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Clomiphene Citrate for Men with Hypogonadism - A Systematic Review & Meta-analysis

MANUSCRIPT

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ABSTRACT

Background – Male hypogonadism is a clinical and biochemical androgen insufficiency syndrome, becoming more prevalent with age. Exogenous testosterone is first choice therapy, with several side-effects, including negative feedback of the hypothalamic-pituitary-gonadal axis, resulting in suppression of intratesticular testosterone production and spermatogenesis. To preserve these testicular functions while treating male hypogonadism clomiphene citrate (CC) is used as off-label therapy. This systematic review and meta-analysis aimed to evaluate the effectiveness and safety of CC therapy for men with hypogonadism.

Methods – The EMBASE, PubMed, Cochrane databases were searched in May 2021, for effectiveness studies of men with hypogonadism treated with CC. Both intervention and observational studies were included. The Effective Public Health Practice Project Quality Assessment Tool, a validated instrument was used to assess methodological study quality. The primary outcome measure was the evaluation of serum hormone concentration. Secondary outcomes were symptoms of hypogonadism, metabolic- and lipid profile, side-effects, safety aspects.

Results – We included 19 studies, comprising four randomized controlled trials and 15 observational studies, resulting in 1642 patients. Seventeen studies were included in the meta-analysis, with a total of 1279 patients. Therapy and follow-up duration varied between one and a half and 52 months. Total testosterone (TT) increased with 2.60 (95% CI 1.82 – 3.38) during CC treatment. An increase was also seen in free testosterone, luteinizing hormone, follicle stimulating hormone, sex hormone-binding globulin and estradiol. Different symptom scoring methods were used in the included studies. The most frequently used instrument was the Androgen Deficiency in Aging Males-questionnaire, which score improved during treatment. Reported side-effects were only prevalent in less than 10% of the study populations and no serious adverse events were reported.

Conclusion – CC is an effective therapy for improving both biochemical as well as clinical symptoms of males suffering from hypogonadism. CC has few reported side-effects and good safety aspects.

Keywords – Clomiphene citrate, male hypogonadism, testosterone deficiency

LIST OF ABBREVIATIONS

ADAM	androgen deficiency in aging males
AI	aromatase inhibitor

BMI	body mass index
CC	clomiphene citrate
E_2	estradiol
EHS	erection hardness scale
FSH	follicle stimulating hormone
FT	free testosterone
hCG	human chorionic gonadotropin
HPG	hypothalamic-pituitary-gonadal
IIEF-5	international index of erectile function
LH	luteinizing hormone
qADAM	quantitative androgen deficiency in aging males

SHBG	sex hormone-binding globulin
TTh	testosterone therapy
TT	total testosterone

BACKGROUND

Hypogonadism is a common medical condition among men.[1,2] Hypogonadism is a clinical and biochemical testosterone insufficiency syndrome, affecting various organ functions and quality of life, according to the European Association of Urology.[3,4] Common symptoms of hypogonadism are erectile dysfunction, reduced sexual activity and -desire, mood changes and loss of muscle strength.[5,6] The prevalence for symptomatic hypogonadism at age 40-79 years, varies between 2.1%-5.7%[2,6] and increases with age and presence of obesity, cardiovascular disease, chronic obstructive pulmonary disease (COPD), Diabetes Mellitus (DM) type 2, human immunodeficiency virus (HIV), chronic kidney disease, malignancies and metabolic syndrome.[7]

Causes of hypogonadism can be classified based on disruptions in various levels of the hypothalamic-pituitary-gonadal (HPG) axis. Primary hypogonadism is the most frequent cause of hypogonadism, resulting in low serum testosterone concentration and high serum gonadotropin concentration.[3] Primary hypogonadism results from direct testicular failure; the most common reasons are Klinefelter syndrome and testicular tumors.[8,9] On the opposite, in secondary hypogonadism the testis are inadequately stimulated by gonadotropins, resulting in hypogonadism, usually with reduced or inappropriately normal serum concentration of gonadotropins.[3] Reasons for secondary hypogonadism are, e.g. hyperprolactinemia, Kallmann's syndrome and obesity.[3,10,11] Adult-onset hypogonadism or late-onset hypogonadism, is a symptomatic testosterone deficiency in middle-aged and older men, with normal HPG-axis function.[6,12]

Testosterone therapy (TTh) is the first-choice treatment for men with hypogonadism.[13] The goal of this treatment aims to increase serum testosterone and restore androgen-dependent functions, e.g.

muscle mass and strength, sexual functions, bone density and general well-being.[4,14] However, TTh has some notable side effects. Subfertility is one of the most crucial side-effects of TTh, especially for men with an active or possible future child wish, because endogenous testosterone is reduced by negative feedback.[15] Other side-effects are, e.g. increase in prostate volume, increase in prostate specific antigen (PSA), elevated hematocrit (Ht) and serum estrogen concentration and serum lipid alterations.[15–17]

Preserving fertility and costs are important reasons to not prescribe TTh for men with hypogonadism. Other medications used are human chorionic gonadotropin (hCG), aromatase inhibitors and selective estrogen/androgen receptor modulators (SERMS and SARMS).[18–20] Clomiphene citrate (CC) is a SERM occupying estrogen receptors in the hypothalamus and pituitary leading to gonadotropin release, which leads to increased testicular stimulation and testosterone production.[21] CC is used since 1960 for ovulation induction in women. It has been used off-label for men because the US Food And Drug Administration (FDA) did not approve the medicine, because unclear effectiveness.[22,23]

Several studies and reviews are published about the effects of CC on subfertility. Few of these studies specifically examined the effect of CC in men with hypogonadism.[24–26] The purpose of this study was to determine if CC is an effective and safe therapy for men with hypogonadism. For this purpose, we conducted a systematic review and meta-analysis to provide oversight of the current literature in the effectiveness and safety of CC therapy for men with hypogonadism.

METHODS

This systematic review and meta-analysis adhered to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[27] PRISMA aims to improve the reporting of systematic reviews for randomized controlled trials (RCTs) and observational studies. This study was registered in PROSPERO under registration number *CRD42021246588*.

Search strategy

A systematic search was performed using the electronic databases of EMBASE, PubMed, Cochrane in May 2021. The search strings for each database are provided in Appendix 1. Search terms covered all the research on the intended population (hypogonadism) combined with the intervention (CC). On purpose, search terms for outcomes were not used, to research all possible results. Additionally, reference lists of included articles and relevant reviews were hand-searched for relevant additional studies.

Eligibility criteria and study selection

Both intervention and observational studies written in English or Dutch, on the effectiveness of CC in men with hypogonadism ≥ 18 years, were included. Outcomes had to contain at least hormonal assessment and preferably evaluation of symptoms of hypogonadism during treatment with CC. Treatment with enclomiphene, zuclomiphene or CC combined with another medicine, were excluded. Specific disorder populations, such as chronical diseases (HIV, cancer, osteoporosis, severe kidney/liver disease, depression, hemochromatosis, acromegaly, polycythemia, Alzheimer, eating disorder, sickle cell disease, retardation), genetic disorders (e.g. Klinefelter, Prader Willi, Kallman, Bardet Biedl) were excluded. Case series n<5, letters to the editor, pilot studies, reviews, comments and animal studies were excluded. No restrictions were imposed on the year of publication, the dosage of therapy and duration of intervention. Two reviewers (HvB and MH) independently performed study selection according to the predefined eligibility criteria. Differences in judgement were resolved by discussion. The selection was divided into three phases. First, studies were selected by title and duplications were removed. Second, abstract screening was performed. Third, articles were screened full-text for eligibility. Thereafter, the resultant articles were included.

Data extraction and methodological quality assessment

Data were individually collected by two reviewers (HvB and MH) for the following data: authors, year of publication, study design, type of study, single/multi-centre, number of patients, presence of subgroup, therapy dosage, follow-up duration, presence of subfertility, mean age, comorbidities.

The primary outcome was hormonal assessment before and during treatment. Secondary outcomes were: symptoms of hypogonadism, metabolic- and lipid profile, side-effects and safety aspects. Missing values of primary or secondary outcomes were reported as 'not available' in tables. Study quality assessment was conducted of all included studies independently by two reviewers (HvB and MH) using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP).[28] This instrument has been described as suitable to be used in systematic reviews of effectiveness and has been demonstrated to have content and construct validity.[28–30] Moreover, this tool can evaluate several study designs (e.g. RCTs, before and after studies, observational studies), with an inter-assessor coefficient of 0.77 (95% CI, 0.51 -0.90).[31] The inter-assessor coefficient of 0.77 is considered an excellent consensus.[32]

Statistical analysis

Data were reported as counts, percentages or means with standard deviations (SD). Outcomes reported by three or more studies were pooled in a meta-analysis, Review Manager (RevMan) 5.4 was used.[33] Studies were eligible for meta-analysis if mean with SD was reported. Standard errors were converted to standard deviations.[34] Data reported as median with interquartile range were converted to mean with SD.[35] The inverse-variance weighting method was used to calculate the pooled effects of before and during treatment outcomes, presented as mean differences or standardized mean differences with confidence intervals (CI).[34] The standardized mean difference was used when studies use different units for their outcomes, e.g. nmol/L or ng/dL for TT.[34] Heterogeneity across studies was assessed by inspecting the forest plots and by statistical analysis using the χ^2 test and I^2 statistic. The I^2 value as most important quantitative assessment, with interpretation 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.[34] 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

Study selection

The systematic search yielded a total of 569 studies (Fig. 1). After removing duplicates and articles based on title, 415 studies remained. Of these studies, 383 were excluded based on abstract or on the basis of the predetermined exclusion criteria, yielding 32 studies. During screening for eligibility, full-text was assessed, leading to the exclusion of another 13 studies. In 9 out these 13 studies, full-text was not available, another three studies were excluded based on methods used, and one was excluded based on the outcome. One study exclusion was because therapy dosage was not described[36], and the study population seemed to interfere with the included study of Ramasamy *et al.* (2014).[37] A second study was excluded because this study was a 10-day clomiphene challenge test.[38] The third study was excluded because patients were included based on men with subfertility.[39] The last excluded study did not clearly describe serum testosterone and symptoms.[40] In the end, 19 studies were included in the systematic review.[37,41–58] Seventeen of these studies were included in the meta-analysis.[37,41-46,48,,50-57] Two studies were not included in meta-analysis because no standard deviations nor interquartile range were available.[47,49]

Study characteristics

A total of four RCTs and 15 observational cohort studies, of which 11 were retrospective, and four were prospective (Table 1). See Appendix 2 for an extended oversight of study characteristics. After contact with the authors it was confirmed that there was little overlap in the study populations of Patel et al. (2015) and Keihani et al. (2020), and between Katz et al. (2012), Moskovic et al. (2012) and Mazolla et al. (2014).[41,43–45,57] Despite the overlap between these studies, therapy duration and outcomes differed between these studies. In the 19 included studies, 1642 patients were treated with CC. Seventeen studies, containing 1279 patients treated with CC, reported mean with SD and were included in the meta-analysis. Two out of these 17 studies presented outcomes in subgroups based on age. For the meta-analysis, the subgroup with the largest sample size was chosen in those two studies.[44,51] Mean therapy duration of CC and follow-up differed between one and a half and 52 months. The mean age of patients treated with CC was between 29 and 62 years. One study only observed young patients with obesity, with age between 19 and 21 years.[58] Dosage of CC therapy differed between 25-50 mg per day or 25, 50 or 100 mg every other day.

Methodological quality assessment

According to the EPHPP tool, of the 19 included studies, three studies were assessed as strong quality[42,50,53], five studies as moderate quality[37,45,47,48,56] and eleven studies were assessed as weak quality[41,43,44,46,49,51,52,54,55,57,58] (Table 1). Details regarding quality assessment can be found in Appendix 3.

Hormonal evaluation

Table 2 and 3 provide an overview of serum hormone concentration before and during treatment. Mean (SD) total testosterone (TT) ranged at baseline between 179.0 ng/dL (72.0) and 310.3 ng/dL (96.0) and during treatment between 467.0 ng/dL (190.0) and 687.9 ng/dL (276.7).[37,41–48,50–58] Data of TT before and during treatment for meta-analysis were available in 17 of the 17 included studies (98%, n = 1256 patients).[37,41–46,48,50–58] One study reported TT in median (IQR), converted into mean (SD).[41] Outcomes of mean TT were published in different units (nmol/L and ng/dL), so the meta-analysis presented TT in standardized mean difference. TT was higher during treatment with a standardized mean difference of 2.60 (95% CI, 1.82, 3.38; $P < 0.00001$; $I^2 = 98\%$) (Fig. 2). In four studies, an improvement was found in TT during CC treatment compared with anastrozole, placebo or no therapy (Table 2).[37,42,50,53] The overall response rate, described in three studies, ranged between 62 to 81% and defined as an improvement of TT of at least 200 ng/dL over baseline and above 400-450ng/dL.[41,43,51] Mean (SD) free testosterone (FT) before and during treatment was reported in five studies (17%, n = 222).[42,43,45,50,53] Outcomes of mean FT were published in different units (pmol/L and ng/dL), so in the meta-analysis, FT was presented in standardized mean difference. FT was higher during treatment with a standardized mean difference of 1.78 (95% CI, 0.65, 2.91; $P = 0.002$; $I^2 = 95\%$) (Fig. 2).

Mean (SD) luteinizing hormone (LH) before and during treatment was reported in eight studies (24%, n = 301).[42–45,50,53,54,58] LH was higher during treatment with a mean difference of 4.67 IU/L (95% CI, 3.67, 5.68; $P < 0.00001$; $I^2 = 77\%$) (Fig. 3). Mean (SD) follicle stimulating hormone (FSH) before and during treatment was reported in six studies (14%, n = 180).[42,44,50,53,54,58] FSH was higher during treatment with a mean difference of 4.25 IU/L (95% CI, 2.70, 5.81; $P < 0.00001$; $I^2 = 72\%$) (Fig. 3). One study found during treatment a higher LH and FSH for CC compared with placebo, another study showed no difference between CC and anastrozole treatment in LH and FSH.[53,57]

Eight studies reported mean (SD) serum estradiol concentration before and during treatment (47%, n = 595).[42,43,45,48,51,53,57] Estradiol was higher during treatment with a mean difference of 17.69 pg/mL (95% CI, 12.46, 22.92; $P < 0.00001$; $I^2 = 82\%$) (Fig. 4). A difference was found during treatment compared with placebo and anastrozole.

In three studies, hormonal outcomes were compared between age subgroups.[46,48,50] In one study (1%, n = 17) there was a difference in during treatment TT between younger males (median 53 years) and older males (median 66 years).[50] This result was also found in another study (8%, n = 125) who showed a higher testosterone increase during CC therapy in younger patients (30-50yr) compared to patients above 50 years.[46] The third study (2%, n = 36) showed no higher TT in one of the two groups.[48]

Symptoms of hypogonadism

Twelve studies describe symptoms by various questionnaires (49%, n = 798), the Androgen Deficiency in Aging Males (ADAM), quantitative ADAM-score (qADAM), International Index of Erectile Function (IIEF-5), Erection Hardness Scale (EHS) and the number of intercourse events per month.[37,41,42,44,45,47,50,52,53,55–57] Table 4 provides oversight of symptoms of hypogonadism before and during treatment with CC. There was an improvement in ADAM scores during CC treatment in four studies (14%, n = 176).[44,47,53,55] ADAM-scores improved (a lower score is better), during CC treatment with a mean difference of -3.13 (95%, 4.16, 2.10; $P < 0.00001$; $I^2 = 80\%$) (Fig. 5). One of these studies (5%, n = 86) described an improvement on five out of ten items on the ADAM-questionnaire, during CC treatment.[45] However, an improvement of ADAM-score was also found in another study's placebo group (2%, n = 34).[53] There was no difference between CC and anastrozole treatment on the qADAM score (1%, n = 13).[42]. There was a difference ($P = 0.028$) between increasing age and the decreasing response of CC on attempts of sexual intercourse below and above 55 years of age (11%, n = 178).[49] A difference was found in the subjective improvement of symptoms, which increase more in younger patients (<55 years of age) (5%, n = 86).[46] There was a difference in sexual satisfaction, tip rigidity, nocturnal tumescence, intercourse attempts, for the younger group (median 53, range 42 – 61) who responded better to CC (1%, n = 17). In this double-blind, placebo-controlled trial patients were unable to distinguish for symptoms between CC and placebo.[50]

Lipid and metabolic profile

Four studies published BMI results before and during treatment (11%, n = 184).[44,52,53,58] Only one study showed a decrease in BMI after three years of CC treatment.[44] There was no difference in BMI before and during treatment. Three studies reported total cholesterol before and during treatment (14%, n = 224).[46,47,53] Only one study (8%, n = 125) found a decrease in total cholesterol during treatment with CC.[46] Table 5 provides an oversight of the lipid and metabolic profile outcomes.

Safety aspects and side-effects

Table 6 provides information from four studies on hemoglobin (Hb), Ht, PSA, International Prostate Symptom Score (IPSS), blood pressure (BP), bone density before and during treatment.[44,47,51,53] There was no difference found in Hb, Ht, total PSA, IPSS, BP before and during treatment. Only one study (24%, n = 400) found one patient with an elevated Ht during CC treatment with no clinical significance.[51] Bone density before and during treatment was measured in one study (2.8%, n = 46). They found an improvement in the femoral neck and lumbar spines' bone density over one, two and three years. Bone density increased with the years; the presence of patients with osteoporosis decreased over the years.[44] Seven studies (20%, n = 332) reported no side effect of CC therapy.[42–45,47,48,55] Four studies (36%, n = 590) reported side effects between 4-11% of the population, e.g. mood changes, blurred vision, breast/nipple tenderness, fatigue.[46,51,54,57] One study (2%, n = 34) did not find a difference between self-reported side effects (somnolence, weight gain, acne, asthenia,

irritability, changes in bowel habits, anxiety, increased appetite, urethral candidiasis, headache, perception of testicle reduction, snoring, cramps) between CC and placebo.[53]

Sensitivity analyses

In the sensitivity analyses on study design, four RCTs were included.[42,50,52,53] In the analyses on methodological quality, three studies were included.[42,50,53] The analysis for ADAM-score was not possible to repeat because only one study was left for analysis. The other five analyses (TT, FT, estradiol, LH and FSH) were repeated with the included studies. All results remained in favour of during treatment and held statistical significance.

DISCUSSION

This systematic review and meta-analysis show that men with hypogonadism treated with CC, have an improvement of TT and symptoms of hypogonadism on the ADAM questionnaire. With an overall response rate between 62 to 81% for TT. This is to our knowledge, the first meta-analysis of the current literature on this subject with the inclusion of both RCTs and observational cohort studies.

Besides the increase of TT, also FT, LH, FSH, and estradiol increased. These elevations of testosterone and gonadotrophins show that CC is effective in improving endogenous testosterone secretion by stimulating the HPG-axis in men with hypogonadism. During CC treatment, serum TT achieved the reference value (15.6-20.8 nmol//L) sufficient for treating hypogonadism, according to the guidelines of the American Urology Association.[59] Different studies comparing CC with testosterone gel concluded the same. Taylor *& Levine* (2010) (n = 103), demonstrated no difference in biochemical outcome of serum TT between CC or usage of testosterone gel.[47] Ramasamy *et al.* (2014) (n = 124) supported this finding between the effect of CC and testosterone gel but found a higher increase of serum TT in patients who used testosterone injections compared to CC or testosterone gel.[37] They found no difference in outcomes on the ADAM questionnaire between TTh or CC therapy.[37] However, there are several advantages of CC over TTh to mention, i.e. less expensive, non-invasive, fertility sparing. Furthermore, testosterone injections cause a high-peak increase of exogenous TT with potential higher risk of more side-effects.[37]

It has yet to be established what the most effective dosage of CC therapy is and by which patient characteristics this may be influenced. In the included studies, the dosage varied between 25-50mg/day and 25, 50 or 100 mg every other day. Keihani *et al.* (2020) based the dosage of CC on bioavailable testosterone, BMI, patient preferences and symptom severity.[41] However, there is lack of evidence for relevance of these variables. Four included studies titrated the dosage of CC based on TT level, measured after some time.[47,51,54,57] In our opinion, the best treatment strategy for this moment is to start with the lowest dosage, 25 mg every other day and titrating the dosage based on reached serum TT concentration or symptom improvement.[38,60]

Considering the duration of CC therapy, the total follow-up differed between the included studies from 1.5 to 52 months. Most studies described in the first month an effective biochemical response. A clomiphene challenge test supports this, where TT after seven days of treatment reached above 400 ng/dL and after ten days above 500 ng/dL.[38] An important question is whether there is a prolonged effect after discontinuing CC and CC's effectiveness on the long-term. If we focus on biochemical response, three included studies (n = 29 - 120) did find sustained responses of serum hormone concentration after 24 till 52 months of CC usage.[44,47,51] To our knowledge, these are the

longest and largest studies conducted on the long-term effectiveness of CC therapy for male hypogonadism.

Another critical question is whether TT level remains high after discontinuation of CC therapy. Guay *et al.* (2003) proposed that CC can be stopped without decrease of serum TT, however evidence lack, because the effect was not tested.[49] On the contrary, Patel *et al.* (2015) (n = 27) demonstrated the opposite with a trial stop of CC therapy. Of the 27 patients, 78% had decreased serum TT (<300ng/dL) after three months, and all patients had reduced serum TT (<300ng/dL) after six months.[56] This finding was supported in a study with five patients, after 5-7 months of discontinuation of CC: in three patients serum TT decreased but remained above 400ng/dL, in two patients serum TT dropped to before treatment concentration.[61] In another study in 12 out of 16 patients, serum TT remained normal six months after ending CC therapy, in four patients serum TT dropped to before treatment concentration.[62] The biochemical response results after stopping CC therapy are contrary, with most studies reporting a decrease in TT after stopping CC therapy.

Another gap in current knowledge is what predictors are influencing the response on CC. Mazzola *et al.* (2014) (n = 76) stated that a low LH and greater testicular volume predict a better CC response.[43] Guay *et al.* (2003) (n = 178) described age and the presence of diabetes as predictors for the response to CC. In their study population, they found that younger patients respond 2.3 as likely to CC treatment as patients of 56 years and older. However, their success rate was defined as the percentage of successful intercourse attempts.[49] Another study expressed success rate in biochemical response, a higher increase of TT was found in the younger population against the elderly population, 100% and 32%, respectively.[63] Thereby, in the clomiphene challenge test of 10 days, a 60 ng/dL points higher TT was found in the study population below 50 years of age.[38] On the contrary, another included study (n = 36), found an opposite effect of a better TT response in older males. However, their cut-off value for age was remarkable lower (40 years). Three other included studies did not find any association between gonadotrophins, age, BMI, estradiol or testicular axis on changes in testosterone.[41,57,64]

Besides the biochemical response, the clinical response is equally important in the definition of hypogonadism.[60] Nevertheless, most included articles did not clearly described and reported symptoms of hypogonadism as most important finding, next to the biochemical response. Krzastek *et al.* (2019) (n = 400), reported in >75% of the patients subjective hypogonadal symptom improvement (FU > 3 years).[51] The ADAM questionnaire (with relatively high sensitivity but low specificity) is one of the most used and validated screening instrument.[6566] In our meta-analysis the ADAM score improved. One of the included studies (n = 86) reported that there was an improvement in the items: 'decreased libido', 'lack of energy', 'decreased life enjoyment', 'sad/grumpy' and 'decreased sports performance'. However, 10% of the patients did not experience symptom improvement.[45] These results of symptoms of hypogonadism should be interpreted with caution. A placebo-controlled RCT (n = 17) from 1995 reported that the population could not

discriminate for symptom improvement when they used CC and when they were in the placebo period.[50] Another included RCT with placebo found a comparable improvement in both the CC group and placebo groups.[53] This could be due to the lack of gradation in the severity of symptoms.[67] However, when this RCT discriminated between items, they found an improvement in the CC group in 'erection strength' and an improvement in 'libido improvement' in both groups. These contradictory effects of CC on symptoms of hypogonadism bring us to the conclusion that symptoms of hypogonadism are of multifactorial origin and complex to summarize in one questionnaire. Therefore, we advocate for the development of the implementation of a new or updated questionnaire.

Conclusive evidence of the possible effects on the lipid and metabolic profile is still lacking. Few included studies did measure some of these potential effects. Results from our review show that BMI before and during treatment differed only in one out of four studies. In one included study (n = 125) total cholesterol decreased during treatment. [46] This effect was not found in two other included studies.[47,53] Data is missing in several studies from a large part of the patient population. Therefore, more research is necessary to indicate whether CC influences the metabolic and lipid profile.

Some side-effects have been reported in the included studies, but most studies did not report any. Most frequent side-effects were: mood changes, blurred vision, breast/nipple tenderness, weight gain, headache. The incidence and type of side-effects are comparable in comparison with the usage of CC in women, where clomiphene is an acknowledged therapy.[68] Elevated hematocrit, potentially leading to thrombo-embolic events, is one of the most concerning side-effects for using CC. However, in the included studies, only one patient was described with elevated hematocrit.[51] An earlier study with 200 patients on CC showed that prevalence of polycythemia was lower in CC therapy than TTh and did not develop a hematocrit high enough to require phlebotomy.[69] In women case reports on CC therapy, development of thrombosis was described, which was associated by ovarian hyperstimulation caused by CC.[70] Attention should be paid for a reversed effect of CC on the testicular function. This paradoxical effect was described in two patients of one included study.[57] The underlying pathology is unclear but has been reported before in case series.[70,71] Further long-term follow-up (above five years) on CC has to be done, to see whether on the long-term CC is causing side-effects.

There are several limitations to mention for this systematic review, meta-analysis and the included studies. First, meta-analysis results may be influenced by missed studies in our search. However, an extensive search was performed, and reference list were searched for additional studies. Second, with the limited amount of studies on this subject, most of our analyses exhibited substantial heterogeneity. The different study designs, the variation in CC dosage between studies, the different laboratory measurements of serum hormone concentration and the unclear described in- and

exclusion criteria of the studies are reasons for this heterogeneity. Furthermore, heterogeneity could have been caused by several included studies with no strict in- and exclusion criteria. Third, the methodological quality of the included studies differed. With the inclusion of retrospective studies, there is a risk of confounding because of the retrospective study design and risk of detection bias with researchers' awareness of the treatment

To our knowledge, this is the first systematic review with meta-analysis of this subject, with various strengths and a large study population. With a limited number of studies on this subject with different study designs, it was difficult to find a reliable quality assessment tool. However, one of the strengths is that we found a validated instrument, suitable for all type of study designs. Furthermore, with the inclusion of both RCTs and observational studies, the study population in our study may cause a better representation of the patient population in daily clinical practice. Another strength is that with the sensitivity analysis for study design and study quality the results were still consistent.

CONCLUSION

CC for men with hypogonadism improves both clinical symptoms and the biochemical testosterone insufficiency. CC therapy has few reported side effects and good safety aspects. It is probably necessary to stay on CC therapy to keep the biochemical and clinical effect. In our opinion, CC is a potential effective and safe treatment and should be considered as a therapy in men with symptomatic hypogonadism, especially for those with an active or future child wish.

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Supporting Information

OTHER INFORMATION

1. Registration

This review was registered on PROSPERO under the registration number CRD42021246588 on 15-05-2021. A review protocol was not previously published.

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COMPETING INTERESTS

The authors have no conflicts of interest. See for all conflict of interest statements the supplementary material.

AUTHORS' CONTRIBUTION

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

AVAILABILITY OF DATA, CODE, AND OTHER MATERIALS

Data on search results, study selection, data collection and quality assessment available on request.

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Table 1. Study- and patient characteristics and quality assessment with the global EPHPP.

First author, year	Study type	n of CC and other subgroups	Dosage of therapy	Mean FU in months (SD)
Keihani, 2020	Cohort	CC = 332	50mg/2day (50%), 25 mg/2day (27%), 50mg/day (18%) and 25mg/day (5%)	Median 1.4 (IQR: 0.9 - 2.1
Krzastek, 2019	Cohort	CC = 400	25 mg/day with titration to 50 mg/day*	≤3 year = 12.8 (9.52) >3 year = 52.0 (10.5)
Habous, 2018	RCT	CC = 90 CC + hCG = 76 hCG = 78	CC = 50mg/day CC + hCG = 50mg + (5000IU) 2/week hCG = (5000IU) 2/week	3.0

Soares, 2018	RCT	CC = 34 Placebo = 33	CC = 50mg/day Placebo = placebo tablets/day	3.0
Liel, 2017	Cohort	CC = 18	25mg-50mg 3days/week*	1.6 (range, 1.4 - 1.8)
Tan, 2017	Cohort	CC = 10	50mg/day	n.a. (range, 0.7 - 7.0)
Marconi, 2016	Cohort	CC = 27	50mg/day	1.8
Patel, 2015	Cohort	CC = 47	50mg/2day* - 50mg/day	Median 3.0 (IQR, 2.3 - 3.6
Bendre, 2015	Cohort	CC = 11	25mg/2day	3.0
Helo, 2015	RCT	CC = 13 Anastrozole = 13	CC = 25mg/day Anastrozole = 1mg/day	3.0 3.0
Mazzola, 2014	Cohort	CC = 76	25mg /2day (42%), 50mg /2day (22%), 50mg/day (36%)	6.0
Ramasamy, 2014	Cohort	CC = 31 T injections = 31 T gel = 31 No therapy = 31	CC = 25mg/day T injections = T cypionate100 - 200 mg/week i.m. T gel = Testim® 1% or Androgel® 1.62%, 2-4 pumps/day	n.a.
Moskovic, 2012	Cohort	CC = 46	25 mg/2day	n.a. (>12.0 months)
Katz, 2012	Cohort	CC = 86	25 mg/2day (70%) and 50 mg/2day (30%)	19.0 (14.0)
Da Ros, 2012	Cohort	CC = 125	25 mg/day	6.0
Taylor, 2010	Cohort	CC = 65 T gel = 38	CC = 50mg /2day* to 25 - 100 mg /2day T gel = 5g 1% Androgel® or 5g 1% Testim® *	CC = 23.0 (range, 8-40) T gel = 46.0 (range 6.0-14
Shabsigh, 2005	Cohort	CC = 36	25mg/day	12.0
Guay, 2003	Cohort	CC = 178	(50mg) 4/week	4.0

Guay, 1995	RCT, placebo cross-over	CC = 17	(50mg) 3/week or placebo tablets 3/week	2.0

n = number of patients; IQR = interquartile range; SD = standard deviation; RCT = randomized controlled trial; CC = clomiphene citrate; FU = follow-up; hCG = human chorionic gonadotropin; T = testosterone, TTh = testosterone therapy; i.m. = intramuscular; n.a. = not available; EPHPP = Effective Public Health Practice Project.

* titration until a normal level of testosterone (> 300/350 ng/dL) was achieved

Table 2. Hormonal assessment testosterone and gonadotrophic hormones before and during treatment

Author (year)	**n**	**Mean TT before (ng/dL, SD)**	**Mean TT during (ng/dL, SD)**	**Mean free T before (ng/dL, SD)**	**Mean free during (ng/dL, SD)**	**Mean LH (mIU/m**
Keihani (2020)	CC = 332	Med 249.5 (IQR 200.5 - 298.0) Mean 249.4 (16.3)	Med 553.5 (IQR: 433.0-706.5) Mean 561.6 (45.6)	n.a.	n.a.	Med 4.2 6.2) (n=
Krzastek (2019)	CC = 400 FU ≤3 yr (n= 280) FU > 3yr (n= 120)	 217.18 (56.41) (n= 280) 218.29 (60.06) (n=120)	 579.28 (219.58) (n=280) 524.40 (212.48) (n=120)	n.a.	n.a.	n.a.
Habous (2018)	G1: CC = 90 G2: CC + hCG = 76 G3: hCG = 78	243 (78) 226 (57) 222 (59)	548 (209) * G3 531 (n.a.) * G3 460 (121)	n.a. n.a. n.a.	n.a. n.a. n.a.	n.a. n.a. n.a.
Soares (2018)	CC = 34	225.54 (72.49) (n=35)	687.94 (276.66) (n=35) p <.001 BA	191.47 (60.08) (n=30) pmol/L	565.97 (217.93) (n=30) **B-A/BG	4.25 (1.8 (n=35)

	PLB = 33	220.28 (69.30) (n=36)	220.19 (48.46) (n=36)	193.61 (67.28) (n=31) pmolL	184.52 (41.12) b(n=31)	5.10 (2.8 (n=36)
Liel (2017)	CC = 18	219.0 (74.9)	556.2 (148.9) **	n.a.	n.a.	2.7 (2.1)
Tan (2017)	CC = 10	246 (76)	548 (281) p <.01	n.a.	n.a.	n.a.
Marconi (2016)	CC = 27	244.9 (52.9) (n=30)	654.2 (233.4) (n=27)***	n.a.	n.a.	4.3
Patel (2015)	CC = 47	246.8 (97.6)	527.6 (221.5) (n=23) p = 0.0001	n.a.	n.a.	5.8 (4.8)
Bendre (2015)	CC = 11	233 (66)	581 (161) p<.0001	n.a.	n.a.	3.3 (1.6)
Helo (2015)	CC = 13 Anastrozole = 13	253 (17) 248 (18)	571 (SE 51) 3 mnths 408 (SE56) p=.04 BG	8.3 (SE 0.85) 9.3 (SE 0.9)	17 (SE 1.8) 3 mnths 14 (SE 2.0) groups	3.9 (SE 0 4.8 (SE 0
Mazzola (2014)	CC = 76	179 (72)	467 (190)***	26 (190)	76 (54)***	5.2 (5.6)
Ramasamy (2014)	G1: CC = 31 G2: Tinj = 31 G3: Tgel = 31 G4: NT = 31	247.0 (66.5) 223.4 (182.5) 230.0 (151.0) n.a.	503.5 (306.8) *** G4 1104.0 (866.5) ** G1/3/4 412.0 (339.0) 310.0 (136.0)	n.a. n.a. n.a. n.a.	n.a. n.a. n.a. n.a.	n.a. n.a. n.a. n.a.
Moskovic (2012)	CC = 46	228 (48)	1 yr 612 (212) (n=46) 2 yr 562 (201) (n=37) 3 yr 582 (227) (n=29)**	n.a.	n.a.	2.0 (1.6)
Katz (2012)	CC = 86	192 (87)	485 (165) p< 0.01	22 (16)pg/L	95 (35)***	2.6 (2.2)
Da Ros (2012)	CC = 125	310.27 (95.95)	669.03 (239.68) ** BA	n.a.	n.a.	n.a.

	G1: ≤ 50 yr G2: 50-70yr G3: >70 yr	329.18 (87.76) 296.41 (85.53) 335.30 (124.08)	794.59 (231.05) 648.35 (238.13) p =.04 G1 624.03 (224.53) p =.006 G1			
Taylor (2010)	G1: CC = 65 G2: T gel = 38	277 (range, 15 - 381) 221 (range, 27 – 363) p<0.05 BG	573 (n.a.) 553 (n.a.)	n.a. n.a.	n.a. n.a.	3.6 (0.0- 7.5 (1.8- p<.05BG
Shabsigh (2005)	CC = 36 G1: ≤ 40 yr G2: > 40 yr	247.6 (39.8) 251.4 (38.9) 242.2 (41.8)	610.0 (178.6) p<.00001 579.7 (152.7) 652.4 (207.6)	n.a.	n.a.	2.3 (2.3)
Guay (2003)	CC = 178	n.a.	n.a.	9.3 (n.a.)	21.2 (n.a.) **	3.3 (n.a.
Guay (1995)	CC = 17 G1: Med 53 yr G2: Med 67 yr PLB = 17	237.6 (38.3) 263 (20) 222 (36) p<.014 G1 n.a.	527.0 (149.9) *** BA/PLB 489 (150) 577 (145) n.a.	10.0 (2.5) 10.3 (2.7) 9.3 (1.8) n.a.	17.8 (5.0)*** BA 17.9 (5.6) 18.8 (4.0) n.a.	6.4 (1.5) n.a. n.a. n.a.

n = total number of patients, n.a. = not available, yr = year, CC = clomiphene citrate, T = testosterone, TT = total testosterone, TTh = testosterone therapy , n.s. = no significance, IQR = inter quartile range, FU = follow-up. B-A, plac = placebo, Luteinizing hormone (LH), FSH = follicle stimulating hormone, BA = before after treatment, BG= between groups, PLB = placebo, G = group, Med = median. NT = no therapy, mnth = months

* p<0.002, **p<0.001, ***p<0.01

Author (year)	n	Estradiol before (pg/mL, SD)	Estradiol during (pg/mL, SD)	T/E ratio before	T/E ratio during

Table 3. Hormonal assessment – Estradiol, testosterone-estradiol ratio, SHBG before and during treatment

Keihani (2020)	CC = 332	Median 18.9 (14.2-23.1) (n=265)	n.a.	n.a.	n.a.
Krzastek (2019)	CC = 400 FU ≤3 yr (n=280) FU > 3yr (n=120)	 24.24 (9.59) 25.73 (14.06)	 44.10 (14.47) ** 45.76 (19.71) p=.001	n.a.	n.a.
Soares (2018)	CC = 34 Placebo = 33	32.48 (12.59) (n=35) 33.45 (12.57) (n=34)	89.44 (47.85) **BA/BG (n=35) 35.77 (11.51) (n=34)	n.a. n.a.	n.a. n.a.
Patel (2015)	CC = 47	20.8 (8.8) (n=47)	32.0 (15.1)** (n=23)	n.a.	n.a.
Helo (2015)	CC = 13 Anastrozole = 13	27.6 (SE 0.9) 26.7 (SE 0.9)	50 (SE 4.2) 3 mnths 25 (SE 0.1)**BG	9.3 (SE 2.5) 9.7 (SE 3.1)	12.0 (SE 1.3) 17.0 (SE 1.5) p=.005
Mazzola (2014)	CC = 76	29 (31)	42 (20)***BA	6.2 (n.a.)	11.2
Ramasamy (2014)	CC = 31 T injections = 31 T gel = 31 No therapy = 31	n.a. n.a. n.a. n.a.	20.0 (10.0) 60.0 (58.0)***BG 20.0 (10.0) 20.0 (10.0)	n.a. n.a. n.a. n.a.	n.a. n.a. n.a. n.a.
Moskovic (2012)	CC = 46	37 (16)	1 yr 48 (22) (n=46) 2 yr 42 (13) (n=37) 3 yr 50 (30) (n=29)p<.02	n.a.	n.a.
Katz (2012)	CC = 86	26 (22)	39 (18.) p<.05	n.a.	n.a.
Shabsigh (2005)	CC = 36 G1 ≤ 40 yr G2 > 40 yr	32.3 (10.9) 31.0 (12.4) 34.5 (8.1)	46.3 (16.6)p=.001 52.7 (16.6) 39.0 (13.9)	8.7 (3.5) 9.5 (4.1) 7.4 (1.9)	14.2 (5.1) p=.001 BA 11.7 (4.4) p=0.003 G 17.0 (4.5)

n = total number of patients, n.a. = not available, CC = clomiphene citrate, T = testosterone, T/E= testosterone-estradiol-ratio, TTh = testosterone therapy , n.s. = no significance, FU = follow-up. B-A, SHBG = sex hormone binding globulin, Prl = prolactin, B-A = before after comparison, BG= between groups

** p<0.001

Table 4. Hypogonadal symptoms before and during treatment due to ADAM, IIEF-5, EHS questionnaires and no. of intercourse.

Author (year)	n	Mean ADAM scores before 1-10 (SD)	Mean ADAM scores after 1-10 (SD)	Mean qADAM scores before 10-50	Mean qADAM scores after 10-50 (SD)	Mean IIEF-5 before	Mean after
Keihani (2020)	CC = 332	4.0 (range, 2.0-6.0)	n.a.	n.a.	n.a.	n.a.	n.a.
Habous (2018)	CC = 90 CC + hCG = 76 hCG = 78	n.a. n.a. n.a.	n.a. n.a. n.a.	20.5 (3.8)	Marginally higher qADAM scores in hCG +CC compared with hCG or CC.	n.a. n.a. n.a.	n.a. n.a. n.a.
Soares (2018)	CC = 34 Placebo = 33	5.26 (2.67) 5.00 (2.15)	3.38 (2.74)*p<0.001 3.12 (2.63)	n.a. n.a.	n.a. n.a.	n.a. n.a.	n.a. n.a.
Tan (2017)	CC = 10	5.9 (1.9)	1.7 (1.1) p=0.10	n.a.	n.a.	n.a.	n.a.
Marconi (2016)	CC = 27	n.a.	n.a.	n.a.	n.a.	Median 18.0 (range 11.0-24.0) (n = 27) Median 8.0 (range, 17.0-21.0) (n=3, ED)	22.0 (24.0) ED)
Patel (2015)	CC = 47	55% had ≥3 positive symptoms	n.a.	n.a.	n.a.	n.a.	n.a.
Helo (2015)	CC = 13 Anastrozole = 13	n.a. n.a.	n.a. n.a.	37.0 (SE 1.9) 36.0 (SE	49.0 (SE 1.3) 38.0 (SE 1.3) p=0.634	13.4 (SE 0.5) 12.1 (SE 0.7)	13.7 (12.48 0.4)

				1.6)			
Ramasamy (2014)	CC = 31 T injections = 31 T gel = 31 No therapy = 31	n.a. n.a. n.a. n.a.	n.a. n.a. n.a. n.a.	n.a. n.a. n.a. n.a.	35.0 (8.0) 39.0 (8.0) 36.0 (9.0) 34.0 (9.0)	n.a. n.a. n.a. n.a.	n.a. n.a. n.a. n.a.
Moskovic (2012)	CC = 46	7 (2)	1yr = 3 (2) 2yr = 5 (2.5) 3yr = 5.0 (3) p=.01BA	n.a.	n.a.	n.a.	n.a.
Katz (2012)	CC = 86	5 (IQR, 2-7) Mean 4.75 (SD, 2.25)	2 (IQR, 1-4) Mean 2.25 (SD, 1.25)	n.a.	n.a.	n.a.	n.a.
Taylor (2010)	CC = 65 T gel = 38	4.9 (n.a.) n.a.	2.1 (n.a.) p<0.05 (n=22) n.a.	n.a. n.a.	n.a. n.a.	n.a. n.a.	n.a. n.a.
Guay (1995)	CC = 17 Placebo = 17	n.a. n.a.	n.a. n.a.	n.a. n.a.	n.a. n.a.	n.a. n.a.	n.a. n.a.

n = total number of patients, n.a. = not available, yr = year, CC = clomiphene citrate, T = testosterone, TTh = testosterone suppletion therapy , ED = erectile dysfunction , n.s. = no significance

Table 5. Metabolic and lipid profile before and during treatment.

Author (year)	**n**	**Mean BMI before (kg/m2, SD)**	**Mean BMI during (kg/m2, SD)**	**Mean HbA1c before (%, SD)**	**Mean HbA1c during (%, SD)**	**M b**
Keihani (2020)	CC= 332	Median 30.3 (range 24.4 – 35.1) (n=317)	n.a.	n.a.	n.a.	n
Habous (2018)	CC = 90 CC + hCG = 76	30.9 (n.a.) 31.6 (n.a.)	30.4 (n.a.) 31.0 (n.a.)	n.a. n.a.	n.a. n.a.	n n

	hCG = 78	30.1 (n.a.)	29.7 (n.a.)	n.a.	n.a.	n.
Soares (2018)	CC = 34 Placebo = 33	45.80 (11.51)(n=37) 46.28 (8.62) (n=36)	47.71 (8.97) (n=37) 46.28 (8.62) (n=36)	5.8 (0.8) 5.7 (0.7)	5.9 (0.8) 5.8 (0.7)	1 1
Liel (2017)	CC = 18	29.9 (4.5; range, 18.6 - 37.6)	n.a.	n.a.	n.a.	n.
Patel (2015)	CC = 47	30.2 (n.a.)	n.a.	n.a.	n.a.	n.
Bendre (2015)	CC = 11	35.22 (4.8)	35.29 (4.63)	n.a.	n.a.	n.
Helo (2015)	CC = 13 Anastrozole = 13	32.0 (SE 7.5) 33.0 (SE 9.8)	n.a. n.a.	n.a. n.a.	n.a. n.a.	n n
Moskovic (2012)	CC = 46	32 (8)	1 yr = 31 (9) 2 yr = 29 (11) 3 yr = 28 (4) p<0.05	n.a.	n.a.	n.
Da Ros (2012)	CC = 125	n.a.	n.a.	n.a.	n.a.	1
Taylor (2010)	CC = 65 T gel = 38	n.a.	n.a.	n.a.	n.a.	1 1

n = total number of patients, n.a. = not available, yr = year, CC = clomiphene citrate, T = testosterone, BMI = body mass index, HbA1c = hemoglobin A1c, n.s. = no significance

Table 6. Safety aspects before and during treatment.

Author (year)	**n**	**Mean Ht before % (SD)**	**Mean Ht during % (SD)**	**Mean Hb before mmol/L**	**Mean Hb during mmol/L**	**Mean PSA before ng/mL (SD)**	**Mean PSA during ng/mL (SD)**	**Mean IPSS before 0-35 (SD)**	**Mean IPSS during 0-35 (SD)**	**Mean BP mmHg (S**

Krzastek (2019)	CC = 400	Normal	1 patient with ↑ Ht	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Soares (2018)	CC = 34	43.9 (2.4)	44.9 (5.7)	n.a.	n.a.	0.6 (0.4)	0.8 (0.5)	8.4 (5.2)	8.6 (5.2)	SPB 126.5 DBP 81.9
	Placebo = 33	43.9 (2.6)	44.1 (2.7)	n.a.	n.a.	0.6 (0.5)	0.6 (0.4)	9.9 (6.0)	8.5 (5.8)	SBP 123.9 DBP 79.4
Moskovic(2012)	CC = 46	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Taylor (2010)	CC = 65	n.a.	n.a.	15.0	14.5	0.8 (n.a.)	1.0 (n.a.)	n.a.	n.a.	n.a.
	T gel = 39	n.a.	n.a.	14.9	15.2	0.9 (n.a.)	1.14 (n.a.)	n.a.	n.a.	n.a.

n = total number of patients, CC = clomiphene citrate, Ht = hematocrit, Hb = hemoglobin, PSA = prostate specific antigen, IPSS = international prostate symptom score, BP = blood pressure, SBP = systolic blood pressure DBP = diastolic blood pressure, n.a. = not available, yr = year, T = testosterone

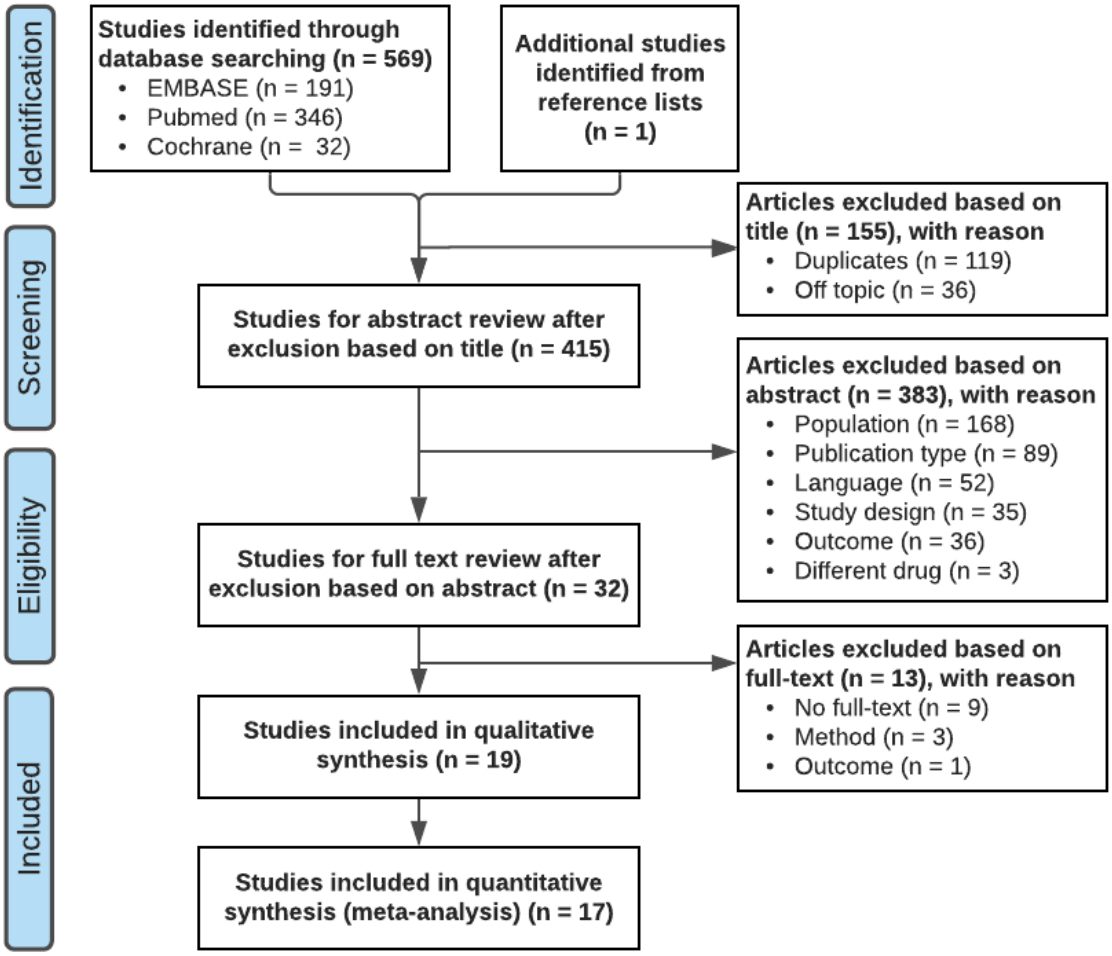
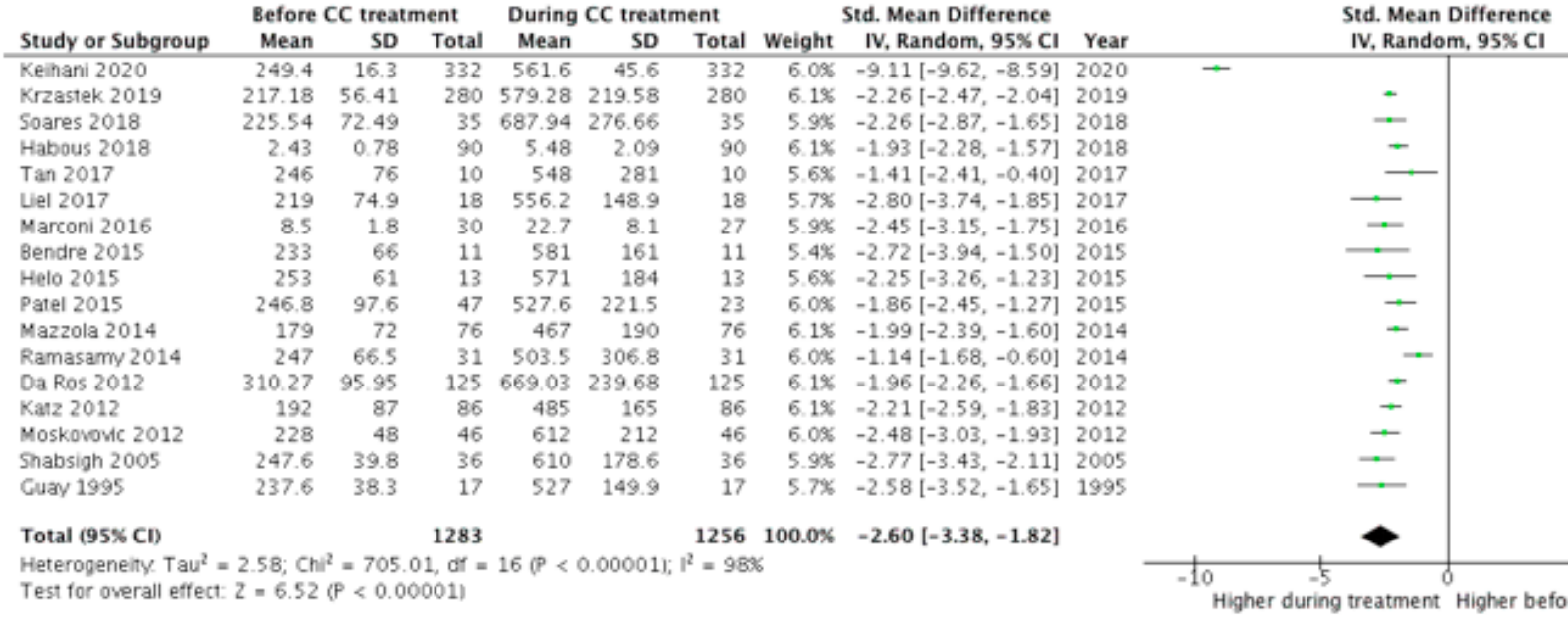
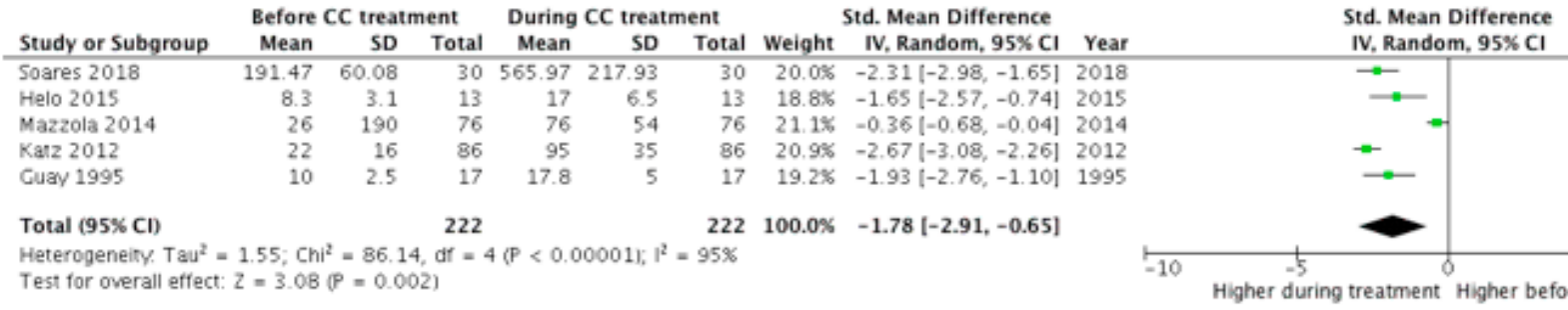


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.
Search and screen process for studies about effectiveness of clomiphene citrate for hypogonadal males

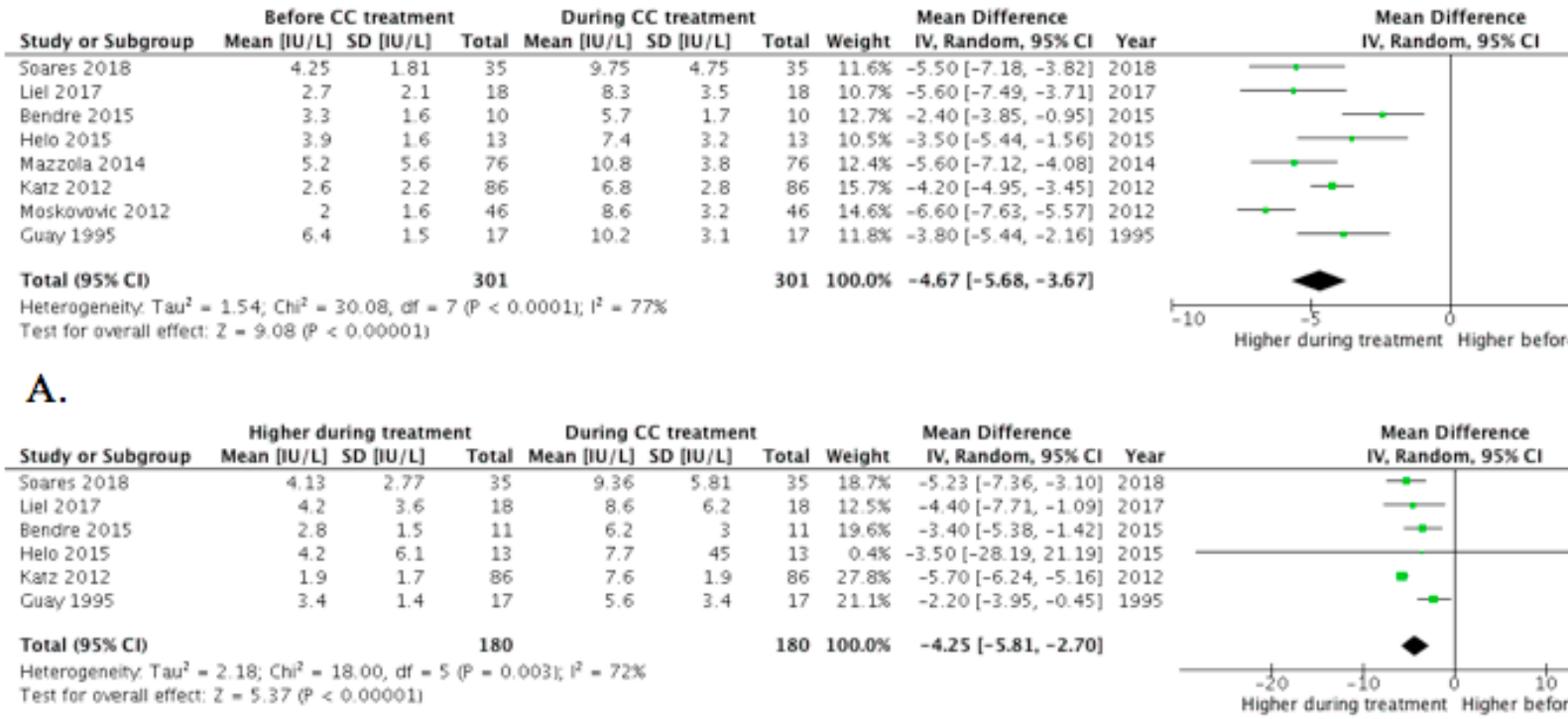


A.



B.

Figure 2. Effect of clomiphene citrate on testosterone: total testosterone (A) and free testosterone (B).
Forrest plot comparison of testosterone in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.



A.

B.

Figure 3. Effect of clomiphene citrate on gonadotropins: luteinizing hormone (A) and follicle stimulating hormone (B). Forrest plot comparison of gonadotropins in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.

Study or Subgroup	Before CC treatment Mean [pg/mL]	SD [pg/mL]	Total	During CC treatment Mean [pg/mL]	SD [pg/mL]	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Krzastek 2019	24.24	9.59	280	44.1	14.47	280	16.6%	-19.86 [-21.89, -17.83]	2019
Soares 2018	32.48	12.59	35	89.44	47.85	35	6.4%	-56.96 [-73.35, -40.57]	2018
Patel 2015	20.8	8.8	47	32	15.1	23	13.4%	-11.20 [-17.86, -4.54]	2015
Helo 2015	27.6	3.2	13	50	15.1	13	11.9%	-22.40 [-30.79, -14.01]	2015
Mazzola 2014	29	31	76	42	20	76	11.9%	-13.00 [-21.29, -4.71]	2014
Katz 2012	37	16	46	48	22	46	12.3%	-11.00 [-18.86, -3.14]	2012
Moskovovic 2012	26	22	86	39	18	86	13.9%	-13.00 [-19.01, -6.99]	2012
Shabsigh 2005	32.43	10.9	36	46.3	16.6	36	13.5%	-13.87 [-20.36, -7.38]	2005
Total (95% CI)			**619**			**595**	**100.0%**	**-17.69 [-22.92, -12.46]**	

Heterogeneity: Tau² = 41.69; Chi² = 38.56, df = 7 (P < 0.00001); I² = 82%
Test for overall effect: Z = 6.63 (P < 0.00001)

-5
High

Figure 4. Effect of clomiphene citrate on estradiol. Forrest plot comparison of estradiol in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.

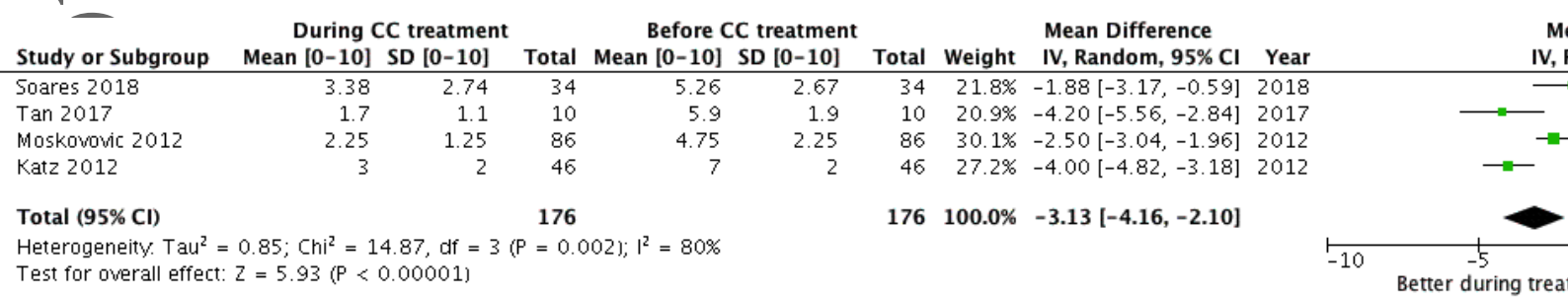


Figure 5. Effect of clomiphene citrate on the Androgen Deficiency in the Aging Male (ADAM) questionnaire. Forrest plot comparison of ADAM questionnaire in patients before- and during CC treatment. SD, standard deviation; STD, standardized; IV, inverse variance; CI, confidence interval.