Clomiphene Citrate for Male Infertility

A Systematic Review and Meta-Analysis

Short title:

Clomiphene Citrate for Male Infertility

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ABSTRACT

BACKGROUND – Male infertility is a prevalent and worldwide problem with various difficulties in treatment. Clomiphene citrate (CC) is a selective estrogen receptor modulator and may improve semen quality by stimulating hormone synthesis and spermatogenesis. There is lack of evidence on the efficacy of CC as therapy for male infertility.

OBJECTIVES - Therefore, a systematic review and meta-analysis was performed to assess the efficacy of CC on sperm quality in infertile men.

METHODS – A search was conducted in the PubMed, EMBASE and Cochrane databases for effectiveness in infertile males treated with CC. Both intervention and observational studies were included. Primary outcome measures were semen parameters (concentration, motility and morphology). Secondary outcomes included hormonal evaluation, pregnancy rate and side effects. Studies were included for meta-analysis if they provided absolute numbers for outcomes before and during treatment with appropriate SD or SE.

RESULTS – 1799 studies were identified during the search, 18 studies remained for qualitative analysis (n = 731) and 15 studies for meta-analysis (n = 566). Study populations ranged between 11 and 140 participants. Sperm concentration was higher during treatment with a mean difference 8.38 x10^6/mL (95% CI, 5.17, 11.59; $P < 0.00001$; $I^2 = 87\%$). Total sperm motility was higher during treatment with a mean difference of 8.14% (95% CI, 3.83, 12.45; $p < 0.00001$; $I^2 = 76\%$). There was no difference in sperm morphology before and during treatment. Total testosterone, follicle stimulating hormone, luteinizing hormone and estradiol were higher during CC treatment. During follow-up no serious adverse effects occurred. In ten studies pregnancy rate was reported and yielded a mean of 17% during CC treatment (range, 0 – 40%).

CONCLUSIONS – Clomiphene citrate increased sperm concentration and -motility and could be considered as a safe therapy for improving sperm parameters in infertile males.

INTRODUCTION

According to The International Glossary on Infertility and Fertility Care (2017), infertility is a 'disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner'.[1] Infertility affects an estimated 48 to 186 million people worldwide.[2,3] Male factor is the sole cause approximately one-third of all cases of infertility.[4,5] Congenital anomalies, urogenital infections and trauma, systemic disorders and varicocele are some of the causes and associated factors with male infertility.[6] In about 30-40% of the cases, infertile men have normal findings on physical examination and hormonal laboratory test. This so-called idiopathic infertility, which has no known etiology, is difficult to treat.[6]

An unfulfilled child wish is the reason that infertile couples are frequently treated with assisted reproductive techniques such as intrauterine insemination, in vitro fertilization, testicular sperm extraction, and intracytoplasmic sperm injection.. Empirical therapies such as selective estrogen receptor modulators (SERMs) and antioxidants are a potential treatment option to improve

spermatogenesis. Although, there is lack of supporting data on the efficacy of these medications, empirical therapies are necessary in the treatment of idiopathic infertility.[5]

Clomiphene citrate (CC) is a SERM, it occupies estrogen receptors in the hypothalamus and pituitary, and so stimulates the hypothalamic-pituitary-gonadal (HPG) axis, resulting in release of gonadotropins and improves testosterone production and may theoretically improve spermatogenesis. [7] CC has been used in women for ovulatory dysfunction since the 1960s.[8] Although, the U.S.A. Food and Drug Administration (FDA) never approved CC therapy for male infertility and hypogonadism, it has been used as an off-label medication. The advantage of CC over testosterone therapy, is that it maintains spermatogenesis in case of hypogonadal males and may improve spermatogenesis in infertile males. CC results from previous studies demonstrated safety on long-term use with minor side-effects and costs.[9]

Even though it is an off-label medication, many urologists utilize CC to treat male infertility. According to the survey conducted by the American Urological Association in 2012 and revised in 2020, 78% and 93%, of male fertility fellowship-trained urologists used CC, as well as other empirical therapies and surgery to treat infertile males.[10,11]

Even though, CC is commonly used as empirical treatment, the efficacy of therapy with CC for male infertility is insufficiently established. According to the FDA, appropriate or well-controlled trials demonstrating the efficacy of CC in the treatment of male infertility are needed.[12] We conducted a systematic review and meta-analysis to provide an overview of the published studies on efficacy of CC therapy on sperm parameters in the treatment of male infertility.

METHODS

3.1 Search Strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[13] This study was registered in PROSPERO under registration number CRD42021241644. PubMed, EMBASE and Cochrane databases were searched for relevant publications from the beginning of the study collecting up to December 2022 using the Medical Subject Headings and Keywords [Infertility OR Subfertility OR Aspermia OR Asthenozoospermia OR Azoospermia OR Oligospermia OR Teratozoospermia] AND [Clomiphene] AND [Male OR Men]. The full search strategy for PubMed and EMBASE is provided in Supplementary Materials (Appendix 1). Additionally, reference lists of included studies were searched for potentially eligible studies not identified by our database search.

3.2 Selection process

Two reviewers (MH and RH) independently screened and assessed eligibility of identified publications. Disagreements were resolved by consensus of a third independent reviewer (HB). Publications were included if they assessed the effect of clomiphene citrate on semen parameters in semen analysis in normogonadotropic or hypogonadal men ≥18 years old with clinical infertility, defined as the inability to conceive a pregnancy following regular unprotected sexual intercourse with a healthy female partner, with or without associated hypogonadism. Semen parameters for semen analysis included volume, sperm count, sperm concentration, sperm motility, and sperm morphology. Publications were excluded if treatment with CC was combined with other testosterone suppletion therapy, or if patients were treated with enclomiphene or zuclomiphene. Other exclusion criteria were studies in a female study population, studies in populations with specific disorders (HIV, malignancy, liver cirrhosis, renal failure), patients with syndromic disorders (Klinefelter, Prader Willi, Kallman, Bardet Biedl), animal studies, case reports, case series (that were not cohort-based), literature reviews, studies not published as full reports (i.e. conference abstracts, letters to editor), studies with no full-text availability, and publications in languages other than English or Dutch.

3.3 Data collection

Data extraction was performed in duplicate and independently by two authors (MH and RH) using a standardized data extraction sheet. Data items were then compared for correctness and completeness. Disagreements were resolved by consensus. Data items that were extracted as primary outcomes were semen analysis parameters, including sperm concentration, sperm motility, and sperm morphology before and after therapy with CC. Data elements that were extracted as secondary outcomes were endocrinologic parameters in blood samples, including total testosterone (TT), estradiol, luteinizing hormone (LH), and follicle stimulating hormone (FSH) before and after therapy with CC, pregnancy rate, and side effects. All applicable data items were sought in each study, and all results were included. All treatment periods were included. Missing values of primary or secondary outcomes were reported as 'not available' in tables.

3.4 Quality assessment

Two authors (MH and RH) independently assessed methodological quality and risk of bias of studies using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies.[14] The EPHPP tool can be used to compare studies using different study designs and has previously been validated as suitable for quality assessment in systematic reviews.[14–16] Component ratings were summarized into global rating of 'strong', 'moderate', or 'weak' for each publication. Disagreements were resolved by consensus.

3.5 Statistical analysis

All data items from primary studies were reported in primary Tables or Supplementary Materials. Dichotomous and categorical data were presented as frequencies and percentages. Continuous data were presented as mean and standard deviation (SD) or standard error (SE), or median and interquartile range (IQR). Studies were included for meta-analysis if they provided absolute numbers for before and during treatment with appropriate SD or SE. Meta-analysis was performed using Review Manager 5.4.[17] Data presented in included studies as median with interquartile range were converted to mean with SD to be used in meta-analysis.[18] Standard error (SE) values were converted

to SD values.[19] Pooled effects of before and during treatment outcomes were calculated using the inverse-variance weighting method and were presented as mean differences with 95% confidence intervals (95% CI).[19] Main outcome was mean difference between before and during treatment. Standardized mean differences with 95% CI were presented when different units of measurements were used between studies.[19]

Heterogeneity across studies was assessed by visually inspecting forest plots and using the χ^2 test and I^2 statistic. The I^2 statistic was interpreted as follows: 0-40% might not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity, and 75-100% may represent considerable heterogeneity.[19] Sensitivity analyses were performed after the primary analyses. In the sensitivity analyses for study design, only RCTs were included. In the sensitivity analyses for methodological quality, only studies with strong quality were included.

RESULTS

4.1 Search results

The initial search identified 1799 studies, of which 1409 studies were potentially eligible for inclusion (Fig. 1). After screening, 66 studies were assessed for full-text eligibility. In total, 48 studies were excluded. Exclusion reasons for the 48 studies are provided in Figure 1. Eventually, 18 studies were included for qualitative analysis (n = 731).[20–37] Off those, 15 studies (retrospective-, prospective and randomized clinical trials) presented data sufficiently to be included in meta-analysis (n =566).[21–35] The three studies were excluded from meta-analysis because they provided percentage improvement of semen parameters after treatment rather than absolute numbers or because they provided no SD or SE for their data (Fig. 1).[20,36,37] Study characteristics are provided in Table 1 and Supplementary Materials (Appendix 2). The 18 studies were published over a time period of 40 years. Dosage of CC therapy differed between 25-50 mg per day to 25-50 mg every other day. The number of study participants differed between 11 and 140. Therapy duration of CC and mean follow-up was around 5 months.

4.2 Quality Assessment

Global quality assessment rating for each study is presented in Table 1, and detailed quality assessment including scores across all domains in Supplementary Materials (Appendix 3).

Methodological quality of included studies was considered 'strong' in 3 studies [21,26,36] 'moderate' in 10 studies [22–25,27–29,32,34,35] and 'weak' in 5 studies.[20,30,31,33,37]

4.3 Semen analysis

Appendix 4 of the Supplementary Materials provide information on semen analysis before and during CC treatment. Data of sperm concentration before and during treatment was reported in 15/18 studies (n = 566).[21–35] Three studies reported no standard median or standard deviation and were therefore not included in meta-analysis.[20,36,37] Sperm concentration was higher during treatment with a mean difference of 8.38 x10^6/mL (95% CI, 5.17, 11.59; $P < 0.00001$; $I^2 = 87\%$) (Fig. 2A). Mean sperm concentration in these studies before treatment was 14.11 x10^6/mL (SD 27.10 and during treatment 21.56x10^6/mL x10^6/mL (SD 30.16). Data of sperm motility (progressive and total motility) before and during treatment was reported in 13 studies (n =537).[21–29,32–34,37] Five studies were excluded from meta-analyses because no standard deviation was provided.[21,30,31,36,37] Sperm motility was better during treatment with a mean difference of 8.14% (95% CI, 3.83, 12.45; p < 0.00001; $I^2 = 76\%$) (Fig. 2B). Mean percentage of progressive and total sperm motility in these studies was before treatment 30.79% 31.08% (SD 17.64) and during treatment 36.98% (SD 18.13).Sperm motility was better during treatment with a mean difference of (Fig. 2B). Data of sperm morphology before and during treatment was reported in six studies (n = 221).[21,23,25,32–34] There was no significant difference in sperm morphology, with a slightly better morphology during treatment with a mean difference of 2.59% (95% CI, 0.98, 6.17; $P = 0.15$; $I^2 = 42\%$) (Fig. 2C). Mean percentage of useful sperm morphology in these studies before treatment was 37.79% (SD 24.45) and during treatment 41.23% (SD 26.05).

4.4 Hormonal assessment

Seventeen out of 18 studies reported on hormonal assessment.[20-22,24–37] One study published only on semen parameters.[23] Appendix 5 of the Supplementary Materials give an oversight of hormonal levels before and during treatment. Mean (range) TT was at baseline 16.1 nmol/L (5.2 – 20.7) and during treatment 32.2 nmol/L (19.8 - 49.4) across these 17 studies.[20-22,24–37] Data of TT before and during treatment usable for meta-analysis were available in seven out of the 17 included studies publishing on hormonal outcomes (n = 274).[21,25,26,28–31] TT was higher during treatment with a standardized mean difference of 2.05 (95% CI, 1.65, 2.44 $P < 0.00001$; $I^2 = 59\%$) (Fig. 3). Mean total testosterone in these studies was 13.809 nmol/L (SD 6.84) before treatment and 25.78 nmol/L (SD

12.093) during treatment. Data of FSH before and during treatment was reported in five studies (n = 209).[21,26,29–31] FSH was higher during treatment with a mean difference of 10.32.04 mIU/mL (95% CI, 5.59, 15.05; $P < 0.0001$; $I^2 = 83\%$) (Fig. 4A). Mean FSH in these studies before treatment was 5.93 mIU/mL (SD 3.85) and 13.26 mIU/mL (SD 9.3) during treatment. Data of LH before and during treatment was reported in four studies (n = 209).[21,26,29–31] LH was higher during treatment with a mean difference of 10.06 mIU/mL (95% CI, 5.55, 14.57; $P < 0.0001$; $I^2 = 92\%$) (Fig. 4B). Mean LH in these studies was before treatment 6.17 mIU/mL (SD 3.35) and 14.13 (SD 12.51) during treatment. Data of estradiol before and during treatment was reported in four studies (n = 98).[21,25,26,30] Estradiol was higher during treatment with a standardized mean difference of 2.04 (95% CI, 1.03, 3.05; $P < 0.0001$; $I^2 = 85\%$) (Fig. 5). Mean estradiol in these studies was during treatment 18.67 pg/mL (SD 10.91) and 45.31 pg/mL (SD 28.40) during treatment.

4.5 Sensitivity analysis

In the sensitivity analyses on study design, ten randomized- and controlled clinical trials were included. In the analyses on methodological quality, 13 strong and moderate rated studies were included. [21-29,32,34–36] The analyses on sperm concentration, motility, TT, LH, FSH, estradiol were repeated with the included studies. All results remained in favor of during CC treatment and held statistical significance.

4.6 Clinical outcomes

Ten studies reported a mean pregnancy rate of 17% during CC treatment (range, 0 – 40%) between 3 and 12 months of CC treatment, Table 1.[28–30,36,38–43] Three out of nine studies reported in 2-27% of their population side effects which included, headache, gynecomastia, dizziness, visual changes, mood changes, fatigue.[27,35,36] The other six studies reported in 0% of the population any side effects. Eight studies did not report on side effects.

DISCUSSION

According to the results of this systematic review and meta-analysis, CC therapy enhances sperm concentration and motility without causing major side effects. As far as we know, this is the most recent and comprehensive systematic review and meta-analysis that includes both clinical trials and observational studies.

Fifteen of the eighteen included studies indicated that CC therapy led to improvement of sperm concentration and motility.[21–35] Sperm morphology did not change during CC therapy. [21,23,25,32–34] According to the WHO manual on semen analysis (2021) sperm morphology is a limited prognostic value regarding spontaneous pregnancies.[38] The total number of spermatozoa per ejaculate and sperm concentration are related to pregnancy and pregnancy rates and are predictors of conception according to the WHO manual.[38] As a result, it is reasonable to assume that at least increased sperm concentration will result in higher pregnancy rates. According to this updated manual, it is recommended for future research to focus besides sperm concentration on total number of spermatozoa per ejaculate. Only two included studies described that the effect of different dosage of CC on sperm parameters and did not find a difference.[31,34] With these few outcomes, it is hard to draw a conclusion on CC dosage difference and sperm parameters.

In the current study, the average pregnancy rate was 17%. As the pregnancy rate in infertile couples in the second year of trying to conceive is 8%, the results with CC treatment is much more favorable.[39] In a previous meta-analysis of Chua *et al.* (2013), patients on CC treatment had a 2.4 times higher likelihood of conception than no or placebo therapy.[40] This is might be explained by the fact that CC leads to gonadotropin release and theoretically stimulates spermatogenesis, leading to higher concentration and total number of spermatozoa per ejaculate, important predictors for conception.[38]. No difference in pregnancy rate was found with different dosages of CC.[31,32,34] However, our systematic review and search strategy were not directed at pregnancy rates as primary goal, and because conception is multifactorial, it is still not completely certain that treatment of infertile males with CC leads to greater pregnancy rates.[41]

We found that during treatment testosterone levels increased in all seven studies included in the meta-analysis.[21,25,26,28-31] Also, FSH, the gonadotropin essential for spermatogenesis, increased in all

five studies included in the meta-analysis.[21,26,29-31] An increase in FSH, with a lower to normal FSH before treatment, supposedly stimulates spermatogenesis and may lead to improvement of semen parameters. Previous studies in hypogonadal males also found a rise in gonadotropins during CC therapy.[42]

As sperm parameters did not improve in all men, it is interesting to identify potential predictors for treatment response. In a previous study on CC, low FSH was thought to be a predictor of improved outcomes on sperm quality.[43] In the current review only one of the included studies described predictive factors for success of CC treatment (age, BMI, FSH, LH, estradiol, testis volume) and found no predictors for success. However, these were potential predictors for bioavailable testosterone, not for sperm quality. So no conclusion can be drawn from these results with respect to fertility.[25] In contrast for the CC effect on hypogonadism the study of Mazzolla *et al.* (2014), who reported that low LH (<6ml/L) and a testis volume >14cc were predictors of a better biochemical response to CC therapy in male hypogonadism.[44] These potential predictors in previous studies on hypogonadism and perhaps for infertility, were supported by an AUA 2020 survey, suggesting various potential predictors of poor CC treatment response, such as increased FSH, testis volume < 10cc, BMI > 35kg/mg2 and sperm concentration <5 milj/ml.[10]

Two previously reported small case series described a lower sperm count, worsened sperm motility and non-bacterial pyospermia as a result of CC therapy, in contrast to the findings of this systematic review.[45,46] This have led to the hypothesis, that CC might have a paradoxical effect on sperm parameters. One of the included studies in our review investigated this potential paradoxical negative effect of CC therapy on total motile count and sperm concentration in 47 patients, but could not confirm any paradoxical effect.[25] A natural variation in sperm production could be an explanation for decrease in sperm concentration, but there is currently no satisfactory explanation.[47] In hypogonadal males a paradoxical effect of CC on testosterone was described before in only few patients, neither without a satisfactory explanation.[42] We think it is advisable during usage of CC therapy for infertile males, to monitor TT levels for early detecting this potential paradoxical effect on both sperm quality and testosterone levels.

The current study shows no major adverse events nor development of testicular tumors. In a 2012 report, the FDA indicated that testicular tumors and gynecomastia were reported in infertile males who used CC.[12] Previous large and long-term cohort studies, such as in our study, did not reported this risk of developing testicular tumors during CC treatment.[48] In a 2012 study with 650 infertile

men two young patients developed a testis tumor, one of them even 21 months after discontinuing CC.[49] According to the American Cancer Society 1 out of 250 men develop testicular cancer during their life, at an average age of 33 years.[50] Thus, the possibility of developing testis tumor during CC treatment seems comparable with the normal population. Furthermore, infertile males seem to have a double or triple life-time risk of developing testicular cancer in comparison with the fertile population.[51] Taking this in account 2/650 infertile patients is even a low prevalence of developing a testis tumor in this patient group.

In three out of nine of the included studies who reported on adverse events, 2-27% of the patients had mild side effects, such as gynecomastia, headache, dizziness and mood changes, similar to of those seen in previous studies on CC.[42] No serious adverse events, such as thromboembolic complications were reported.

Finally, there are a few potential limitations for this study to consider. First, despite the extended search, studies could have been missed for inclusion. Second, this review demonstrates a biochemical efficacy of CC on semen parameters in infertile males, as a proxy for pregnancy rates. Third, with the inclusion of retrospective study designs, there is risk of confounding and detection bias. Fourth, there is notable heterogeneity across the included studies, with varying; dosage, laboratory measurements and in- and exclusion criteria. As last to mention, demographic- and predictive factors were not well investigated or documented so it is difficult to draw conclusions regarding to potential predictive factors for success. In further research, there is a need for documentation on demographic, patient specific factors and potential predictors in order to be able to determine who will benefit from CC therapy.

Importantly, there is difference in methodological quality of the included studies. Most important reasons for rating 'moderate' or 'weak' quality were; retrospective study design, unclear described study population, undescribed important differences between groups prior to intervention in case of controlled clinical trials. With only three 'strong' rated studies.[21,26,36], conclusion of our results should be interpreted with caution. A future study with a more homogenous population, such as idiopathic infertility, is needed to further investigate the effect of CC on male infertility.

CONCLUSIONS

This systematic review on the use of CC to treat male infertility indicated that CC therapy enhanced sperm motility and concentration, with presence of minor side effects. Future studies should be conducted to help the FDA reevaluate its approval of CC as therapy option for infertile men.

AUTHOR CONTRIBUTIONS

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AUTHOR CONTRIBUTIONS

M.H., R.H., T.L., V.d.K., L.d.K.,H.v.B., contributed to the design, to the analysis of the results and to the writing of the manuscript. M.H., R.H. and H.v.B. contributed to the data search and selection. See supplementary material for signed contribution forms of all authors.

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FIGURES

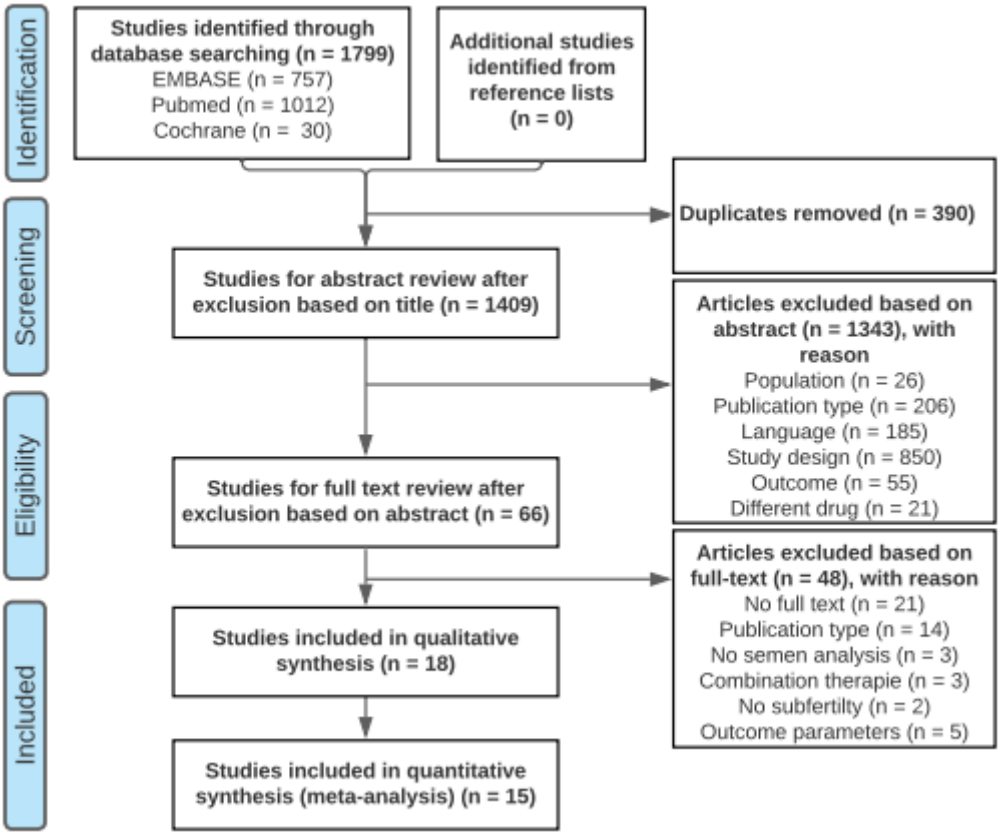
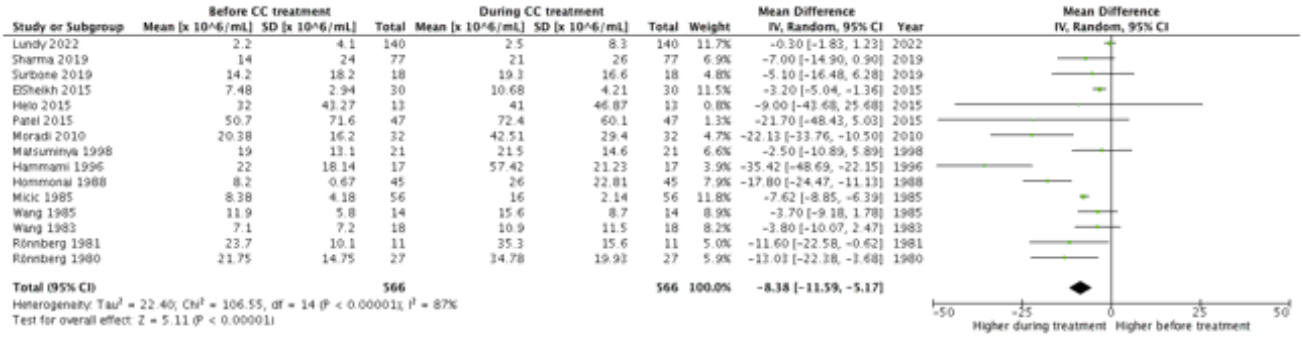
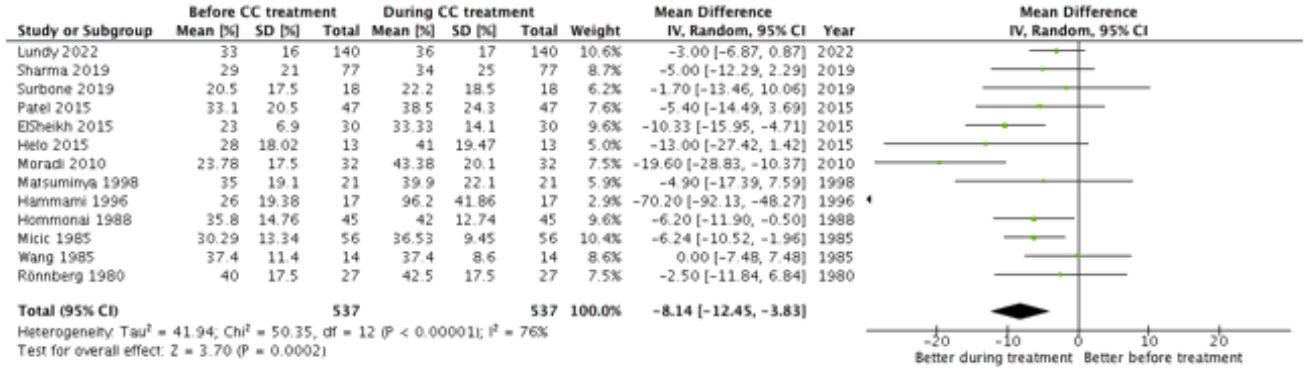


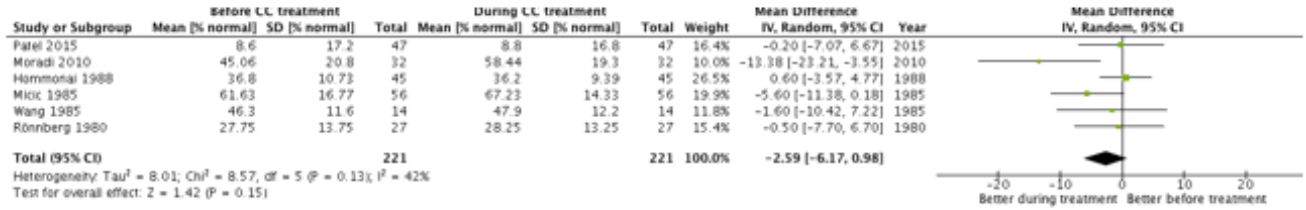
Figure 1. Flowchart of identification, screening for eligibility and inclusion of relevant publications.



A. Sperm concentration



B. Sperm motility



C. Sperm morphology

Figure 2. Effect of clomiphene citrate on semen: sperm concentration (A), total sperm motility (B), sperm morphology (C). Forrest plot comparisons of semen in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.

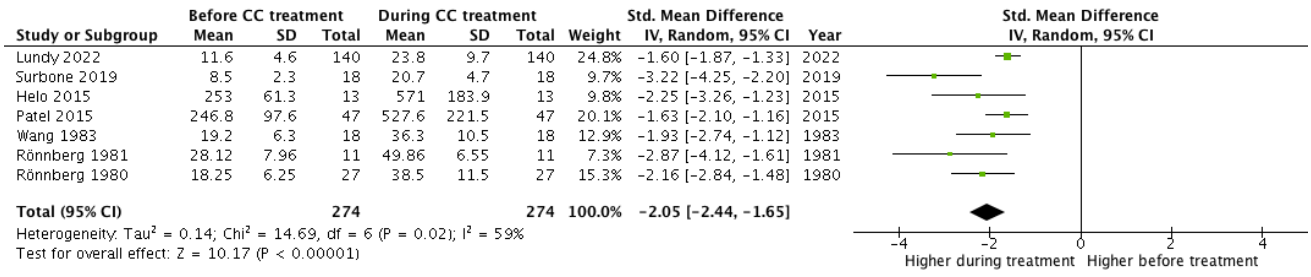
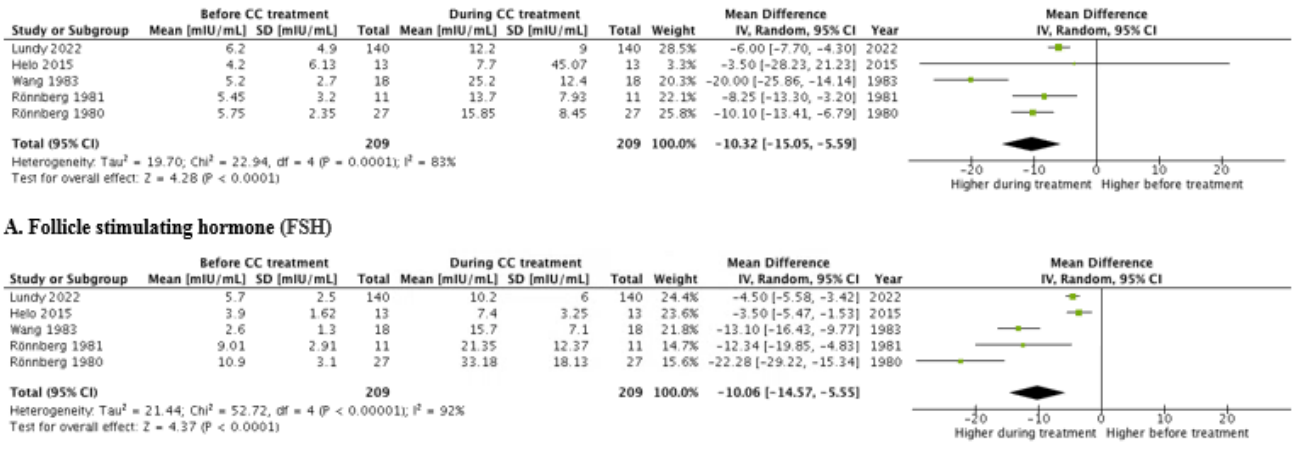


Figure 3. Effect of clomiphene citrate on total testosterone (TT). Forrest plot comparisons of TT in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.



A. Follicle stimulating hormone (FSH)

B. Luteinizing hormone (LH)

Figure 4. Effect of clomiphene citrate on Gonadotrophins (A. follicle stimulating hormone (FSH) and B. luteinizing hormone (LH)). Forrest plot comparisons of FSH in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.

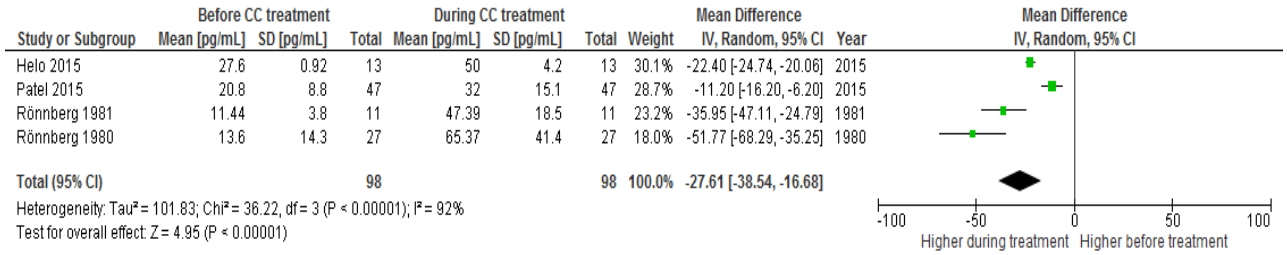


Figure 5. Effect of clomiphene citrate on estradiol (E2) Forrest plot comparisons of E2 in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.

TABLES

Table 1. Study characteristics of included studies for qualitative synthesis

First author (year	Study type	Study size (n)	Population description	CC dosage	Mean CC duration (months)	Global EPHPP rating	Mean pregnancy rate (%)
Jones (1980)	Cohort	20	Oligospermic infertile men	25mg/day 3 weeks on, 1 week off	6	Weak	40
Rönnberg (1980)	RCT placebo controlled cross-over	27	Normogonadotropic infertile men	50mg/day	3	Strong	11
Rönnberg (1981)	Cohort	11	Normogonadotropic infertile men	50mg/day	3	Weak	n.a.
Wang (1983)	RCT	28	Idiopathic oligospermic men	25mg/day or 50mg/day	6	Weak	36 vs. 22
Mićić (1985)	CCT	56	Idiopathic oligospermic men	50mg/day	6-9	Weak	13
Wang (1985)	Cohort	24	Idiopathic oligospermic men	25mg/day or 50mg/day	6	Moderate	8
Sokol (1988)	RCT double-blind placebo controlled	11	Normogonadotropic infertile men	25mg/day	12	Moderate	9

Hommonai (1988)	CCT	89	Normogonadotropic oligospermic men	25mg/2day or 25mg/day 25 days per month	4.8	Moderate	27 vs. 21
WHO (1996)	RCT double blind placebo controlled	70	Idiopathic oligospermic and asthenozoospermic men	25mg/day	6	Strong	10
Hammami (1996)	Cohort	17	Idiopathic oligospermic men	25mg/day 25 days per month	>4	Weak	n.a.
Matsuminya (1998)	CCT	21	Idiopathic Normogonadotropic oligoastenozoospermic men	50mg/day	>3	Moderate	0
Moradi (2010)	RCT	32	Idiopathic infertile men	25mg/day	3	Moderate	n.a.
Helo (2015)	RCT double blind	13	Hypogonadal infertile men	25mg/day	3	Strong	n.a.
ElSheikh (2015)	CCT	30	Idiopathic oligoasthenozoospermic men	25mg/day	6	Moderate	n.a.
Patel (2015)	Cohort	47	Hypogonadal subfertile men	50mg/2 days or 50mg/day	Median = 3	Moderate	n.a.

Sharma (2019)	Cohort	77	Hypogonadal and/or infertile oligospermic, azoospermic, normozoospermic men	25-50mg/day	no limitation n.a.	Moderate	n.a.
Surbone (2019)	Cohort	18	Oligospermic infertile men	50mg /2days	3	Moderate	17
Lundy (2022)	Cohort	140	Idiopathic oligo- and azoospermic men	50mg/2days	3.7	Moderate	n.a.

N = study size, CC = clomiphene citrate, RCT = randomized controlled trial, CCT = clinical controlled trial, n.a. = not available, EPHPP = Effective Public Health Practice Project