Review / Derleme

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What is the effect of sildenafil citrate intake on women undergoing assisted reproduction? A systematic review and meta-analysis of randomized controlled trials

Sildenafil sitrat alımının yardımcı üreme teknikleri uygulanan kadınlar üzerinde etkisi nedir? Randomize kontrollü çalışmaların sistematik bir incelemesi ve meta-analizi

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Abstract

Assisted reproductive technologies (ART) have become a vital option for women facing fertility challenges. One of the potential interventions being explored is the use of sildenafil citrate (SC) to improve clinical outcomes in ART procedures. The aim of this study was to assess the impact of SC on clinical outcomes in women undergoing ART. A comprehensive literature search was conducted using multiple databases, including PubMed, Scopus, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. The search covered studies from inception until April 15, 2023, and identified relevant randomized controlled trials (RCTs) for inclusion in the analysis. The endpoints were summarized as risk ratio (RR) or standardized mean difference (SMD) with 95% confidence interval (CI). After meticulous analysis, twenty-eight RCTs comprising 3,426 women were included in the study. The results revealed significant findings regarding the impact of SC on clinical pregnancy (CP) rates. Women receiving SC demonstrated a significantly higher probability of CP compared to the control group (n=21 RCTs, RR=1.43; 95% CI: 1.29, 1.59). Additionally, when SC was combined with other medications like clomiphene citrate (CC) or estradiol valerate, it further improved the likelihood of CP compared to these medications alone (RR=1.35, 95% CI: 1.19, 1.53; RR=1.55, 95% CI: 1.08, 2.22, respectively). Furthermore, the study observed that the mean endometrial thickness (ET) was significantly higher in women who received SC compared to the control group, which involved other active interventions or placebo (SMD=0.77, 95% CI: 0.20, 1.34). Particularly, the administration of SC resulted in a notably higher ET level compared to the placebo (SMD: 1.33, 95% CI: 0.15, 2.51). The findings suggest that luteal supplementation of SC can be considered a beneficial approach to enhance ET and improve the CP rate in women undergoing ART.

Keywords: Assisted reproduction technology, sildenafil citrate, endometrial thickness, chemical pregnancy, clinical pregnancy

Öz

Yardımcı üreme teknolojileri (YÜT), doğurganlık sorunları yaşayan kadınlar için hayati bir seçenek haline geldi. Araştırılan potansiyel müdahalelerden biri, YÜT prosedürlerinde klinik sonuçları iyileştirmek için sildenafil sitratın (SS) kullanılmasıdır. Bu çalışmanın amacı, YÜT uygulanan kadınlarda SS'nin

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klinik sonuçlar üzerindeki etkisini değerlendirmektir. PubMed, Scopus, Embase, Web of Science ve Cochrane Central Register of Controlled Trials dahil olmak üzere birçok veri tabanı kullanılarak kapsamlı bir literatür araştırması yapıldı. Araştırma, başlangıçtan 15 Nisan 2023'e kadar olan çalışmaları kapsadı ve analize dahil edilecek ilgili randomize kontrollü çalışmaları (RKÇ'ler) belirledi. Sonlanım noktaları, risk oranı (RR) veya %95 güven aralığı (GA) ile standartlaştırılmış ortalama fark (SOF) olarak özetlendi. Titiz bir analizin ardından çalışmaya 3.426 kadını kapsayan 28 RKÇ dahil edildi. Sonuçlar SS'nin klinik gebelik (KG) oranları üzerindeki etkisine ilişkin önemli bulgular ortaya çıkardı. SS alan kadınlar, kontrol grubuyla karşılaştırıldığında anlamlı olarak daha yüksek KG oranı gösterdi (n=21 RKÇ, RR=1,43; %95 GA: 1,29, 1,59). Ek olarak SS, klomifen sitrat veya östradiol valerat gibi diğer ilaçlarla birlikte kullanıldığında, KG olasılığını bu ilaçların tek olarak kullanımı ile karşılaştırıldığında daha da artırdı (sırasıyla, RR=1,35, %95 GA: 1,19, 1,53; RR=1,55, %95 GA: 1,08, 2,22). Ayrıca bu çalışmada, diğer aktif müdahaleleri veya plaseboyu içeren kontrol grubuyla karşılaştırıldığında SS alan kadınlarda ortalama endometrial kalınlığın (EK) anlamlı derecede daha yüksek olduğu gözlemlendi (SOF=0,77, %95 GA: 0,20, 1,34). Özellikle SS'nin uygulanması, plaseboya kıyasla belirgin şekilde daha yüksek bir EK seviyesiyle sonuçlandı (SOF: 1,33, %95 GA: 0,15, 2,51). Bulgular, SS'nin luteal takviyesinin, YÜT uygulanan kadınlarda EK'yi artırmak ve KG oranını iyileştirmek için yararlı bir yaklaşım olarak değerlendirilebileceğini göstermektedir.

Anahtar Kelimeler: Yardımcı üreme teknolojisi, sildenafil sitrat, endometrial kalınlık, kimyasal gebelik, klinik gebelik

Introduction

The global use of advanced techniques such as assisted reproductive technology (ART) has expanded, leading to noteworthy advancements in the treatment of infertility. However, despite these achievements, complex challenges persist in comprehending the intricate process of implantation and enhancing the outcomes of ART. Further research and advancements are necessary to address these complexities and improve the overall success of ART procedures[1].

It is crucial to conduct additional research on current therapeutic approaches to augment the success rates of ART due to the consistently low worldwide frequencies of embryo implantation and gestation[2]. Among the intricate aspects of ART, implantation is one of the most vulnerable and complex processes[3]. It depends on numerous local and systemic elements, including immune agents and hormonal cues[4]. Before being implanted, the embryo needs to produce substances that encourage the attachment site, whereas the decidua, conversely, should emit substances that support the differentiation and initial growth of the embryo. Consequently, exploring and understanding these factors are crucial for improving the success of ART[5,6]. Synchronization of endometrial receptivity and embryonic competence in a timely manner is of utmost importance for successful embryo implantation. It is crucial that the mentioned mediators operate within a normal range and at the appropriate time to ensure optimal conditions for this process[7]. Achieving adequate endometrial growth is a vital requirement for successful implantation. However, the precise understanding of the factors influencing endometrial growth remains limited and requires further investigation[8].

In recent times, significant numbers of studies have focused on investigating angiogenesis and vascularization within the endometrium. These studies have revealed that women with thin endometrium often exhibit poor uterine receptivity, which is potentially attributable to compromised blood flow impedance through the endometrium[9]. Over the past 10 years, several approaches have been examined to improve endometrial thickness among poor endometrial responders[10-14]. Along these lines, sildenafil citrate (SC) has been extensively examined in previous clinical trials to gage its impact on enhancing the success rate of ART. This is attributed to its well-documented vasodilatory and antithrombotic activities, making it one of the most thoroughly researched medications in this regard[15,16]. Numerous clinical trials have been conducted, and a mounting body of evidence suggests a beneficial effect of SC on ART outcomes[17-19].

To date, 28 randomized clinical trials (RCTs) have been performed to investigate the effect of SC on ART outcomes. However, despite these efforts, a definitive conclusion regarding its efficacy remains elusive, and prior studies have not yielded strong evidence[20]. Considering the substantial debate surrounding the effectiveness of SC, we conducted a contemporary systematic review and meta-analysis of RCTs specifically targeted at appraising the influence of SC on various clinical endpoints of ART.

Methods

This investigation was conducted following the guidelines outlined in the preferred reporting items for systematic reviews and meta-analyses statement[21] and the Cochrane handbook for systematic reviews of interventions[22]. This investigation was registered in the international prospective register of systematic reviews under the identifier CRD42023433884.

Databases and Search Strategy

To identify potential studies, a systematic search was conducted using several databases, including PubMed, Scopus, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. The search encompassed the period from the inception of each database to April 15, 2023. In addition, we manually inspected the reference lists of pertinent published studies with the intention of discovering any extra suitable RCTs. The search query comprisedthe following: ("in vitro fertilization" OR "intracytoplasmic sperm injection" OR "IVF" OR "Embryo Transfer" OR "ICSI" AND "Sildenafil" OR "SC" OR "Hydroxyhomosildenafil" OR "Revatio" OR "Homosildenafil" OR "Acetildenafil" OR "Viagra"). Supplement Table 1 provides comprehensive information regarding the search strategy employed, including the specific terms used and database-specific indexing terminology. No limitations were set based on the year of publication or language during the search process.

Table 1. Study characteristics

Study	Country	Study design	Population	Sample size		Intervention(s)	Control	Outcome measures
				Case	Control			
Moini et al.[17] 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,
El-Sayed et al.[25] 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 et al.[43] 2018	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 et al.[26] 2018	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 et al.[24] 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 et al.[27] 2018	Egypt	Randomized clinical trial	Unexplained infertility, 18-35 years.	45	45	CC 100 mg/d from 2nd to 6th day of cycle, oral sildenafil citrate 25 mg every 8 h from 2nd day of the cycle	CC 100 mg/d from 2nd to 6th day of cycle	Chemical pregnancy, endometrial thickness
Reddy et al.[38] 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	CC 100 mg/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.	CC 100 mg/d from 3nd to 7th day of cycle	Chemical pregnancy, endometrial thickness
AbdelKader Fahmy et al.[28] 2015	Egypt	Randomized clinical trial	Women aged between 18 and 40 years with primary or secondary infertility and with regular menstrual cycles.	35	35	CC 50 mg orally 3 times/day from 3rd to 7th day of the cycle with sildenafil citrate 25 mg (Viagra, Pfizer) orally 3times/day from	CC 50 mg orally 3 times/day from 3rd to 7th day of the cycle	Chemical pregnancy, endometrial thickness

Ashoush and Abdelshafy[29] 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 et al.[30] 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 et al.[44] 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
Vardhan et al.[39] 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 and Mehirishi[40] 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
Dehghani Firouzabadi et al.[19] 2019	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

Alieva et al.[48] 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 et al.[49] 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
Abdullah et al.[45] 2021	Iraq	Randomized clinical trial	Infertile female patients who undergo stimulated intra-uterine insemination	25	25	Sildenafil citrate 50 mg vaginally every 12 hours from day 5 of the cycle for 8 days + letrozole 5 mg at cycle day 2 for 5 days	Letrozole 5 mg at cycle day 2 for 5 days	Clinical pregnancy, endometrial thickness
Belapurkar et al.[42] 2022	India	Randomized clinical trial	Infertile women with primary or secondary infertility	35	35	Self-administer non-clinically vaginal sildenafil citrate 25 mg every six hours from day seven to day 12 of the menstrual cycle	intrauterine G-CSF injection (300 mcg/1 mL) four days after the last day of menses	Endometrial thickness
Mohammed et al.[46] 2023	Iraq	Randomized clinical trial	Infertile women who were undergoing intracytoplasmic sperm injection	30	30	Sildenafil citrate 25 mg vaginally every 6 hours from day of stopping of cycle to day of HCG	Nothing	Clinical pregnancy
Dawood et al.[47] 2020	Iraq	Randomized clinical trial	Women with unexplained, primary or secondary infertility who have thin endometrium	30	30	Sildenafil citrate 25 mg vaginally every 6 hours	Estradiol valerate 2 mg tablet 12 hourly	Clinical pregnancy, Endometrial thickness
Mohamed et al.[18] 2022	Eygept	Randomized clinical trial	PCOS women, aged 20-35 years, with primary or secondary infertility	50	50	Sildenafil (seldin 25 mg tab), oral tab was given every 12 hours every day starting from day 3 of the period till leading follicle size reaches about 18-20 mm + clomiphene citrate (clomid 50 mg tab) two tablets every 24 hours	Clomiphene citrate (clomid 50 mg tab) two tablets every 24 hours	Clinical pregnancy
Gupta et al.[41] 2021	India	Randomized clinical trial	Infertile women with primary or secondary infertility	38	42	Sildenafil citrate 25 mg vaginally every 6 hours + 50 mg clomiphene citrate in tablet form orally once daily from days 1-5 of the cycle	50 mg clomiphene citrate in tablet form orally once daily from days 1-5 of the cycle	Clinical pregnancy

Abbas et al.[32] 2021	Eygept	Randomized Clinical trial	Infertile women with PCOS women undergoing induction of ovulation	216	216	Sildenafil citrate 25 mg vaginally every 6 hours + 50 mg clomiphene citrate in tablet form orally once daily from days 1-5 of the cycle	50 mg clomiphene citrate in tablet form orally once daily from days 1-5 of the cycle	Clinical pregnancy
ELkhouly et al.[33] 2022	Eygept	Randomized clinical trial	Infertile women aged between 18 and 35 years old diagnosed with PCO	100	100	Patients who were given sildenafil, 20 mg coated tablets from the seventh day to 1^{1th} day of the cycle three times per day orally + clomiphene citrate 50 mg was given from the 3rd day to seventh day of the same cycle two times per day orally.	Patients who were given clomiphene citrate 50 mg from the third day to seventh day of the cycle two times per day orally	Chemical pregnancy, live birth and miscarriage
El-Asbaa et al.[34] 2021	Eygept	Randomized clinical trial	Infertile women undergoing induction by clomiphene citrate attending infertility and unit	22	22	Sildenafil citrate 25 mg was given every 8 hour from 2nd day of the cycle till the day of trigger of ovulation	Oral estradiol valerate 2 mg, one tablet every 12 hour from day 8th of the cycle till triggering of ovulation	Clinical pregnancy, endometrial thickness
Abdel Hamid et al.[35] 2021	Eygept	Randomized clinical trial	Infertile women aged between 18 and 35 years with primary or secondary infertility	29	29	Vaginal sildenafil tablets 25 mg/12 h daily was given from day 8 up to ovulation trigger + 50 mg CC (clomid) orally 2 times/day from day 3 to day 7 of the cycle.	50 mg CC (clomid) orally 2 times/day from day 3 to day 7 of the cycle.	Chemical pregnancy, endometrial thickness
Wafa et al.[24] 2022	Egypt	Randomized clinical trial	Infertile women aged between 18 and 35 years with primary or secondary infertility	75	75	Sildenafil citrate, 20 mg from cycle day 8 till cycle day 13 in dose of 20 mg every 8 hours	Placebo tablets from cycle day 8 till cycle day 13 orally every 8 hours	Chemical pregnancy, endometrial thickness
El-ghany et al.[37] 2022	Egypt	Randomized clinical trial	Infertile women aged between 20 and 35 years with primary or secondary infertility	100	100	Aromatase inhibitor (letrozole 2.5 mg) 1 tablet twice daily for induction of ovulation for five-days, beginning from the 2nd day of cycle, and Sildenafil citrate: 1 tablet three times per day from with the start of Letrzole therapy until the day of HCG administration.	Aromatase inhibitor (letrozole 2.5 mg) 1 tablet twice daily for induction of ovulation for five-days, starting from the 2nd day of cycle and Placebo tablets: 1 tablet three times per day from with the start of letrzole therapy until the day of HCG administration.	Clinical pregnancy, Endometrial thickness

CC: Clomiphene citrate, PCOS: Polycystic ovary syndrome, HCG: Human chorionic gonadotropin, FSH: Follicle stimulating hormone, BMI: Body mass index, IVF: In vitro fertilization

Inclusion and Exclusion Criteria

In our review, studies were analyzed if they met the following conditions: (i) the study comprised subfertile patients undergoing ART, (ii) the intervention group received SC alone or in combination with other agents, (iii) the comparator (control) group received a placebo, no treatment or an active agent other than SC, (iv) the study reported at least one of the desired endpoints such as endometrial thickness, chemical pregnancy, clinical pregnancy, live birth or miscarriage and (v) the study design was an RCT. In contrast, our review excluded studies that were in any of the following categories: (i) the study was not an RCT, (ii) the study involved animals, and (iii) the study lacked adequate information on the study methodology or findings.

Study Selection, Data Collection, and Quality Assessment

Following the retrieval of all citations, duplicates were eliminated. Subsequently, the titles/abstracts of the residual citations were examined, and any unrelated citations were excluded. Then, the full-text citations of the residual ones were screened to establish their final eligibility. Two coauthors independently selected the studies, and any disagreements were resolved via consensus.

Data collection involved two distinct categories. The initial category encompassed the fundamental attributes of the eligible RCTs, such as the name of the primary author, year of publication, country, study arms, participant count, specifics of treatment arms, and reported results. The subsequent category comprised the clinical endpoints, namely, endometrial thickness, rate of chemical pregnancy, and rate of clinical pregnancy. The task of collecting data was carried out by two sets of coauthors who worked independently, and disputes were resolved via consensus within each pair.

The Cochrane risk of bias tool was used to assess the methodological quality of RCTs[23]. Each of the seven domains was assessed as unclear, low, or high risk of bias. Two coauthors completed the study appraisal independently, and disputes were resolved by discussion with a third co-author.

Statistical Analysis

The Mantel-Haenszel method was used to compute the risk ratio (RR) and its 95% confidence interval (CI) for the contrasting findings of chemical and clinical pregnancy rates.

In contrast, the standardized mean difference (SMD) was used to compute the continuous result of the average thickness of the endometrium, along with its 95% CI, employing the inverse-variance method. The random-effects model was employed for all calculations. The heterogeneity of the RCTs was assessed visually through forest plots and statistically using the chi-square-based Q statistic and I^2 value. Significant heterogeneity was established when the p-value of the chi-square-based Q statistic measured <0.10 or I^2 measured >50%. Stata software (version 17) was used to perform all statistical analyses. Subgroup analyses were conducted to explore the impact of SC on ART outcomes, considering related study features. These features included intervention type (e.g., SC alone, SC with clomiphene citrate (CC), SC with estradiol valerate, and SC with letrozole), population type (e.g., recurrent implantation failure (RIF) or other infertility categories), and control type (e.g., CC, estradiol, letrozole, or placebo), which were considered potential sources of variation.

Results

Summary of the Database Screening

In total, 935 records were found across all databases after eliminating duplicates. Of these, 89 records underwent a complete text examination, and among them, 61 records were excluded for specific reasons. Eventually, 28 RCTs were included in the meta-analysis (Figure 1).

Summary of Baseline Characteristics of Eligible RCTs

All RCTs had a parallel design and were performed between 2010 and 2023. The RCTs were conducted in various countries, including Egypt (n=14)[24-37], India (n=5)[38-42], Iran (n=4)[17,19,43,44], Iraq (n=3)[45-47], Russia (n=1)[48], and Korea (n=1)[49]. Seven RCTs compared SC with placebo, ten RCTs compared the combination of SC and CC with CC, 7 RCTs compared the blend of SC and estradiol valerate with estradiol valerate, three RCTs compared the combination of SC and letrozole with letrozole, and one RCT compared SC with placebo. Table 1 displays the range of sample sizes, with participant numbers varying from 44 to 850. Among the seven RCTs, the focus was on women with recurrent implantation failure. On the other hand, the remaining RCTs examined different forms

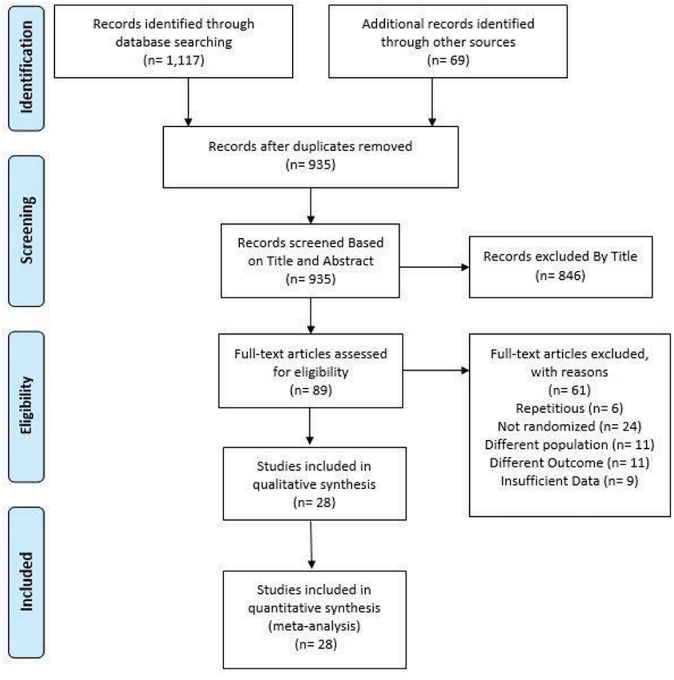

Figure 1. Flow diagram of study selection for the analysis

of infertility, including patients with narrow endometria or undetermined causes of infertility.

Summary of the Study Quality of the Included RCTs

Supplement Table 2 presents an overview of the bias risk of the RCTs that were included. With the exception of 15 RCTs, all other RCTs were determined to have a low risk regarding random generation. Uncertainty regarding random allocation was observed in 13 RCTs. For allocation concealment, 14 RCTs were deemed to have a high risk of bias, whereas eight RCTs had an unclear risk of bias. Performance bias was rated as a high and unclear risk of bias in 16 and four RCTs, respectively. Detection bias was rated as high and unclear risk of bias in 10 and 7 RCTs, respectively. Attrition bias was rated as a high and unclear risk of bias in four and six RCTs, respectively. Fifteen RCTs were concluded to exhibit an unclear risk of bias for the domain of reporting bias.

Meta-analysis of the Rate of Chemical Pregnancy

Chemical pregnancy data were pooled from 11 RCTs with a total of 982 individuals (485 cases and 497 controls). The probability of chemical pregnancy (RR=1.54; 95% CI: 1.27, 1.87) was significantly higher in the intervention group (i.e., SC alone or combination with other treatments) than in the placebo group (i.e., any other active treatment, no treatments, or placebo), without significant heterogeneity (I^2=0%; p=0.679) (Figure 2). A counter funnel plot and Egger's test showed no sign of publication bias (β=0.83, 95% CI: -1.05, 2.73; p=0.343, Supplement Figure 1). The sensitivity analysis indicated that the calculated combined risk RR ranged between 1.50 (95% CI: 1.23, 1.83) and 1.62 (95% CI: 1.32, 1.97). This suggests that none of the individual RCTs had a substantial influence on the overall effect size (Supplement Figure 2).

The impact size was more pronounced in a subgroup of RCTs that provided subcutaneous injections (SC) to RIF women (n=3 RCTs, RR=2.08, 95% CI: 1.22, 3.54, I^2=0%), compared with women with other infertility types (n=8 RCTs, RR=1.48, 95% CI: 1.20, 1.81, I^2=0%) (Supplement Figure 3). There was no distinction between the subgroup of RCTs that administered SC doses of ≤50 mg (n=5 RCTs, RR: 1.66, 95% CI: 1.25, 2.20, I^2=0%) and those that administered SC doses of more than 50 mg (n=6 RCTs, RR=1.45, 95% CI: 1.12, 1.89, I^2=0%) (Supplement Figure 4).

Three RCTs with participants experiencing RIF were conducted to compare subcutaneous SC intervention with placebo. Additionally, four RCTs compared the combination of SC and CC with CC alone, three RCTs compared the blend of SC and estradiol valerate with estradiol valerate alone, and one RCT compared the combination of SC and letrozole with letrozole alone. The forest plots, using random-effects analysis, for all the RCTs that compared SC with placebo showed a noteworthy improvement in the chemical pregnancy rate in the SC intervention group compared with the control arm (RR=2.08, 95% CI: 1.22, 3.54, I^2=0%). Furthermore, a significantly substantial change was noticed in the subgroup of RCTs that contrasted the blend of SC and CC with CC alone (RR=1.47, 95% CI: 1.15, 1.88, I^2=0%). However, no significant change was observed in the subgroup of RCTs that compared the blend of SC and estradiol valerate with estradiol valerate alone (RR=1.31, 95% CI: 0.85, 2.01, I^2=6.42%) (Figure 2).

Meta-analysis of the Rate of Clinical Pregnancy

Data on clinical pregnancy were gathered from 21 RCTs involving 2.816 patients (1.401 cases and 1.415 controls). The intervention group, which received either SC treatment alone or in combination with other therapies, exhibited a significantly higher likelihood of clinical pregnancy (RR=1.43; 95% CI: 1.29, 1.59) compared with the control group, which consisted of other active interventions, no intervention, or placebo. No significant heterogeneity was identified (I^2=2.36%; p=0.716) (Figure 3). A counter funnel plot and Egger's test indicated no evidence of publication bias (β=0.74, 95% CI: -0.01, 1.50; p=0.054, Supplement Figure 5). Sensitivity analysis demonstrated that the combined RR estimates varied from 1.40 (95% CI: 1.27, 1.55) to 1.51 (95% CI: 1.33, 1.71), indicating that no individual RCT exerted a significant influence on the overall effect size (Supplement Figure 6).

No significant changes were noticed between the subgroup of RCTs that provided SC treatment to RIF women (n=6 RCTs, RR=1.63, 95% CI: 1.13, 2.33, I^2=0%) and those with different infertility causes (n=15 RCTs, RR=1.41, 95% CI: 1.26, 1.56, I^2=72%) (Supplement Figure 7). The subset of RCTs that used SC doses of ≤50 mg (n=9 RCTs, RR=1.62, 95% CI: 1.36, 1.93, I^2=0%) showed a stronger effect size compared with those that used SC doses of more than 50 mg (n=12 RCTs, RR=1.32, 95% CI: 1.17, 1.49, I^2=0%) (Supplement Figure 8).

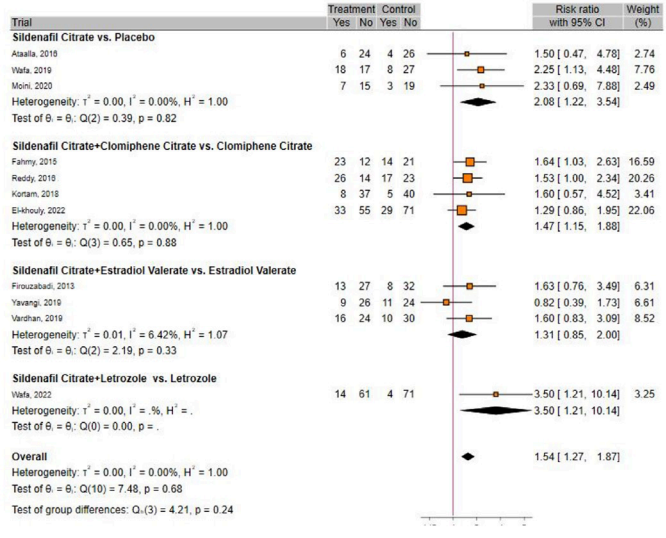

Figure 2. Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of chemical pregnancy in women who received sildenafil citrate versus control regarding intervention and control type

Six RCTs assessed the use of SC (n=183 patients) in contrast to a placebo (n=183 patients). Furthermore, seven RCTs investigated the combination of SC and CC (n=890 patients) compared with CC alone (n=893 patients). Six RCTs examined the combined administration of estradiol valerate and SC versus estradiol valerate alone, encompassing 203 participants in the experimental group and 209 participants in the control group. Lastly, two RCTs compared the combined use of letrozole and SC versus letrozole alone, involving 125 participants in the experimental group and 125 participants in the control group.

Pooling the outcomes of six RCTs that compared the rates of successful pregnancies between the SC (study compound) and placebo groups revealed a considerably higher likelihood of achieving clinical pregnancy in the SC group (RR=1.59, 95% CI: 1.10, 2.30, I^2=0%). Women who received both SC and CC had significantly higher chances of clinical pregnancy compared with those who received monotherapy CC (RR=1.35, 95% CI: 1.19, 1.53, I^2=0%). Remarkably, women who received both SC and estradiol valerate experienced a notable increase in clinical pregnancy rates compared with those who only received estradiol valerate (RR=1.55, 95% CI: 1.08, 2.22, I^2=0%). Conversely, no statistically significant change was observed between the intervention and control groups in a subset of RCTs that administered the combination of letrozole and SC versus letrozole alone (n=2, RR=1.78, 95% CI: 0.98, 3.24, I^2=45.42%) (Figure 3).

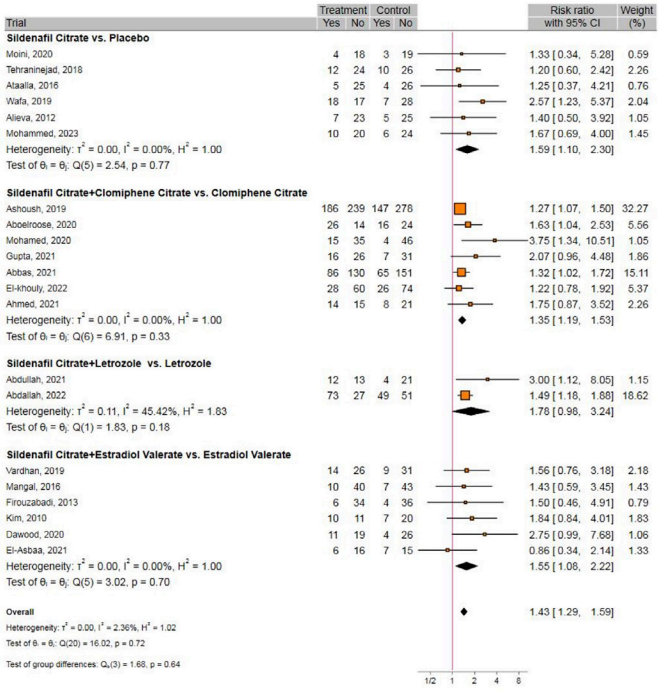

Figure 3. Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of clinical pregnancy in women who received sildenafil citrate versus control regarding intervention and control type

Meta-analysis of the Diameter of the Endometrial Thickness

Data regarding the thickness of the endometrium were gathered from ten RCTs involving 748 participants, with 374 being cases and 374 being controls. The findings revealed that women who received an intervention, either subcutaneous administration alone or in combination with other treatments, had a considerably higher average endometrial thickness (SMD=0.77, 95% CI: 0.20, 1.34; I^2=92.72%) than the control group. The control group included various interventions such as other active treatments, no intervention, or a placebo (Figure 4). A counter funnel plot and Egger's test were conducted, which indicated no indication of publication bias (β=5.40, 95% CI: -9.02, 19.84; p=0.413). Sensitivity analysis demonstrated that the combined RR estimates varied from 0.58 (95% CI: 0.12, 1.03) to 0.89 (95% CI: 0.39, 1.47), implying that no individual RCT had a substantial impact on the overall effect size (Supplement Figure 9).

There was a notable distinction observed between a specific group of RCTs that used SC treatment in patients experiencing RIF (consisting of 4 RCTs, with a SMD of 1.33, 95% CI: 0.15, 2.51, and an I^2 value of 94.35%) and another group that administered SC treatment to patients with different forms of infertility (comprising 6 RCTs, with an SMD of 0.43, 95% CI: -0.02, 0.88, and an I^2 value of 83.35%, Supplement Figure 10). The magnitude of the effect was more pronounced in the subset of RCTs that used SC doses exceeding 50 mg (including 7 RCTs, with an SMD of 0.65, 95% CI: 0.08, 1.22, and an I^2 value of 89.89%) than in those that employed SC doses of 50 mg (consisting of 3 RCTs, with an SMD of 1.09, 95% CI: -0.42, 2.67, and an I^2 value of 96.37%, Supplement Figure 11).

Four RCTs conducted a comparison between SC administration and placebo, with a total of 127 patients in the case group and 127 participants in the control group. Among them, one RCT compared the combined use of SC and CC (n=45 patients) with the use of CC alone (n=45 patients). Furthermore, another RCT contrasted the combined use of SC and letrozole with the use of letrozole alone, with 75 cases and 75 controls. Moreover, an additional RCT compared SC (n=35 patients) with G-CSF (n=35 patients). Lastly, one RCT compared the combined use of estradiol valerate and SC (n=40 patients) with the use of estradiol valerate alone (n=40 patients).

After the intervention, patients who were administered SC experienced an increase in endometrial thickness in comparison with those who received a placebo (n=4 RCTs, SMD=1.33, 95% CI: 0.15, 2.51, I^2=94.35%). The average endometrial thickness was significantly higher in women who received both SC and CC than in those who only received CC (n=1 RCT, SMD=0.92, 95% CI: 0.49, 1.36). No notable change between patients who received a blend of SC and estradiol valerate versus those who received estradiol valerate alone was noted (n=1 RCT, SMD=0, 95% CI: -0.43, 0.43). Additionally, women who received SC exhibited a significantly higher endometrial thickness compared

with those who received G-CSF (n=1 RCT, SMD=0.67, 95% CI: 0.19, 1.14) (Figure 4).

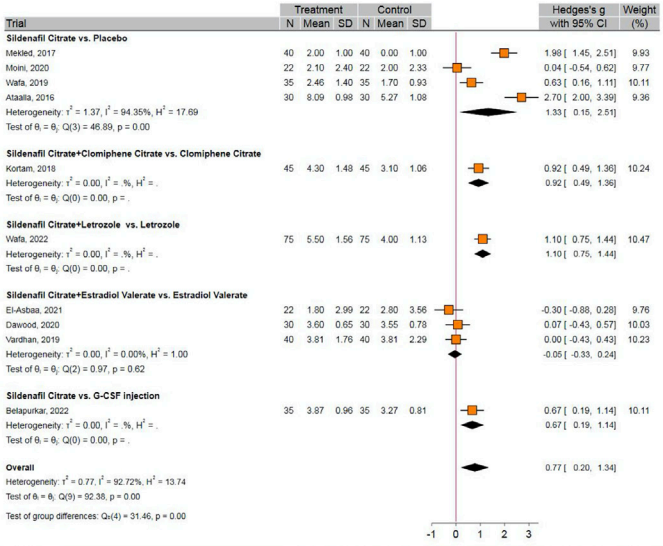

Figure 4. Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the mean of endometrial thickness in women who received sildenafil citrate versus control regarding intervention and control type

SD: Standard deviation

Discussion

Understanding the specific function and operational method of SC in the implantation process is an intricate issue. However, various potential theories have been proposed. Initially, SC hinders the activity of phosphodiesterase 5 (PDE5), an enzyme responsible for breaking down cyclic guanosine monophosphate (cGMP). Through the application of SC, the levels of cGMP remain heightened, resulting in the relaxation of blood vessels and an augmented blood circulation toward the endometrium[50]. Second, SC could influence vasoactive cytokines responsible for governing the growth of the uterine lining or the attachment of the embryo[19]. Third, the use of SC can improve the readiness of the uterus by aiding in the growth of spiral arteries and augmenting the flow of arterial blood within the uterine region. Fourth, SC may increase natural killer cell activity in addition to the role of SC in promoting endometrial growth facilitation[51]. The fifth point is that SC can trigger the angiogenic reactions of the vascular endothelial growth factor. This involvement in the formation of new blood vessels and heightened vascular penetrability in the middle secretory stage is fundamental to the achievement of satisfactory implantation[52].

In our current systematic review and meta-analysis, we examined 28 RCTs involving 3.426 women with subfertility. Among these participants, 1.702 were assigned to receive the intervention, whereas 1.724 were placed in the control group. All individuals underwent ART. Based on the collective findings, it is evident that the use of SC, either alone or in conjunction with other active treatments such as CC, estradiol valerate, or letrozole, can lead to higher chemical pregnancy rate, clinical pregnancy rate, and endometrial thickness compared with the control group. However, it is essential to approach these findings with concern because the quality of the RCTs included was not up to par. When subgroup analysis was conducted, it was found that women with RIF experienced the most significant increase in chemical and clinical pregnancy rates compared with patients with other infertility causes. Various RCTs included infertile patients with unexplained infertility or narrow endometrium. Considering the various sources of infertility investigated in the eligible RCTs and the inadequate number of available RCTs, it was impossible to conduct a proper subgroup analysis. Therefore, it is important to be cautious when interpreting the results of this analysis.

Furthermore, due to inadequate information on the methodologies used in the included studies, we could not perform subgroup analysis considering various potential factors contributing to heterogeneity, such as the specific dose of SC, the stage of embryos during transfer, or the type of protocol employed[24-26]. Moreover, although we did identify a noteworthy distinction between women who were administered SC and those who received a placebo, the available evidence of endometrial thickening was of extremely poor quality, exhibiting imprecise results and significant heterogeneity. Lastly, none of the RCTs included in our analysis offered data on live birth rates or side effects, resulting in a lack of conclusive evidence regarding differences between the groups in these aspects.

Prior to our investigation, many systematic reviews and meta-analyses had examined the effectiveness of various treatments (such as gonadotropin-releasing hormone agonist[53], aspirin[12], human chorionic gonadotrophin[54], and a mixture of alpha-tocopherol plus pentoxifylline[55] in preparing the endometrium for patients experiencing ART. Nonetheless, the existing evidence was insufficient to establish a specific procedure for preparation of the endometrium. We came across only one meta-analysis that assessed the clinical utility of vasodilation-promoting agents in patients undergoing ART. This analysis spanned six data sources and encompassed 15 studies and 1.326 patients. All meta-analyzed RCTs contrasted a vasodilator with a control group comprising no treatment or placebo. Three of the RCTs examined the clinical utility of SC. Two of the RCTs judged the efficacy of monotherapy SC compared with placebo, while the other RCT assessed the blend of SC and estradiol valerate compared with no treatment. The meta-analysis of the two articles comparing SC alone with placebo indicated no discernible differences between the two treatments. Likewise, an investigation comparing the blend of SC and estradiol valerate indicated no significant changes between the two interventions[20]. In addition to these three

RCTs, we identified 25 additional RCTs that evaluated the efficacy of SC either alone or in conjunction with other active therapies. The most extensive RCT to date, conducted in Egypt, examined the effectiveness of combining SC and CC compared with CC alone and was well-executed.

At Ain-Shams University Women's Hospital, an RCT was conducted involving 850 women diagnosed with PCOS who had previously experienced failure with CC. The study compared two groups, one receiving SC treatment and the other receiving CC treatment. The SC group demonstrated a greater thickness of the endometrial lining and had a higher likelihood of achieving a clinical pregnancy than the CC group[29].

The methodological quality and similarity of the studies included have a sizable influence on the reliability of the meta-analysis results. In our study, the quality of the trials included was comparatively poor, but there was little variation in the analysis of clinical and chemical pregnancy rates. However, we found high heterogeneity in the analysis of endometrial thickness. Although we did not find any statistical heterogeneity in the main outcomes across the trials, we cannot disregard the potential impact of clinical heterogeneity on the study findings. While most RCTs examined in the review had clearly defined criteria for including and excluding participants, a small number of RCTs failed to specify their precise criteria. In addition, the RCTs lacked consistent or unreported information about the primary source of infertility and the history of RIF or repeated abortion among the women included in the research. There was also variation across the RCTs with respect to the methods used for luteal stage stimulation, endometrial setup, and ovarian hyperstimulation regimens, with some studies failing to report these specific details. Moreover, there were notable variations in the dosage of SC, a crucial element that significantly impacts the efficacy of the given medication, across the various studies. Unfortunately, most studies did not report miscarriage rates, drug-related adverse events, or pregnancy outcomes, thereby limiting our understanding of these important factors.

Regarding the effects of SC on frozen-thawed embryo transfer (FET) cycles in the setting of ART, our results from included studies advocate that SC may positively affect endometrial receptivity, potentially enhancing blood flow to the uterus and improving the implantation rates of embryos during FET[19]. The medication is thought to exert influence by relaxing uterine smooth muscles and increasing blood flow, which could contribute to a more favorable environment for embryo implantation[56]. However, research on this topic is ongoing, and while some studies have shown promising results, further investigation is needed to establish the optimal dosage, timing, and overall efficacy of SC in the context of FET cycles[57].

There were various shortcomings in our review. First, the majority of the RCTs we analyzed depicted inadequate methodological quality and harbored a small number of patients. These factors can affect the reliability of the studies. Second, there was significant variability in some results, especially with regard to endometrial thickness. However, we did not perform subgroup analyses to investigate the potential causes of this variability, such as the specific dose of SC, stage of embryo transfer, or type of protocol used. This was because the analyzed studies did not offer sufficient detailed data about their methods.

Conclusion

The present systematic review and meta-analysis revealed that luteal administration of SC, whether orally or vaginally, either alone or as an adjuvant therapy, may enhance endometrial thickness and clinical pregnancy rate in women experiencing ART. Considering the methodological limitations of the analyzed RCTs, this evidence does not yet endorse the routine use of SC in clinical practice. To establish its efficacy and safety more conclusively, future high-quality RCTs with larger sample sizes are necessary. Future RCTs should prioritize different elements, including processing methods, embryo stage, embryo quality, dosage, administration timing, and the composition of the control group. These studies aim to pinpoint particular patient groups that would derive the greatest advantages from this drug administration and establish the ideal dose, timing, and type of SC that would produce the most favorable outcomes while minimizing potential adverse events.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: S.B., A.A-Z., Design: S.B., A.A-Z., Data Collection or Processing: S.B., M.A., M.S.A., H.T.S., W.H.A., E.B., A.Y.A., I.A.B., A.A., O.A., A.A-Z., Analysis or Interpretation: S.B., M.A., O.A., A.A-Z., Literature Search: M.A., M.S.A., H.T.S., W.H.A., E.B., A.Y.A., I.A.B., A.A., O.A., Writing: S.B., A.A-Z.

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Supplement **Table 1.** Detailed search strategy

Domains	Descriptors
Population	Reproductive Techniques, Assisted OR Assisted Reproductive Technique OR Reproductive Technique, Assisted OR Technique, Assisted Reproductive OR Assisted Reproductive Technics OR Assisted Reproductive Technology OR Assisted Reproductive Technologies OR Reproductive Technologies, Assisted OR Fertilization in Vitro OR In Vitro Fertilization OR In Vitro Fertilizations OR IVF OR ICSI OR Sperm Injections, Intracytoplasmic OR Injection, Intracytoplasmic Sperm OR Intracytoplasmic Sperm Injection OR Injections, Intracytoplasmic Sperm OR in-vitro fertilization OR Recurrent in Vitro Fertilization failure OR recurrent in-vitro fertilization failure OR Recurrent IVF failure OR recurrent implantation failure OR Recurrent failure of implantation OR Recurrent failure of in vitro fertilization OR RIF OR Repeated implantation failure OR failed cycle OR implantation failure OR recurrent failure to implant OR repeat failure to implant OR recurrent failed implantation OR repeat failed implantation OR recurrent reproductive failure OR repeat reproductive failure OR poor implantation
Intervention	Sildenafil Citrate OR Citrate, Sildenafil OR Sildenafil OR Homosildenafil OR Hydroxyhomosildenafil OR Revatio OR Viagra OR Acetildenafil OR Sildenafil Lactate OR Lactate, Sildenafil OR Sildenafil Nitrate OR Nitrate, Sildenafil OR Desmethyl Sildenafil OR Sildenafil, Desmethyl OR Desmethylsildenafil
Design	Randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single blind method OR clinical trial OR clinical trials OR placebos OR placebo OR random

PubMed
Number of localized studies: 99
Limits: Clinical Trial, Humans

	Descriptors	Number of studies reached
#1	((((((((((((((((((((((((((((((((((((“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “reproductive techniques, assisted”[All Fields]) OR (“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“assisted”[All Fields] AND “reproductive”[All Fields] AND “technique”[All Fields]) OR “assisted reproductive technique”[All Fields])) OR (“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“reproductive”[All Fields] AND “technique”[All Fields] AND “assisted”[All Fields]))) OR (“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“technique”[All Fields] AND “assisted”[All Fields] AND “reproductive”[All Fields]))) OR (“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“assisted”[All Fields] AND “reproductive”[All Fields] AND “technics”[All Fields]) OR “assisted reproductive technics”[All Fields])) OR (“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“assisted”[All Fields] AND “reproductive”[All Fields] AND “technology”[All Fields]) OR “assisted reproductive technology”[All Fields])) OR (“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“assisted”[All Fields] AND “reproductive”[All Fields] AND “technologies”[All Fields]) OR “assisted reproductive technologies”[All Fields])) OR (“reproductive techniques, assisted”[MeSH Terms] OR (“reproductive”[All Fields] AND “techniques”[All Fields] AND “assisted”[All Fields]) OR “assisted reproductive techniques”[All Fields] OR (“reproductive”[All Fields] AND “technologies”[All Fields] AND “assisted”[All Fields]))) OR (“fertilisation in vitro”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields])) OR (“in vitro fertilisation”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilization”[All Fields]) OR “in vitro fertilization”[All Fields])) OR (“fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilizations”[All Fields]) OR “in vitro fertilizations”[All Fields])) OR (“sperm injections, intracytoplasmic”[MeSH Terms] OR (“sperm”[All Fields] AND “injections”[All Fields] AND “intracytoplasmic”[All Fields]) OR “intracytoplasmic sperm injections”[All Fields] OR (“sperm”[All Fields] AND “injections”[All Fields] AND “intracytoplasmic”[All Fields]) OR “sperm injections, intracytoplasmic”[All Fields])) OR (“sperm injections, intracytoplasmic”[MeSH Terms] OR (“sperm”[All Fields] AND “injections”[All Fields] AND “intracytoplasmic”[All Fields]) OR “intracytoplasmic sperm injections”[All Fields] OR (“injection”[All Fields] AND “intracytoplasmic”[All Fields] AND “sperm”[All Fields]))) OR (“sperm injections, intracytoplasmic”[MeSH Terms] OR (“sperm”[All Fields] AND “injections”[All Fields] AND “intracytoplasmic”[All Fields]) OR “intracytoplasmic sperm injections”[All Fields] OR (“intracytoplasmic”[All Fields] AND “sperm”[All Fields] AND “injection”[All Fields]) OR “intracytoplasmic sperm injection”[All Fields])) OR (“sperm injections, intracytoplasmic”[MeSH Terms] OR (“sperm”[All Fields] AND “injections”[All Fields] AND “intracytoplasmic”[All Fields]) OR “intracytoplasmic sperm injections”[All Fields] OR (“injections”[All Fields] AND “intracytoplasmic”[All Fields] AND “sperm”[All Fields]))) OR (“J In Vitro Fert Embryo Transf”[Journal] OR “ivf”[All Fields])) OR (“in vitro fertilisation”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilization”[All Fields]) OR “in vitro fertilization”[All Fields])) OR (“in vitro fertilisation”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilization”[All Fields]) OR “in vitro fertilization”[All Fields])) OR (“sperm injections, intracytoplasmic”[MeSH Terms] OR (“sperm”[All Fields] AND “injections”[All Fields] AND “intracytoplasmic”[All Fields]) OR “intracytoplasmic sperm injections”[All Fields] OR “icsi”[All Fields])) OR (“sperm injections, intracytoplasmic”[MeSH Terms] OR (“sperm”[All Fields] AND “injections”[All Fields] AND “intracytoplasmic”[All Fields]) OR “intracytoplasmic sperm injections”[All Fields] OR (“intracytoplasmic”[All Fields] AND “sperm”[All Fields] AND “injection”[All Fields]) OR “intracytoplasmic sperm injection”[All Fields])) OR (“in vitro fertilisation”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilization”[All Fields]) OR “in vitro fertilization”[All Fields])) OR (Recurrent[All Fields] AND (“in vitro fertilisation”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilization”[All Fields]) OR “in vitro fertilization”[All Fields]) AND failure[All Fields])) OR (recurrent[All Fields] AND (“in vitro fertilisation”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilization”[All Fields]) OR “in vitro fertilization”[All Fields]) AND failure[All Fields])) OR (Recurrent[All Fields] AND (“J In Vitro Fert Embryo Transf”[Journal] OR “ivf”[All Fields]) AND failure[All Fields])) OR (recurrent[All Fields] AND (“embryo implantation”[MeSH Terms] OR (“embryo”[All Fields] AND “implantation”[All Fields]) OR “embryo implantation”[All Fields] OR “implantation”[All Fields]) AND failure[All Fields])) OR (Recurrent[All Fields] AND failure[All Fields] AND (“embryo implantation”[MeSH Terms] OR (“embryo”[All Fields] AND “implantation”[All Fields]) OR “embryo implantation”[All Fields] OR “implantation”[All Fields]))) OR (Recurrent[All Fields] AND failure[All Fields] AND (“in vitro fertilisation”[All Fields] OR “fertilization in vitro”[MeSH Terms] OR (“fertilization”[All Fields] AND “vitro”[All Fields]) OR “fertilization in vitro”[All Fields] OR (“vitro”[All Fields] AND “fertilization”[All Fields]) OR “in vitro fertilization”[All Fields]))) OR (“Rev Infect”[Journal] OR “rif”[All Fields])) OR (Repeated[All Fields] AND (“embryo implantation”[MeSH Terms] OR (“embryo”[All Fields] AND “implantation”[All Fields]) OR “embryo implantation”[All Fields] OR “implantation”[All Fields]) AND failure[All Fields])) OR (failed[All Fields] AND cycle[All Fields])) OR ((“embryo implantation”[MeSH Terms] OR (“embryo”[All Fields] AND “implantation”[All Fields]) OR “embryo implantation”[All Fields] OR “implantation”[All Fields]) AND failure[All Fields])) OR (recurrent[All Fields] AND failure[All Fields] AND implant[All Fields])) OR (repeat[All Fields] AND failure[All Fields] AND implant[All Fields])) OR (recurrent[All Fields] AND failed[All Fields] AND (“embryo implantation”[MeSH Terms] OR (“embryo”[All Fields] AND “implantation”[All Fields]) OR “embryo implantation”[All Fields] OR “implantation”[All Fields]))) OR (repeat[All Fields] AND failed[All Fields] AND (“embryo implantation”[MeSH Terms] OR (“embryo”[All Fields] AND “implantation”[All Fields]) OR “embryo implantation”[All Fields] OR “implantation”[All Fields]))) OR (repeat[All Fields] AND (“reproduction”[MeSH Terms] OR “reproduction”[All Fields] OR “reproductive”[All Fields]) AND failure[All Fields])) OR ((“poverty”[MeSH Terms] OR “poverty”[All Fields] OR “poor”[All Fields]) AND (“embryo implantation”[MeSH Terms] OR (“embryo”[All Fields] AND “implantation”[All Fields]) OR “embryo implantation”[All Fields] OR “implantation”[All Fields]))	176,256

PubMed
Number of localized studies: 99
Limits: Clinical Trial, Humans

	Descriptors	Number of studies reached
#2	((((((((((("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields]) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR ("citrate"[All Fields] AND "sildenafil"[All Fields]))) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "sildenafil"[All Fields])) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "homosildenafil"[All Fields])) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "hydroxyhomosildenafil"[All Fields])) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "revatio"[All Fields])) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "acetildenafil"[All Fields])) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR ("sildenafil"[All Fields] AND "lactate"[All Fields]) OR "sildenafil lactate"[All Fields])) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR ("lactate"[All Fields] AND "sildenafil"[All Fields]))) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR ("nitrate"[All Fields] AND "sildenafil"[All Fields]))) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR ("desmethyl"[All Fields] AND "sildenafil"[All Fields]) OR "desmethyl sildenafil"[All Fields])) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR ("sildenafil"[All Fields] AND "desmethyl"[All Fields]))) OR ("sildenafil citrate"[MeSH Terms] OR ("sildenafil"[All Fields] AND "citrate"[All Fields]) OR "sildenafil citrate"[All Fields] OR "desmethylsildenafil"[All Fields])	8,513
#3	**#1** AND **#2**	99

Web of Science
Number of localized studies: 196
Limits: no limit

	Descriptors	Number of studies reached
#1	(Reproductive Techniques, Assisted) OR TOPIC: (Assisted Reproductive Technique) OR TOPIC: (Reproductive Technique, Assisted) OR TOPIC: (Technique, Assisted Reproductive) OR TOPIC: (Assisted Reproductive Technics) OR TOPIC: (Assisted Reproductive Technology) OR TOPIC: (Assisted Reproductive Technologies) OR TOPIC: (Reproductive Technologies, Assisted) OR TOPIC: (Fertilization in Vitro) OR TOPIC: (In Vitro Fertilization) OR TOPIC: (In Vitro Fertilizations) OR TOPIC: (IVF) OR TOPIC: (ICSI) OR TOPIC: (Sperm Injections, Intracytoplasmic) OR TOPIC: (Injection, Intracytoplasmic Sperm) OR TOPIC: (Intracytoplasmic Sperm Injection) OR TOPIC: (Injections, Intracytoplasmic Sperm) OR TOPIC: (in-vitro fertilization) OR TOPIC: (Recurrent in Vitro Fertilization failure) OR TOPIC: (recurrent in-vitro fertilization failure) OR TOPIC: (Recurrent IVF failure) OR TOPIC: (recurrent implantation failure) OR TOPIC: (Recurrent failure of implantation) OR TOPIC: (Recurrent failure of in vitro fertilization) OR TOPIC: (RIF) OR (Repeated implantation failure) OR TOPIC: (failed cycle) OR TOPIC: (implantation failure) OR TOPIC: (recurrent failure to implant) OR TOPIC: (repeat failure to implant) OR TOPIC: (recurrent failed implantation) OR TOPIC: (repeat failed implantation) OR TOPIC: (recurrent reproductive failure) OR TOPIC: (repeat reproductive failure) OR TOPIC: (poor implantation)	162,807
#2	TOPIC: (Sildenafil Citrate) OR TOPIC: (Citrate, Sildenafil) OR TOPIC: (Sildenafil) OR TOPIC: (Homosildenafil) OR TOPIC: (Hydroxyhomosildenafil) OR TOPIC: (Revatio) OR TOPIC: (Viagra) OR TOPIC: (Acetildenafil) OR TOPIC: (Sildenafil Lactate) OR TOPIC: (Lactate, Sildenafil) OR TOPIC: (Sildenafil Nitrate) OR TOPIC: (Nitrate, Sildenafil) OR TOPIC: (Desmethyl Sildenafil) OR TOPIC: (Sildenafil, Desmethyl) OR TOPIC: (Desmethylsildenafil)	12,869
#3	#1 AND #2	196

Scopus
Number of localized studies: 336

	Descriptors	Number of studies reached
#1	((TITLE-ABS-KEY (reproductive AND techniques, AND assisted) OR TITLE-ABS-KEY (assisted AND reproductive AND technique) OR TITLE-ABS-KEY (reproductive AND technique, AND assisted) OR TITLE-ABS-KEY (technique, AND assisted AND reproductive) OR TITLE-ABS-KEY (assisted AND reproductive AND technics) OR TITLE-ABS-KEY (assisted AND reproductive AND technology) OR TITLE-ABS-KEY (assisted AND reproductive AND technologies) OR TITLE-ABS-KEY (reproductive AND technologies, AND assisted) OR TITLE-ABS-KEY (fertilization AND in AND vitro) OR TITLE-ABS-KEY (in AND vitro AND fertilization) OR TITLE-ABS-KEY (in AND vitro AND fertilizations) OR TITLE-ABS-KEY (ivf))) OR ((TITLE-ABS-KEY (icsi) OR TITLE-ABS-KEY (sperm AND injections, AND intracytoplasmic) OR TITLE-ABS-KEY (injection, AND intracytoplasmic AND sperm) OR TITLE-ABS-KEY (intracytoplasmic AND sperm AND injection) OR TITLE-ABS-KEY (injections, AND intracytoplasmic AND sperm) OR TITLE-ABS-KEY (in-vitro AND fertilization) OR TITLE-ABS-KEY (assisted AND reproductive AND technologies) OR TITLE-ABS-KEY (recurrent AND in AND vitro AND fertilization AND failure) OR TITLE-ABS-KEY (recurrent AND in-vitro AND fertilization AND failure) OR TITLE-ABS-KEY (recurrent AND ivf AND failure) OR TITLE-ABS-KEY (recurrent AND implantation AND failure) OR TITLE-ABS-KEY (recurrent AND failure AND of AND implantation) OR TITLE-ABS-KEY (recurrent AND failure AND of AND in AND vitro AND fertilization) OR TITLE-ABS-KEY (rif) OR TITLE-ABS-KEY (repeated AND implantation AND failure) OR TITLE-ABS-KEY (failed AND cycle) OR TITLE-ABS-KEY (implantation AND failure) OR TITLE-ABS-KEY (recurrent AND failure AND to AND implant) OR TITLE-ABS-KEY (repeat AND failure AND to AND implant) OR TITLE-ABS-KEY (recurrent AND failed AND implantation) OR TITLE-ABS-KEY (repeat AND failed AND implantation) OR TITLE-ABS-KEY (recurrent AND reproductive AND failure) OR TITLE-ABS-KEY (repeat AND reproductive AND failure) OR TITLE-ABS-KEY (poor AND implantation)))	202,497
#2	(TITLE-ABS-KEY (sildenafil AND citrate) OR TITLE-ABS-KEY (citrate, AND sildenafil) OR TITLE-ABS-KEY (sildenafil) OR TITLE-ABS-KEY (homosildenafil) OR TITLE-ABS-KEY (hydroxyhomosildenafil) OR TITLE-ABS-KEY (revatio) OR TITLE-ABS-KEY (viagra) OR TITLE-ABS-KEY (acetildenafil) OR TITLE-ABS-KEY (sildenafil AND lactate) OR TITLE-ABS-KEY (lactate, AND sildenafil) OR TITLE-ABS-KEY (sildenafil AND nitrate) OR TITLE-ABS-KEY (nitrate, AND sildenafil) OR TITLE-ABS-KEY (desmethyl AND sildenafil) OR TITLE-ABS-KEY (sildenafil, AND desmethyl) OR TITLE-ABS-KEY (desmethylsildenafil))	22,447
#3	#1 AND #2	336

Cochrane
Number of localized studies: 88
Limits: No limits

	Descriptors	Number of studies reached
#1	Reproductive Techniques, Assisted OR Assisted Reproductive Technique OR Reproductive Technique, Assisted OR Technique, Assisted Reproductive OR Assisted Reproductive Technics OR Assisted Reproductive Technology OR Assisted Reproductive Technologies OR Reproductive Technologies, Assisted OR Fertilization in Vitro OR In Vitro Fertilization OR In Vitro Fertilizations OR IVF OR ICSI OR Sperm Injections, Intracytoplasmic OR Injection, Intracytoplasmic Sperm OR Intracytoplasmic Sperm Injection OR Injections, Intracytoplasmic Sperm OR in-vitro fertilization OR Recurrent in Vitro Fertilization failure OR recurrent in-vitro fertilization failure OR Recurrent IVF failure OR recurrent implantation failure OR Recurrent failure of implantation OR Recurrent failure of in vitro fertilization OR RIF OR Repeated implantation failure OR failed cycle OR implantation failure OR recurrent failure to implant OR repeat failure to implant OR recurrent failed implantation OR repeat failed implantation OR recurrent reproductive failure OR repeat reproductive failure OR poor implantation in Title Abstract Keyword - (Word variations have been searched)	37,144
#2	Sildenafil Citrate OR Citrate, Sildenafil OR Sildenafil OR Homosildenafil OR Hydroxyhomosildenafil OR Revatio OR Viagra OR Acetildenafil OR Sildenafil Lactate OR Lactate, Sildenafil OR Sildenafil Nitrate OR Nitrate, Sildenafil OR Desmethyl Sildenafil OR Sildenafil, Desmethyl OR Desmethylsildenafil	2,274
#3	#1 AND #2	88

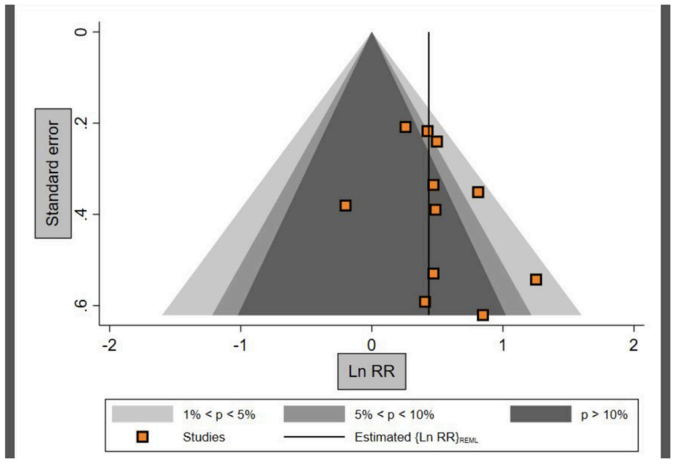
Embase
Number of localized studies: 398
Limits: No limits

	Descriptors	Number of studies reached
#1	reproductive AND techniques, AND assisted OR (assisted AND reproductive AND technique) OR (reproductive AND technique, AND assisted) OR (technique, AND assisted AND reproductive) OR (assisted AND reproductive AND technics) OR (assisted AND reproductive AND technology) OR (assisted AND reproductive AND technologies) OR (reproductive AND technologies, AND assisted) OR (fertilization AND in AND vitro) OR (in AND vitro AND fertilization) OR (in AND vitro AND fertilizations) OR ivf OR icsi OR (sperm AND injections, AND intracytoplasmic) OR (injection, AND intracytoplasmic AND sperm) OR (intracytoplasmic AND sperm AND injection) OR (injections, AND intracytoplasmic AND sperm) OR ('in vitro' AND fertilization) OR (recurrent AND in AND vitro AND fertilization AND failure) OR (recurrent AND 'in vitro' AND fertilization AND failure) OR (recurrent AND ivf AND failure) OR (recurrent AND implantation AND failure) OR (recurrent AND failure AND of AND implantation) OR (recurrent AND failure AND of AND in AND vitro AND fertilization) OR rif OR (repeated AND implantation AND failure) OR (failed AND cycle) OR (implantation AND failure) OR (recurrent AND failure AND to AND implant) OR (repeat AND failure AND to AND implant) OR (recurrent AND failed AND implantation) OR (repeat AND failed AND implantation) OR (recurrent AND reproductive AND failure) OR (repeat AND reproductive AND failure) OR (poor AND implantation)	196,523
#2	sildenafil AND citrate OR (citrate, AND sildenafil) OR sildenafil OR homosildenafil OR hydroxyhomosildenafil OR revatio OR viagra OR acetildenafil OR (sildenafil AND lactate) OR (lactate, AND sildenafil) OR (sildenafil AND nitrate) OR (nitrate, AND sildenafil) OR (desmethyl AND sildenafil) OR (sildenafil, AND desmethyl) OR desmethylsildenafil	24,812
#3	#1 AND #2	398

Records from electronic databases: 1,117
Records from other resources: 69
Total with duplicates: 1,184
Duplicates: 249
Final records for review: 535

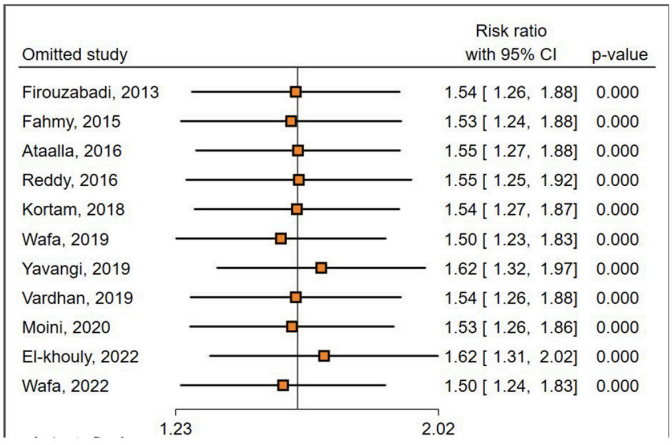
Supplement Table 2. Assessment of the risk of bias in the included trials

Author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Moini et al.[17] 2020	-	+	?	?	+	-	-
El-Sayed et al.[25] 2017	?	+	_	_	?	?	_
Tehraninejad et al.[43] 2018	?	+	+	_	?	_	_
Ataalla et al.[26] 2018	_	+	_	_	_	_	_
Wafa et al.[24] 2019	_	+	_	_	_	_	_
Kortam et al.[27] 2018	_	_	+	?	+	?	_
Reddy et al.[38] 2016	?	+	+	_	+	?	_
AbdelKader Fahmy et al.[28] 2015	_	_	+	?	+	?	_
Ashoush and Abdelshafy[29] 2019	_	_	_	_	_	_	_
Aboelroose et al.[30] 2020	_	_	_	_	_	_	_
Yavangi et al.[44] 2019	_	_	_	?	_	_	_
Vardhan et al.[39] 2019	?	+	+	?	_	?	_
Mangal and Mehirishi[40] 2019	?	+	+	?	_	?	_
Dehghani Firouzabadi et al.[19] 2019	_	?	?	_	_	_	_
Alieva et al.[48] 2012	?	?	?	?	?	?	?
Kim et al.[49] 2010	?	?	?	_	_	?	_
Abdullah et al.[45] 2021	?	+	+	+	_	?	?
Belapurkar et al.[42] 2022	_	?	+	+	_	_	_
Mohammed et al.[46] 2023	?	+	+	+	_	?	?
Dawood et al.[47] 2020	?	+	+	+	_	?	?
Mohamed et al.[18] 2022	_	?	+	+	_	_	_
Gupta et al.[41] 2021	?	+	+	+	?	?	?
Abbas et al.[32] 2021	_	?	+	+	_	_	_
ELkhouly et al.[33] 2022	_	?	+	+	_	_	?
El-Asbaa et al.[34] 2021	_	?	+	+	_	_	?
Abdel Hamid et al.[35] 2021	_	_	+	+	_	?	?
Wafa et al.[24] 2022	?	+	_	_	?	?	_
El-ghany et al.[37] 2022	?	+	_	_	?	?	_



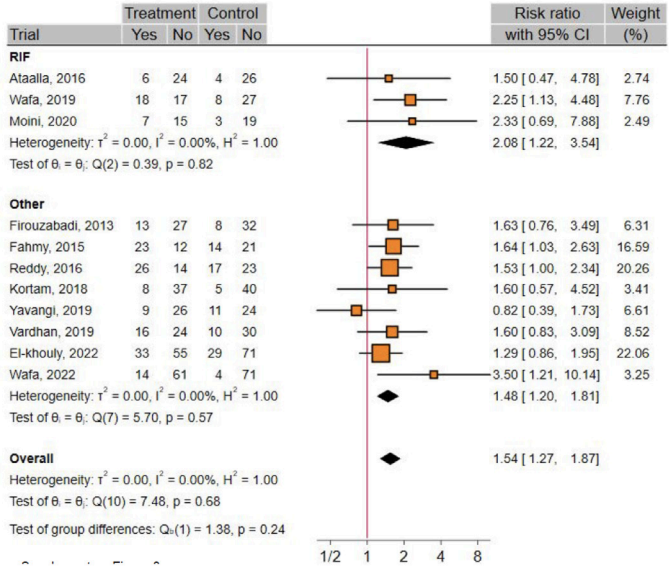
Supplement Figure 1. Funnel plot showing publication bias in trials that evaluated the risk of chemical pregnancy in women who received treatment versus control

RR: Risk ratio

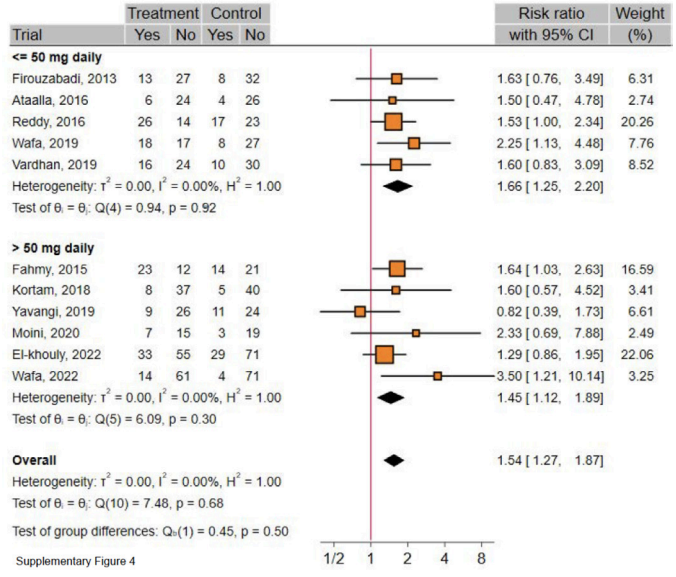


Supplement Figure 2. Leave-one-out plot showing the effect of each study on pooled estimate in subset of trials that evaluated the risk of chemical pregnancy in women who received treatment versus control

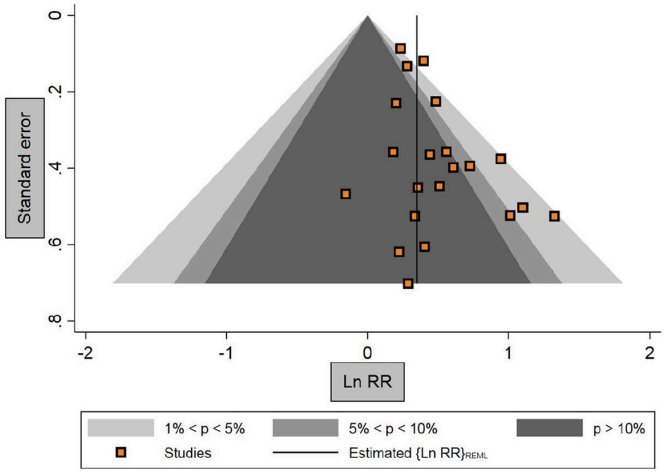
CI: Confidence interval



Supplement 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 intervention versus control regarding population type

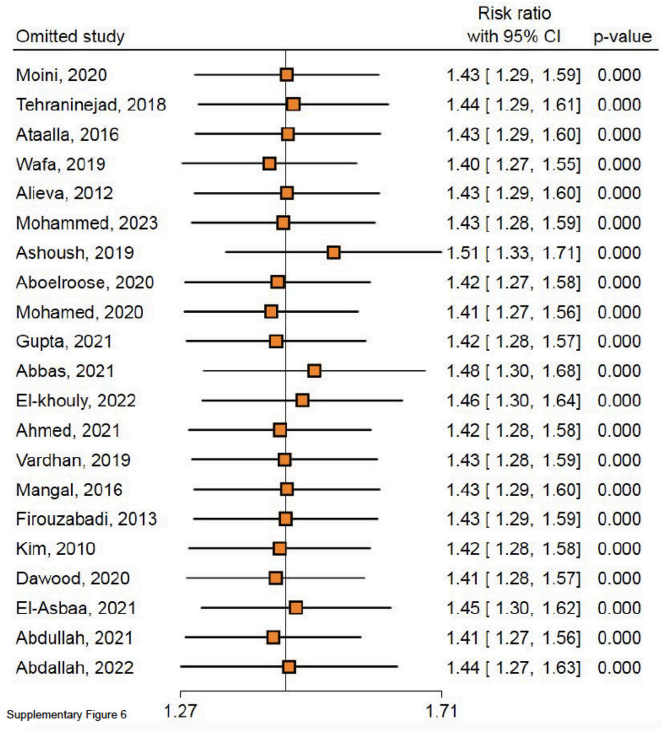


Supplement Figure 4. Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of chemical pregnancy in women who received intervention versus control regarding dose of sildenafil citrate



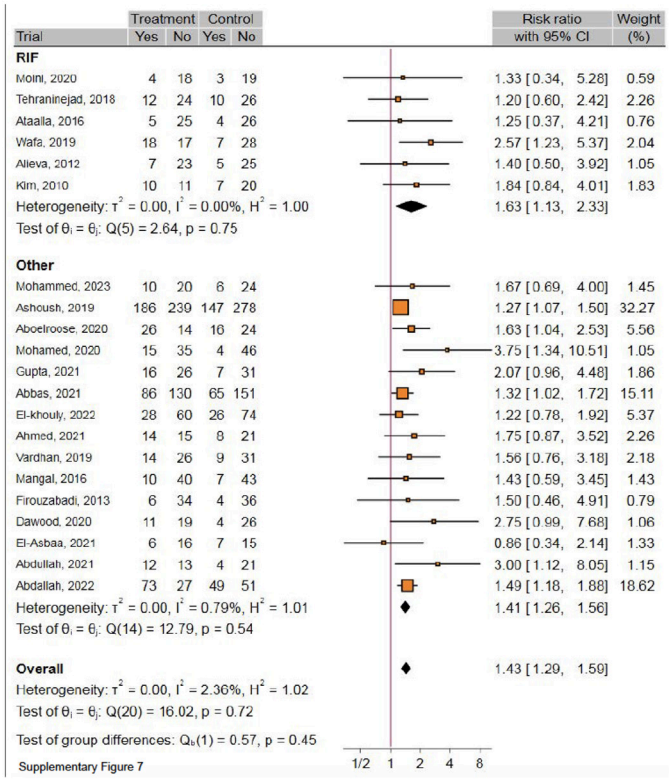
Supplement Figure 5. Funnel plot showing publication bias in trials that evaluated the risk of clinical pregnancy in women who received treatment versus control

RR: Risk ratio

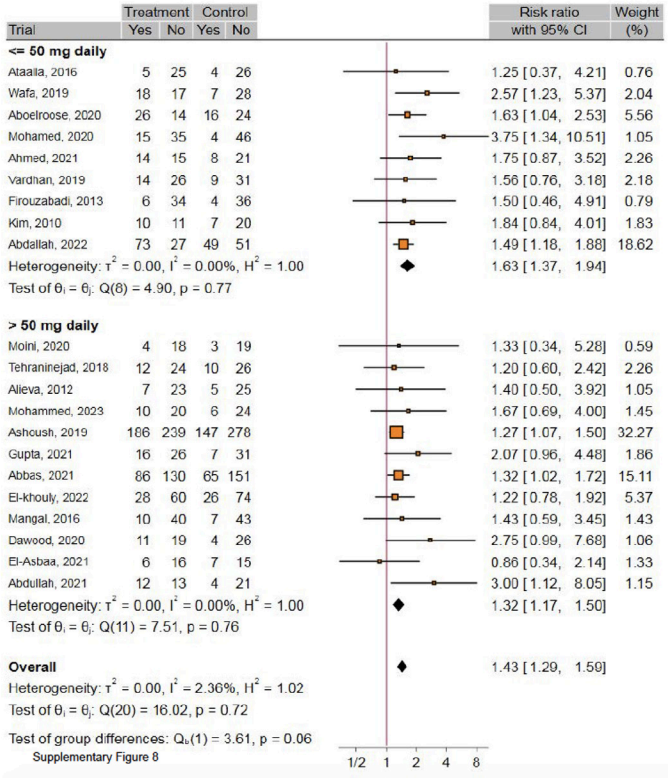


Supplement Figure 6. Leave-one-out plot showing the effect of each study on pooled estimate in subset of trials that evaluated the risk of clinical pregnancy in women who received treatment versus control

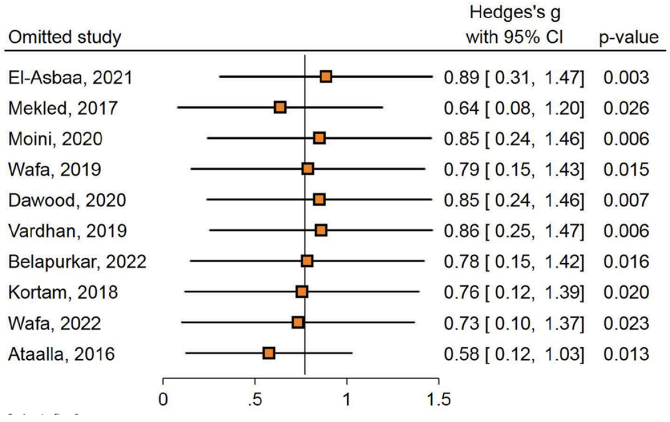
CI: Confidence interval



Supplement Figure 7. 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 intervention versus control regarding population type

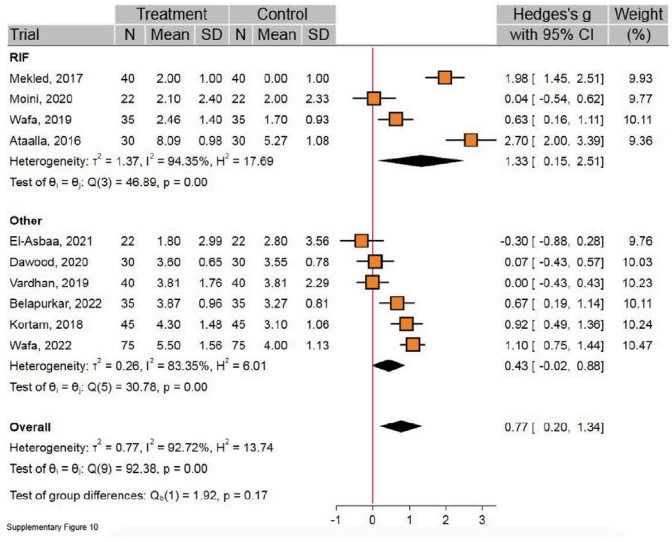


Supplement Figure 8. Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in trials that evaluated the risk of clinical pregnancy in women who received intervention versus control regarding dose of sildenafil citrate



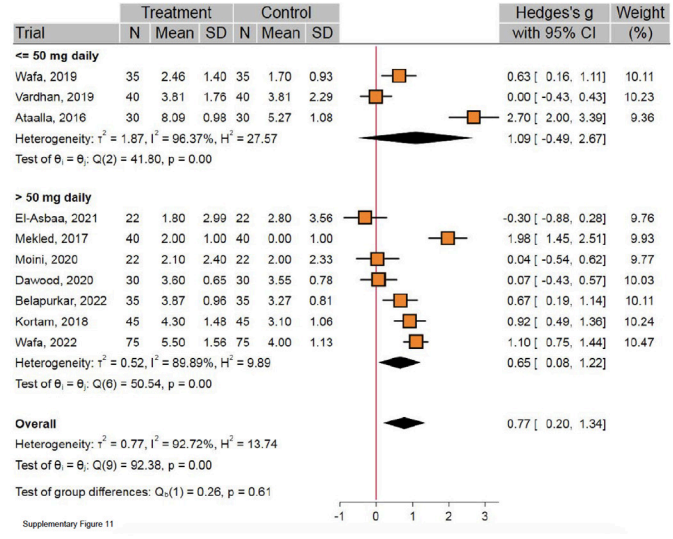
Supplement Figure 9. Leave-one-out plot showing the effect of each study on pooled estimate in subset of trials that evaluated the mean of endometrial thickness in women who received treatment versus control

CI: Confidence interval



Supplement Figure 10. 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 intervention versus control regarding population type

SD: Standard deviation



Supplement Figure 11. 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 intervention versus control regarding dose of sildenafil citrate

SD: Standard deviation