Title

Temporal Changes of Clomiphene on Testosterone Levels and Semen Parameters in Subfertile Men

Journal

The World Journal of Men's Health, 40(1)

ISSN

2287-4208

Authors

Jiang, Tommy
Sigalos, John T
Osadchiy, Vadim
et al.

Publication Date

2023

DOI

10.5534/wjmh.220010

Peer reviewed

Original Article
Male reproductive health and infertility

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2023 Jan 41(1): 198-203
https://doi.org/10.5534/wjmh.220010

The World Journal of MEN's HEALTH

Temporal Changes of Clomiphene on Testosterone Levels and Semen Parameters in Subfertile Men

Tommy Jiang, John T. Sigalos, Vadim Osadchiy, Alvaro Santamaria, Michael H. Zheng, Neilufar Modiri, Keith V. Regets, Jesse N. Mills, Sriram V. Eleswarapu

Division of Andrology, Department of Urology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

Purpose: Clomiphene citrate (CC) is prescribed off-label in men to improve testosterone and sperm parameters, but the duration of treatment needed to reach maximal benefit remains unclear. Our objective was to examine temporal effects of CC on total testosterone (TT) and semen analysis (SA) using longitudinal follow-up data in treated men.
Materials and Methods: We analyzed an IRB-approved database of men treated with CC (25 mg q.d. or 50 mg q.o.d.) from January 2016 through May 2021. We identified patients with 3, 6, 9, and 12 month follow-up data for TT and 3, 6, and 9 month follow-up SA. Mean absolute changes in TT and sperm concentration compared to baseline were calculated, along with 95% confidence intervals. Men with prior genitourinary procedures or hormone therapy were excluded. Paired t-tests were used to compare TT and sperm concentration at each time point to baseline (alpha=0.05).
Results: One hundered thirty-four men received CC, mean age 37.7 years (SD 6.7, range 24–52). TT at all follow-ups (3, 6, 9, and 12 months) were available for 25 men, and SA at 3, 6, and 9 months for 26 men. Baseline TT was 358±145 ng/dL and sperm concentration was 13±17.2 M/mL. Significant improvement in TT was identified at 3 months (62.7 ng/dL, 95% CI: 0.49–125.0, p=0.048), additional benefit at 6 months (181.8 ng/dL, 95% CI: 114.1–249.5, p<0.01), and plateau at 9 and 12 months. Improvement in sperm concentration was first observed at 9 months (20.7 M/mL, 95% CI: 10.2–31.2, p<0.01). Semen volume and sperm motility did not change.
Conclusions: Duration of treatment with clomiphene may impact testosterone and sperm concentration, and the historical 3 month milestone may be insufficient for clinical and research evaluation. Men taking CC may experience plateau in TT at 6 months and first benefit in sperm concentration at 9 months.

Keywords: Clomiphene citrate; Male infertility; Selective estrogen receptor modulator; Semen analysis; Testosterone

INTRODUCTION

Approximately 15% of couples fail to achieve pregnancy within one year of attempted conception with over 50% having a male contribution [1]. For men contending with subfertility, reproductive urologists depend upon lifestyle counseling, empiric medical therapy, and targeted surgical management to improve fertility outcomes. Clomiphene citrate (CC), an oral selective estrogen receptor modulator, is commonly pre-

Received: Jan 22, 2022 **Revised:** Apr 2, 2022 **Accepted:** Apr 8, 2022 **Published online** Jun 13, 2022
Correspondence to: Sriram V. Eleswarapu https://orcid.org/0000-0003-1852-4833
Division of Andrology, Department of Urology, David Geffen School of Medicine, University of California, 10945 Le Conte Avenue, Ueberroth #3361, Los Angeles, CA 90095, USA.
Tel: +1-310-794-3058, **Fax:** +1-310-206-2369, **E-mail:** Seleswarapu@mednet.ucla.edu

scribed to hypogonadotropic men [2] in an attempt to improve serum total testosterone (TT; reference range: 200–1,000 ng/dL) and semen parameters through the modulation of luteinizing hormone (LH; reference range: 2–12 miU/mL) and follicle stimulating hormone (FSH; reference range: 1.6–9 miU/mL). Despite widespread prescribing of CC by reproductive urologists, discussion of CC is sparse within both the American Urological Association [3] and European Association of Urology [4] guidelines on male hypogonadism and infertility. Data supporting the use of CC vary widely: the largest randomized clinical trial by the World Health Organization (WHO) showed no improvement in pregnancy rates or sperm concentration (reference range >15 M/mL) with CC use compared to placebo at 6 months [5], whereas other retrospective studies have shown variable improvements in semen parameters with stricter initial sperm concentration and gonadotropin inclusion criteria [6,7]. Of note, few studies have evaluated outcomes of CC use in men beyond 3 months [8,9], and no temporal pattern of hormonal or seminal response has been identified. We sought to determine the magnitude of improvement in TT and sperm concentration in men taking CC for fertility optimization with long-term interval follow-up to investigate if and when patients may experience a plateau with CC monotherapy.

MATERIALS AND METHODS

We retrospectively evaluated men presenting to an academic andrology clinic for fertility evaluation who were prescribed CC (25 mg q.d. or 50 mg q.o.d.) from January 2016 through May 2021. We identified men with 3, 6, 9, and 12 month follow-up data for TT and 3, 6, and 9 month follow-up semen analysis (SA). Men with previous genitourinary surgeries, previous or concurrent hormone therapies, and patients without interval TT, LH, FSH, or SA were excluded from the analysis. Our primary endpoint was magnitude of improvement at each time point for TT and sperm concentration compared to baseline. We generated 95% confidence intervals (CIs) for each parameter at each time point. Paired t-tests were calculated to compare change in TT, sperm concentration, semen volume, and sperm motility (reference range: >40%) at each time point compared to baseline. RStudio v. 1.1.463 (RStudio, Inc., Boston, MA, USA) was used for statistical analysis, with $p<0.05$ considered statistically significant.

Ethics statement

All protocols, extractions, and analyses were approved by the UCLA Institutional Review Board (IRB#20-000710). The written informed consent was waived by the board owing to the retrospective design of the study.

RESULTS

CC was prescribed to 134 men seeking fertility optimization during the 5-year period. Mean age was 37.7 years (standard deviation [SD], 6.7 y; range, 24–52 y). Of these 134, data for TT at 3, 6, 9, and 12 months were available for 25 men, and SA at 3, 6, and 9 months were available for 26 men. Demographics of the analyzed patients are included in Table 1 and Table 2.

In the subset of 25 men with long-term follow-up data, a statistically significant improvement in TT was identified at 3 months (62.7 ng/dL; 95% CI, 0.5–125.0 ng/dL; p=0.048), and additional benefit was seen at 6 months (181.8 ng/dL; 95% CI, 114.1–249.5 ng/dL; p<0.01), without additional statistical improvement at 9 or 12 months (Fig. 1A). Of note, these trends did not change when doing the same analysis on a subset of 40 men with only 3 and 6 month follow-up and in a subset of

Table 1. Patient demographics

Characteristic	Value
Age (y)	37.7±6.7
Baseline LH (miU/mL)	5.0±2.6
Baseline FSH (miU/mL)	5.3±2.9
Baseline TT (ng/dL)	358±145
% TT <350	17 (65.4)
Sperm concentration (M/mL)	13.0±17.2
% Severe oligozoospermia (0–5)	10 (38.5)
% Moderate oligozoospermia (5–10)	8 (30.8)
% Mild oligozoospermia (10–15)	2 (7.7)
% Normospermia (>15)	6 (23.1)
Average testicle volume (mL)	36.5±9.4
Left testicle	18.1±4.9
Right testicle	18.4±5.6
% Patient with a varicocele	16 (61.5)

Values are presented as mean±standard deviation or number (%).
LH: luteinizing hormone, FSH: follicle stimulating hormone, TT: total testosterone.
All patients (n=26) had semen analyses at 3, 6, and 9 month follow-ups.

The World Journal of MEN's HEALTH

Table 2. Patient demographics

Characteristic	Value
Age (y)	37.6±6.7
Baseline LH (miU/mL)	5.1±2.6
Baseline FSH (miU/mL)	5.3±2.9
Baseline TT (ng/dL)	352±145
% TT <350	17 (68.0)
Sperm concentration (M/mL)	12.8±17.1
% Severe oligozoospermia (0–5)	10 (40.0)
% Moderate oligozoospermia (5–10)	8 (32.0)
% Mild oligozoospermia (10–15)	2 (8.0)
% Normospermia (>15)	5 (20.0)
Average testicle volume (mL)	36.5±9.4
Left testicle	18.1±4.9
Right testicle	18.4±5.6
% Patient with a varicocele	16 (64.0)

Values are presented as mean±standard deviation or number (%).
LH: luteinizing hormone, FSH: follicle stimulating hormone, TT: total testosterone.
All patients (n=25) had TT labs at 3, 6, 9, and 12 month follow-ups.

32 men with 3, 6, and 9 month follow-up. No patients reported adverse effects of changes in mood, blurred vision, or breast tenderness at any follow-up.

Improvement in sperm concentration was first noted at 9 months of CC use (20.7 M/mL; 95% CI, 10.2–31.2 M/mL; p<0.01), without improvement at earlier time points (Fig. 1B). These trends were further confirmed when doing the same analysis on 49 patients with only 3 and 6 month follow-up data and 134 patients with only 3 month follow up data. At no point were there improvements in semen volume or sperm motility (Fig. 1C, 1D).

DISCUSSION

1. Longitudinal effect of clomiphene citrate on testosterone

CC has been shown consistently to improve both TT [10] and symptoms of hypogonadism [10,11] with a lim-

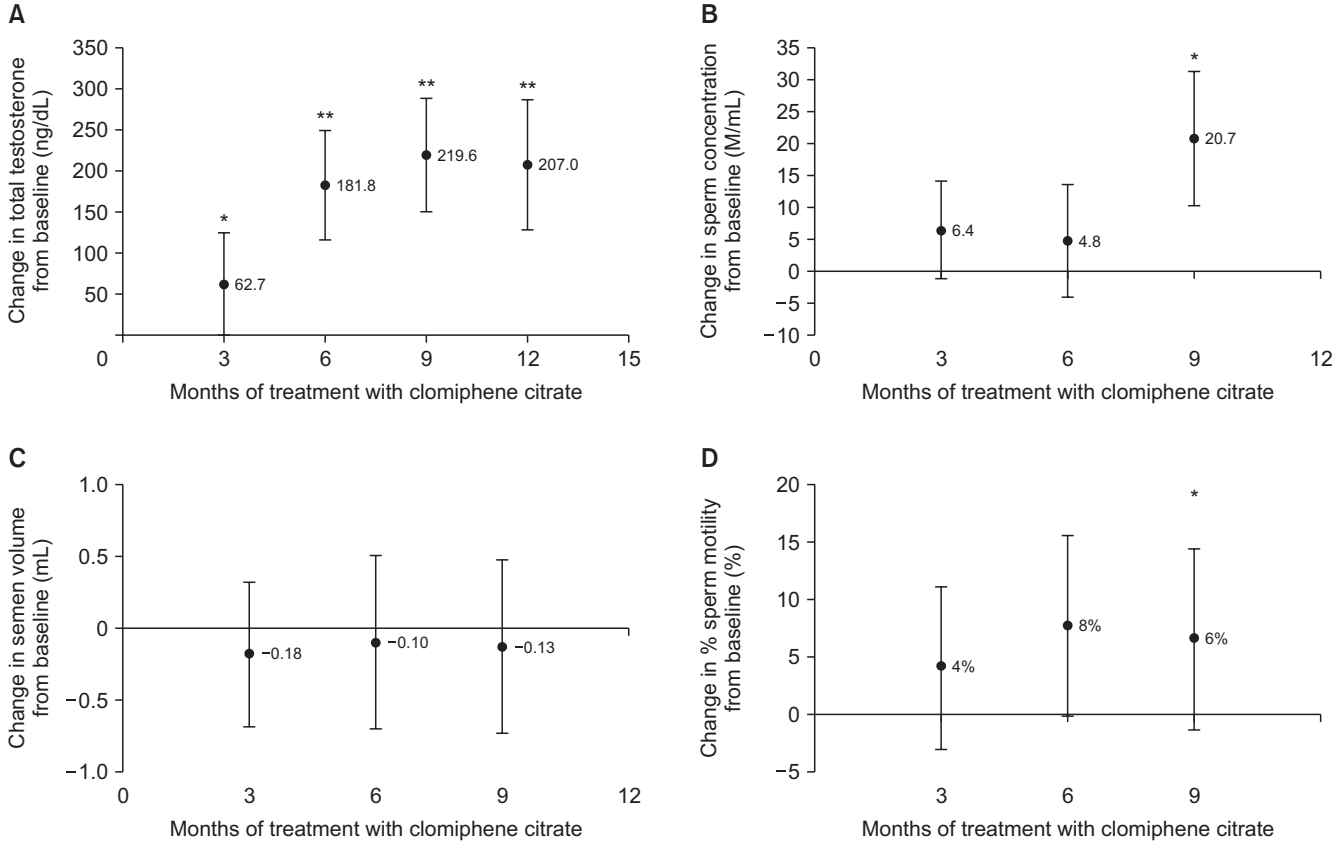

Fig. 1. Changes in (A) total testosterone, (B) sperm concentration, (C) semen volume, and (D) percent sperm motility across duration of clomiphene citrate treatment. Differences between interval follow-ups and baseline total testosterone and semen parameters. Interval follow-up data for total testosterone were available for 3, 6, 9, and 12 months of treatment, while semen parameters were available for 3, 6, and 9 months of treatment. 95% confidence interval are shown. Paired t-tests were calculated at each interval time point with significance set at p<0.05. *Statistical improvement compared to baseline. **Statistical improvement compared to baseline and compared to 3-month follow up.

ited side effect profile [9]. AUA guidelines currently recommend CC to improve low testosterone in infertile men with the common practice of using 3 months as the primary endpoint in evaluating efficacy. Our study suggests men may experience the full benefit of CC with longer duration of use, as we observed maximal benefit in TT at 6 months of CC monotherapy before a plateau at the 9 and 12 month follow-up dates. There are some data in the literature to suggest benefit with longer durations of CC in hypogonadism. Krzsatek et al [8] found that a majority of hypogonadal men became eugonadal with at least 3 years of CC use; however, interval data was not provided in this study. Additionally, some studies have reported longitudinal data showing sustained TT response with CC alone; however, these studies do not specifically explore the temporal pattern of response and allowed for up-titration of CC when TT was not maintained at a certain threshold [9,10,12]. Taken together with our results, the data from these studies suggest that 6 months may be a more suitable endpoint in studying CC efficacy than the typical 3-month milestone historically evaluated in the scientific literature. Such data may be helpful in counseling patients regarding expectations for CC treatment duration during shared decision-making conversations in the clinical context.

2. Longitudinal effect of clomiphene citrate on sperm parameters

The efficacy of CC for sperm parameters in subfertile men remains less clear. Gundewar et al [13] reported that up to 24% of men may experience a paradoxical decline in sperm concentration during 3-month follow-up, with 17% of patients never recovering to baseline upon discontinuation of CC. Studying CC in male fertility has been stymied by a lack of knowledge on predictors of efficacy; multiple studies have reported that even baseline LH and FSH poorly correlate with sperm parameter improvement at 3-month follow-up [14]. Our data suggest that 3 months may not be a sufficient duration of treatment to experience a fertility benefit from CC. Our cohort of patients first showed statistical improvement in sperm concentration at 9 months. These data may be useful in setting timing expectations for couples trying to conceive, since 9 months (or longer) may be too burdensome a timeline before opting for intrauterine insemination or *in vitro* fertilization. Indeed, one of the reasons we observe a diminishing sample size at longer durations of treatment with CC is that couples tend to move forward with advanced reproductive technologies after the frustrating experience of seeing no meaningful improvement in sperm parameters after 3 months of CC, which is typically the timing of first follow-up SA.

The relationship between serum testosterone and sperm parameters continues to be an important topic of study in the male fertility research community. For example, dual therapy of CC with anastrozole has been studied with the idea that improving TT and the testosterone-to-estradiol ratio provides a lateral effect on fertility optimization [15]. Other groups have shown that optimizing TT may improve sperm retrieval rates in microsurgical sperm extraction in men with azoospermia [16,17]. While it remains unclear if CC alone is definitively effective in optimizing fertility parameters in subfertile men, longer intervals of treatment will likely be needed to answer this question.

3. Limitations

Our study is not without limitations. Data were limited by retrospective analysis and the inability to account for differences that may not be captured in the electronic medical record. This was a single-arm study without a control group and without randomization and was not powered to any single outcome. Patients were offered CC with a dosing regimen of 25 mg q.d. or 50 mg q.o.d., but no distinction was made between the dosing regimens in our retrospective analysis. In prior studies, one research group has evaluated response to CC titration from 25 mg q.o.d. to 50 mg q.o.d. and 50 mg q.d [12]. The same group identified an approximately 7% rate of tachyphylaxis defined as a return to a level within 50 ng/dL from baseline TT [18]. In our study, we found no patients who experienced tachyphylaxis by this definition. Our study was also limited by a small sample size due to inclusion criteria that eliminated patients who did not have all interval time assessments. We therefore could not account for patients who may have achieved benefit with CC at earlier intervals but either terminated therapy or were lost to follow-up. To address this question, we performed independent subset analyses on men with complete data for 3 and 6 months, and on men with complete data for 3, 6, and 9 months. As noted in the Results section, statistical significance did not change on these subset analyses despite the expanded sample sizes.

CONCLUSIONS

Overall, our study raises the question of what a suitable endpoint may be when studying CC monotherapy in the context of male subfertility and hypogonadism. We pose that 6 months of CC may be needed to achieve maximal benefit in TT while 9 months may be necessary to observe statistical benefit in sperm concentration. The findings from this work may serve as additional data for reproductive urologists to use to counsel men regarding the potential benefits of CC monotherapy for subfertility.

Conflict of Interest

Jesse N. Mills and Keith V. Regets are consultants for Antares Pharma, Boston Scientific, and Endo Pharmaceuticals. Sriram Eleswarapu, Tommy Jiang, Vadim Osadchiy, Alvaro Santamaria, Michael H. Zheng, Neilufar Modiri, and John T. Sigalos have no disclosures.

Funding

None.

Author Contribution

Conceptualization: TJ, VO, JNM, SVE. Data curation: TJ, NM, AS. Formal analysis: TJ, VO, MHZ. Funding acquisition: N/A. Investigation: TJ, JTS. Methodology: TJ, JTS, VO. Project administration: KVR, JNM, SVE. Resources: N/A. Software: VO, MHZ. Supervision: KVR, JNM, SVE. Validation: All authors. Visualization: TJ. Writing – original draft: TJ, VO, SVE. Writing – review & editing: All authors.

Data Sharing Statement

The data required to reproduce these findings cannot be shared at this time due to personal information protection policy.

REFERENCES

1. Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, et al. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988-1989). Hum Reprod 1991;6:811-6.
2. Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES Jr. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. J Urol 2012;187:973-8.
3. Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. J Urol 2021;205:36-43.
4. Dohle GR, Colpi GM, Hargreave TB, Papp GK, Jungwirth A, Weidner W; EAU Working Group on Male Infertility. EAU guidelines on male infertility. Eur Urol 2005;48:703-11.
5. A double-blind trial of clomiphene citrate for the treatment of idiopathic male infertility. World Health Organization. Int J Androl 1992;15:299-307.
6. Mićić S, Dotlić R. Evaluation of sperm parameters in clinical trial with clomiphene citrate of oligospermic men. J Urol 1985;133:221-2.
7. Rŏnnberg L. The effect of clomiphene treatment on different sperm parameters in men with idiopathic oligozoospermia. Andrologia 1980;12:261-5.
8. Krzastek SC, Sharma D, Abdullah N, Sultan M, Machen GL, Wenzel JL, et al. Long-term safety and efficacy of clomiphene citrate for the treatment of hypogonadism. J Urol 2019;202:1029-35.
9. Moskovic DJ, Katz DJ, Akhavan A, Park K, Mulhall JP. Clomiphene citrate is safe and effective for long-term management of hypogonadism. BJU Int 2012;110:1524-8.
10. Katz DJ, Nabulsi O, Tal R, Mulhall JP. Outcomes of clomiphene citrate treatment in young hypogonadal men. BJU Int 2012;110:573-8.
11. Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. J Sex Med 2010;7(1 Pt 1):269-76.
12. Mazzola CR, Katz DJ, Loghmanieh N, Nelson CJ, Mulhall JP. Predicting biochemical response to clomiphene citrate in men with hypogonadism. J Sex Med 2014;11:2302-7.
13. Gundewar T, Kuchakulla M, Ramasamy R. A paradoxical decline in semen parameters in men treated with clomiphene citrate: a systematic review. Andrologia 2021;53:e13848.
14. Sharma D, Zillioux J, Khourdaji I, Reines K, Wheeler K, Costabile R, et al. Improvements in semen parameters in men treated with clomiphene citrate-a retrospective analysis. Andrologia 2019;51:e13257.
15. Alder NJ, Keihani S, Stoddard GJ, Myers JB, Hotaling JM. Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hypoandrogenic subfertile men. BJU Int 2018;122:688-94.
16. Reifsnyder JE, Ramasamy R, Husseini J, Schlegel PN. Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. J Urol 2012;188:532-6.
17. Hussein A, Ozgok Y, Ross L, Niederberger C. Clomiphene

administration for cases of nonobstructive azoospermia: a multicenter study. J Androl 2005;26:787-91; discussion 792-3.
18. Mazzola CR, Logmanieh N, Katz DJ, Mulhall JP. Defining the rate of tachyphylaxis in patients using daily clomiphene citrate. J Urol 2012;187(4 Suppl):e607.