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SHORT COMMUNICATION

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A paradoxical decline in semen parameters in men treated with clomiphene citrate: A systematic review

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Abstract

Clomiphene, a selective oestrogen receptor modulator, has been utilised in managing male sub-fertility since 1967. Numerous controlled and uncontrolled studies have been published regarding the efficacy of clomiphene citrate in male sub-fertility cohorts. Although the primary intention of treating men with clomiphene citrate is to improve sperm parameters and testosterone levels, some studies have reported paradoxical decline in semen parameters. The information available on decline in sperm parameters following treatment with clomiphene is sparse. We conducted a systemic review using PubMed, Embase, Cochrane Library and Scopus databases for original studies reporting adverse effects of clomiphene citrate therapy on sperm parameters. This systematic review includes 384 men from 11 different studies that reported adverse effects of clomiphene citrate therapy. Of the men included in these studies, 19%, 21%, 17% and 24% of clomiphene-treated men demonstrated a decrease in sperm count, concentration, motility and total motile sperm count respectively. In up to 17% of patients, deterioration of semen parameters did not recover following discontinuation of therapy. In the future, more studies should report on this aspect so the magnitude of this effect can be more clearly understood.

KEYWORDS

adverse effects, azoospermia, clomiphene citrate, infertility, male infertility, oligozoospermia, semen parameters, side effects, sperm parameters

1 | INTRODUCTION

Clomiphene citrate is a selective oestrogen receptor modulator initially developed for the treatment of female infertility in the 1960s (Wheeler et al., 2019). Due to its mechanism of action, many have also advocated for its use to treat hypogonadal men who wish to preserve fertility. Selective oestrogen receptor modulators function by inhibiting the negative feedback of oestrogen on the hypothalamus and pituitary to promote spermatogenesis and testosterone production (Krzastek et al., 2019; Wheeler et al., 2019). While its use for male hypogonadism is off label due to a lack of long-term data, its usage has been supported by the American Urological Association guidelines (Krzastek et al., 2019). Treatment with clomiphene citrate has consistently demonstrated increases in testosterone levels as well as improvement in hypogonadal symptoms (Bendre et al., 2015; Katz et al., 2012; Moskovic et al., 2012; Ramasamy et al., 2014; Taylor & Levine, 2010). Many studies have also reported improvements in fertility, but still a paucity of data exists with regard to the true fertility outcomes in hypogonadal men treated with clomiphene citrate (ElSheikh et al., 2015; Hussein et al., 2013; Mićić & Dotlić, 1985; Moradi et al., 2010; Wheeler et al., 2019). While clomiphene citrate has generally been regarded as a safe drug, minimal evidence concerning adverse side effects is available (Wheeler et al., 2019).

In contrast to the notion of fertility preservation and improvement in semen parameters in men treated with clomiphene citrate therapy, few studies have reported adverse effects on fertility parameters (Pasqualotto et al., 2008; Shanis, Check, & Bollendorf, 1991). Negative effects on sperm concentration, motility, total motile

sperm count and morphology have been reported (Heller et al., 1969; Jungck et al., 1964; Pasqualotto et al., 2008; Ross et al., 1980; Rŏnnberg, 1980; Shanis et al., 1991). A previous meta-analysis also demonstrated that while clomiphene citrate therapy is associated with an increase in sperm concentration, reported changes in these parameters are highly variable due to inconsistency in study design (Bridges et al., 2015). Due to the variability in reporting and paucity of data, descriptions on adverse effects on semen parameters in men treated with clomiphene have not been clearly elucidated. We conducted a systematic review to organise evidence reporting adverse effects of clomiphene citrate therapy on semen parameters.

2 | MATERIALS & METHODS

This systematic review was conducted with the objective of identifying evidence concerning adverse effects on semen parameters in men treated with clomiphene citrate (Figure 1). A systematic and qualitative review was performed according to the Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Search was made through PubMed, MEDLINE, Embase, Cochrane Library, Scopus, Google Scholar and ProQuest databases from inception until 31 May 2020. Medical subject headings (MeSH) terms along with keywords were used during the search through all the fields of the records. Search was done using the following terms: "Clomiphene" AND ("Male infertility" OR "Male sub-fertility" OR "Oligozoospermia" OR "Low sperm count" OR "Asthenozoospermia" OR "Teratozoospermia" OR "Abnormal spermatozoa" "Oligoasthenoteratozoospermia" OR "Worsening of Semen Quality" OR "Worsening of Semen analysis"). Additional manual search was done using the reference lists of relevant studies. Reference list of related literatures and abstracts from major meetings of Urology, Andrology, Reproductive Medicine, Obstetrics and Gynecology was searched on the ISI Web of Knowledge: http://isiwebofknowledge.com/ (last searched 31 May 2020). "Fertility and Sterility", "Human Reproduction" and "Andrology" journals which contains abstract supplements for the "American Society for Reproductive Medicine" "European Society of Human Reproduction and Embryology" and "American Society for Andrology" were handsearched. Ongoing and recently completed trials were searched from the World Health Organization International Trials Registry Platform search portal' (www.who.int/trialsearch/) (last searched 31

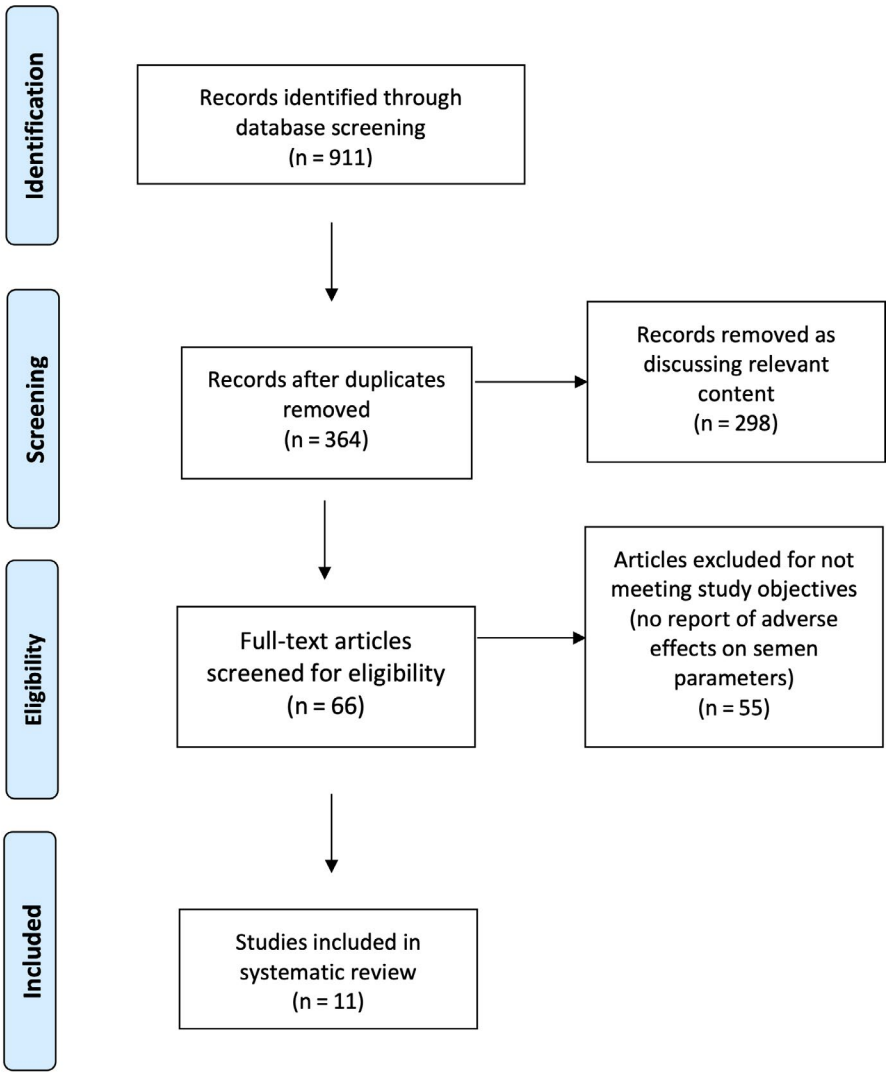

FIGURE 1 Flow chart of studies included in systematic review

May 2020). Studies were excluded if they reported men with identifiable male factor infertility such as inflammatory disease, testicular trauma, epididymal factor, varicocele, anti-sperm antibodies or genetic problems.

Two authors (T.G and M.K) performed all aspects of search strategy. Each author independently examined the relevance of abstracts according to the study objective. Relevant articles (full-text articles and abstracts) tagged by either reviewer were ordered for full-text copy. The two authors (T.G. and M.K.) independently extracted the data for subsequent analysis, and one author functioned as a referee in case of ambiguities (R.R.). When a foreign language article was encountered for inclusion, article abstract was translated through Google Translator and then evaluated to assess its relevance. A standardised form was used to summarise and extract data from each study.

3 | RESULTS

Overall, there were no major disparities between reviewers with regard to study inclusion, exclusion and data extraction. Minor disparities in extraction of clinical characteristics were resolved by consensus and intervention by a third independent reviewer. In total, eleven studies reported adverse effects on sperm parameters (Table 1). 315 eligible males, ranging from age 20–50, were included in this systematic review. Men included were either healthy volunteers ($n = 26$) or patients with sub-fertility ($n = 289$). Sub-fertile patients had a diagnosis of either idiopathic sub-fertility ($n = 85$) or idiopathic oligospermia ($n = 204$). Men received treatment with either clomiphene citrate ($n = 304$) or cis-clomiphene ($n = 11$). Clomiphene citrate was administered in doses ranging from 25–400 mg/day, while cis-clomiphene was administered in doses of 5–10 mg/day. Duration of treatment ranged from 2–15 months with a follow-up period up to 6 months.

3.1 | Sperm count

Five studies reported adverse effects of clomiphene citrate therapy on sperm count (Table 2). Jungck et al. enrolled healthy volunteers ($n = 12$) and oligospermic patients ($n = 29$). Healthy volunteers and 20 oligospermic patients were treated with 50 mg/day of CC for 8 weeks and the remaining 9 oligospermic patients were treated with 25 mg/day of CC for 8 weeks. In all, 10 out of these experienced an average of 51% decrease in sperm count. In a trial by Mellinger et al., three oligospermic males had progressive decrease in sperm count and one eventually developed azoospermia. The sperm counts recovered in one patient with continued therapy in one patient and recovered in the other two following discontinuation. In a study by Mroueh et al., four oligospermic sub-fertile males experienced an average of 51% decline in sperm count after 6 weeks with 50 mg/day of clomiphene citrate therapy. Paulson et al. assessed the effect of 25 mg/day of CC on 22 idiopathic sub-fertile males. Four patients experienced an average of 53% decrease in sperm count following six months of treatment. In another study a year later, Paulson et al. enrolled 35 idiopathic oligospermic patients to evaluate the effect of 25 mg/day of CC given over 12 months or till pregnancy. Two patients experienced worsening of sperm count. Overall, of studies that reported adverse effects of CC therapy on sperm count, 19% of mean experience an average decrease in sperm count of 52%.

3.2 | Sperm concentration

Five studies reported adverse effects of clomiphene citrate therapy on sperm concentration (Table 3). Heller et al. evaluated the effect of varying clomiphene dosages on sperm concentration in healthy volunteers. One participant who received the lowest dose of 50 mg/day had a decrease in concentration at 2 months, but subsequently recovered to baseline levels. Six other participants who received higher dosage (ranging from 100–400 mg/day) had a reduction in sperm concentration. The average percentage decrease in concentration was 62% and was dose dependent. Both patients whom received 400 mg/day experienced a decline in concentration. Recovery in sperm concentration was seen within 3 months of discontinuing clomiphene treatment for some participants; however, 60% of participants experiencing a decrease did not demonstrate recovery in concentration by 6 months. In another study by Wieland et al., 11 males with idiopathic oligospermia received cis-clomiphene 5 mg or 10 mg daily for 12 weeks. Three of the participants had a decrease in sperm concentration by an average of 66% at 12 weeks. In a study by Halim et al. of 25 oligospermic men, four men demonstrated a mean decrease in sperm concentration by an average of 77% following 8 weeks of 50 mg/day of CC therapy. Ross et al. evaluated 53 idiopathic sub-fertile males; nine patients experienced a decrease in sperm concentration after receiving 100 mg of clomiphene on alternate days for a period of 3–15 months. The average decrease in concentration was 48% for these men. Pasqualotto et al. reported three patients of severe oligospermia becoming azoospermic after a mean duration of 4.5 months treatment with clomiphene. Upon discontinuation of clomiphene therapy and re-evaluation at 3 months, sperm concentration recovered to a mean concentration of 2.5 ± 1.1 million/ml. In all the studies that reported worsening in sperm concentration, 21% of clomiphene-treated males demonstrated an average of 68% decrease in sperm concentration. Additionally, when the dose range was constrained to those who received 50 mg/day or less, analysis of the data revealed that 17% of men experienced an average of 66% decrease in sperm concentration.

3.3 | Sperm motility

Four studies reported worsening sperm motility after CC treatment (Table 4). In a study by Mellinger et al. of 13 oligospermic sub-fertile men, two patients (15%) experienced worsening of sperm motility. In a trial by Mroueh et al. of 13 oligospermic sub-fertile men who

TABLE 1 Summary of studies reporting adverse effects of clomiphene citrate therapy on sperm parameters which were included in the systematic review

Study	Design	Patients	Intervention	Outcome measures	Follow-up
Jungck et al. (1964)	Prospective case–control	Healthy volunteers ($n = 12$) and oligospermic patients ($n = 29$)	For 8 weeks, CC 50 mg/day (healthy volunteers), CC 50 mg/day (20 oligospermic) or CC 25 mg/day (9 oligospermic)	Semen volume and sperm concentration	No
Mellinger and Thompson (1966)	Prospective cohort	Idiopathic oligospermic sub-fertile males ($n = 13$)	CC (dose and duration—N/A)	Semen characteristics and hormonal response (FSH, LH, T, urinary 17-ketosteroids)	N/A
Mroueh et al. (1967)	Prospective cohort	Idiopathic oligospermic sub-fertile males ($n = 13$)	CC 50 mg/day for 6 weeks	Semen characteristics and testicular biopsy	No
Heller et al. (1969)	Prospective cohort	Healthy volunteers ($n = 14$)	CC 50 mg/day, 100 mg/day, 200 mg/day and 400 mg/day for 2–12 months	Sperm concentration	6 months
Wieland et al. (1972)	Prospective cohort	Idiopathic oligospermic sub-fertile males ($n = 11$)	Cis-clomiphene 5 mg/day or 10 mg/day for 12 weeks	Sperm concentration, FSH, LH, testosterone	12 weeks
Halim et al. (1973)	Prospective cohort	Idiopathic oligospermic sub-fertile males ($n = 25$)	CC 50 mg/day for 60 days	Sperm concentration	No
Paulson et al. (1975)	Prospective cohort	Idiopathic oligospermic sub-fertile males ($n = 22$)	CC 25 mg/day for 25 days a month for 6 months	Semen characteristics, FSH, LH, testosterone	No
Paulson and Wacksman (1976)	Prospective cohort	Idiopathic oligospermic sub-fertile males ($n = 35$)	CC 25 mg/day for 25 days a month for 12 months or until pregnancy	Semen characteristics, FSH, LH, testosterone	No
Ross et al. (1980)	Prospective cohort	Idiopathic oligospermic sub-fertile males ($n = 53$)	CC 100 mg/day 3× a week for 3–15 months (dependent upon response or pregnancy)	TMC, sperm concentration, motility, FSH, LH, testosterone	No
Pasqualotto et al. (2008)	Case series	Severe idiopathic oligospermia ($n = 3$)	CC (dose and duration— N/A)	Sperm concentration	3 months
Samplaski et al. (2014)	Prospective cohort	Idiopathic sub-fertile males ($n = 85$)	CC 25 mg/day (duration— N/A)	Total motile sperm count, adverse effects to CC	No

Abbreviations: CC, clomiphene citrate; FSH, follicle-stimulating hormone; LH, luteinising hormone; and N/A, not available.

TABLE 2 Studies reporting worsening in sperm count following clomiphene citrate therapy

Study	Dose and drug formulation	Patients with decrease in sperm count (*n*)	Mean % decrease
Jungck et al. (1964)	Overall	24.39% (10)	51.39%
	CC 25 mg/day	33.33% (3)	43.08%
	CC 50 mg/day	21.87% (7)	55.55%
Mellinger and Thompson (1966)	N/A	23.07% (3)	N/A
Mroueh et al. (1967)	CC 50 mg/day	30.76% (4)	51.21% ± 21.12
Paulson et al. (1975)	CC 25 mg/day	18.18% (4)	53% ± 22.18
Paulson and Wacksman (1976)	CC 25 mg/day	5.71% (2)	N/A
Overall		18.54% (23)	51.86% ± 0.98

Abbreviations: CC, clomiphene citrate and N/A, not applicable.

received 50 mg dose of CC daily for 6 weeks, three patients (23%) experienced an average decline in sperm motility of 34%. Furthermore, three patients (13%) experienced an average decrease in motility by 40% in a study by Paulson et al. In a trial by Ross et al., 9 men (16%) experienced worsening of sperm motility with a mean decrease in motility by 27%. In the studies that have reported adverse effects of CC on motility, 17% of CC-treated males demonstrated an average of 34% decrease in sperm motility.

3.4 | Total motile sperm count

Two studies described adverse outcomes of clomiphene therapy on total motile sperm count (TMSC) (Table 5). Ross et al. evaluated 53 idiopathic sub-fertile males who received 100mg dose of clomiphene on alternate days for a period of 3 to 15 months. Of these patients, six patients (11%) demonstrated a decrease in TMSC at 6 months of follow-up. Five of them subsequently recovered despite continuing therapy. In another study by Samplaski et al., 85 infertile males were treated with 25 mg dose of clomiphene citrate daily. 27 patients (32%) demonstrated worsening of TMSC at 3 months of follow-up. Overall, in the studies that reported adverse effects of CC therapy on total motile sperm count, 24% of males demonstrated an average of 49% decrease in total motile sperm count.

4 | DISCUSSION

The aim of this study was to summarise available evidence reporting worsening of semen parameters following clomiphene citrate therapy. To our knowledge, no review article or meta-analysis is available which sheds light on this important aspect. Our results find that a significant number of men treated with clomiphene citrate have negative effects on semen parameters—the parameters it has long been believed to preserve. Our analysis found that in studies reporting adverse impacts, 19%, 21%, 17% and 24% of men demonstrated a decrease in sperm count, concentration, motility and total motile sperm count (TMSC) respectively. In the men who experienced worsening in these parameters, sperm count, concentration, motility and TMSC decreased by a mean of 52%, 68%, 35% and 49% respectively.

TABLE 3 Studies reporting worsening in sperm concentration following clomiphene citrate therapy

Study	Dose and drug formulation	Patients with decrease in sperm concentration (*n*)	Mean % decrease
Heller et al. (1969)	Overall	42.87% (6)	61.72% ± 34.65
	100 mg/day	100% (1)	*12.38%
	200 mg/day	50% (3)	69.43%
	400 mg/day	100% (2)	94.49%
Wieland et al. (1972)	Overall	27.27% (3)	56.43% ± 22.84
	Cis-clomiphene 5 mg/day	20% (1)	*81.81%
	Cis-clomiphene 10 mg/day	33.33% (2)	43.75%
Halim et al. (1973)	CC 50 mg/day CC	16% (4)	76.5% ± 20.77
Ross et al. (1980)	CC 100 mg on A/D	16.98% (9)	47.9% ± 35.44
Pasqualotto et al. (2008)	N/A	N/A	$100%
Overall		21.35% (22)	68.44 ± 20.44

Abbreviations: CC, clomiphene citrate; N/A, not applicable; A/D, alternate days; *not an average value as it was only one patient; and $all patients became azoospermic.

TABLE 4 Studies reporting worsening in sperm motility following clomiphene citrate therapy

Study	Patients reporting decrease in sperm motility (*n*)	Mean % decrease
Mellinger and Thompson (1966)	15.38% (2)	N/A
Mroueh et al. (1967)	23.07% (3)	34.35% ± 22.26
Paulson et al. (1975)	13.63% (3)	40.46% ± 20.32
Ross et al. (1980)	16.98% (9)	27.4% ± 18.01
Overall	16.83% (17)	34.4% ± 6.33

TABLE 5 Studies reporting worsening in total motile sperm count (TMSC) following clomiphene citrate therapy

Study	Patients reporting decrease in TMSC (*n*)	Mean % decrease
Ross et al. (1980)	11.32% (6)	57.14% ± 35.61
Samplaski et al. (2014)	31.76% (27)	40.9%
Overall	23.91% (33)	49.02% ± 11.48

Among the patients experiencing a decrease in semen parameters with follow-up data, complete recovery in sperm count after stopping therapy occurred in 48% of men, partial recovery (improvement but not above baseline) in 35%, and no recovery was recorded in 17%. In men who recovered parameters, recovery was commonly seen within 3 months of treatment discontinuation.

Clomiphene, a selective oestrogen receptor modulator, has been used to manage male sub-fertility for more than six decades despite a lack of FDA approval for this indication (Krzastek et al., 2019). According to a 2010 American Urological Association survey of 387 urologists, clomiphene citrate, human chorionic gonadotropin and anastrozole were the most commonly prescribed agents, though clomiphene was by far the most commonly used drug for male sub-fertility (>90% of respondents) (Ko et al., 2012). As a result of increased use, numerous studies evaluating the efficacy of clomiphene citrate in male sub-fertility have been conducted, but only a minority report paradoxical effects in semen parameters following treatment.

Plausible mechanisms explaining the deterioration in semen parameters are technical errors in analysis, direct effects of clomiphene on testicular histology and increases in oestrogen concentration due to CC therapy. Semen parameters are highly variable biological measures. Unlike other body fluids, semen parameters are not subjected to homeostatic regulations. There is significant intra-individual variability of seminal parameters—it can vary as much as 10.3% to 26.8% (Alvarez et al., 2003). According to Opsahl et al., 10.4% of men with an abnormal semen at first analysis eventually had a normal sperm count upon subsequent analyses without intervention (Opsahl et al., 1996). Thus, there is a possibility that changes

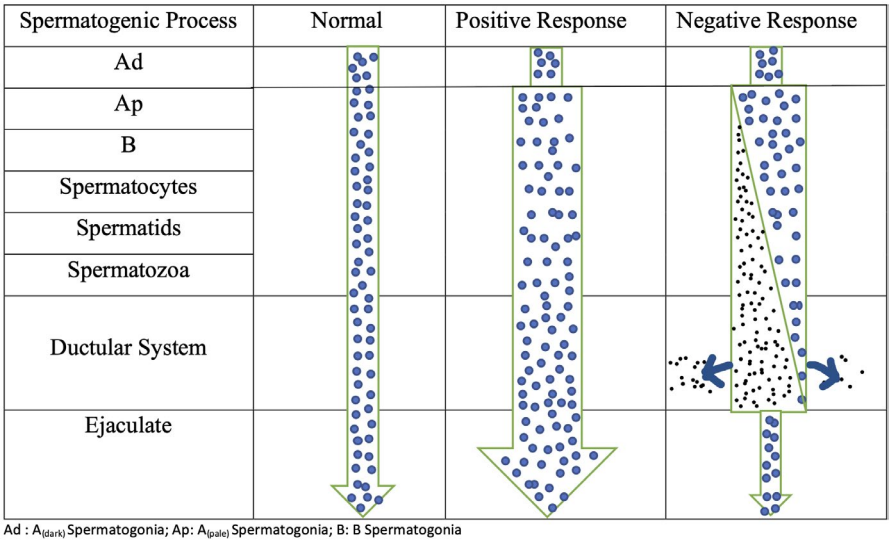

FIGURE 2 Adapted using information data from Heller et al. (Heller & Heller, 1970). Diagrammatic representation of effect of clomiphene on spermatogenesis. Normal arrow indicates a normal process with a consistent flow of cells. The middle arrow indicates a positive response; there is an increase in the $A_{(pale)}$ spermatogonia and subsequent cell types resulting in increased sperm output. The right arrow indicates a negative response due to high dose or increased sensitivity of the subject; $A_{(pale)}$ spermatogonia and subsequent cell types are increased in number, but abnormal forms are increased. Abnormal forms are maximum in mature spermatids and spermatozoa. These abnormal cells are reabsorbed by Sertoli cells or the epididymis, and consequently, sperm output is decreased. (Large circles indicate normal germ cells; smaller circles indicate abnormal germ cells)

in semen parameters may result from a natural variation in semen production.

Clomiphene can have a direct effect on germ cells or an indirect effect from alteration in peri-tubular membrane structure to adversely affect germinal cells. Heller et al. quantified abnormal germinal cells following administration of clomiphene citrate in normal men. Clomiphene directly stimulates division of spermatogonia, evidenced by an increase in $A_{(pale)}$, type B spermatogonia and spermatocytes occurring at all doses of clomiphene regardless of the resultant sperm count. It also results in increased synthesis of abnormal germinal cells primarily at high doses, with maximum effect on mature spermatids followed by immature spermatids, spermatocytes and spermatogonia. These abnormal cells are reabsorbed during their passage through the ductular system eventually resulting in a decrease in sperm output (Figure 2). Production of abnormal germinal cells can be a result of either direct effect of clomiphene on germ cells or indirect effect from alteration in peri-tubular membrane structure or function leading to nutrient blockage adversely affecting their growth. Some credence to the hypothesis that clomiphene leads to a barrier in nutrient supply is the observation that at the higher dose levels some hyalinisation of the basement membrane has been seen (Heller & Heller, 1970). Thus, sperm count variation is a direct result of the number of abnormal cells produced by the individual and is related to the clomiphene citrate dose administered or sensitivity of an individual to the clomiphene dose (Heller & Heller, 1970). Variations in sensitivity can be due to genetic polymorphisms and these subjects can serve as a source of pharmacogenomic research in the future.

Clomiphene citrate is associated with increase in oestrogen levels. According to a study by Keihani et al., 25.47% patients treated with clomiphene citrate 50 mg/day or every other day experienced hyperoestrogenaemia (defined as oestradiol > 50 pg/ml) 4 weeks after treatment initiation (Keihani et al., 2020). Supraphysiological oestrogen levels have a deleterious effect on spermatogenesis (Morrish et al., 1990; O'Marcaigh et al., 1995; Sharpe & Skakkebaek, 1993; Young et al., 1996). There are different postulated mechanisms by which raised oestrogens affect sperm production. Elevated oestradiol levels result in vacuolisation and increased glycoprotein production impairing Sertoli cell function. It also disturbs communication with germ cells, increases collagen synthesis and fatty degeneration in the testicular connective tissue. All these actions collectively result in induction of germ cell death (Leavy et al., 2017). Oestradiol also plays a critical role in round spermatid chromatin reorganisation during spermiogenesis through its action on Estrogen Receptor Alpha (ERα) present on Sertoli cells (Cacciola et al., 2013). Overexposure to oestrogens reduces expression of ERα on Sertoli cells, impacting this critical action. Moreover, it has been recognised that supraphysiological concentrations of oestrogen act as powerful apoptotic triggers which induce germ cell apoptosis (Correia et al., 2015). Consequently, increased oestrogen levels due to clomiphene citrate therapy may result in impaired spermatogenesis and worsening of sperm parameters.

The results of our study bring light to adverse effects resulting from clomiphene citrate therapy. These should be considered when initiating treatment due to the limited availability of robust research evaluating the safety and efficacy of this medication. Close follow-up should be maintained with patients following initiation and treatment to monitor for deterioration of fertility or any other side effects. Ultimately, our study has strengths and limitations. A strength of this study is that it is the first to systematically review available evidence regarding adverse effects of clomiphene therapy on sperm parameters. Published evidence has been compiled in one place so future studies can easily identify and utilise the data that are available. Limitations of this study include the paucity of data that has been published about this topic; therefore, conclusions may be limited due to small sample populations. Some studies have evaluated the effect of clomiphene on sperm concentration. However, sperm concentration is vulnerable to wide variations due to sensitives of ejaculate volume. Raised testosterone levels following clomiphene citrate itself can increase seminal volume. Additionally, semen analysis is a subjective evaluation. Attempts have been made by WHO to standardise semen analysis; however, adoption among laboratories is still low. Thus, it is possible to have variations in sperm parameter data due to subjective variations as opposed to repercussions of clomiphene citrate treatment. Finally, pregnancy rate was not our outcome measure and hence we did not analyse if pregnancies occurred despite fall in seminal parameters.

5 | CONCLUSION

Treatment with clomiphene citrate can be associated with a decrease in semen count, concentration, motility, morphology and total motile sperm count in up to 20% of patients. Among men who had a decline in semen parameters, 17% of them may not recover following discontinuation of therapy. The benefits of therapy should be weighed against potential negative impacts on fertility, and close follow-up should be maintained. More studies should report on decline in semen parameters so the magnitude of this effect can be more easily measured by reproductive specialists in the future.

DATA AVAILABILITY STATEMENT

Data sharing upon request.

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