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Clomiphene citrate effect on testosterone level and semen parameters in 18 infertile men with low testosterone level and normal/low gonadotropines level

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ABSTRACT

Objective: To determine the effect of a 3-month course of clomiphene citrate (CC) on plasma testosterone (T) level and on semen parameters in 18 infertile men with low T level and normal or low gonadotropines level.

Study design: A retrospective study was conducted by reviewing the medical records of men referred to a university fertility medicine unit for infertility management between January 2010 and March 2015. Men treated with CC for at least 3 months were included if they presented with:

- infertility
- plasma T level less than 11 nmol/l and low or normal FSH and LH levels
- sperm concentration >0.1 millions/ml.

Results: 18 patients met the inclusion criteria. CC was prescribed for 3 months at the dose of 50 mg every 48 h. Plasma T level was assessed at baseline and after 1 month of CC administration. Semen parameters were assessed at baseline and after 3 months of CC administration.
The median pre-treatment T level was 9.1 nmol/l; after 1 month of CC treatment the median post-treatment T level increased to 20.2 nmol/l ($p = <0.001$). Median baseline sperm concentration was 7 millions/ml with a median progressive motility of 18%. After 3 months of CC, the median post-treatment sperm concentration was 17.5 millions/ml ($p = 0.024$) and the median post-treatment progressive sperm motility was 18% ($p = 0.40$). Three natural pregnancies occurred during the treatment period.
Conclusion: CC is an effective and inexpensive treatment to increase plasma T level in infertile men with low T level and normal or low gonadotropines level. Our study suggests that CC could increase sperm concentration even in oligospermic infertile men, without, however, a significant effect on progressive sperm motility. More powered randomized controlled trials are needed to definitively assess CC effect on sperm parameters and on natural pregnancy rates.

Introduction

Clomiphene citrate (CC), a selective estrogen receptor modulator, binds to the hypothalamic estrogen receptors resulting in blockade of the estradiol negative feedback and causing an endogenous increase in follicle stimulating hormone (FSH) and luteinising hormone (LH) secretion. Clomiphene citrate is

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currently recommended to induce follicular development and ovulation in women with polycystic ovarian syndrome with chronic anovulation [1]. Since CC has been shown to increase testosterone (T) secretion by Leydig cells and potentially improve spermatogenesis by increasing FSH and LH secretion, its administration in infertile men with hypogonadism could represent an interesting therapeutic option [2]. The present study retrospectively determines the effect of CC administration on plasma T level and on semen parameters in 18 infertile men with low T level and normal or low gonadotropines level.

Subjects and method

Study design

A retrospective study was conducted by reviewing the medical records of men referred to a university fertility medicine unit for infertility management between January 2010 and March 2015.

Men treated with CC for at least 3 months were included if they presented with:

- infertility defined as the absence of pregnancy despite one year of unprotected regular intercourses
- Low plasma T level and low or normal FSH and LH levels
- sperm concentration >0.1 millions/ml.

The exclusion criteria were a history of genitourinary cancer, primary hypogonadism, secondary causes of hypogonadism such as Kallmann syndrome, previous cranial radiotherapy or intracranial neoplasia, testicular atrophy, anomaly of the epididymis or of the vasa deferens, abnormal karyotype, chromosome Y microdeletions, homozygous CFTR gene mutation, active genital or urinary tract infections and the presence of a clear female infertility factor (bilateral tubal occlusion, chronic anovulation, Ashermann syndrome, FIGO 0-2 fibroid, endometrial polyp or uterine septum).

Demographic data and clinical characteristics were collected for all patients including: age, body mass index (BMI), ethnicity, relevant comorbidities, duration and diagnosis of infertility, baseline and 3 months post CC treatment sperm assessment, baseline and 1 month post CC treatment hormonal measurements. Symptoms of hypogonadism were available in all patients at baseline, but in only 1 patient after CC treatment, thus precluding any statistical evaluation.

The main study outcome was to assess the difference between baseline and post-treatment T level, sperm concentration and progressive motility.

Statistical analysis

All descriptive statistics for baseline, 1 month and 3 months follow-up variables are recorded as mean, standard deviation (SD), median (p50), interquartile range (IQR), lowest value (Min) and highest value (Max). As T level and sperm concentration and motility did not follow a normal distribution, the non-parametric Wilcoxon signed-rank test was used to test the difference between baseline and post-treatment values. The Spearman's rank correlation coefficient was used to determine the correlation coefficient between the variation in plasma T level and sperm concentration, plasma T level and sperm progressive motility, sperm concentration and sperm progressive motility.

Ethics committee approval

The local ethics committee gave his approval for this retrospective study.

Results

Out of 284 patients referred to the university reproductive medicine unit for infertility assessment, 78 were diagnosed with low T level (<11 nmol/l). Of these 78 patients, 58 were excluded by

Table 1
Clinical single patient characteristics.

Patient	Age (Years)	BMI (kg/m^2)	Comorbidities	Infertility (years)	Baseline Symptoms
1	36	28	Perianal Paget disease, glaucoma, hypothyroidism, gastritis	6 (secondary)	–
2	28	24.8	Smoking	5	Reduced libido, asthenia
3	37	25.8	–	10	–
4	42	31.9	Hypertension, hypercholesterolemia	6 (secondary)	Reduced libido, Erectile dysfunction
5	43	28.1	Major depressive disorder	2	Reduced libido, irregular ejaculation, Asthenia
6	32	36.8	Previous correction of left varicocele	5	Reduced libido, Erectile dysfunction
7	31	29.1	Hypertension	10	–
8	40	25.1	–	4 (secondary)	–
9	23	28.1	Previous tonsillectomy, heterozygous CFTR mutation (G551D + normal)	2	↓ libido, premature ejaculation, normal vasa deferens, no epididymal dilatation
10	36	27.4	Previous left meniscectomy, previous cystoscopic correction of membranous urethral stenosis	1.5	↓ libido, asthenia, depressed mood
11	37	20.9	Left varicocele	2	–
12	45	?	Previous correction of left varicocele in 1991, mumps orchitis when child	2 (secondary)	–
13	28	24.2	Tonsillectomy, mumps orchitis when teenager	2	–
14	40	26	Hypertension	5 (secondary)	Erectile dysfunction, Depressive mood
15	30	26.1	Appendicitis with peritonitis, correction of left varicocele in 2005	2	–
16	48	33.8	Hypertension, type 2 diabetes, hepatic steatosis, previous appendicectomy, Thrombotic Thrombocytopenic Purpura	1.5	↓ libido
17	30	32.7	Previous meniscectomy	2 (secondary)	↓ libido, asthenia
18	42	31.2	Previous circumcision	2	↓ libido,

Abbreviation: BMI: body mass index.

the exclusion criteria. The remaining 20 patients presented with normal or low LH and FSH, and 18 of them met the inclusion criteria of a sperm concentration over 0.1 millions/ml.

The mean age of the patients was 36 years (range 23–48) with a mean BMI of 28.2 kg/m^2 (range 20.9–36.8). Primary infertility was diagnosed in 12/18 patients. The mean infertility duration was 3.9 years (range 1.5–10). All but 4 patients were Caucasian (1 patient was Somalian, 2 were Maghrebis and 1 was Hispanic).

Relevant comorbidities included metabolic syndrome, isolated high blood pressure, major depressive disorder, unilateral varicocele, obesity (BMI > 30 kg/m^2), hypothyroidism, previous mumps orchitis, previous urologic surgery and active smoking >10 cigarettes/day.

Oligospermic patients with <10 millions spermatozoids/ml underwent genetic investigations including karyotype and search for chromosome Y microdeletions. Search for CFTR gene mutations was performed when semen concentration was <5 millions/ml. Only 1 patient was found carrying a heterozygous CFTR mutation (G551D + normal).

All patients were assessed by a single urologist with a specific training in male infertility.

Clomiphene citrate was prescribed for 3 months at the dose of 50 mg every 48 h, corresponding to 25 mg/day. This dosage was chosen based on previous studies on CC in males and also because CC 25 mg is not available in Switzerland. Semen assessment and hormonal measurements were performed at baseline as part of the couple infertility investigations, within a month of the first visit. Plasma T level was then reassessed after 1 month of CC administration and semen assessment after 3 months of CC administration.

While data on post treatment semen progressive motility were missing in 4 patients, data on all other variables were available for all patients.

Clinical single patient characteristics are summarized in Table 1.

Laboratory assessments

Blood samples for plasma T, FSH and LH were collected between 7:00 and 10:00 AM. Testosterone, LH and FSH were measured by the university endocrine laboratory through, respectively, a competitive one-step immunoassay using a chemiluminescent microparticle technology (T) and an electrochemiluminescent immunoassay using two monoclonal antibodies (sandwich immunoassay) (FSH and LH). The laboratory reference ranges are 11–30 nmol/l for T, 2–9 U/l for LH and 2–12 U/l for FSH.

Semen assessment was performed in the university laboratory of andrology and reproductive biology. Semen samples were collected by masturbation after 2–5 days of sexual abstinence and examined following 30 min liquefaction at 37 °C. The samples were manually evaluated for volume and pH, and then assessed using optical microscopy for concentration and morphology. Concentration and motility (total and progressive) were also analyzed using the computer-assisted sperm analysis tool CASA SCA (5.4, Microptic SL, Barcelona, Spain). The 2010 World Health Organization (WHO) laboratory manual for the examination and processing of human semen – 5th ed., was strictly followed.

Effect on testosterone level

The median pre-treatment T level was 9.1 nmol/l (range 3.8–11.3). Median LH level was 3.5 IU/l (range 1.8–9) and median FSH level was 4.1 IU/l (range 1.8–16.8). As shown in Figs. 1 and 2, after 1 month of CC treatment, plasma T level increased in all patients with a median post treatment T of 20.2 nmol/l (range 14.4–33.4) and a median increment of 11.5 nmol/l (IQR 4.4, p = <0.001).

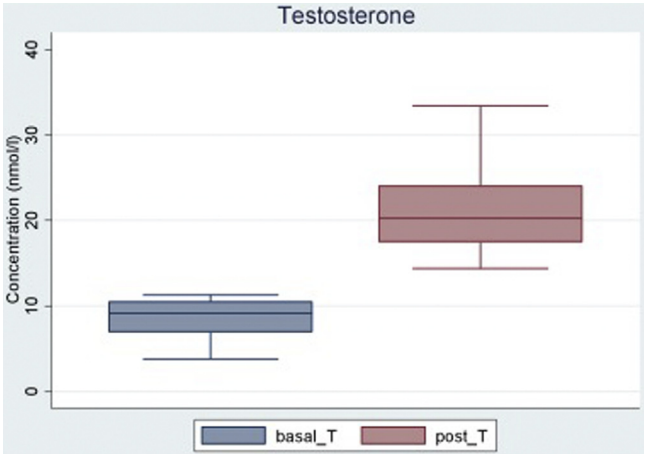

Fig. 1. Median T level, IQR and Min-Max range at baseline and after 1 month of treatment (*abbreviations:* T: testosterone).

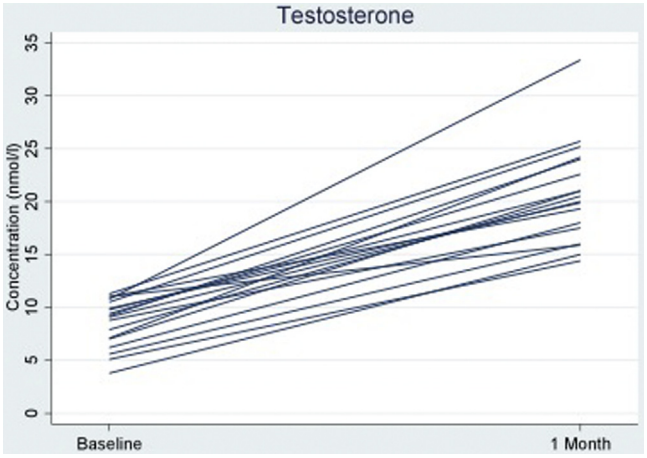

Fig. 2. T level variation for every patient.

Effect on semen parameters

The median baseline sperm concentration was 7 millions/ml (range 0.1–61). After 3 months of CC, the sperm concentration increased in 11/18 patients with a median post treatment sperm concentration of 17.5 millions/ml. The median increment was 3.1 millions/ml (IQR 9, p = 0.024). Despite this statistically significant increment, there is a slight variability in the sample population with 3 patients experiencing a decrease in sperm concentration. It must be noticed, however, that no normozoospermic patient became oligozoospermic while 5 out of the 13 patients presenting with oligozoospermia became normozoospermic at the end of the treatment (Figs. 3 and 4).

The median baseline progressive motility was 18% (range 0–68). After 3 months of CC, the median progressive sperm motility was 18% (range 1–68) with a clinically and statistically not relevant median increment of 0.5% (IQR 13, p = 0.40). We observed a marked variability in the results with an increase in the sperm progressive motility in 7/18 patients, a decrease in 5 of the men and stability in all the others (Figs. 5 and 6).

All baseline and post treatment statistics for T level, sperm concentration and progressive motility are summarised in Table 2, while Table 3 describes the single patient baseline and post treatment results.

After applying the Spearman's rank correlation coefficient, no correlation was found between the variation in plasma T level and

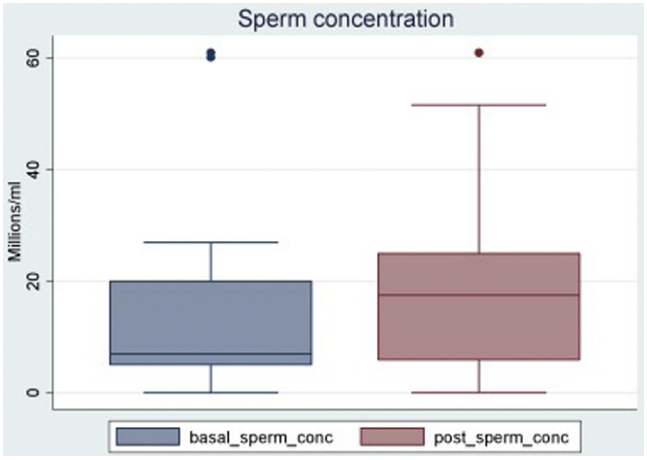

Fig. 3. Median sperm concentration, IQR and Min-Max range at baseline and after 3 month of treatment (*abbreviations:* conc: concentration).

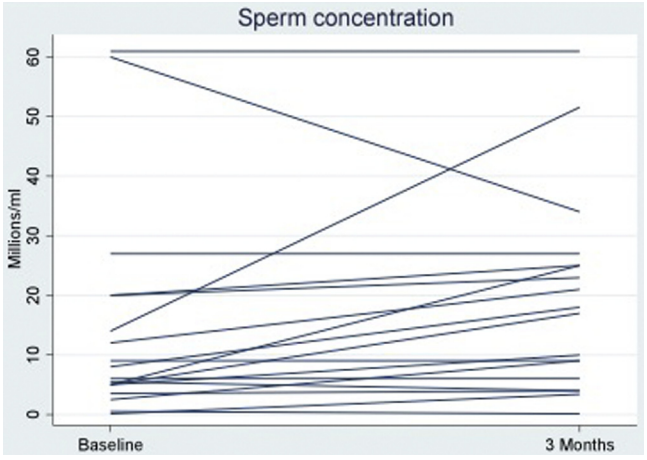

Fig. 4. Single patient sperm concentration variation.

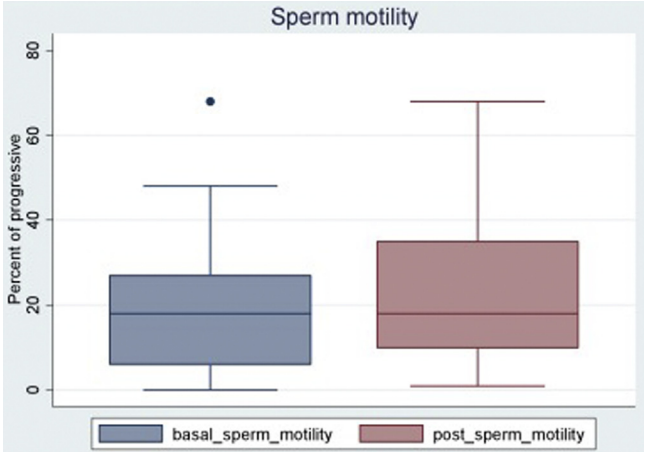

Fig. 5. Median value, IQR and Min-Max range for sperm progressive motility at baseline and after 3 months of treatment.

sperm concentration (Spearman's rho 0.17, p = 0.50), the variation in plasma T level and sperm progressive motility (Spearman's rho 0.18, p = 0.54) and the variation in sperm concentration and sperm progressive motility (Spearman's rho 0.16, p = 0.58).

Other results

Three natural pregnancies occurred during the treatment period with the delivery of 3 healthy babies at term and without any reported complication during gestation. All the couples that conceived naturally presented infertility duration of no more than 2 years. Two of the male partners (patients number 9 and 10) showed normozoospermia at the baseline semen assessment, while 1 patient (number 17) presented with oligozoospermia (9 millions/ml) that remained stable during the treatment period.

Data on post treatment symptoms were available for only 1 patient (number 9), who reported a slight improvement in libido after 3 months of CC treatment. There was no reported side effect during the treatment period and no patients reported weight gain or change in muscular mass.

Discussion

In the present study, 18 infertile men with low T level and normal or low gonadotropines level were prescribed CC 50 mg every other day. All patients experienced a significant increase in median plasma T level after 1 month of treatment. Data on the pre and post treatment semen assessment were collected for each patient and 11/18 patients showed an increase in sperm concentration, with a significant median increment of 3.1 millions/ml (p = 0.024). Despite a slight heterogeneity in the results, this increase in sperm concentration is statistically significant with 5 out of the 13 patients presenting with oligozoospermia becoming normozoospermic at the end of the treatment period.

No effect was observed on sperm progressive motility.

The effect of CC on T level is well established. As presented in a recent review of the literature, all studies published so far assessing T level after CC treatment (25–50 mg/day) have shown a significant increase in endogenous T, even after 36 months of treatment [3]. Use of CC in infertile men has been the object of several publications, with conflicting results. Following a preliminary study showing a beneficial effect of CC on sperm concentration in normogonadotropic infertile men [4], the World Health Organisation (WHO) conducted the first placebo-controlled trial looking the effect of CC administration (25 mg/day) in 142 couples with idiopathic infertility and oligoasthenozoospermia. After 6 months of treatment, CC failed to induce an increase in sperm parameters and pregnancy rate despite a significant increase in T level [5]. Helo S et al. obtained similar results in a randomized prospective double-blind comparison trial of CC and anastrozole in hypogonadal infertile men. They observed that both CC and anastrozole could raise T and LH level after 12 weeks of treatment, but without any significant change in FSH, semen parameters and patient-reported symptoms [6]. In contrast to these results, another randomized placebo-controlled trial has shown a significant increase in sperm concentration and progressive motility and a higher pregnancy rate after 6 months of treatment with CC 25 mg/day associated with vitamin E (400 mg/day) [7]. These results were confirmed by Moradi M et al. who observed a significant increase in sperm count and motility after 3 months of CC treatment (25 mg/day) in 32 men with idiopathic infertility [8]. A more recent prospective randomized study comparing CC 25 mg/day with vitamin E has shown similar results. The authors observed a significant increase in sperm concentration and total motility after 6 months of treatment with CC and vitamin E [9].

Evidence of a beneficial effect of CC on hypogonadism symptoms is lacking as no randomized controlled trial has been published on the subject. In our study, this effect was not evaluated since data on hypogonadism symptoms after CC treatment were not collected.

Concerning the safety profile, CC has been safely used in women since 1960' for ovulation induction. The long-term study

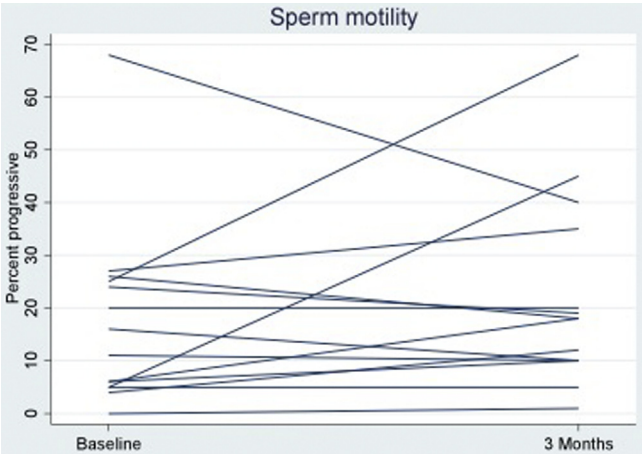

Fig. 6. Single patient sperm progressive motility variation.

conducted by Moskovic DJ et al. on infertile men has not shown any major adverse events up to 3 years of follow-up and has even observed an improvement in bone mineral density [10]. Only 2 cases of VTE have been reported in men under CC treatment, one of which in a patient carrier of factor V Leiden mutation [3]. In general, very few mild side effects have been reported including gastrointestinal complaints, headaches, hot flushes, reversible visual changes and breast tenderness or gynecomastia [11]. Only 3 case reports describe psychiatric side effects in men, 2 of which in patients with a history of psychiatric disease [12]. In our series, no side effects were reported. Clomiphene citrate has thus a very good safety profile without any need for biochemical monitoring of hepatic function, lipid profile, Prostate Specific Antigen or hematocrit, in contrast to T replacement therapy.

Clomiphene citrate is simple to administer (orally and once a day) and represents a very cost-effective therapy. A cost analysis study performed by Taylor et al. demonstrated that using CC allowed to save 190 $ (about 70%) per month compared with T prescription (5 mg/day), with comparable elevation in T serum level [13].

Our retrospective study has several limitations, in particular a short follow-up, a small sample size, the absence of a control population and the lack of data about symptoms of hypogonadism after CC therapy. However, it has several noteworthy strengths. To our knowledge, this is the first study addressing the effect of CC as a single therapy on semen parameters in infertile men with low T level and normal or low gonadotropines level. Our non-selected and heterogeneous population of young infertile men is very close to the real clinical practice. Despite this, the raise in plasma T concentration is consistent and homogeneous. The availability of

Table 2
Patients' characteristics, testosterone level and semen parameters (baseline and post treatment).

Variable	Number of patients	Mean	SD	p50	IQR	Min	Max	*P* value
Age (years)	18	36	6.8	36.5	12	23	48	
BMI (Kg/m^2)	17	28.2	3.9	28	5.4	20.9	36.8	
Infertility length (years)	18	3.9	2.7	2	3	1.5	10	
Baseline LH (IU/l)	18	4.2	2.3	3.5	2.2	1.8	11	
Baseline FSH (IU/l)	18	4.8	3.3	4.1	2.3	1.8	16.8	
Baseline T (nmol/l)	18	8.5	2.3	9.1*	3.5	3.8	11.3	*0.0002
Post treatment T (nmol/l)	18	20.7	4.7	20.2*	6.5	14.4	33.4	
Baseline sperm concentration (Millions/ml)	18	14.7	18.2	7°	15	0.1	61	°0.024
Post treatment sperm concentration (Millions/ml)	18	19.3	16.6	17.5°	19	0.1	61	
Baseline sperm progressive motility (%)	18	20.5	17.5	18•	21	0	68	•0.395
Post treatment sperm progressive motility (%)	14	22.2	18.5	18•	25	1	68	

Abbreviations: BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinising hormone; T: testosterone; Min: lowest value; Max: highest value; IQR: interquartile range; p50: median; SD: standard deviation.
*, ° and • refer to the statistical significance, expressed as P value, of the difference between pre-and post-treatment results for the median T level, sperm concentration and sperm progressive motility.

Table 3
Sngle patient baseline and post treatment results.

Patient	Baseline LH (IU/l)	Baseline FSH (IU/l)	Baseline T (nmol/l)	Post-treatment T (nmol/l)	Baseline sperm concentration (millions/ml)	Post-treatment sperm concentration (millions/ml)	Baseline sperm progressive motility (%)	Post-treatment sperm progressive motility (%)	Spontaneous pregnancy
1	4.4	4.6	5.6	16	3.5	4	6	10	
2	2.7	4.8	9.1	20	5.5	4	4	12	
3	9	16.8	9.4	22.6	0.5	0.1	5	5	
4	1.8	3.4	9.9	19.9	20	23	26	18	
5	2.3	4.9	3.8	15	6	6	32	?	
6	2.1	2.6	7.1	24.2	2.5	9	20	20	
7	3.5	6.6	7.9	20.5	5	25	25	68	
8	4.8	3.9	9.8	21	5	17	11	10	
9	6.5	3.1	10.8	33.4	60	34	13	?	yes
10	4.4	1.8	10.5	25.2	20	25	34	?	yes
11	3	4.3	8.8	17.5	8	18	27	35	
12	3.6	6.6	7	21	5	10	5	45	
13	6.8	6	9.2	24	12	21	0	1	
14	2.3	3.2	6.2	18	27	27	48	?	
15	2.6	2.5	11.3	25.7	14	51.6	16	10	
16	2.7	4	11	19.3	61	61	68	40	
17	7.4	2	11	15.9	9	9	24	19	yes
18	4.3	5.4	5.1	14.4	0.1	3.4	6	18	

Abbreviations: T: testosterone; FSH: follicle stimulating hormone; LH: luteinising hormone.

semen assessment at baseline and at the end of the treatment period for all the participants allowed us to evaluate the effect of CC on sperm concentration and progressive motility. In our series, despite some heterogeneity in the results, we found a statistically significant increase in sperm concentration. Three natural pregnancies occurred during the 3 months treatment period but no conclusion can be drawn. Even if natural pregnancy rate should be the primary outcome when evaluating the effect of CC in male partners of infertile couples, this outcome is rarely evaluated in studies investigating the effect of CC in infertile men and the results available are controversial [7,5]. All studies published so far are underpowered and the follow-up is too short to definitively conclude on a significant effect on the pregnancy rate.

Conclusion

In conclusion, CC is an effective and inexpensive treatment to increase T level in patients with low T level and normal or low gonadotropines. Our study suggests that CC could also increase sperm concentration in selected oligospermic infertile men. However, the effect of CC on sperm parameters and on natural pregnancy rates remains to be evaluated [14]. Male infertility with low sperm concentration can be successfully treated with in vitro fertilization and intracytoplasmic sperm injection. This approach is however invasive and expensive and it is therefore important to develop treatments that specifically target the cause of infertility to increase the chance of a natural pregnancy. In selected infertile male patients with low T level and normal or low gonadotropines, use of CC might represent a valid alternative to more invasive treatment, but more powered randomized controlled trials are needed.

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