Effect of sildenafil citrate in women undergoing assisted reproduction: a meta-analysis based on randomized controlled trials

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Research

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Abstract

Background

to evaluate whether the sildenafil citrate in women undergoing assisted reproduction ameliorate the clinical outcomes.

Methods

We performed a comprehensive literature search for published randomized controlled trials (RCT) in Medline, Embase, Scopus, Web of Science and Cochrane Central Register of Controlled Trials from inception to 25 Jun 2020. Literature screening, selection of relevant studies, assessment risk of bias and data extraction was conducted independently by two reviewers. We combined study data using the random-effects model.

Results

Sixteen trials including 1,589 women (771 cases and 818 controls) were included in meta-analysis. Pooling results from five trials, which compared clinical pregnancy between sildenafil citrate and placebo, showed a significantly higher probability of clinical pregnancy in sildenafil citrate group (RR: 1.57, 95% CI: 1.05, 2.36, I^2 = 0%). The probability of clinical pregnancy was significantly higher in women who received the combination of sildenafil citrate and clomiphene citrate compared with clomiphene citrate alone (RR: 1.31, 95% CI: 1.12, 1.53, I^2 = 0%). Following the intervention, clinical pregnancy significantly increased in women who received the combination of estradiol valerate and sildenafil citrate compared to estradiol valerate (RR: 1.59, 95% CI: 1.05, 2.43, I^2 = 0%). Following the intervention, endometrial thickness (ET) increased in women who received sildenafil citrate compared to women who received placebo (SMD: 1.32, 95% CI: 0.30, 2.34, I^2 = 92.41%). The mean of ET was significantly higher in women who received the combination of sildenafil citrate and clomiphene citrate compared to women who received clomiphene citrate (SMD: 0.92, 95% CI: 0.49, 1.36).

Conclusion

Our systematic review and meta-analysis showed that luteal supplementation of sildenafil citrate (oral or vaginal), alone or adjuvant therapy can be used for improving the EM and clinical pregnancy rate in women undergoing assisted reproduction. However, given the methodological limitations the current evidence does not support its use in clinical practice yet.

Background

According to the reports from the national survey of family growth, the prevalence of infertility among the men and women aged 15–44 years is about 6.4% [1, 2]. Advanced technologies to overcome infertility like assisted reproductive technologies (ART) has increased worldwide and significant progress has been made, but, still, there are complex problems in understanding the implantation process and improving the outcomes of ART. A study published by word health organization (WHO) at the end of 2012, has shown that the total infertility rate in women from 190 countries was similar in comparison to levels and trends from 1990 to 2010 [3]. So since the embryo implantation and pregnancy rate remains low globally we still need further studies on existing interventions and treatments to improve the outcomes of ART[4]. One of the most vulnerable and complicated concepts in ART is implantation [5]. Because it depends on several local and systemic factors such as immunologic mediators and hormonal signals [6]. Before the implantation, on one hand, the embryo should secret factors that can stimulate the implantation site and on the other hand, the decidua should secrete factors that stimulate embryonic differentiation and early development [7, 8]. It is very critical for normal embryo implantation that the endometrial receptivity and embryonic competence follow a timely synchronized pattern and the mentioned mediators should act in a normal range and at the right time [9]. So, adequate endometrial growth is considered essential for successful implantation, although factors affecting the growth of endometrium are still not well understood [10]. Recently the majority of studies has focused on the angiogenesis and vascularization within the endometrium and found that a poor uterine receptivity in women with thin endometrium may be due to the impairment of blood flow impedance through the endometrium [11]. During the last decade various strategies have been studied to try increase the ET in poor endometrial responders [12–16]. Sildenafil citrate (Viagra) has been one of the most studied agents in previous clinical trials, aimed to evaluate its potential role in increasing

ART success rate due to its antithrombotic and vasodilatory effects. Several studies have been conducted and there is growing evidence that sildenafil citrate may positively affect the outcomes of ART, and, up to now, 16 trials have been conducted to evaluate the effect of it on the clinical outcomes of ART, but there is still no definitive conclusion, and previous reviews have failed to provide robust evidence [17]. Given the considerable controversy regarding the efficacy of sildenafil citrate and serious consequences of infertility, in this systematic review and meta-analysis, we evaluated the effect of sildenafil citrate on clinical outcomes of ART.

Materials And Methods

Main aim

This study addressed the efficacy of sildenafil citrate alone or in combination with other treatments compared with control (other treatments, placebo or nothing) in subfertile women for improving clinical outcome after assisted reproduction.

Data sources and search strategy

Potential studies were identified by conducting a systematic search using Medline, Embase, Scopus, Web of Science and Cochrane Central Register of Controlled Trials (from inception to 25 Jun 2020). In addition, reference and the citation lists of published articles were hand-searched in order to identify additional eligible studies. Search terms included: ("in Vitro Fertilization" OR "IVF" OR "intracytoplasmic sperm injection" OR "ICSI" OR "Embryo Transfer" AND "Sildenafil Citrate" OR "Citrate, Sildenafil" OR "Sildenafil" OR "Homosildenafil" OR "Hydroxyhomosildenafil" OR "Revatio" OR "Viagra" OR "Acetildenafil" OR "Sildenafil Lactate"). Full details of the search strategy used terms and database-specific indexing terminology are provided in supplementary file 1. There were no limits on language and year of publication.

Eligibility criteria

Studies were considered in our review if they fulfilled the following criteria: (□) the study was a RCT in parallel or crossover design, (□) the intervention was administration of sildenafil citrate vaginal or orally or combination of sildenafil citrate and other treatments, (□) the control group was any other active intervention, no intervention or placebo, (□) the outcomes of interest were ET or pregnancy endpoints (live birth, clinical pregnancy, chemical pregnancy and miscarriage) and, (□) the population of interest was subfertile women, undergoing assisted reproduction, with any ovarian stimulation protocol. Studies were excluded if those were (□) case-control, case series, cross-sectional, (□) animal or cell culture studies, (□) did not report adequate details of study methodology or results, and (□) presented only as abstracts, conference paper, letters to the editor and editorials.

Study selection, data extraction, and quality appraisal

Two trained methodological reviewers (M.S. and M.R.), with enormous experience in conducting systematic reviews and meta-analysis, scrutinized the retrieved articles based on predefined eligibility criteria. Any disagreement resolved by discussion with third reviewer (S.R.). The following data were extracted from each eligible study and cross-checked by two reviewers (M.R. and A.A.): first author's name, year, the country where the study was conducted, study design, number of participants, type and duration of treatment. The methodological quality of trials assessed by Cochrane risk of bias tool.

Statistical analysis

The effect size for clinical and chemical pregnancy were measured as the risk ratios (RRs) with corresponding 95% confidence intervals (CIs) obtained by Mantel-Hansel method. The effect size for ET was measured as the standardized mean difference (SMDs) with corresponding 95% CIs obtained by inverse variance method. Data were combined using the random-effects model. Heterogeneity of the studies was assessed graphically with forest plots and statistically by chi-square-based Q statistic and I^2 value. Heterogeneity was considered significant at a P-value of < 0.10 in Q-test or $I^2 > 40\%$. Statistical analyses were performed using STATA software (Version 16.0) (STATA Corp, College Station, Texas). Subgroup analyses were used to identify the effect of sildenafil citrate administration on ART outcomes considering relevant study characteristics (Intervention type (sildenafil citrate alone, sildenafil citrate in combination with clomiphene citrate, sildenafil citrate in combination with estradiol valerate), population type (recurrent implantation failure (RIF), other type of infertility), control type (placebo, clomiphene citrate, estradiol valerate) as possible sources of heterogeneity.

Results

Summary of the literature search

The initial search yielded 872 publications. Finally after reading the full text of retrieved articles (24 studies), eight studies excluded and eight eligible trials were included in meta-analysis. Four were non-RCT; one didn't report our desired outcomes; one was repetitive; one study had a different population and one didn't provide sufficient data, thus leaving eight RCTs to be included in the meta-analysis (Fig. 1).

Study characteristics

Trials were conducted between 2010 and 2020, of which 11 trials were published after 2016. The trials were conducted in Iran (4 trials) [18–21], Egypt (7 trial) [22–28], India (3 trials)[29–31], Korea (1 trial)[32], and one in Russia [33]. All trials were parallel. Six studies compared sildenafil citrate with placebo, five studies compared combination of sildenafil citrate and clomiphene citrate with clomiphene citrate and five studies compared combination of sildenafil citrate and estradiol valerate with estradiol valerate. The study population of seven trials were women with RIF and the study population of remaining studies were other type of infertility such as women with thin endometrium or women with unexplained infertility. The sample size ranged from 44 to 517 participants (Table 1).

Table 1
Study characteristics

Study	Country	Study design	Population	Sample size		Intervention(s)	Control	Outcome Measures
				Case	Control			
Moini, 2020	Iran	Randomized Clinical trial	Women had normal ovarian reserve with at least two prior consecutive failed IVF/ICSI attempts with at least a transfer of two good quality fresh or frozen-thawed embryos	22	22	Sildenafil (vaginal suppositories, 100 mg/day, were administered from the first day of the FSH injection until the day of oocyte retrieval.	Placebo (vaginal suppositories)	Chemical pregnancy, Clinical pregnancy, Miscarriage, Endometrial thickness Implantation Rate,
Mekled, 2017	Egypt	Randomized Clinical trial	Women have experienced two or more implantation failure attributed to inadequate endometrial development. Age 20–40 years, (BMI):20–29	40	40	Oral sildenafil citrate at dose 25 mg tab /6 h daily from day six of induction of ovulation until day of HCG administration	Nothing	Endometrial thickness
Tehraninejad, 2017	Iran	Randomized Clinical trial	Women who had previously at least two IVF failure attempts and women aged below 45 years of age.	36	36	100 mg vaginal sildenafil suppositories daily, starting on day 3 of menstruation	Routine medication for frozen thawed cycle	Clinical pregnancy
Ataalla, 2016	Egypt	Randomized Clinical trial	Patients with previous low response to controlled ovarian hyper stimulation using antagonist protocol.	30	30	Sildenafil 50 mg/day orally	Placebo 50 mg/day orally	Chemical pregnancy, Clinical pregnancy, Endometrial thickness Implantation Rate,
Wafa, 2019	Egypt	Randomized Clinical trial	Women have experienced two or more implantation failure attributed to inadequate endometrial development, Age 18–35 years.	35	35	Sildenafil 25 mg orally twice daily	Nothing	Clinical pregnancy
Kortam, 2018	Egypt	Randomized Clinical trial	Unexplained infertility, 18–35 years.	45	45	CC100mg/d from 2nd to 6th day of cycle, oral sildenafil citrate 25 mg every 8 h from 2nd day of the cycle	CC100mg/d from 2nd to 6th day of cycle	Chemical pregnancy,, Endometrial thickness

Study	Country	Study design	Population	Sample size		Intervention(s)	Control	Outcome Measures
				Case	Control			
Reddy, 2016	India	Randomized Clinical trial	Age less than 40 years and more than 18 years, Primary or Secondary infertility, with regular menstrual cycles, and normal semen parameters of the husband	40	40	CC100mg/d from 3nd to 7th day of cycle, oral sildenafil citrate Sildenafil (Viagra, Pfizer) 25 mg twice daily was given from Day 8 up to ovulation trigger.	CC100mg/d from 3nd to 7th day of cycle	Chemical pregnancy,, Endometrial thickness
Fahmy, 2015	Egypt	Randomized Clinical trial	Women aged between 18 and 40 years with primary or secondary infertility and with regular menstrual cycles.	35	35	Clomiphene citrate (CC) 50 mg orally 3times/day from 3rd to 7th day of the cycle with sildenafil citrate 25 mg (Viagra, Pfizer) orally 3times/day from	Clomiphene citrate (CC) 50 mg orally 3times/day from 3rd to 7th day of the cycle	Chemical pregnancy,, Endometrial thickness
Ashoush, 2019	Egypt	Randomized Clinical trial	PCOS women, aged 21–35 years, With clomiphene failure	239	278	Clomiphene citrate 50 mg, on the 2nd day of the menstrual cycle for 5 days for a maximum of six induction cycles.25 mg of sildenafil citrate orally every 6 hours till the end of the cycle	Clomiphene citrate 50 mg, on the 2nd day of the menstrual cycle for 5 days for a maximum of six induction cycles	Clinical pregnancy,, Endometrial thickness
Aboelroose, 2020	Egypt	Randomized Clinical trial	Infertile women with primary or secondary infertility aged 18–40 years	40	40	100 mg clomiphene citrate in tablet form orally once daily from days 3–7 of the cycle and 25 mg sildenafil citrate orally twice daily from days 8–12 of the same cycle.	100 mg clomiphene citrate in tablet form orally once daily from days 3–7 of the cycle	Clinical pregnancy,, Endometrial thickness
Yavangi, 2019	Iran	Randomized Clinical trial	Infertile women with primary or secondary infertility	35	35	25 mg vaginal sildenafil four times a day + 6 mg E2 from the second or third day of the cycle	6 mg E2 from the second or third day of the cycle	Chemical pregnancy

Study	Country	Study design	Population	Sample size		Intervention(s)	Control	Outcome Measures
				Case	Control			
Vardhan, 2019	India	Randomized Clinical trial	Infertile women with primary or secondary infertility	40	40	From the first day to the fourth day, 2 mg estradiol Valerate tablets, and from the 5th to the 8th day, 4 mg estradiol tablets, and from the 9th to the 12th day of the menstrual cycle, 6 mg estradiol Valerate and sildenafil citrate tablets orally 25 mg TDS daily from day 1 of the cycle until the 12th day.	From the first day to the fourth day, 2 mg estradiol Valerate tablets, and from the 5th to the 8th day, 4 mg estradiol tablets, and from the 9th to the 12th day of the menstrual cycle, 6 mg estradiol Valerate	Chemical pregnancy, Clinical pregnancy, Endometrial thickness
Mangal, 2019	India	Randomized Clinical trial	Infertile women with primary or secondary infertility	50	50	Sildenafil citrate 25 mg vaginally every 6 hours for 5 days from day 8th of the cycle and tablet estradiol Valerate 2 mg 6–8 hourly	Tablet estradiol valerate 2 mg 6–8 hourly	Clinical pregnancy, Endometrial thickness
Firouzabadi, 2013	Iran	Randomized Clinical trial	Infertile women with primary or secondary infertility	40	40	First to the fourth day of the menstrual cycle, 2 mg estradiol valerat tablets, from the 5th to the 8th day of the menstrual cycle, 4 mg estradiol valerat tablets, and from the 9th to the 12th day of the menstrual, 6 mg estradiol valerat tablets were given daily and sildenafil citrate tablets (50 mg) daily	First to the fourth day of the menstrual cycle, 2 mg estradiol valerate tablets, from the 5th to the 8th day of the menstrual cycle, 4 mg estradiol valerat tablets, and from the 9th to the 12th day of the menstrual, 6 mg estradiol valerat tablets were given daily.	Clinical pregnancy, Endometrial thickness

Study	Country	Study design	Population	Sample size		Intervention(s)	Control	Outcome Measures
				Case	Control			
Alieva, 2012	Russia	Randomized Clinical trial	Women with tubal infertility who had undergone at least 2 unsuccessful IVF and embryo transfer attempts when transferred embryos were of high quality and disturbances in uterine hemodynamics were present	23	25	Sildenafil citrate in the IVF cycle	Nothing	Clinical pregnancy, Endometrial thickness
Kim, 2010	Korea	Randomized Clinical trial	Women with a thin endometrium (< 8 mm: range 5 to 7.9 mm) at the time of embryo transfer undergoing IVF	21	27	Vaginal sildenafil 25 mg/d + oral estradiol valerate 4 mg/d from Day of embryo transfer until pregnancy test (11 days)	Nothing	Clinical pregnancy

Risk of bias assessment

The summary of risk of bias assessments was shown in supplementary file 2. All the trials except seven were judged to be at low risk of bias for random allocation. The random allocation was unclear in seven studies. Allocation concealment was judged to be at low risk of bias for five trials but the concealment in half of trials (8 trials) assessed at high risk of bias. Six of trials assessed to be at high risk for performance bias and blinding of participants and personnel was unclear in four trials. All of trials except seven reported an appropriate blinding of outcome assessment and blinding of outcome assessment was unclear in seven trials. Four trials were judged to be at high risk of bias for attrition bias. Eight trials were judged to be unclear for reporting bias. One trial were judged to be at unclear risk for other bias.

Chemical pregnancy

Chemical pregnancy data were obtained from nine included trials with a total of 644 participants (322 cases and 322 controls). Three trials compared the sildenafil citrate with placebo (87 cases and 87 controls), three trials compared the combination of sildenafil citrate and clomiphene citrate with clomiphene citrate (120 cases and 120 controls) and three trials compared combination of estradiol valerate and sildenafil citrate with estradiol valerate (115 cases and 115 controls). The random effects forest plot for all included trials that compared sildenafil citrate with placebo showed a significant improvement in chemical pregnancy with sildenafil citrate intervention group versus control group (RR = 2.08, 95% CI: 1.22, 3.54, I^2 = 0%). Also a significant difference was observed in the subset of trials that compared the combination of sildenafil citrate and clomiphene citrate with clomiphene citrate (RR = 1.58, 95% CI: 1.17, 2.14, I^2 = 0%), but there was no difference in the subset of trials that compared the combination of estradiol valerate and sildenafil citrate with estradiol valerate (RR = 1.31, 95% CI: 0.86, 1.98, I^2 = 0%) (Fig. 2). The effect size was stronger in the subset of trials that administered sildenafil citrate in patients with RIF (n = 3, RR: 2.08, 95% CI: 1.22, 3.54, I^2 = 0%), rather those administered it in patients with other type of infertility (n = 6, RR: 1.48, 95% CI: 1.16, 1.89, I^2 = 0%) (Fig. 3). There was no evidence of publication bias in this regard (Egger's regression intercept: 0.12, 95%CI: -2.24, 2.48, P = 0.91). Sensitivity analysis showed that the estimates of the pooled RR range from 1.50 (95% CI: 1.18, 1.90) to 1.69 (95% CI: 1.33, 2.15), suggesting that no one study is substantially influencing the pooled estimate.

Clinical pregnancy rate

Clinical pregnancy data were obtained from 11 included trials with a total of 1,904 participants (1,129 cases and 775 controls). Five trials compared the sildenafil citrate with placebo (153 cases and 153 controls), two trials compared the combination of sildenafil citrate and clomiphene citrate with clomiphene citrate (465 cases and 465 controls) and four trials compared the combination of estradiol valerate and sildenafil citrate with estradiol valerate (151 cases and 157 controls). Pooling results from five trials, which compared clinical pregnancy between sildenafil citrate and placebo, showed a significantly higher probability of clinical pregnancy in sildenafil citrate group (RR: 1.57, 95% CI: 1.05, 2.36, I^2 = 0%). The probability of clinical pregnancy was significantly higher in women who received the combination of sildenafil citrate and clomiphene citrate compared with clomiphene citrate alone (RR: 1.31, 95% CI: 1.12, 1.53, I^2 = 0%). Following the intervention, clinical pregnancy significantly increased in women who received the combination of estradiol valerate and sildenafil citrate compared to estradiol valerate (RR: 1.59, 95% CI: 1.05, 2.43, I^2 = 0%) (Fig. 4). The effect size was stronger in the subset of trials that administered sildenafil citrate in patients with RIF (n = 6, RR: 1.63, 95% CI: 1.13, 2.33, I^2 = 0%), rather those administered it in patients with other type of infertility (n = 5, RR: 1.32, 95% CI: 1.14, 1.54, I^2 = 0%) (Fig. 5). There was no evidence of publication bias in this regard (Egger's regression intercept: 0.85, 95%CI: -0.33, 2.04, P = 0.13). Sensitivity analysis showed that the estimates of the pooled RR range from 1.33 (95% CI: 1.15, 1.53) to 1.59 (95% CI: 1.24, 2.03), suggesting that no one study is substantially influencing the pooled estimate.

Endometrial thickness

Changes in ET following sildenafil citrate administration were examined in six trials (212 cases and 212 controls). Four trials compared the sildenafil citrate with placebo (127 cases and 127 controls), one trial compared the combination of sildenafil citrate and clomiphene citrate with clomiphene citrate (45 cases and 45 controls) and one trial compared the combination of estradiol valerate and sildenafil citrate with estradiol valerate (40 cases and 40 controls). Following the intervention, ET increased in women who received sildenafil citrate compared to women who received placebo (SMD: 1.32, 95% CI: 0.30, 2.34, I^2 = 92.41%). The mean of ET was significantly higher in women who received the combination of sildenafil citrate and Clomiphene Citrate compared to women who received Clomiphene Citrate (SMD: 0.92, 95% CI: 0.49, 1.36). There was no difference between women who received the combination of estradiol valerate and sildenafil citrate compared to women who received estradiol valerate (SMD: 0, 95% CI: -0.43, 0.43) (Fig. 6). The SMD was significant in the subset of trials that administered sildenafil citrate in patients with RIF (n = 4, SMD: 1.32, 95% CI: 0.30, 2.34, I^2 = 92.41%), but non-significant in those administered it in patients with other type of infertility (n = 2, SMD: 0.46, 95% CI: -0.18, 1.10, I^2 = 77.21%) (Fig. 7). There was no evidence of publication bias in this regard (Egger's regression intercept: 12.16, 95%CI: -10.76, 35.08, P = 0.21). Sensitivity analysis showed that the estimates of the pooled SMD range from 0.67 (95% CI: 0.44, 0.89) to 1.12 (95% CI: 0.88, 1.36), suggesting that no one study is substantially influencing the pooled estimate.

Discussion

At the present systematic review and meta-analysis, we included 16 RCTs investigated the effect of sildenafil citrate alone or in combination with other active treatments for 1,589 subfertile women undergoing assisted reproduction. The overall results showing that sildenafil citrate administration alone can increase chemical pregnancy, clinical pregnancy and ET compared to the control group. Also, the combination of sildenafil citrate with other active treatment such as clomiphene citrate and estradiol valerate can improve chemical pregnancy, clinical pregnancy and ET. Considering poor methodological quality of included trials, our findings should be interpreted with caution. The results of subgroup analysis showed that the highest increase in chemical and clinical pregnancy rates was in the subgroup of women with RIF compared to the women with other types of infertility. Some trials included infertile women with a thin endometrium or women with unexplained infertility. Since the causes of infertility were various in included studies and due to the small number of studies it was not possible to perform accurate sub-group analysis. Therefore, the results of this subgroup analysis should be interpreted with caution. We did not perform sub-group analysis considering other possible source of heterogeneity such as exact dose of sildenafil citrate, stage of the embryo at transfer, type of performed protocol, because the included studies did not report sufficient detail about their method. Even though we found a significant difference between women who received sildenafil citrate and women who received placebo, evidence for the thickened endometrium was of very low quality, and low precision and high heterogeneity. Last, we found no clear evidence to suggest differences between groups for live birth and side effects regarding no study reported these outcomes.

Before our study, several systematic review and meta-analysis have studied the efficacy of different treatments (gonadotrophin-releasing hormone (GnRH) agonist [34], aspirin [14], human chorionic gonadotrophin (hCG)[35], combination of pentoxifylline and vitamin E [36]) in endometrial preparation for women undergoing assisted reproduction. However, evidence is insufficient to perform a

particular protocol for endometrial preparation. We found only one systematic review and meta-analysis that evaluate the effectiveness and safety of vasodilators in women undergoing assisted reproduction. In this review six databases searched until Oct 2017, and finally 15 studies including 1,326 women included in meta-analysis. All included studies compared a vasodilator versus placebo or no treatment. Three included trials reported the effectiveness of sildenafil citrate. Two assessed sildenafil citrate alone versus placebo, and another the combination of sildenafil citrate and estradiol valerate versus no treatment. The meta-analysis of two studies that compared sildenafil citrate alone versus placebo showed no evidence of differences between two groups (RR: 1.47, 95%CI: 0.68, 3.20, I^2 = 0%). Similarly, the study that compared combination of sildenafil citrate and estradiol valerate showed no evidence of differences between two groups (RR: 1.84, 95%CI: 0.84, 4.01) [17]. In addition to these three clinical trials, we found 13 other trial that assessed the effectiveness of the sildenafil citrate alone or in combination with other active treatments. The largest clinical trial to date that compare the effectiveness of the combination of sildenafil citrate and clomiphene citrate with clomiphene citrate alone was a well-designed study that conducted in Egypt. A double-blinded RCT was conducted in Ain-Shams university women's hospital on 850 women with polycystic ovary syndrome and clomiphene failure. The sildenafil group developed higher ET (10.6 ± 1.3 vs 9.4 ± 1.5; $p < 0.001$), and probability of clinical pregnancy compared to clomiphene citrate (RR: 1.27, 95%CI: 1.07, 1.50) [27].

The accuracy of meta-analysis findings depend largely on the methodological quality and homogeneity of included studies. The methodological quality of included trials was relatively low, but low heterogeneity was found in the analysis of chemical and clinical pregnancy rate. Although high heterogeneity was found in the analysis of ET. Although we found no evidence of statistical heterogeneity in main outcomes among trials, we could not rule out the effects of clinical heterogeneity on study results. In most of the reviewed studies, the inclusion and exclusion criteria were well-defined, but a number of studies did not list the exact criteria. Additionally, the main cause of infertility and history of RIF or recurrent miscarriage in the women recruited were either not reported or not identical among the studies. The luteal phase support, endometrial preparation, and ovarian hyper-stimulation protocols used varied between the studies and were not reported in some of them. Also, the dose of sildenafil citrate, as an important factor influencing the effectiveness of administered drugs, is very different between the studies. Unfortunately, miscarriage rates, complications, adverse pregnancy outcomes, and side effects were not reported in most of the studies.

Clarifying the exact role and the action mechanism of sildenafil citrate in the process of implantation is complicated, but, several possible mechanisms have been proposed as following: (1) enhances the effect of nitric oxide by inhibiting phosphodiesterase 5 (PDE5), which is responsible for degradation of cyclic guanosine monophosphate (cGMP). With the use of sildenafil, cGMP remains elevated, which leads to vascular relaxation and increased blood flow to the endometrium, [37] (2) have an effect on vasoactive cytokines that regulate endometrial development or implantation, [21] (3) increases uterine receptivity by the development of spiral arteries and increasing uterine arterial blood flow, [38] (4) reduce natural killer cell activity in addition to the endometrial growth facilitating effect, [39] (5) stimulated the angiogenic responses of Vascular endothelial growth factor (VEGF), a signaling protein produced by the epithelial cells that promotes the growth of new blood vessels, contributes to angiogenesis and increased vascular permeability in the mid-secretory phase, which is necessary for successful implantation [40].

Several limitations existed in our review as following: first, most of the included trials had poor methodological quality with small sample sizes, which may influence internal validity, second, significant heterogeneity was found in some results, especially ET, however we did not perform sub-group analysis considering possible source of heterogeneity such as exact dose of sildenafil citrate, stage of the embryo at transfer, type of performed protocol, because the included studies did not report sufficient detail about their method, third, our meta-analysis was not registered, but our meta-analysis was done in strict accordance with the guidelines in the Cochrane Handbook for Systematic Reviews.

Conclusion

Our systematic review and meta-analysis showed that luteal supplementation of sildenafil citrate (oral or vaginal), alone or adjuvant therapy can be used for improving the EM and clinical pregnancy rate in women undergoing assisted reproduction. However, given the methodological limitations the current evidence does not support its use in clinical practice yet. Future high-quality RCT with large sample size to evaluate the sildenafil citrate effect in women undergoing assisted reproduction are needed. Future RCTs should focus on type of processing, stage of embryo, embryo quality, dosage, time of administration, type of control group, in order to identify the groups of patients who would benefit the most from this intervention and the most appropriate dosage, time, and type of sildenafil citrate which would have the most positive effect and the less possible side effects.

Abbreviations

ARTs: Assisted reproduction techniques; RCT: randomized controlled trials; CI: Confidence interval; ET: endometrial thickness; RR: risk ratio; SMD: Standardized mean difference; WHO: word health organization; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RIF: recurrent implantation failure; VEGF: Vascular endothelial growth factor, cGMP: cyclic guanosine monophosphate; PDE5: phosphodiesterase 5.

Declarations

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None.

Authors' contributions

SR, MR1, MR2, MS, and AN were involved in literature search and initial selection of studies and data extraction. SR and MR1 performed quality assessment of studies, data extraction, and statistical analysis. SR, MR1, MR2, MS, and SM were involved in interpretation of results. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

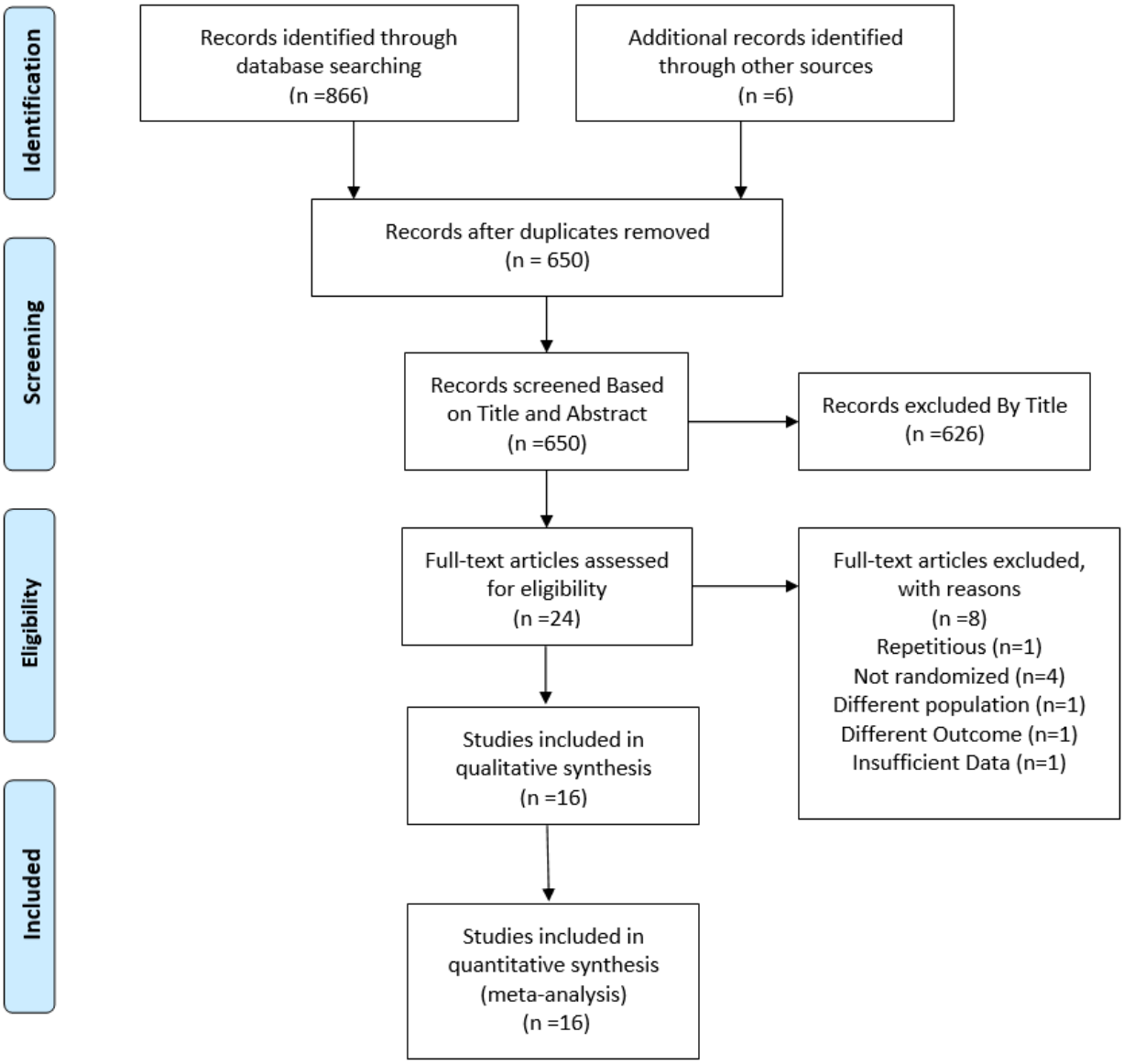

Figure 1

Flow diagram of study selection for the analysis.

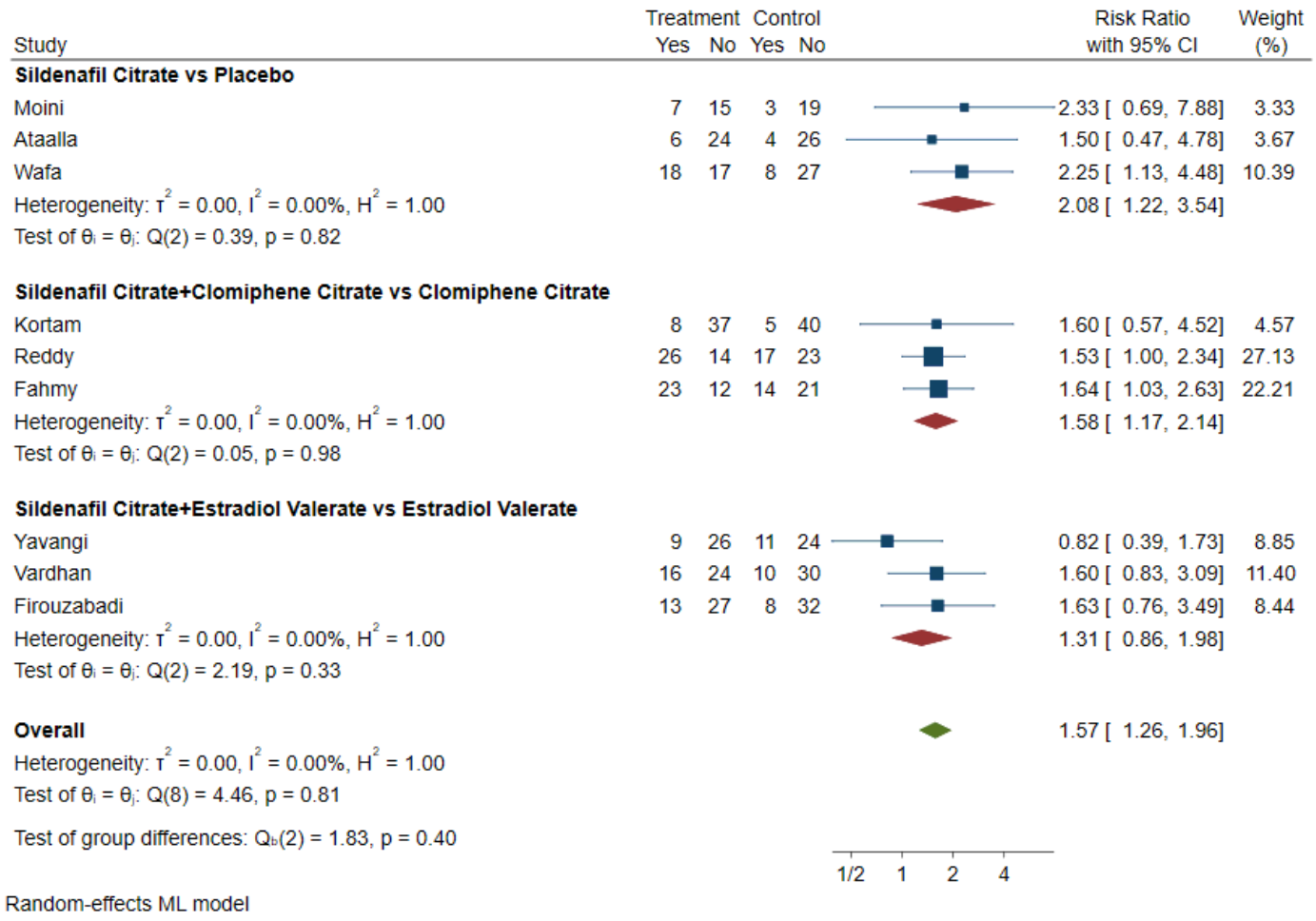

Figure 2

Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of chemical pregnancy in women who received sildenafil citrate versus control regarding intervention and control type.

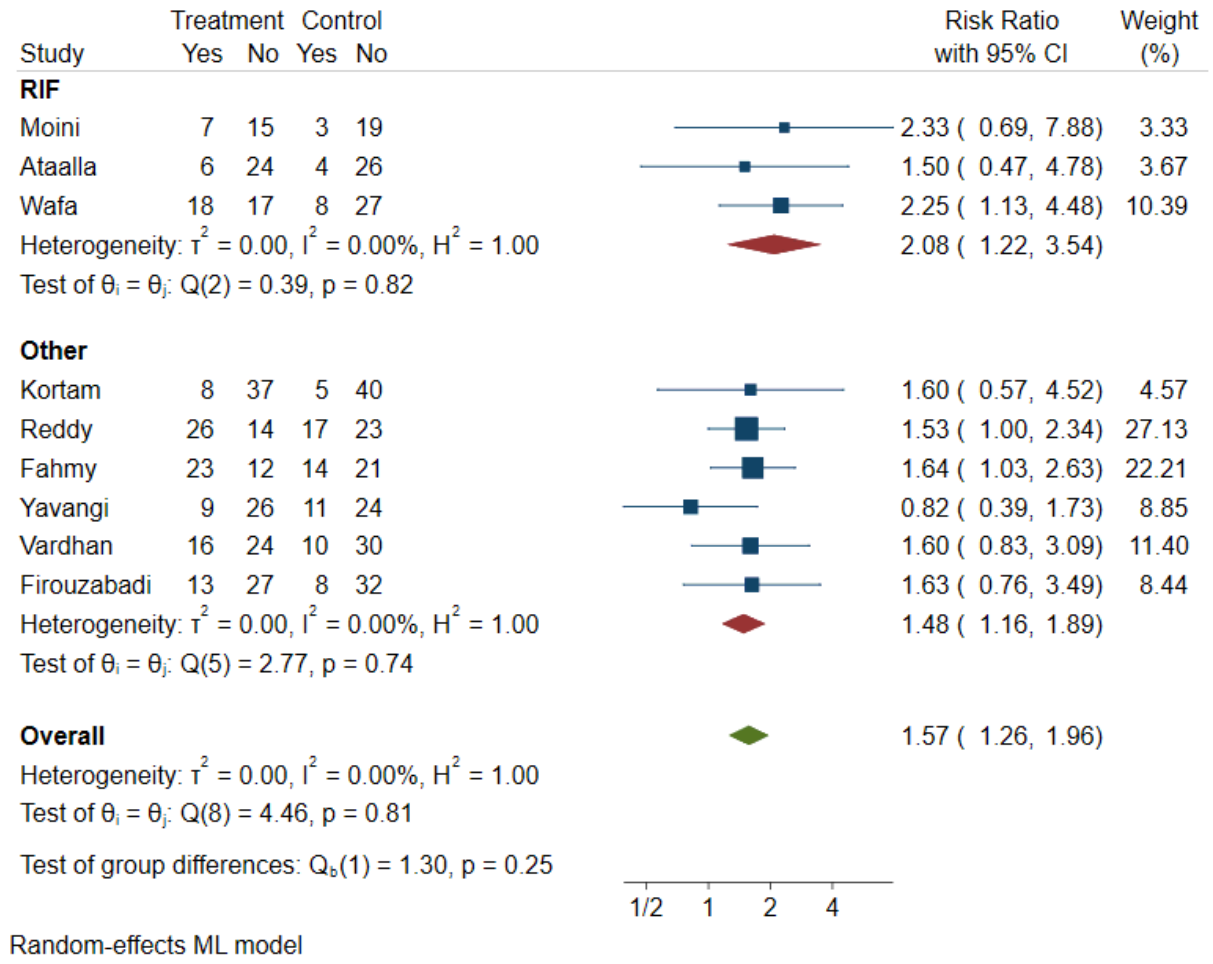

Figure 3

Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of chemical pregnancy in women who received sildenafil citrate versus control population type.

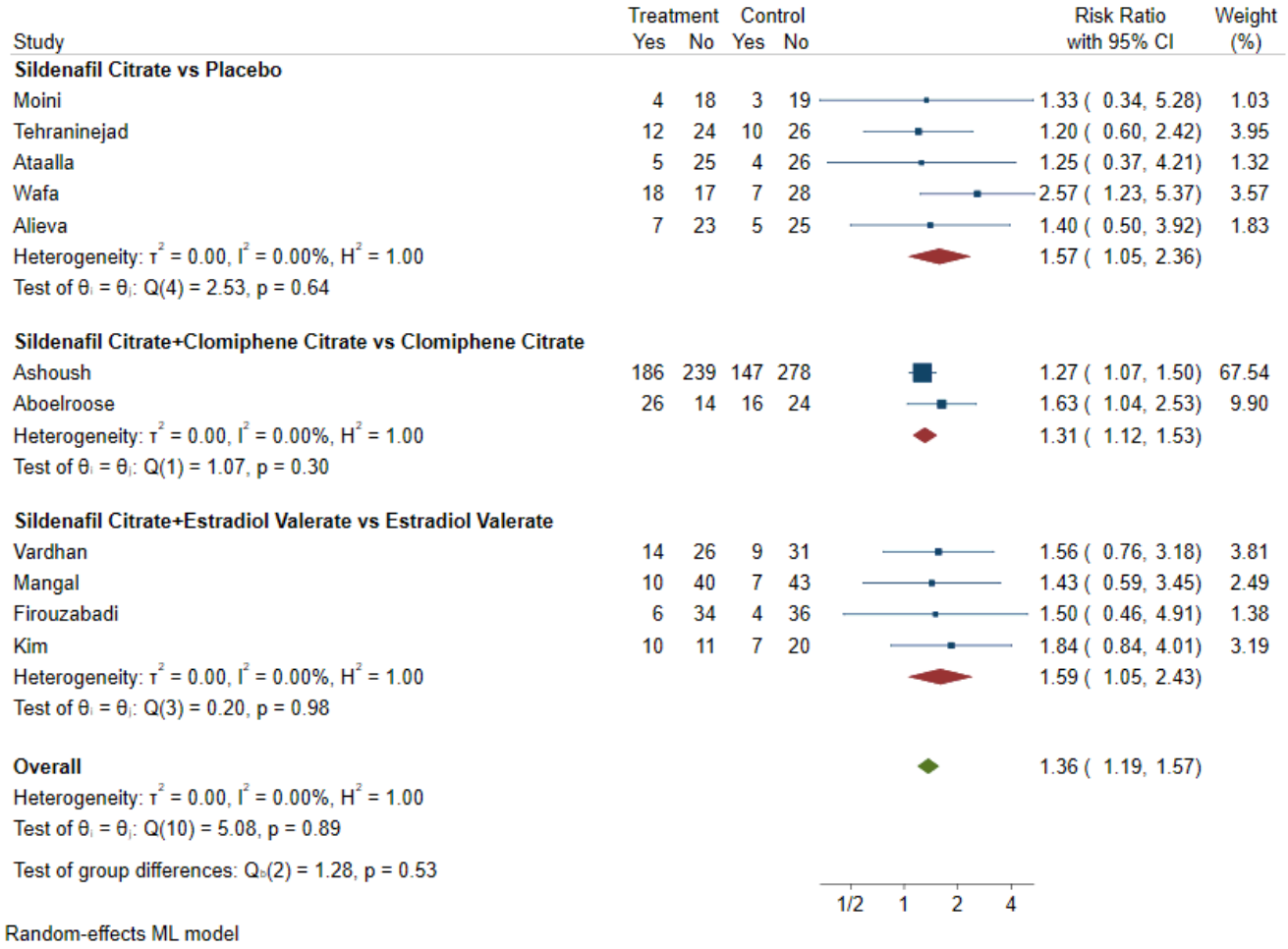

Figure 4

Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of clinical pregnancy in women who received sildenafil citrate versus control regarding intervention and control type.

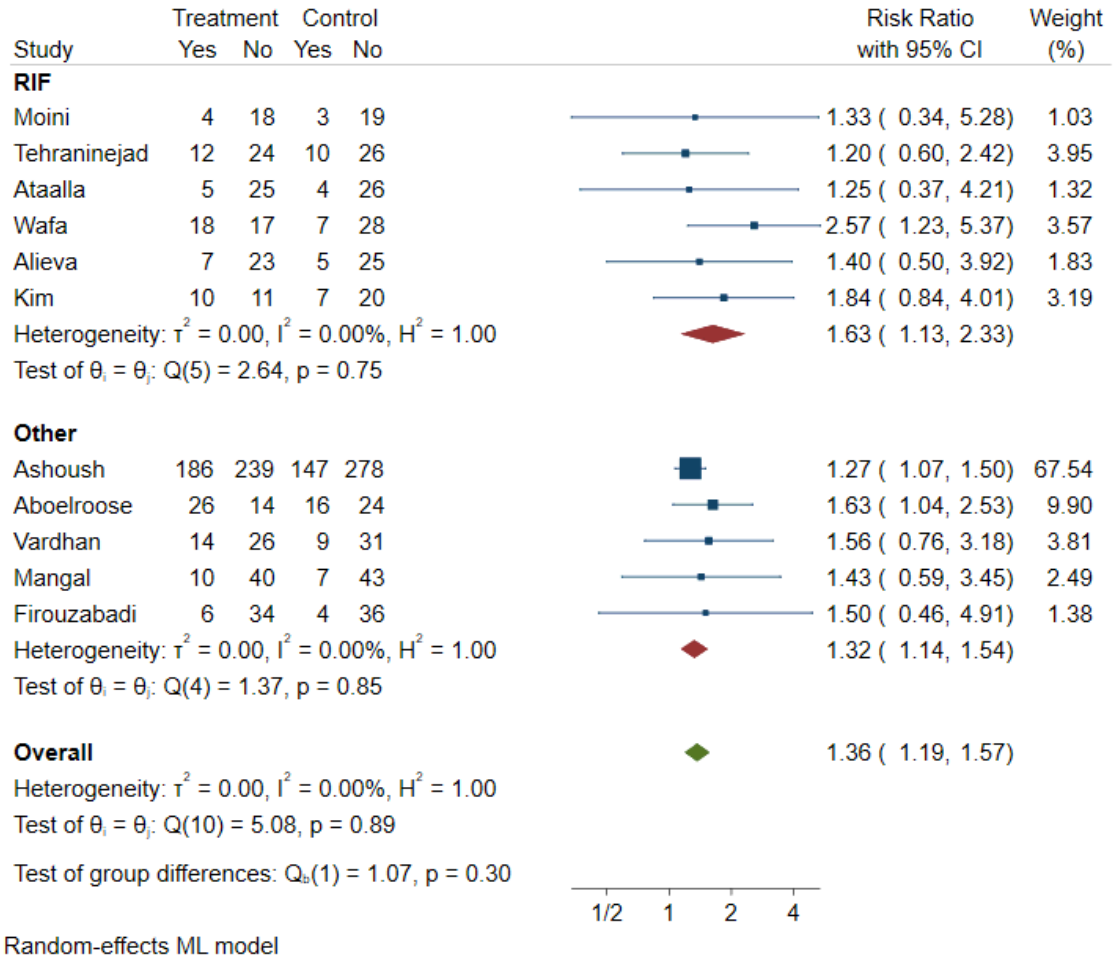

Figure 5

Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of clinical pregnancy in women who received sildenafil citrate versus control population type.

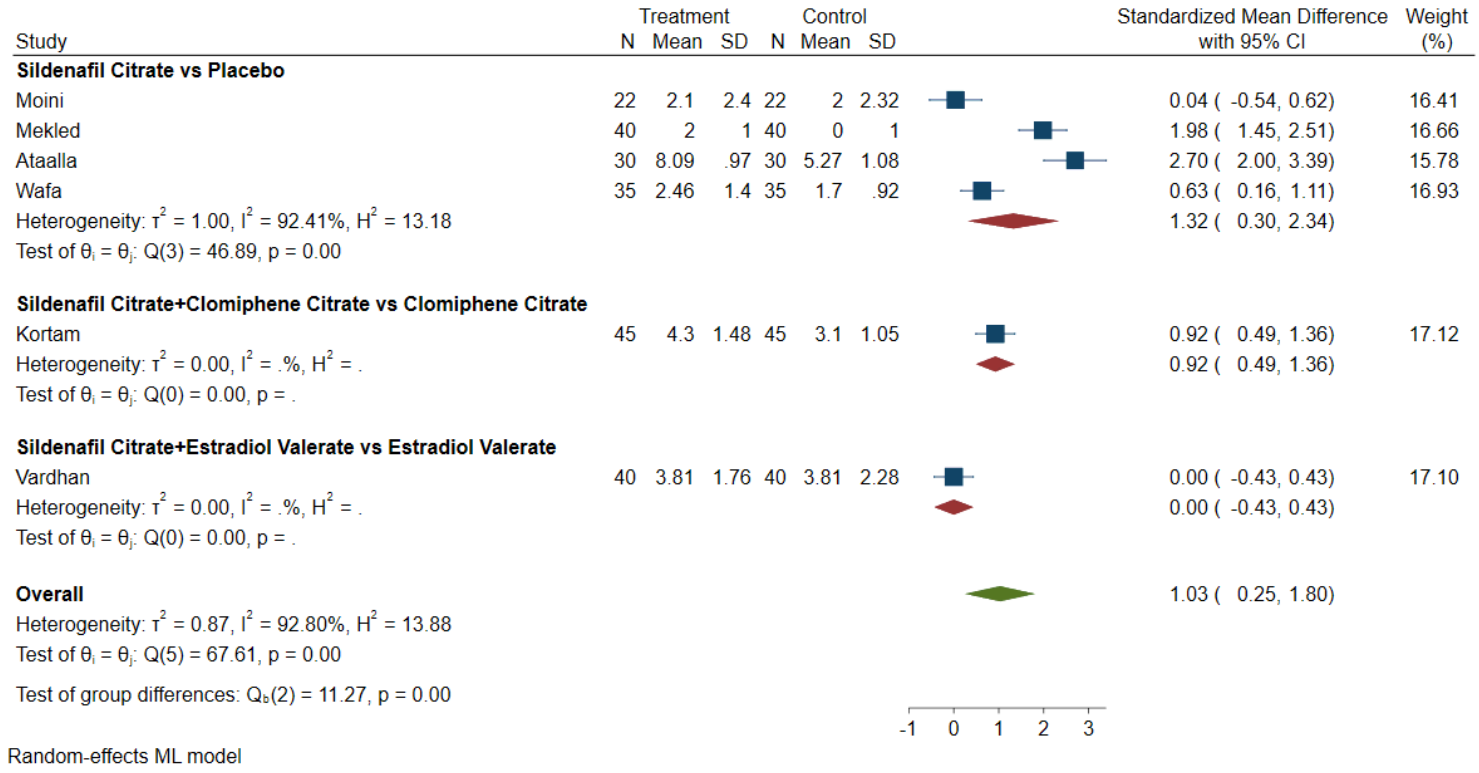

Figure 6

Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the mean of endometrial thickness in women who received sildenafil citrate versus control regarding intervention and control type.

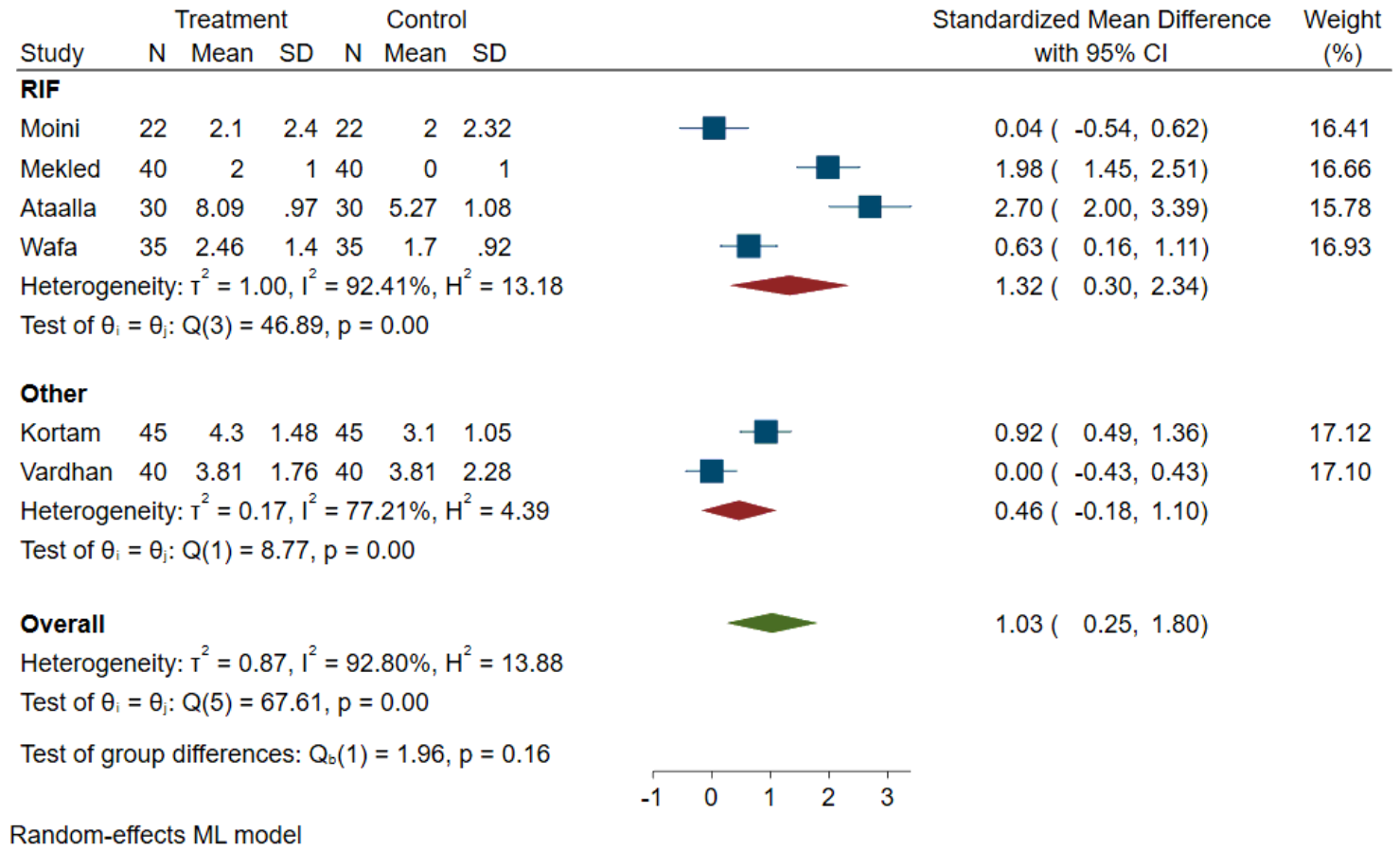

Figure 7

Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the mean of endometrial thickness in women who received sildenafil citrate versus control regarding population type.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile2.docx
- Supplementaryfile1.doc