult to draw conclusion from these results. Notwithstanding these limitations, this study provides valuable insights into the effectiveness of this medication in the population of infertile males and can serve as a guide for future research in this area. The positive outcomes observed suggest potential benefits of CC treatment in particular for patients with FSH levels >4 and <7 IU/L with respect to sperm quality and a higher retrieval rate (75%) enough for ICSI in azoospermic patients who underwent TESE or PESA. CC remains an attractive therapy option due to its effectiveness and minimal side effects. However, further research using a randomized, placebo-controlled crossover design is necessary to determine the effectiveness of CC as inducer or stimulator of spermatogenesis before further ART.

5. Conclusion

This study shows that CC is an effective and safe treatment for infertile men, improving sperm concentration in one-third of men and leading to pregnancy (partly ART) in one-third of couples. One-fifth of the patients had an upgrade in sperm concentration category and one out of six patients who were pre-CC treatment ineligible for IUI became eligible for IUI. CC was more effective in patients with low-normal pretreatment FSH.

Data Availability

The raw data are available from the corresponding author upon request

Conflicts of Interest

There are no conflicts of interest.

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