Asian Journal of Urology 12 (2025) 15–22

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

Review

Efficacy of clomiphene citrate and tamoxifen on pregnancy rates in idiopathic male subfertility: A systematic review and meta-analysis

Shadi Khashaba [a], Shehab Khashaba [b], Anil Krishan [c], Angus Bruce [d], Abdullatif Almaghlouth [e], Jason Huang [f], Mahmoud Mima [f,*], Craig Niederberger [f]

[a] *IVFAustralia, Sydney, Australia*
[b] *King Hamad University Hospital, Busaiteen, Bahrain*
[c] *George Eliot Hospital, Nuneaton, UK*
[d] *Guy's Hospital, London, UK*
[e] *King Faisal University, Riyadh, Kingdom of Saudi Arabia*
[f] *Department of Urology, University of Illinois at Chicago, Chicago, IL, USA*

Received 3 February 2023; accepted 6 November 2023
Available online 17 September 2024

KEYWORDS
Male fertility;
Male infertility;
Clomiphene citrate;
Tamoxifen;
Selective estrogen receptor modulator

Abstract *Objective:* Selective estrogen receptor modulators (SERMs) have demonstrated efficacy in the treatment of hypogonadism in males and male factor infertility. Two SERMs, clomiphene citrate and tamoxifen, are now prescribed for off-label use to treat both conditions in males. However, existing literature compares mixed protocols with active management. We aimed to conduct a meta-analysis to evaluate the effect of clomiphene and tamoxifen versus placebo on natural pregnancy rates.

Methods: We conducted a comprehensive systematic review of electronic databases: MEDLINE, PubMed/PMC, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Google Scholar, and Web of Science. Articles satisfying all selection criteria were analyzed. The primary outcome was the incidence of pregnancy after receiving the treatment. Secondary outcomes included serum follicle-stimulating hormone, luteinizing hormone, and testosterone levels, and sperm count and motility. We calculated the pooled odds ratio, risk ratio, and risk difference to ascertain possible alterations in the direction of the pooled effect size.

Results: Ten randomized controlled trials were ultimately included and underwent data extraction. Clomiphene citrate and placebo groups had similar pregnancy rates (10.4% and 7.1%,

* Corresponding author.
E-mail address: mmima2@uic.edu (M. Mima).
Peer review under responsibility of Tongji University.

https://doi.org/10.1016/j.ajur.2024.09.001

respectively; odds ratio 1.30 [95% confidence interval 0.27—6.17]; $p=0.74$). No meta-analysis could be calculated for pregnancy rates in tamoxifen versus placebo groups. Heterogeneity among the studies of both SERMs ranged from low to high.
Conclusion: Although clomiphene citrate and tamoxifen are often used off-label for the treatment of male infertility secondary to hypogonadism, studies of SERMs in the treatment of idiopathic male factor infertility are limited and heterogenous, preventing this meta-analysis from investigating the efficacy of SERMs on male infertility. The effect of clomiphene citrate or tamoxifen on the pregnancy rate remains uncertain.

1. Introduction

Infertility is a global problem estimated to affect one in six couples trying to conceive [1]. It is defined as the failure to achieve pregnancy naturally after 1 year [2]. The male factor plays a role in 50% of these cases and is solely responsible for couples' infertility in approximately 30% of the cases [3]. The etiology of male infertility with abnormal semen parameters remains unknown in 25% of the men [4].

Spermatogenesis is controlled by the hypothalamic—pituitary—testicular axis. Gonadotropin-releasing hormone is released from the hypothalamus in a pulsatile manner [5]. This pulsatile fashion causes the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. LH directly affects Leydig cells in the testicles to produce testosterone, which is then converted into estrogen in the peripheral tissue. Estrogen provides negative feedback to the hypothalamus and anterior pituitary [5]. FSH directly affects Sertoli cells in the testicles, causing the initiation and maintenance of spermatogenesis [6]. Sertoli cells induce a negative feedback loop in the hypothalamus and pituitary through inhibin production [7].

Selective estrogen receptor modulators (SERMs) have been used off-label for decades to treat male factor infertility. The SERM is a class of drugs that acts on estrogen receptors with agonist or antagonist properties, depending on the target tissue. Clomiphene citrate and tamoxifen are SERMs. They act as estrogen blockers, inhibiting the negative feedback acting on both the hypothalamus and anterior pituitary. For example, SERMs cause the hypothalamus to release more gonadotropin-releasing hormone, which in turn releases more FSH and LH from the anterior pituitary gland [4]. The increased LH secretion raises intratesticular testosterone which acts along with FSH to stimulate and maintain spermatogenesis. The earliest study from 1966 by Mellinger and Thompson [8] showed the benefits of clomiphene citrate in treating male infertility. Other medications within the SERM family are hypothesized to function similarly to clomiphene citrate such as tamoxifen. Tamoxifen was introduced a long time ago as an empiric treatment for idiopathic oligozoospermia [9], and the World Health Organization Working Committee proposed it as the first-line treatment for this condition [10]. The rationale behind its use is similar to that of clomiphene citrate—by inhibition of the estradiol, it enhances gonadotropin-releasing hormone secretion from the hypothalamus and thus LH and FSH from the pituitary, leading to an increase in intratesticular levels and testosterone secretion and subsequently spermatogenesis [11].

A recent review showed the effective role of clomiphene citrate in patients who suffer from both male factor infertility and symptomatic hypogonadism [12]. A systematic review and meta-analysis published by Huijben et al. [13] in 2023 noted an increased sperm concentration and motility with no change in morphology with the use of clomiphene citrate. There were no serious adverse events reported indicating that this could be a safe option for infertile men [13]. While previous studies have focused on semen parameters, we conducted a meta-analysis to evaluate the effect of clomiphene and tamoxifen versus placebo on pregnancy rates, as all recent analyses compared mixed protocols with active management. The main focus of this meta-analysis is to focus on pregnancy rates but we will also look at biochemical effects in the form of hormone levels and the clinical effects in the form of sperm count and motility.

2. Methods

The protocol for our review was determined before the literature search. The methods of study selection, data analysis, data extraction, and analysis of the outcomes were predefined in our initial study protocol. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021229422 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021229422). The study was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) standards [14]. No ethical approval was required.

2.1. Eligibility criteria

We included all randomized controlled trials (RCTs) evaluating the outcomes of idiopathic infertile male patients taking either clomiphene citrate or tamoxifen versus placebo with no age restriction. All studies written in English, focusing on idiopathic male infertility (idiopathic oligoasthenoteratozoospermia, which indicates that the men have an unexplained reduction of semen parameters) with no

date restrictions, were included. The exclusion criteria included manuscripts not in English, unpublished manuscripts, and conference proceedings. Clomiphene citrate or tamoxifen was considered the intervention of interest, and placebo was considered the comparator.

2.2. Outcome measures

The incidence of normal pregnancy after receiving treatment was the primary outcome. Secondary outcomes included serum FSH, LH, and testosterone levels, and sperm count and motility.

2.3. Search strategy

A comprehensive search strategy was devised based on our pre-set study protocol. Two authors (Bruce A and Almaghlouth A) independently performed a comprehensive search using the following electronic databases: MEDLINE, PubMed/PMC, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Google Scholar, and Web of Science. Supplementary Table 1 outlines the literature search strategy. The search was concluded on December 20th, 2022 with no time limitation. The titles and abstracts of the papers identified from the literature search were assessed by two independent authors (Krishan A and Almaghlouth A). The full texts of qualifying articles were retrieved and assessed; these were further screened for those that met eligibility criteria. In case of disagreements between the two authors, a third author (Khashaba S) was consulted to reach a majority verdict. To ensure that our search strategy was as comprehensive as possible, the reference lists of the included studies were screened to identify any additional studies not found in the database search. Further discussions with experts in the field were conducted to identify further studies missed in the database search.

2.4. Data extraction

Two independent authors (Bruce A and Almaghlouth A) extracted data from each study using an electronic spreadsheet produced following the Cochrane recommendations for intervention reviews. These included study-related data (the first author's name, publication year, country of origin, journal, study design, dose of clomiphene or tamoxifen, and duration of treatment), baseline patient characteristics of the study populations (the number of patients, age, semen volume, sperm concentration, sperm motility, and serum FSH, LH, and testosterone levels), and primary and secondary outcomes' data.

2.5. Summary measures

Two authors (Krishan A and Almaghlouth A) independently assessed the results. In case of discrepancies, a third author (Khashaba S)'s opinion was sought to reach a majority verdict. The Review Manager (RevMan version 5.4; the Cochrane Collaboration, Copenhagen, Denmark) was used for the data synthesis. We used random effects modelling for data analysis in the event of low-to-moderate heterogeneity or fixed effects when heterogeneity was high or considerable. The results are displayed using forest plots with 95% confidence intervals (CIs). The mean difference (MD) between groups was calculated for continuous variables, whereas the odds ratio (OR) was calculated for dichotomous variables.

Heterogeneity between studies was assessed, and inconsistencies were calculated using the I^2 statistic. Values of 0–50% represented low heterogeneity; 51%–75% moderate heterogeneity; 76%–100% considerable heterogeneity.

For each dichotomous variable, we calculated the pooled OR, risk ratio, and risk difference to ascertain possible alterations in the direction of the pooled effect size. The influence of each study was assessed by re-evaluating the resultant effect after removing it from the analysis (leave-one-out sensitivity analysis).

The quality and risk of bias assessments were performed by two independent authors (Krishan A and Almaghlouth A) for each included study, using the RoB2 tool that included within the ReviewManager to assess the risk of bias. Again, in case of disagreements between the two authors, a third author (Khashaba S)'s opinion was sought to reach a majority verdict.

3. Results

The electronic search strategy initially identified 233 articles. After screening the titles and abstracts, 204 articles were excluded. Of the 29 articles reviewed in full, 19 were excluded due to either a lack of relevance or the absence of outcomes defined in our study. Ultimately, 10 RCTs [9,15–23] met the eligibility criteria (Fig. 1). The clomiphene citrate studies included a total of 396 patients, and the tamoxifen studies included a total of 234 patients. The baseline characteristics of the studies are displayed in Supplemental Tables 2 and 3 for clomiphene citrate and tamoxifen, respectively. Supplemental Tables 4 and 5 present the baseline patient characteristics of the included studies.

3.1. Methodological quality and risk of bias

The results of the methodological quality assessment are shown in Fig. 2.

3.1.1. Clomiphene citrate versus placebo

3.1.1.1. Pregnancy rate (Fig. 3A). The clomiphene citrate and placebo groups had similar pregnancy rates (10.4% and 7.1%, respectively; OR 1.30 [95% CI 0.27–6.17]; $p=0.74$).

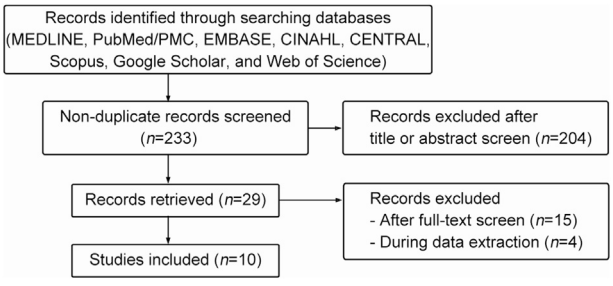

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart for the reviewed articles. CENTRAL, Cochrane Central Register of Controlled Trials.

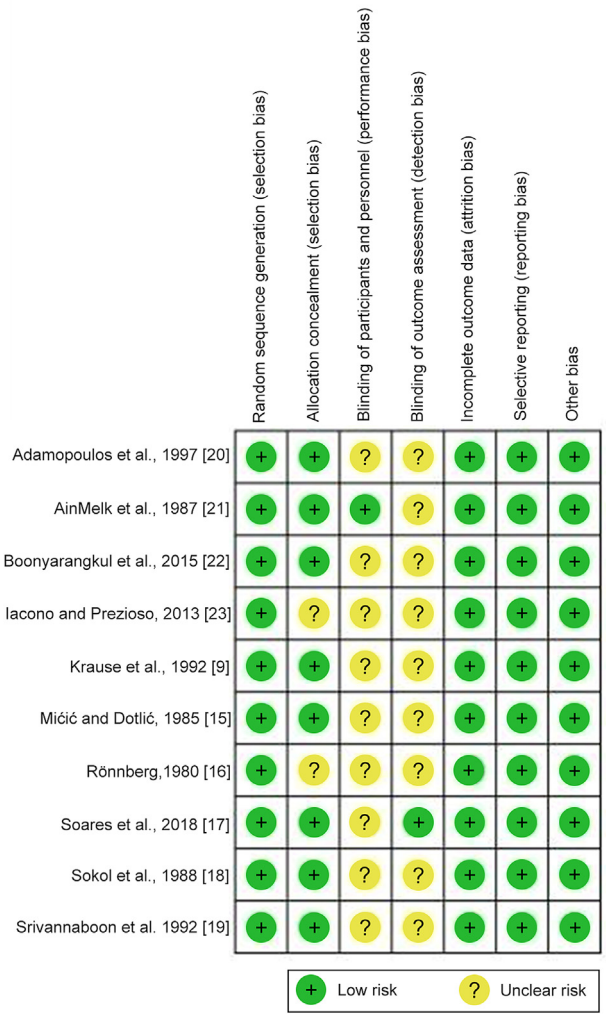

Figure 2 Risk of bias assessment of the included studies.

The moderate heterogeneity was observed among the included studies ($I^2=53\%$, $p=0.09$).

3.1.1.2. Serum FSH level (Fig. 3B). The post-treatment FSH level in the clomiphene citrate group was significantly higher than that in the placebo group (10.67 mIU/mL and 6.36 mIU/mL, respectively; MD 4.30 [95% CI 3.26−5.34]; $p<0.001$). A low level of heterogeneity was observed among the included studies ($I^2=7\%$, $p=0.34$).

3.1.1.3. Serum LH level. Only two studies, Sokol et al. [18] and Soares et al. [17], reported outcomes for LH levels after clomiphene citrate treatment. Therefore, no meta-analysis was performed on this outcome.

3.1.1.4. Serum testosterone. Only two studies, Sokol et al. [18] and Soares et al. [17], reported serum testosterone level outcomes after clomiphene citrate treatment. Therefore, no meta-analysis was performed on this outcome.

3.1.1.5. Sperm count. Only two studies, Sokol et al. [18] and Mićić and Dotlić [15], reported sperm count levels after clomiphene citrate treatment. Therefore, no meta-analysis was performed on this outcome.

3.1.1.6. Sperm motility. Only two studies, Sokol et al. [18] and Mićić and Dotlić [15], reported sperm motility after the clomiphene citrate treatment. Therefore, no meta-analysis was performed on this outcome.

3.1.2. Tamoxifen versus placebo

3.1.2.1. Pregnancy rate. Only one study, Iacono and Prezioso [23], reported total pregnancy rates in their study outcomes. These were 6/30 for the tamoxifen group and 4/30 for the placebo group. No meta-analysis was performed on this outcome.

3.1.2.2. Serum FSH level (Fig. 4A). The measured post-treatment FSH in the tamoxifen group was significantly

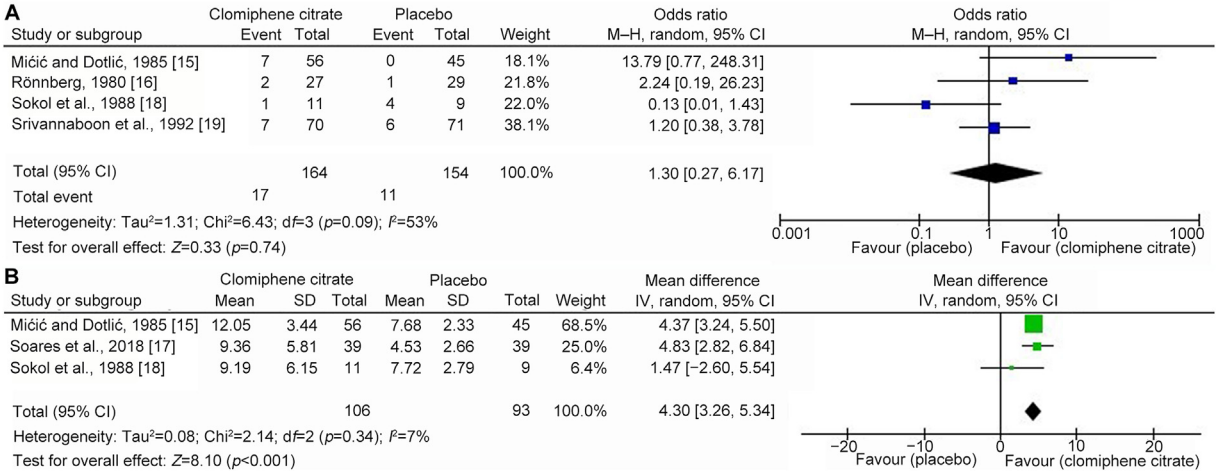

Figure 3 The forest plot analysis following treatment with clomiphene citrate versus placebo. (A) Pregnancy rate; (B) Serum follicle-stimulating hormone level. CI, confidence interval; M−H, Mantel−Haenszel. IV, inverse variance.

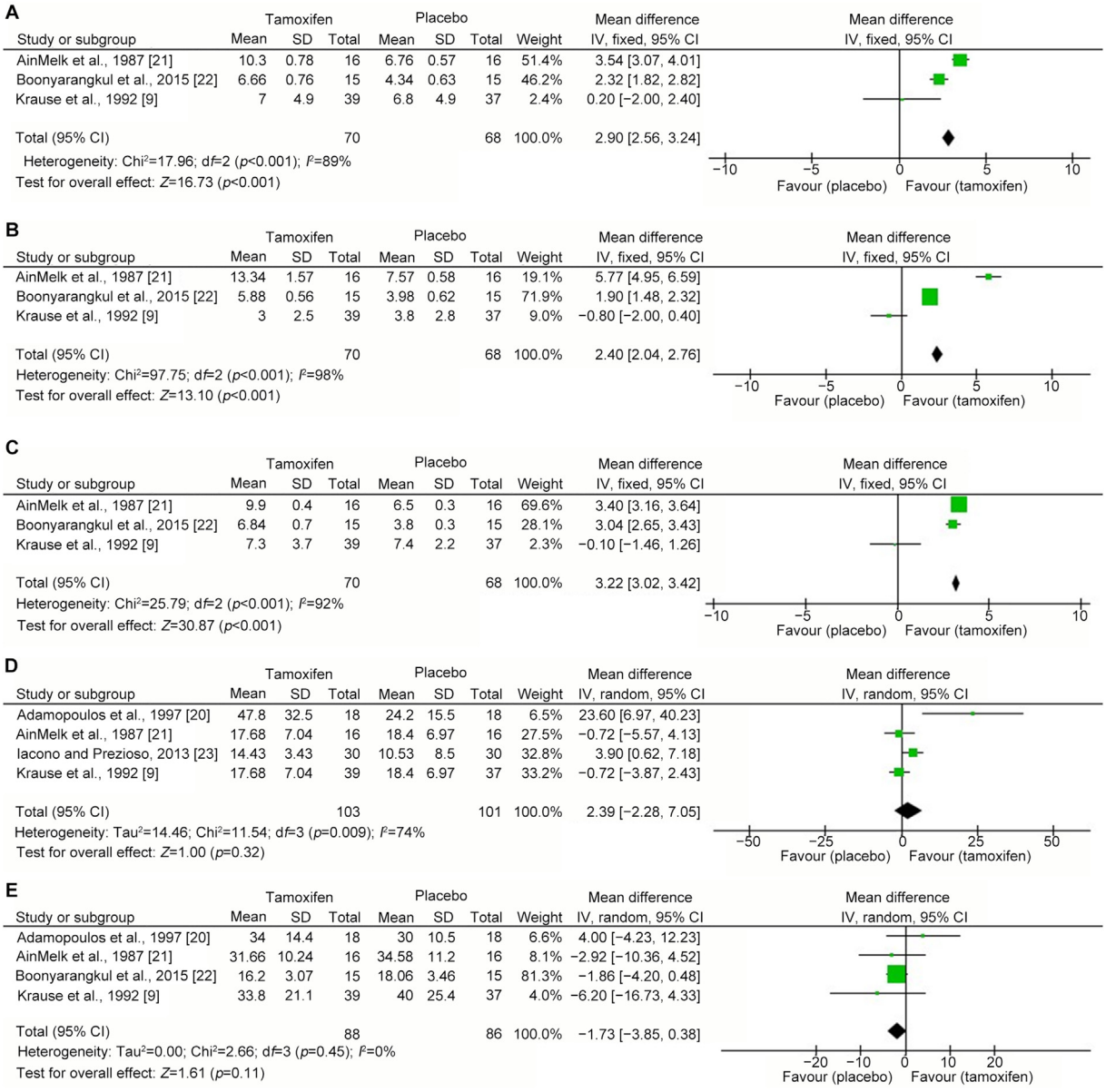

Figure 4 The forest plot analysis following the treatment with tamoxifen versus placebo. (A) Serum follicle-stimulating hormone level; (B) Serum luteinizing hormone level; (C) Serum testosterone level; (D) Sperm count; (E) Sperm motility. CI, confidence interval; IV, inverse variance; SD, standard deviation.

higher than in the placebo group (7.68 mIU/mL *vs.* 6.25 mIU/mL; MD 2.90 [95% CI 2.56–3.24]; $p<0.001$). A high level of heterogeneity was observed among the included studies ($I^2=89\%$, $p<0.001$).

3.1.2.3. Serum LH level (Fig. 4B). The measured post-treatment LH in the tamoxifen group was significantly higher than in the placebo group (5.98 mIU/mL *vs.* 4.73 mIU/mL; MD 2.40 [95% CI 2.04–2.76]; $p<0.001$). A high level of heterogeneity was observed among the included studies ($I^2=98\%$, $p<0.001$).

3.1.2.4. Serum testosterone level (Fig. 4C). The measured post-treatment testosterone in the tamoxifen group was significantly higher than in the placebo group (7.80 ng/dL *vs.* 6.39 ng/dL; MD 3.22 [95% CI 3.02–3.42]; $p<0.001$). A high level of heterogeneity was observed among the included studies ($I^2=92\%$, $p<0.001$).

3.1.2.5. Sperm count (Fig. 4D). Similar sperm counts were measured in the tamoxifen and placebo groups (22.0×10^6 *vs.* 17.1×10^6, respectively; MD 2.39 [95% CI −2.28–7.05]; $p=0.32$). A moderate level of heterogeneity was observed among the included studies ($I^2=74\%$, $p=0.009$).

3.1.2.6. Sperm motility (Fig. 4E). Similar mean sperm motility was noted in the tamoxifen and placebo groups (30.5% *vs.* 33.1%, respectively; MD −1.73 [95% CI

−3.85−0.38]; $p=0.11$). A low level of heterogeneity was observed among the included studies ($I^2=0\%$, $p=0.45$).

3.2. Sensitivity analysis

The use of fixed or random effects modelling for each reported outcome assessment did not significantly alter the calculated outcomes. Similarly, the direction of the pooled effect remained unchanged when OR, risk ratio, or risk difference was calculated from dichotomous variables or MD or standardized MD from continuous variables. The leave-one-out sensitivity analysis was performed only on outcomes reported in more than three studies. The removal of each study did not alter the statistical significance of outcomes.

4. Discussion

This systematic review and meta-analysis aimed to evaluate the effects of the SERMs (clomiphene citrate and tamoxifen) on the idiopathic male infertility and pregnancy rate. In addition, we evaluated the treatment impact on hormonal levels and semen parameters.

4.1. Clomiphene citrate

Clomiphene citrate is a SERM used to treat male infertility with controversial efficacy. The goal of this medication from a fertility standpoint is to block negative feedback loops which ultimately result in an increase in LH and FSH levels that stimulate testosterone release and spermatogenesis [24,25]. In males, this is used as an off-label treatment for hypogonadism due to its indirect stimulation of Leydig cells to produce testosterone, particularly in those wishing to maintain fertility [26].

The effect of clomiphene citrate on pregnancy rates was reported in all studies (OR 1.30 [95% CI 0.27−6.17]; $p=0.74$), with a moderate level of heterogeneity among them ($I^2=53\%$; $p=0.09$). Differences in pregnancy rates among studies could be because the increase in pregnancy rates were achieved in a selected group of infertile males with a longstanding history of infertility [15]. Sokol et al. [18] reported a higher pregnancy rate in the control group, concluding that clomiphene citrate was not a useful drug for the male infertility treatment.

Two studies [17,18] reported significantly higher serum LH and testosterone levels after the daily treatment with 25 mg or 50 mg clomiphene citrate than placebo (any overall mean increase, $p<0.001$). The remaining studies did not report this outcome. The two studies showed some heterogeneity given the differences in the study participant numbers and characteristics and the clomiphene citrate dose used.

We found higher FSH levels following treatment with clomiphene citrate (10.67 mIU/mL) than placebo (6.36 mIU/mL; MD 4.30 [95% CI 3.26−5.34]; $p<0.001$). Although the included studies were RCTs, we found a low level of heterogeneity ($I^2=7\%$; $p=0.34$) given the patient characteristics, treatment dose, and follow-up time. The impact of clomiphene citrate on semen parameters was reported only in two studies [15,18], with some differences between them. Sokol et al. [18] reported no change in sperm parameters following treatment with 25 mg clomiphene citrate once daily, concluding that clomiphene citrate was not a useful drug to treat male infertility. Conversely, Mićić and Dotlić [15] reported a significantly higher mean sperm concentration in the clomiphene citrate than the placebo group (8.38 [standard deviation 4.18] million/mL *vs.* 7.56 [standard deviation 3.64] million/mL; $p<0.05$).

4.2. Tamoxifen

Tamoxifen is a non-steroidal anti-estrogen drug that is also considered a SERM.

Tamoxifen's effect on pregnancy rates was reported in only one study [23], which showed a pregnancy rate of 6/30 for the tamoxifen group and 4/30 for the placebo group. A recent review reported higher pregnancy rates in patients treated with SERMs than placebo-treated or non-treated controls (OR 3.42; 95% CI 1.37−8.52; $p<0.01$); caveats that concern the reported results are the inclusion of non-randomized controlled studies and the high level of heterogeneity among studies [27].

Three studies [9,21,22] reported a significant increase in the mean total serum LH following treatment with tamoxifen over placebo (5.98 mIU/mL *vs.* 4.73 mIU/mL; $p<0.001$). These three studies were noted to have differences in participant characteristics and the tamoxifen doses used ($I^2=98\%$, $p<0.001$). The same three studies also reported a significant increase in FSH level following treatment with tamoxifen over placebo with overall mean of (7.68 mIU/mL *vs.* 6.25 mIU/mL; $p<0.001$). Although all three studies were RCTs, they showed a high level of heterogeneity ($I^2=89\%$, $p<0.001$), primarily due to the patient characteristics, treatment dose, and follow-up time. The impact of tamoxifen on semen parameters was reported in all studies, showing no difference in the sperm concentration or motility between the tamoxifen and placebo groups.

According to the WHO manual on infertility (2021), the sperm count and concentration is the best predictor of fertility [28]. One could debate whether a routine semen analysis just accurately measures sperm production, maturation, and the ejaculatory process [29−31], but not necessarily fertility. Perhaps other independent factors like sperm function play a role in fertility. For this reason, we chose the pregnancy rate as our primary outcome. It is important to note that pregnancy is a multifactorial outcome that does not only depend only on semen parameters. For this reason, it is difficult to study empiric treatment options to improve pregnancy rates. There is a pronounced predilection toward the utilization of clomiphene citrate as opposed to tamoxifen, a preference that is ostensibly associated with the comparatively elevated profile of adverse events affiliated with tamoxifen. The latter encompasses gastrointestinal, cardiovascular, and psychiatric disturbances, which have been predominantly cited as the primary impetus for the discontinuation of tamoxifen therapy [32]. The main strength of this meta-analysis is that it was the first attempt to focus primarily on a clinically useful outcome (the pregnancy rate) as the primary outcome of the study following treatment of

male infertility with the SERMs (clomiphene citrate or tamoxifen).

Our review has certain limitations that warrant mentioning. Unfortunately, we were bound to the existing literature that included only a small number of studies. We performed a systematic review and meta-analysis only on RCTs and compared the available data. We observed an increase in testosterone, FSH, and LH levels with tamoxifen administration and an increase in FSH with clomiphene citrate in most studies, despite the moderate-to-high level of heterogeneity. Moreover, semen parameters were not useful tools for the male fertility assessment.

5. Conclusion

Owing to the paucity of incorporated studies and a prominent level of heterogeneity, this meta-analysis was precluded from thoroughly investigating the efficacy of SERMs on male infertility, specifically pertaining to pregnancy rates and the effect of clomiphene citrate or tamoxifen on the pregnancy rate remains uncertain. Despite the derived outcomes, the off-label utilization of clomiphene citrate and tamoxifen prevails for individuals experiencing male infertility attributable to hypoandrogenism. To ascertain the role of clomiphene citrate or tamoxifen in addressing idiopathic male infertility with elevated assurance, a meticulously designed RCT, endowed with sufficient power and an ample sample size, is indispensably requisite.

Author contributions

Study concept and design: Shadi Khashaba, Shehab Khashaba.
Data acquisition: Anil Krishan, Angus Bruce, Abdullatif Almaghlouth.
Data analysis: Anil Krishan, Angus Bruce, Abdullatif Almaghlouth.
Drafting of manuscript: Shehab Khashaba, Jason Huang, Halsie Donaldson.
Critical revision of the manuscript: Shadi Khashaba, Jason Huang, Mahmoud Mima, Craig Niederberger.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2024.09.001.

References

[1] Harris E. Infertility affects 1 in 6 people globally. JAMA 2023; 329:1443. https://doi.org/10.1001/jama.2023.6251.
[2] Agarwal A, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the globe. Reprod Biol Endocrinol 2015;13:37. https://doi.org/10.1186/s12958-015-0032-1.
[3] Valenti D, La Vignera S, Condorelli RA, Rago R, Barone N, Vicari E, et al. Follicle-stimulating hormone treatment in normogonadotropic infertile men. Nat Rev Urol 2013;10: 55—62.
[4] Siddiq FM, Sigman M. A new look at the medical management of infertility. Urol Clin 2002;29:949—63.
[5] Corradi PF, Corradi RB, Greene LW. Physiology of the hypothalamic pituitary gonadal axis in the male. Urol Clin 2016;43: 151—62.
[6] Wetsel WC, Valença MM, Merchenthaler I, Liposits Z, López FJ, Weiner RI, et al. Intrinsic pulsatile secretory activity of immortalized luteinizing hormone-releasing hormone-secreting neurons. Proc Natl Acad Sci U S A 1992;89:4149—53.
[7] Bilezikjian LM, Blount AL, Leal AM, Donaldson CJ, Fischer WH, Vale WW. Autocrine/paracrine regulation of pituitary function by activin, inhibin and follistatin. Mol Cell Endocrinol 2004; 225:29—36.
[8] Mellinger RC, Thompson RJ. The effect of clomiphene citrate in male infertility. Fertil Steril 1966;17:94—103.
[9] Krause W, Holland-Moritz H, Schramm P. Treatment of idiopathic oligozoospermia with tamoxifen—a randomized controlled study. Int J Androl 1992;15:14—8.
[10] Rowe PJ, Comhaire FH, Hargreave TB, Mahmoud AMA; World Health Organization. WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge, United Kingdom: Cambridge University Press; 2000. p. 37—60.
[11] Smals AG, Pieters GF, Drayer JI, Boers GH, Benraad TJ, Kloppenborg PW. Tamoxifen suppresses gonadotropin-induced 17 alpha-hydroxyprogesterone accumulation in normal men. J Clin Endocrinol Metab 1980;51:1026—9.
[12] Herzog BJ, Nguyen HMT, Soubra A, Hellstrom WJG. Clomiphene citrate for male hypogonadism and infertility: an updated review. Androg Clin Res Ther 2020;1:62—9.
[13] Huijben M, Huijsmans RLN, Lock MTWT, de Kemp VF, de Kort LMO, van Breda JHMK. Clomiphene citrate for male infertility: a systematic review and meta-analysis. Andrology 2023;11:987—96.
[14] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700. https://doi.org/10.1136/bmj.b2700.
[15] Mićić S, Dotlić R. Evaluation of sperm parameters in clinical trial with clomiphene citrate of oligospermic men. J Urol 1985;133:221—2.
[16] Rönnberg L. The effect of clomiphene citrate on different sperm parameters and serum hormone levels in preselected infertile men: a controlled double-blind cross-over study. Int J Androl 1980;3:479—86.
[17] Soares AH, Horie NC, Chiang LAP, Caramelli B, Matheus MG, Campos AH, et al. Effects of clomiphene citrate on male obesity-associated hypogonadism: a randomized, double-blind, placebo-controlled study. Int J Obes 2018;42:953—63.
[18] Sokol RZ, Steiner BS, Bustillo M, Petersen G, Swerdloff RS. A controlled comparison of the efficacy of clomiphene citrate in male infertility. Fertil Steril 1988;49:865—70.
[19] Srivannaboon S, Dhall GI, De Krester DM, Hargreave TB, Comhaire FH, Padron RS, et al. A double-blind trial of clomiphene citrate for the treatment of idiopathic male infertility. Int J Androl 1992;15:299—307.
[20] Adamopoulos DA, Nicopoulou S, Kapolla N, Karamertzanis M, Andreou E. The combination of testosterone undecanoate with tamoxifen citrate enhances the effects of each agent given independently on seminal parameters in men with idiopathic oligozoospermia. Fertil Steril 1997;67:756—62.

[21] AinMelk Y, Belisle S, Carmel M, Jean-Pierre T. Tamoxifen citrate therapy in male infertility. Fertil Steril 1987;48:113—7.
[22] Boonyarangkul A, Vinayanuvattikhun N, Chiamchanya C, Visutakul P. Comparative study of the effects of tamoxifen citrate and folate on semen quality of the infertile male with semen abnormality. J Med Assoc Thai 2015;98:1057—63.
[23] Iacono F, Prezioso D. Treating idiopathic male infertility with a combination of tamoxifen citrate and a natural compost with antioxidant and androgen-mimetic action. J Steroids Horm Sci 2013;S5. https://doi.org/10.4172/2157-7536.S5-002.
[24] Cocuzza M, Agarwal A. Nonsurgical treatment of male infertility: specific and empiric therapy. Biologics 2007;1:259—69.
[25] Kumar R, Gautam G, Gupta NP. Drug therapy for idiopathic male infertility: rationale versus evidence. J Urol 2006;176(4 Pt 1):1307—12. https://doi.org/10.1016/j.juro.2006.06.006.
[26] Lo EM, Rodriguez KM, Pastuszak AW, Khera M. Alternatives to testosterone therapy: a review. Sex Med Rev 2018;6:106—13.
[27] Cannarella R, Condorelli RA, Mongioì LM, Barbagallo F, Calogero AE, La Vignera S. Effects of the selective estrogen receptor modulators for the treatment of male infertility: a systematic review and meta-analysis. Expet Opin Pharmacother 2019;20:1517—25.
[28] Boitrelle F, Shah R, Saleh R, Henkel R, Kandil H, Chung E, et al. The sixth edition of the WHO manual for human semen analysis: a critical review and SWOT analysis. Life 2021;11:1368. https://doi.org/10.3390/life11121368.
[29] Rothmann SA, Bort AM. Sperm morphology. In: Skinner MK, editor. Encyclopedia of reproduction. 2nd ed. Waltham, MA, USA: Elsevier Inc; 2018. p. 85—95.
[30] Lewis SEM. Is sperm evaluation useful in predicting human fertility? Reproduction 2007;134:31—40.
[31] Sikka SC, Hellstrom WJ. Current updates on laboratory techniques for the diagnosis of male reproductive failure. Asian J Androl 2016;18:392—401.
[32] Wibowo E, Pollock PA, Hollis N, Wassersug RJ. Tamoxifen in men: a review of adverse events. Andrology 2016;4:776—88.