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Improvements in semen parameters in men treated with clomiphene citrate—A retrospective analysis

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Abstract

Clomiphene citrate (CC) is commonly used off-label for the treatment of male infertility, yet there is limited data to guide patient selection. To identify a subset of patients more likely to benefit from CC, we aimed to define predictors of improvement in semen parameters among men receiving CC. We retrospectively analysed 151 men treated with at least 25 mg CC daily for male infertility and/or hypogonadism at two institutions between 2004 and 2014. Men previously on testosterone were excluded. The primary outcome was change in semen parameters. Variables included baseline patient characteristics, pre-treatment hormone profiles and pre-treatment semen analyses. A total of 77 men met inclusion criteria. Median length of therapy was 2.8 months. There was significant improvement in sperm concentration (14–21 million/ml; $p = 0.002$) and total motile count (TMC; 13–28 million; $p = 0.04$). One third of patients who began with fewer than 5 million motile spermatozoon improved to a TMC > 5 million, increasing reproductive options to include intrauterine insemination. Patient characteristics, pre-treatment hormone profile and degree of oligozoospermia did not predict treatment response. While no predictors of improvement were identified, clinically useful response rates are described for use in shared decision-making.

KEYWORDS

clomiphene citrate, hypogonadism, male infertility, predictors, semen analysis

1 | INTRODUCTION

Ten to fifteen per cent of couples fail to conceive after 1 year of unprotected intercourse. Male factor infertility is the sole culprit in 20% of infertile couples and a contributing factor in another 40% (Chehab, Madala, & Trussell, 2015; Cocuzza & Agarwal, 2007; Ring, Lwin, & Kohler, 2016). Male infertility and hypogonadism often co-exist. A recent study showed that 20% of infertile men are hypogonadal (Ventimiglia et al., 2017). Others have shown 40%–45% of men with abnormal semen parameters are hypogonadal (Shoshany, Abhyankar, Mufarreh, Daniel, & Niederberger, 2017; Sussman, Chudnovsky, & Niederberger, 2008).

Clomiphene citrate (CC) is a selective oestrogen receptor modulator with an established role in the treatment of both male infertility and hypogonadism. CC is the most commonly prescribed medication for male infertility and has been used as an off-label treatment for hypogonadism since the 1970s (Ko, Siddiqi, Brannigan, & Sabanegh, 2012; Paulson & Wacksman, 1976). This dual indication makes the drug particularly useful for fertility specialists and andrologists alike.

Clomiphene citrate has been well studied as a therapy for hypogonadism despite its off-label use in men. It is effective in raising serum testosterone, safe for long-term use and cost effective when compared to testosterone replacement therapy (TRT) (Bendre, Murray, & Basaria, 2015; Katz, Nabulsi, Tal, & Mulhall,

2012; Moskovic, Katz, Akhavan, Park, & Mulhall, 2012; Ramasamy, Scovell, Kovac, & Lipshultz, 2014; Taylor & Levine, 2010; Wheeler et al., 2017). As opposed to TRT, CC inherently preserves spermatogenesis and testicular size by avoiding suppression of the hypothalamic pituitary gonadal axis. Furthermore, it avoids secondary polycythemia requiring phlebotomy associated with TRT (Wheeler et al., 2017). When presented with this data, hypogonadal men, especially those interested in fertility, often self-select for treatment with CC.

Patient selection for CC in the realm of male infertility is more complex. The best evidence to support CC in treating male infertility comes from a 2013 meta-analysis that showed the odds of pregnancy was five times greater in patients receiving high-dose CC compared to placebo (Chua et al., 2013). While providers should be encouraged by this significant improvement and a number needed to treat of only eight couples for one pregnancy, patients may be discouraged by a pregnancy rate of only 15% with CC therapy (Chua et al., 2013).

The ultimate goal is to find a subset of patients who are more likely to respond to CC as a therapy for male infertility. In an effort to do so, this study aimed to define predictors of improvement in semen parameters in a cohort of patients treated with CC for male infertility and/or hypogonadism at two high-volume institutions. The hypothesis was that pre-treatment elevation of follicle stimulating hormone (FSH) may be a negative predictor of response and that gonadal state (the degree and presence of hypogonadism) and/or degree of oligozoospermia may be predictive of a treatment response.

2 | MATERIALS AND METHODS

A retrospective cohort analysis of 151 men treated with CC for male infertility and/or hypogonadism at the University of Virginia, Charlottesville, Virginia, and Austin Fertility and Reproductive Medicine, Austin, Texas, between 2004 and 2014 was performed. Inclusion criteria consisted of documented pre-treatment hormone profiles and pre- and post-treatment semen analyses. Men previously on TRT were excluded from the analysis. In our clinics, pre-treatment semen analyses were ordered in all men who were interested in fertility preservation to assess baseline fertility prior to therapy. Pre-treatment testosterone values and semen analyses were repeated to confirm deficiencies; all patients had at least two pre-treatment semen analyses. Morning blood draws were standard in all clinics, and semen analyses were obtained concurrently. Laboratories were processed using Abbott Architect (Abbott Laboratories, Abbot Park, IL) and Roche COBAS (Roche Diagnostics, Indianapolis, IN) assays, and semen analyses with Medical Electronic System SQA-V Gold (Medical Electronic System, Los Angeles, CA). Semen analyses were not performed at the same laboratory but all used World Health Organization 2010 standards. Samples were centrifuged at 3,000 *g* for 15 min in order to rule out cryptozoospermia. All patients who were diagnosed with palpable varicoceles on physical examination were offered varicocele repair. Those who declined varicocele repair as a first line treatment and opted for treatment with CC as an initial treatment were included in the data, and those who elected to proceed with varicocele repair as a first line treatment were excluded.

Men were treated with a starting dose of 25 mg of CC daily from one of four providers for male infertility and/or hypogonadism, which was defined as a pre-treatment serum total testosterone (TT) of <300 ng/dl. The dose was titrated up to 50 mg daily when TT did not improve to at least 300 ng/dl after 4 weeks of therapy. No patients were previously or concurrently treated with human chorionic gonadotropin (hCG), which was reserved for severely hypogonadotropic patients as primary treatment instead of CC.

Both sites' institutional review boards approved a retrospective chart review in which baseline patient characteristics (age, race, body mass index [BMI], smoking status and ultrasound-determined testicular volume), pre-treatment hormone profiles (TT, FSH and luteinizing hormone [LH]) and pre- and post-treatment semen analyses (volume, sperm concentration and total motility) were collected. Duration of therapy was calculated using the date of therapy initiation and the date of the last available semen analysis. Change in

TABLE 1 Baseline overall cohort characteristics (n = 77)

Patient characteristics	
Age (years)	35 [31, 40]
Race	
White	55 (71%)
Black	7 (9%)
Unspecified	15 (20%)
Body mass index (kg/m^2)	28 [26, 32]
Current smoker	7 (9%)
Testicular volume (ml)	16 [14, 18]
Hormone profile	
Total testosterone (ng/dl)	242 [191, 317]
Follicle stimulating hormone (mIU/ml)	3 [2, 6]
Luteinizing hormone (mIU/ml)	4 [2, 6]
Semen analysis	
Volume (ml)	2.5 [1.5, 3.5]
Concentration (million/ml)	8 [2, 14]
Total motility (%)	30 [10, 45]
Total motile count (million)	3 [0, 13]
Subgroups	
Eugonadal (TT > 300 ng/dl)	20 (26%)
Hypogonadal (TT < 300 ng/dl)	57 (74%)
Normozoospermic (concentration >15 million/ml)	19 (25%)
Oligozoospermic (concentration >0, <15 million/ml)	44 (57%)
Mildly (concentration >5, <15 million/ml)	28
Severely (concentration >0, <5 million/ml)	16
Azoospermic (concentration = 0)	14 (18%)
Low total motile count (<5 million)	46 (60%)

Note. Values reported as median (IQR) or number (per cent cohort).

semen volume, sperm concentration, motility and total motile count (TMC) was calculated based on the latest pre- and post-treatment semen analyses.

Patients were divided into the following subgroups: hypogonadal, eugonadal (pre-treatment TT of >300 ng/ml), normozoospermic (pre-treatment concentration >15 million/ml), oligozoospermic (pre-treatment concentration >0 and <15 million/ml) ("mildly" oligozoospermic [pre-treatment concentration >5 and <15 million/ml] or severely oligozoospermic [pre-treatment concentration >0 and <5 million/ml]) and azoospermic (pre-treatment concentration = 0 million/ml). Azoospermia was based on two centrifuged samples (3,000 *g* for 15 min) revealing no spermatozoon in the semen or in the concentrated pellet. Obstructive azoospermia was clinically ruled out and excluded. All other azoospermic men underwent karyotype and Y chromosome microdeletion testing and were excluded if they had microdeletions or abnormal karyotypes; in those cases, microdissection testicular sperm extraction was offered. Another subgroup with a pre-treatment TMC below 5 million spermatozoon was identified for analysis. The primary outcome was change in semen parameters. The secondary outcome was change in TT.

Descriptive statistics were reported as mean (standard deviation [*SD*]) or median (interquartile range [IQR] 1st, 3rd quartile) as

TABLE 2 Response to therapy

	All (*n* = 77)	**Eu (*n* = 20)**	**Hypo (*n* = 57)**
Pre-treatment			
Volume (ml)	2.5 (1.4)	2.3 (1)	2.4 (1.5)
Concentration (million/ml)	14 (24)	11 (14)	15 (27)
Total motility (%)	29 (21)	22 (21)	31 (21)
TMC (million)	13 (24)	8 (14)	14 (26)
Post-treatment			
Volume (ml)	2.4 (1.3)	2.4 (1.5)	2.4 (1.2)
Concentration (million/ml)	21 (26)	21 (28)	21 (25)
Total motility (%)	34 (25)	29 (20)	35 (26)
TMC (million)	28 (98)	22 (43)	30 (112)
Change			
Volume (ml)	−0.1 (1)	+0.1 (1)	0 (1.1)
Concentration (million/ml)	+7 (26)*	+10 (21)*	+6 (28)*
Total motility (%)	+5 (17)	+7 (15)	+4 (18)
TMC (million)	+15 (91)*	+14 (37)*	+16 (104)
	Normo (*n* = 19)	**Oligo (*n* = 44)**	**Azo (*n* = 12)**
Pre-treatment			
Volume (ml)	2.4 (1.2)	2.4 (1.3)	2.8 (1.8)
Concentration (million/ml)	42 (36)	6 (4)	0 (0)
Total motility (%)	42 (22)	28 (18)	n/a
TMC (million)	39 (37)	5 (7)	0 (0)
Post-treatment			
Volume (ml)	2.2 (1.3)	2.5 (1.3)	2.5 (1.3)
Concentration (million/ml)	38 (32)	18 (22)	6 (15)
Total motility (%)	42 (29)	33 (21)	20 (26)
TMC (million)	64 (189)	19 (36)	5 (10)
Change			
Volume (ml)	−0.2 (0.8)	+0.1 (1.2)	−0.3 (1.3)
Concentration (million/ml)	−4 (37)	+12 (22)*	+6 (15)
Total motility (%)	0 (16)	+5 (17)	n/a
TMC (million)	+15 (180)	+14 (32)*	+5 (10)

Notes. Azo: azoospermic; Eu: eugonadal; Hypo: hypogonadal; Normo: normospermic; Oligo: oligospermic; TMC: total motile count.
Values reported as mean (*SD*).
*$p < 0.05$.

TABLE 3 Response rates

Category	Definition of response	Response rate
Hypogonadal	Post-TT >400, change-TT >200 ng/dl	79% (45/57)
Oligospermic	Post-concentration >15 million/ml	41% (18/44)
Mildly	Post-concentration >15 million/ml	46% (13/28)
Severely	Post-concentration >15 million/ml	31% (5/16)
Azoospermic	Detectable spermatozoon post-treatment	36% (5/14)
Low total motile count	Post-TMC >5 million spermatozoon	35% (16/46)

Note. Rates reported as per cent responding to therapy (number responders/number in subgroup).

appropriate. Nonparametric comparison tests were performed to analyse treatment effects and compare subgroups. Univariate modelling was performed to identify potential predictors of improvement in semen parameters, with the plan to perform multivariate modelling using those variables found notable on univariate analyses ($p < 0.10$). Variables included baseline patient characteristics, pre-treatment hormone profiles, pre-treatment semen analyses and length of therapy. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed in RStudio Software (Version 1.1.383).

3 | RESULTS

A total of 77 patients met inclusion criteria. The baseline cohort characteristics are described in Table 1. Seventy-four per cent of the cohort was hypogonadal compared to 26% eugonadal. Fifty-seven per cent was oligozoospermic, a third of which were severely oligozoospermic, compared to 25% normozoospermic and 18% azoospermic. Fifty-seven per cent of the cohort was asthenozoospermic (motility <40%), and 55% of the cohort was both hypogonadal and oligozoospermic or azoospermic.

The baseline characteristics of subgroups were compared. There were three significant differences when comparing the baseline characteristics of subgroups. Oligozoospermic patients had lower baseline sperm motility compared to normozoospermic patients (30% vs. 45%, $p = 0.01$). Severely oligozoospermic patients had lower testicular volumes compared to other oligozoospermic patients (16.0 ml vs. 18.5 ml, $p = 0.01$). FSH was slightly higher in the severely oligozoospermic group (5 mIU/ml vs. 3 mIU/ml in mildly ozoospermic group, $p = 0.04$), but still fell within normal limits. All other comparisons showed no significant differences ($p > 0.05$).

The median length of therapy was 2.8 months (IQR 1.8, 4.4 months) for the total cohort. This did not significantly differ between subgroups.

The response to therapy for the total cohort and subgroups is summarised in Table 2. The total cohort had a statistically significant rise in sperm concentration from 14 million/ml to 21 million/ml ($p = 0.002$) and in TMC from 13 million to 28 million ($p = 0.04$). Total sperm motility was not significantly different post-treatment except in patients with a starting TMC below 5 million, in which case it was improved from 17% to 26% ($p = 0.03$). Eugonadal and hypogonadal patients demonstrated similar response to therapy, showing significant improvements in sperm concentration. The only subgroups who had a different treatment effect were the normozoospermic and azoospermic patients, who showed no significant changes in semen parameters after treatment.

In regard to hormonal response, the cohort improved from a mean baseline TT of 258 to 578 ng/dl post-treatment. Eugonadal patients increased TT levels from 393 to 563 ng/dl, while hypogonadal patients increased TT levels from 211 to 582 ng/dl.

Response rates are summarised in Table 3. Using different definitions based on subgroup (see Table 3), the response rates ranged from 31% to 46%. The response rate in regard to improved TT was comparatively higher at 79%.

Baseline patient characteristics (age, race, BMI, smoking status and testicular volume), baseline hormonal profile (TT, FSH and LH) and duration of therapy were not predictive of changes in semen parameters. Lower starting sperm concentration and TMC were predictive of improvement in sperm concentration and TMC, but this did not remain significant after excluding normozoospermic patients. In other words, normozoospermic patients' semen parameters were less likely to respond to therapy, but degree of oligozoospermia was not a predictor of treatment response.

4 | DISCUSSION

While the results suggest a negative study, there are several notable findings that meaningfully contribute to the current literature and should aid shared decision-making with infertile couples. First, this cohort had a statistically significant improvement in semen parameters, enough to create candidates for intrauterine insemination (IUI) based on improvements in TMC. Second, neither pre-treatment hormone profiles nor degree of oligozoospermia were predictive of the improvements seen in sperm concentration and TMC. This suggests providers need not be discouraged by patients' gonadal state or degree of oligozoospermia when considering trialing CC for empirical therapy for infertile men. Third, response rates are modest in regard to clinically meaningful changes in semen parameters. These rates are critical to discuss in shared decision-making with infertile couples considering their various treatment options.

4.1 | Response to therapy

The first step in analysis was to determine the magnitude and significance of the treatment response in this cohort. There was a statistically significant improvement in sperm concentration from a mean of 14 million/ml at baseline to 21 million/ml after an average of just under 3 months of therapy ($p = 0.002$). This treatment effect is consistent with improvements previously reported in some of the literature. The highest level of evidence in support of CC as a therapy for male infertility comes from the 2013 meta-analysis by Chua et al., in which nearly 200 men treated with 25–50 mg of CC daily showed a mean improvement in sperm concentration of 7 million/ml, a statistically significant improvement in the high-dose treatment group and the same effect seen in our cohort (Chua et al., 2013).

A recent randomised trial by El Sheikh et al. (2015) showed 30 infertile men with oligoasthenozoospermia treated with CC 25 mg daily for 6 months had an improvement in sperm concentration from 7.5 to 10.7 million/ml, a more modest but statistically significant change from baseline. This study also showed that the treatment effect was higher at 6 months than it was at 3 months in regard to improvement in sperm concentration and motility. Our cohort had a treatment time course closer to 3 months, raising the question of whether the treatment effect may have been higher after another 3 months of therapy.

The insignificant improvement in total motility seen in our cohort is also consistent with other reports. There was no significant improvement in sperm motility in men treated with CC 25 mg daily in the Chua et al. (2013) meta-analysis, but a significant mean increase of 8% post-treatment in men treated with CC 50 mg daily. The study by El Sheikh et al. (2015) showed a significant improvement from a baseline of 23%–30% after 3 months and to 33% after 6 months.

It is important to note that not all studies have shown CC to improve semen parameters. The largest negative study to date was a multi-centre randomised control trial conducted by the World Health Organization in 1992 (WHO, 1992). Just under 100 infertile men received CC 25 mg daily for 6 months and had no statistically significant changes in their semen analyses (WHO, 1992). Findings from Chua et al. would suggest that these findings may have been different at 50 mg daily. Men in that meta-analysis who received 50 mg daily showed significant improvements in semen parameters compared to baseline and placebo while those who received 25 mg daily did not (Chua et al., 2013). There have also been case reports of paradoxical decreases in sperm concentration (Pasqualotto, Fonseca, & Pasqualotto, 2008).

A more recent retrospective analysis of nearly 50 "subfertile" men who received 50 mg every other day had improvements in sperm concentration from 51 million/ml at baseline to 72 million/ml after 3 months of therapy, but the p-value was only 0.09 (Patel et al., 2015). The clinical significance of this is unclear given the normal baseline sperm concentration in that cohort. This is consistent with the normozoospermic patients in our cohort who showed no improvement in sperm concentration from just under 3 months of therapy. Normozoospermic patients in this cohort were presenting with hypogonadism and were treated with CC for their interest in fertility preservation, not for infertility.

Our cohort also showed a statistically significant improvement in serum TT from a mean baseline of about 260 ng/dl to about 580 ng/dl after therapy. This is very similar to the improvement seen by Shabsign et al. (2005) who analysed hypogonadal men treated with 25 mg of CC daily and saw improvements in TT from about 250 to 610 ng/dl after therapy.

The treatment response in our cohort parallels that seen in the literature in regard to both semen parameters and serum TT. This may increase the external validity and generalisability of the findings.

4.2 | Predictors of change in semen parameters

With the treatment effect well characterised, the aim of this study was to elucidate predictors of improvement in semen parameters. It was hypothesised that pre-treatment elevation of FSH may be a negative predictor of response and that gonadal state (presence and degree of hypogonadism) and/or degree of oligozoospermia may be predictive of a treatment response. Sperm concentration, motility and TMC were treated as continuous variables, and univariate analysis was performed for each predictor to maximise the sensitivity of the analysis.

Despite this approach, patient characteristics (age, race, BMI, smoking status and testicular volume), pre-treatment hormone profiles (TT, FSH and LH) and duration of therapy did not predict the improved parameters seen in the cohort. There was a significant difference between oligozoospermic patients and normozoospermic and azoospermic patients, in that neither of the latter two groups responded to therapy. This was reflected in the univariate analysis when low pre-treatment sperm concentration and TMC were significant predictors of improvement until normozoospermic patients were excluded. In other words, normozoospermic patients' semen parameters did not appear to benefit from CC, but degree of oligozoospermia was not a predictor. Subgroup analysis confirmed that treatment response was no different when comparing mildly oligozoospermic to severely oligozoospermic patients or when comparing eugonadal to hypogonadal patients.

While this does not help identify a subset of patients more likely to respond to CC therapy, it does suggest that there is a fairly diverse range of patients who can respond to CC in a similar manner. Thus, we believe patients should be counselled and offered a trial of CC therapy regardless of pre-treatment characteristics such as age, BMI, testicular volume, TT, FSH or degree of oligozoospermia.

It is unclear whether azoospermic patients benefit from CC. Hussein et al. have previously reported that after 42 men were given CC for azoospermia, 64% showed spermatozoon in their semen analyses; all patients had sufficient spermatozoon for intracytoplasmic sperm injection after extraction even though 36% remained azoospermic (Hussein, Ozgok, Ross, & Niederberger, 2005). A randomised control trial is ongoing to evaluate whether azoospermic patients benefit from CC (clinicaltrials.gov identifier NCT02137265).

No previously published study has looked specifically at predictors of improvement of semen parameters in men treated with CC. An early study on the topic by Micic and Dotlic (1985) suggested younger patients showed greater treatment response, but this did not achieve statistical significance. Boeri et al. (2015) presented an abstract on the topic and were able to show younger age, lower BMI and shorter duration of infertility were all positive predictors of treatment response; unfortunately, these findings were not followed by a peer-reviewed manuscript. Our study was not able to demonstrate any correlation with age or BMI and improvement in semen parameters. Duration of infertility was not tracked for analysis.

4.3 | Response rates

Response rates are not always discussed in regard to CC for men. When they are, the definition is variable and sometimes arbitrary. Mazzola, Katz, Loghmanieh, Nelson, and Mulhall (2014) analysed predictors of improvement in serum testosterone among hypogonadal men treated with CC. They found a testicular volume of >14 ml and a LH of less than or equal to 6 mIU/ml were independent predictors of a treatment response, which they admit was arbitrarily defined as an increase in TT of at least 200 ng/dl and a level of at least 400 ng/dl after 6 months of treatment. Hussein et al. (2005) studied CC use among azoospermic men and defined a response as any detectable spermatozoon post-treatment. Guay, Jacobson, Perez, Hodge, and Velasquez (2003) studied hypogonadal men with erectile dysfunction and defined success as ability to have intercourse. Katz et al. (2012) studied outcomes in young hypogonadal men and reported success rates in relation to symptom improvement.

The best definition of success or response rate for infertile men is achieving a pregnancy and live birth, but few studies report this. A meta-analysis by Chua et al. (2013) found only six randomised control trials that reported pregnancy rates as an outcome, with a response rate of 15% in the high-dose CC group. Pregnancy rates were not reported in our cohort. Semen analysis was used a proxy to fertility. Clinically, semen analysis may help determine early response to therapy and guide dose titration.

Several definitions of treatment response were used, aiming to improve shared decision-making with patients. Two definitions were borrowed from the literature: hormonal response from Mazzola et al. (2014) and response for azoospermic patients from Hussein et al. (2005). The response for oligozoospermic patients was defined as a post-treatment sperm concentration in the normal range, >15 million/ml by 2010 WHO 5th edition criteria. There is little consensus on cut-off values for TMC, but 5 million spermatozoon is commonly used clinically as an important threshold for patients, especially those considering IUI (Hajder, Hajder, & Husic, 2016; Hamilton et al., 2015; Zhang, Tao, Xing, Cai, & Zhang, 2014). Response for those with a baseline TMC of <5 million spermatozoon was defined as a post-treatment TMC >5 million spermatozoon. We considered these definitions to be clinically important changes that could help guide patient counselling.

Response rates in this cohort varied by definition. Hormonal response was 79% using the definition of Mazzola et al., who had a 62% response rate in their own cohort. The response rate from a fertility perspective was considerably lower, ranging from 31% to 46%. This was consistent whether using the definitions for oligozoospermic, azoospermic, or low TMC response. This was lower than the response rate seen in azoospermic patients in the Hussein et al. (2005) study, who had a 64% response rate, possibly due to a higher therapy dose of 50 mg daily. Our cohort had a high BMI, but it is unclear if or how this may affect fertility response in men treated with CC.

By providing several definitions of response, we hope providers can offer more targeted counselling to patients based on their baseline parameters and treatment goals. This may be particularly helpful for couples considering IUI. About one third (35%) of our cohort with a pre-treatment TMC below 5 million improved to >5 million motile spermatozoon after treatment, a more favourable threshold for consideration of IUI (Hajder et al., 2016; Hamilton et al., 2015; Zhang et al., 2014). Providers must be cautious in counselling men on CC given its off-label use and rare side effects including case reports of paradoxical decreases in semen parameters (Pasqualotto et al., 2008).

4.4 | Strengths and limitations

There are several strengths to the study. First, to our knowledge, it is the largest published cohort analysed for predictors of improvement in semen parameters. It includes patients from two high-volume institutions and four different fellowship-trained male fertility providers. The inclusion criteria are broad, allowing patients with any combination and degree of male infertility and hypogonadism, and offering a real-world representation of male candidates for CC. While this led to a heterogeneous cohort, it also improves external validity of the study. Statistical analysis was designed to maximise sensitivity for predictors of change, lending confidence to a true negative finding. Response rates are reported using several definitions, some replicated from the current literature and others chosen for their clinical importance.

Like much of the current literature, a limitation of this study is that pregnancy rates and live birth rates were not captured. The study is inherently limited by its retrospective design. There is some heterogeneity expected based on the practice pattern of the different providers and inter-laboratory variability, particularly with semen analyses. The starting dose may be low for fertility patients and the proportion of patients who had dose titration was not captured. The duration of therapy was a limitation, bordering on just 3 months. There is some evidence that treatment response may be more robust at 6 months (El Sheikh et al., 2015), but this study was limited by its retrospective design. Treatment duration in this analysis was defined based on dates of follow-up semen analyses. Many patients continued treatment beyond 3 months, but repeat semen analysis was not obtained as it was deemed less clinically relevant than achieved pregnancies, which were not captured in our dataset. Our cohort did show improvements in a 3-month time frame; moreover, the mean

duration of therapy exceeded the approximately 74 days needed for spermatogenesis. It is possible that repeat semen analysis later in the treatment course may have shown more robust improvements in semen parameters.

Nonetheless, there is value in providing additional data on the expected treatment response from CC in regard to semen parameters, showing consistency in treatment response among various subgroups and introducing clinically helpful response rates to aid in shared decision-making.

5 | CONCLUSIONS

Clomiphene citrate is a reasonable treatment for men with abnormal semen parameters and/or hypogonadism, with the potential of improving sperm concentration, total motile count and serum testosterone. Patient characteristics, pre-treatment hormone profile and degree of oligozoospermia do not predict treatment response. Patients with a range of abnormalities on baseline hormonal assessment and semen analysis may benefit from therapy. Treatment response is variable based on definition and modest for clinically meaningful changes in semen parameters. Providers should use these findings to help guide patient selection and in shared decision-making.

DISCLOSURES

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