Effectiveness of clomiphene citrate on total motile sperm count and hormonal profile in men with clinical infertility

Connor Roque[1], Yool Ko[1], Maximilian G. Fidel[1], Jainik Shah[1], Sahand Malek Marzban[1], Harliv Dhillon[1], Ahmed Almuhanna[2], Avinash Sarcar[3], Premal Patel[2,3]
[1]Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada; [2]Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; [3]Men's Health Clinic Manitoba, Winnipeg, MB, Canada

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Corresponding Author:
Dr. Premal Patel, Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; ppatel5@hsc.mb.ca

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ABSTRACT

Introduction: Infertility affects 15% of couples worldwide, yet evidence for empiric therapy in idiopathic male factor infertility is limited. Clomiphene citrate (CC), a selective estrogen receptor modulator that stimulates gonadotropins, is widely prescribed, but its impact on total motile sperm count (TMSC) and reproductive hormones remains uncertain. This study evaluated CC therapy and subsequent changes in TMSC and hormones in infertile men.

KEY MESSAGES

- Clomiphene citrate is commonly used for idiopathic male infertility, but real-world data on semen and hormonal response are limited.
- In our single-centre cohort of 60 men, total motile sperm count rose by a mean of 13 million after treatment, with additional increases in testosterone, FSH, LH, estradiol, and 17-OHP.
- Response to therapy was highly variable, and no baseline clinical or hormonal factors reliably predicted change in sperm counts.
- A monitored, time-limited course of clomiphene with a semen check at six months can help identify responders before considering assisted reproduction.

Methods: This single-center, retrospective cohort included 60 men ≥18 years with idiopathic infertility treated with CC between January 2022 and November 2024. The primary outcome was change in TMSC; secondary outcomes were changes in testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and 17-hydroxyprogesterone (17-OHP) before and after CC. Hormonal changes were assessed with paired t-tests; primary vs. secondary infertility with independent t-tests; and predictors of TMSC change with multivariable linear regression.
Results: Sixty men (mean age 35.6±4.6 years) were treated for 12.9±6.1 months. Following CC, mean TMSC increased by 13.1 million (p=0.005), 17-OHP by 1.8 nmol/L, testosterone by 9.9 nmol/L, FSH by 4.9 IU/L, LH by 4.8 IU/L, and estradiol by 53.9 pmol/L (all p<0.001). TMSC change was not linked to age, body mass index (BMI), baseline hormones, or treatment duration. Men with primary (n=46) vs. secondary infertility (n=14) demonstrated similar TMSC and hormonal changes.
Conclusions: CC was associated with higher TMSC and reproductive hormones. Response was independent of age, BMI, baseline hormones, and duration. Larger, prospective studies are needed to confirm findings and guide candidate selection.

INTRODUCTION

Infertility affects approximately 15% of couples worldwide, with male factors contributing to half of all cases.[1] Although targeted treatments exist for defined etiologies, idiopathic male factor infertility accounts for approximately 25% of cases and is generally managed with empiric medical therapy. Male factor infertility refers to abnormal semen parameters or conditions that impair sperm production, function, or delivery that contribute to a couple's difficulty conceiving; importantly, the WHO lower reference limits are 5th-percentile values from fertile men and are not diagnostic thresholds of fertility or infertility. Available treatment options (e.g., clomiphene citrate (CC), aromatase inhibitors, antioxidants) are supported by heterogeneous data, the effects on semen parameters are inconsistent, and benefits on pregnancy remain uncertain.[1,2]

CC, a selective estrogen receptor modulator (SERM), is widely prescribed as an empiric therapy for idiopathic male factor infertility to stimulate endogenous gonadotropin production. CC's oral administration, relatively low cost, and its ability to preserve spermatogenesis make it an appealing treatment option, as compared to alternatives such as aromatase inhibitors.[3] CC acts by competing for estrogen binding at hypothalamic receptors, as such it antagonizes estrogen's physiologic negative feedback on gonadotropin release.[3] As a result, secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary increases, stimulating greater endogenous testosterone production in Leydig cells.[4]

Currently, the diagnostic workup for male factor infertility relies on the medical history, physical examination, semen analysis, and select hormonal or genetic tests. Total motile sperm count (TMSC) is a significant predictor of successful conception, and recent studies even suggest that TMSC is a more reliable predictor of fertility outcomes than the traditional World Health Organization (WHO) semen classification system.[5,6] In addition to TMSC, patients' hormone profiles play a critical role in male factor fertility, with any deviation from normal parameters having the potential to affect sperm motility.[7] For example, serum 17-hydroxyprogesterone (17-OHP), a biomarker of intratesticular testosterone, has been associated with improved semen quality parameters including sperm concentration and TMSC.[8]

Despite the prevalent use of CC, data on how it influences TMSC in conjunction with the male hormonal profile remain limited. This study sought to evaluate (1) the effect of CC on TMSC and (2) the overall reproductive hormonal profile in men with primary or secondary infertility.

METHODS

Study design and patient population

A single-centre retrospective cohort study was conducted at an ambulatory men's health and urology clinic. From January 2022 through November 2024, all consecutive men prescribed CC for idiopathic infertility were identified. Inclusion criteria were age ≥18 years, clinical infertility defined as failure to conceive after at least 12 months of regular unprotected intercourse, and at least one abnormal semen parameter before CC initiation. Eligibility was independent of baseline LH and FSH, and men were enrolled regardless of gonadotropin level. Exclusion criteria were pre-treatment TMSC >20 million per ejaculate, current or recent use of exogenous testosterone, any known syndromic or iatrogenic cause of infertility, non-adherence to CC therapy or loss to follow-up, and absence of a post-treatment semen analysis to assess TMSC. CC was prescribed at 25 mg orally every other day for 6 months with repeat semen analyses and was continued or titrated to 50 mg every other day in select cases for partial responders at the urologist's discretion. The study protocol was reviewed and approved by the University of Manitoba Research Ethics Board (REB; file number HS26886).

Data collection

Baseline (pre-treatment) values were defined as the most recent semen analysis and hormone panel obtained before initiation of CC. Post-treatment values were defined as the first semen analysis and hormone panel measured after a documented period of continuous CC use. Semen analyses were performed in the institutional andrology laboratory following standard operating procedures. Azoospermia was defined as the complete absence of sperm on a standard semen analysis. Hormone analysis included serum total testosterone (nmol/L), FSH (IU/L), LH (IU/L), estradiol (pmol/L), and 17-OHP (nmol/L).

Statistical analysis

The primary outcome was the change in TMSC after CC treatment. Secondary outcomes were changes in testosterone, FSH, LH, estradiol, and 17-OHP; change in azoospermia status; comparison of TMSC change between men with primary and secondary infertility (primary: no prior successful conception; secondary: at least one prior spontaneous conception). Continuous variables were summarized as mean ± standard deviation (SD). Paired two-tailed t-tests were used for pre–post CC comparisons and mean differences with 95% CI were presented. McNemar's test was used to assess changes in azoospermia. Change in TMSC between primary and secondary infertility were compared using independent-samples t-tests, reporting with 95% CI for the mean difference. To examine predictors of change in TMSC, a multiple linear regression was fit with prespecified baseline covariates: age, body mass index, treatment duration, and pre-treatment 17-OHP, total testosterone, FSH, LH, and estradiol. Each analysis used complete cases for that endpoint, with sample sizes reported in the tables. All tests were two-sided with $\alpha = 0.05$. Analyses were conducted in IBM SPSS Statistics, version 29 (IBM Corp., Armonk, NY).

RESULTS

Between January 2022 and November 2024, 108 men received CC (Fig. 1). Overall, 31 (28.7%) patients were excluded for missing post-treatment semen analysis and 17 (15.7%) with baseline TMSC >20 million. A total of 60 men met the inclusion criteria for this retrospective analysis and were treated with CC for an average duration of 12.9 ± 6.1 months. The mean age of the cohort was 35.6 ± 4.6 years, and the mean BMI was 30.5 ± 6.9 kg/m². Because follow-up semen analyses were performed at variable intervals, time-to-response could not be assessed.

Following CC therapy, the mean TMSC increased from 5.69 ± 5.62 to 18.82 ± 37.19 million, accounting for a mean increase of +13.14 million (CI: 4.06–22.22; p = 0.005) (Table 1). Of the 7/60 (11.7%) men who were azoospermic at baseline, 4/7 (57%) had detectable motile sperm on follow-up. Conversely, 4/53 (7.5%) of those with motile sperm at baseline were azoospermic on follow-up. Overall azoospermia prevalence was unchanged (7/60 [11.7%] at both time points; McNemar p=1.00) (Table 2). All measured hormones increased after CC (all p<0.001; Table 1): testosterone rose by 9.9 nmol/L; LH by 4.8 IU/L; FSH by 4.9 IU/L; estradiol by 53.9 pmol/L; and 17-OHP by 1.8 nmol/L.

A multiple linear regression (complete cases, n=23) found no significant associations between change in TMSC and prespecified baseline factors, including age, BMI, pre-treatment hormone levels (17-OHP, testosterone, FSH, LH, estradiol), and duration of CC therapy (all p > 0.05) (Table 3).

Men with primary infertility (n = 46) and those with secondary infertility (n = 14) experienced similar improvements in TMSC and hormone levels (Table 4). There were no

significant differences between the primary and secondary infertility groups in the magnitude of TMSC increase or in any of the hormonal changes (all $p > 0.05$).

No serious adverse events were reported over the course of CC treatment. The medication was generally well-tolerated, with most patients completing therapy without significant side effects.

DISCUSSION

In this cohort of men with idiopathic infertility, CC therapy was associated with a significant improvement in TMSC. On average, TMSC increased by approximately 13.1 million after CC treatment, rising from a mean of 5.7 million pre-treatment to 18.8 million post-treatment ($p=0.005$). This improvement is clinically meaningful, as even modest gains in TMSC can elevate a couple's chance of conception, potentially delaying more invasive adjunctive therapies. For example, boosting TMSC above thresholds may allow some couples to pursue intrauterine insemination (IUI) instead of in vitro fertilization (IVF), or even achieve natural pregnancy, given the strong correlation between TMSC and natural conception rates.[6] CC appears to be an effective empiric therapy for enhancing intrinsic semen quality in men without other targetable etiologies.

Exclusion criteria of pre-treatment TMSC >20 million per ejaculate was deliberately chosen to enrich the cohort for clinically meaningful mild to moderate male-factor infertility rather than those with fertility prognosis approaching normal. WHO lower reference limits of TMSC 9 million are derived from 5th percentile values of fertile men, rather than a diagnostic cut-off. By comparison, previous studies show increasing pregnancy rates with rising TMSC levels up to approximately 10 million, with diminishing returns thereafter.[9–11] Thus, our exclusion criteria of TMSC >20 million serves as a conservative cut-off for a near-normal zone above these thresholds in a clinically significant context.

As a SERM, CC blocks estrogen's negative feedback at the hypothalamus, thereby increasing gonadotropin release and stimulating intratesticular testosterone production and spermatogenesis.[12] The documented rises in FSH, LH, and total testosterone levels following CC treatment are consistent with other studies investigating the efficacy of CC.[12] Average serum testosterone nearly doubled with CC, accompanied by similar rises in FSH and LH compared to baseline. These findings also align with recent literature, which suggests that longer durations of CC therapy may enhance sperm parameters in appropriately selected patients.[12,13] Consistent with the need for longer therapy, the mean CC duration in our cohort was 13 months, longer than the 3–6 months in early trials and may have contributed to the magnitude of the TMSC increase.

Although mean TMSC improved, individual responses to CC varied widely, consistent with previous studies.[12,13] Of 53 men with sperm present at baseline, 4/53 (7.5%) became azoospermic during therapy; conversely, of the seven azoospermic patients at baseline, 4/7 (57.1%) achieved detectable sperm post-treatment. This shift resulted in no net change in the

proportion of azoospermic men (7/60 [11.7%] before and after; p=1.00), highlighting the heterogeneous nature of CC's effect on semen parameters. Such declines under CC have been reported previously. Gundewar et al. conducted a systematic review of adverse outcomes with CC and found that approximately one in four men (24%) had a decrease in TMSC during treatment.[14] The mechanism behind these negative responses is not fully understood, but could relate to excessive elevation of estradiol or other feedback disruptions in certain individuals. In our study, higher baseline estradiol was associated with a non-significant trend towards a smaller TMSC increase, suggesting that men with elevated estrogen may not be ideal candidates for CC (or might benefit from adjunct aromatase inhibition). Overall, the variability in response underscores the importance of monitoring semen analyses during CC therapy. No serious adverse events were documented during CC use over a mean of 13 months; however, safety was not a predefined outcome. Clinicians should verify that a patient is responding appropriately within a reasonable timeframe (e.g. 6–9 months) and be prepared to discontinue CC if no benefit or deterioration is observed.

Our data indicating 4/53 (7.5%) of men becoming azoospermic with CC therapy suggests the utility of discussing sperm cryopreservation before initiating treatment, particularly for men with abnormal baseline semen parameters or sperm counts near thresholds for assisted reproductive technologies. Sperm cryopreservation serves as an effective strategy for fertility preservation men at increased risk of deterioration of spermatogenesis.[15] It is also important to note that semen parameters demonstrate a high degree of within-subject variability when examining both fertile and subfertile men.[16–18] Thus, the observed data in this study pertaining to TMSC deterioration may partially be attributed to the natural fluctuation of sperm parameters rather than a direct pharmacological consequence of CC.

Multiple baseline factors were explored, including age, BMI, treatment duration, and pre-treatment hormones (17-OHP, total testosterone, FSH, LH, estradiol), but none significantly predicted TMSC change. In contrast, a study by Lima et al. found that men with low 17-OHP levels (≤55 ng/dL) were far more likely to achieve substantial TMSC increases and "upgrade" their fertility category (e.g. from needing IVF to being eligible for IUI) than men with higher 17-OHP.[8] Although this association was not confirmed in our cohort, it raises the hypothesis that CC may benefit men with secondary hypogonadism or lower intratesticular androgen tone.

CC antagonizes estrogen feedback at the hypothalamus, increasing pituitary FSH and LH and thereby intratesticular testosterone, which supports spermatogenesis.[12] However, excess estradiol may blunt semen response in some men. Clinically, unlike exogenous testosterone, CC preserves spermatogenesis, but therapy should be monitored with periodic hormones and semen analyses, with aromatase inhibition reserved for men with elevated estradiol and suboptimal response.[12]

Limitations

This retrospective, single-centre study lacked a control group, limiting causal inference and leaving room for natural variation and regression to the mean. The sample size (n=60) was sufficient for the primary comparison but small for subgroup and predictor analyses; incomplete hormone data required complete-case analyses, which may have introduced bias. Management occurred within routine care without a standardized protocol for dose or duration; adherence and co-interventions were not controlled, and nonrandomized prescribing may have introduced selection bias and confounding. Eligibility criteria (excluding specific etiologies and TMSC >20 million) improved internal validity but restricted generalizability to men with idiopathic oligozoospermia of mild to moderate severity. Adverse events were not systematically collected. Following treatment, semen analyses and hormone panels were obtained at the discretion of the physician. Thus, variability exists in the number of post-treatment semen analyses performed for each patient and their respective timing relative to treatment initiation, averting calculation of 3-month post-treatment averages. Pregnancy and live-birth outcomes were not consistently measured in the cohort; therefore, any fertility benefit is inferred from TMSC.[6] Accordingly, these findings should be considered with caution, and randomized trials are needed to determine effects on pregnancy and live-birth outcomes.[19]

CONCLUSIONS

In this single-centre cohort of men with idiopathic infertility, CC was associated with improvement in TMSC and increases in FSH, LH, and testosterone. Responses ranged from marked gains to no change or decline, and no baseline clinical or hormonal factor predicted change in TMSC. These findings support a monitored, time-limited empiric trial with semen recheck at 6 months and continuation to 9–12 months only if counts improve. Pregnancy or live birth was not assessed; randomized studies are needed to confirm effects and refine patient selection.

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Competing interests: *Dr. Premal Patel, MD, has been a consultant for Boston Scientific. The remaining authors do not report any competing personal or financial interests related to this work.*

FIGURES AND TABLES

Figure 1. Study cohort for men prescribed clompohene citrate, January 2022 to November 2024.

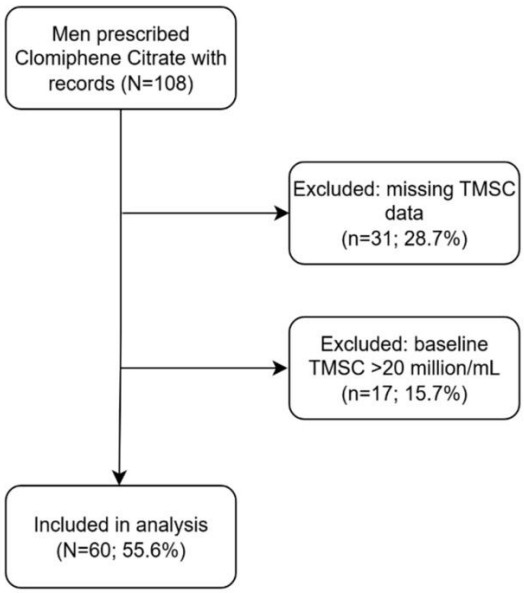

Figure 2. Pre- and post-treatment distributions by outcome. (a) total motile sperm count (TMSC, millions; (b) 17- hydroxyprogesterone (17-OHP, nmol/L); (c) testosterone (nmol/L); (d) follicle-stimulating hormone (FSH, IU/L); (e) luteinizing hormone (LH, IU/L); and (f) estradiol (pmol/L).

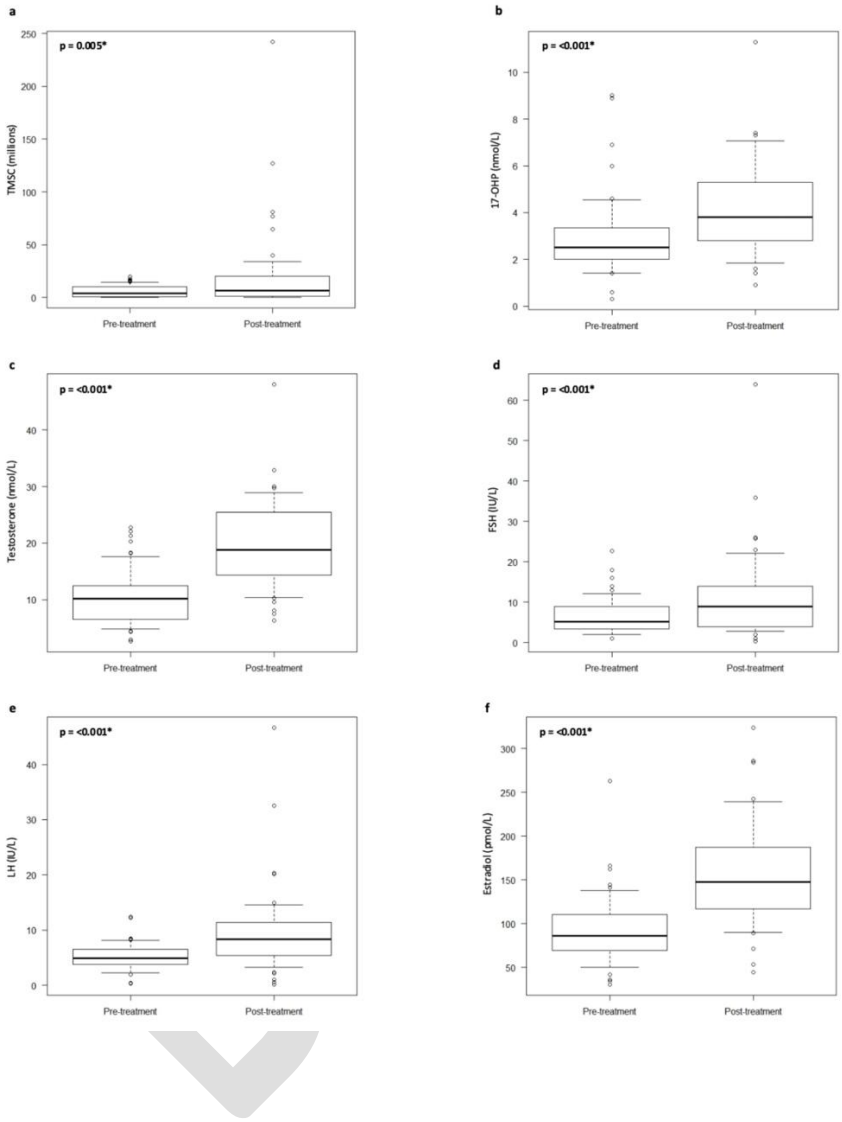

Table 1. Hormonal outcomes before and after clomiphene citrate treatment					
	n	**Pre (mean ± SD)**	**Post (mean ± SD)**	**Mean Δ (95% CI)**	**p**
TMSC (millions)	60	5.69±5.62	18.82±37.19	+13.14 (4.06–22.22)	0.005*
17-OHP (nmol/L)	21	2.78±1.43	4.55±2.06	+1.78 (1.08–2.47)	<0.001*
T (nmol/L)	50	10.05±5.00	19.90±7.75	+9.86 (7.46–12.26)	<0.001*
FSH (IU/L)	49	6.59±4.73	11.46±10.64	+4.87 (2.40–7.33)	<0.001*
LH (IU/L)	47	4.92±2.54	9.70±7.81	+4.78 (2.72–6.83)	<0.001*
Estradiol (pmol/L)	24	89.21±36.15	143.08±64.03	+53.88 (26.91–80.85)	<0.001*

Asterisk denotes statistical significance. CI: confidence interval; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SD: standard deviation; T: testosterone; TMSC: total motile sperm count; 17-OHP: 17-hydroxyprogesterone; Δ: change (post−pre).

Table 2. Changes in azoospermia status from pre- to post-treatment			
	Post: Not azoospermic	**Post: Azoospermic**	**Total, n (%)**
Pre: Not azoospermic	49	4	53 (88.3%)
Pre: Azoospermic	4	3	7 (11.7%)
Total, n (%)	53 (88.3%)	7 (11.7%)	60

McNemar's test: p=1.00.

Table 3. Predictors of change in total motile sperm count (n=23)			
	B (95% CI)	**β**	**p**
Age	-0.27 (-5.98–5.45)	-0.03	0.921
BMI	0.91 (-2.65–4.47)	0.17	0.593
Pre-17-OHP	2.92 (-5.01–10.84)	0.25	0.443
Pre-T	0.83 (-3.13–4.79)	0.15	0.660
Pre-FSH	-0.62 (-5.21–3.98)	-0.08	0.778
Pre-LH	-3.12 (-10.51–4.28)	-0.31	0.381
Pre-estradiol	-0.45 (-0.94–0.05)	-0.55	0.076
Treatment duration	-0.86 (-3.76–2.04)	-0.19	0.535

Multiple linear regression of change in total motile sperm count. Outcome is ΔTMSC (post − pre). No predictor reached statistical significance ($p<0.05$). B: unstandardized coefficient; β: standardized coefficient; BMI: body mass index; CI: confidence interval; FSH: follicle-stimulating hormone; LH: luteinizing hormone; T: testosterone; TMSC, total motile sperm count; 17-OHP: 17-hydroxyprogesterone.

Table 4. Independent-samples t test comparing changes in semen and hormonal parameters between primary and secondary infertility groups					
Outcome	**1° Infertility (Mean Δ ± SD)**	**2° Infertility (Mean Δ ± SD)**	**Mean difference (95% CI)**	**t (df)**	**p**
TMSC	12.06±38.57 (n=46)	16.69±20.97 (n=14)	-4.64 (-26.26–16.99)	-0.43 (58)	0.669
17-OHP	1.90±1.55 (n=17)	1.25±1.45 (n=4)	+0.65 (-1.14–2.44)	+0.76 (19)	0.455
T	10.10±8.85 (n=39)	9.00±7.18 (n=11)	+1.10 (-4.75–6.95)	+0.38 (48)	0.707
FSH	5.24±9.42 (n=38)	3.58±4.72 (n=11)	+1.66 (-4.29–7.60)	+0.56 (47)	0.578
LH	5.01±7.86 (n=37)	3.92±1.56 (n=10)	+1.09 (-2.59–5.88)	+0.43 (45)	0.668
Estradiol	54.26±67.52 (n=19)	52.40±54.21 (n=5)	+1.86 (-66.21–69.93)	+0.06 (22)	0.955

Values are mean change (post−pre) ± SD for each group. Mean difference is primary minus secondary with 95% CI; two-sided independent-samples t tests were used (Welch's correction when variances were unequal). No comparison reached statistical significance ($p<0.05$). CI: confidence interval; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SD: standard deviation; T: testosterone; TMSC: total motile sperm count; 17-OHP: 17-hydroxyprogesterone.