The Effect of Sildenafil Citrate on Fetal and Maternal Ultrasound Indices in IUGR-complicated Pregnancies; A Systematic Review and Meta-analysis of Randomized Clinical Trials

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Research Article

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Abstract

Intrauterine growth restriction (IUGR) is a common complication of pregnancy and is associated with a higher risk of perinatal mortality and morbidity. We aimed to systematically review the studies that evaluated the efficacy of sildenafil citrate on improving the ultrasonographic changes in the middle cerebral artery (MCA) and umbilical artery (UA) in pregnancies complicated with IUGR. We performed a systematic search of PubMed, Scopus, Embase, Pro-Quest, Web of Science, and Google scholar (from inception to 30 June 2020), of randomized clinical studies evaluating the efficacy of sildenafil citrate on different outcomes of IUGR-complicated pregnancies. Mean differences (SD) were extracted and pooled using random and fixed effects models based on their heterogeneity. Six studies were identified for quantitative meta-analysis. Seven outcomes, including MCA resistive index (RI)， MCA pulsatility index (PI)， MCA systolic to the diastolic ratio (S/D), UA RI， UA PI， UA S/D, and cerebroplacental ratio (CPR) have been evaluated in these studies. The pooled results for the efficacy of treatment on MCA RI (Pooled MD = 0.07, 95% CI:0.03 to 0.1,p-value < 0.001) and MCA S/D (Pooled MD = 0.8, 95% CI0.18 to 0.45,p-value < 0.001) were statistically significant. The changes in other outcomes were comparable between the study groups. Overall, our meta-analysis on RCT showed that sildenafil citrate might improve MCA RI and MCA S/D in IUGR-complicated pregnancies. Regarding the other outcomes, our meta-analysis did not provide significant results.

Introduction

Intrauterine growth restriction (IUGR) is a common complication of pregnancy and is associated with an increased risk of perinatal mortality and morbidity [1, 2]. The risk of mortality in IUGR-complicated pregnancies is affected by several factors, such as the etiology, gestational age, and early evaluation using doppler ultrasound [1–3]. Early diagnosis of IUGR using doppler ultrasound in high-risk pregnant women decreases mortality risk [3]. Ultrasound findings of IUGR-complicated pregnancies result from reduced uteroplacental and fetus blood supply or increased blood flow resistance, which are known to be the primary pathogenesis of this disorder [4]. Abnormality in several ultrasound indices, including pulsatility index (PI) of the middle cerebral artery (MCA) and umbilical artery (UA), resistance index (RI) of MCA and UA, systolic to the diastolic (S/D) of MCA and UA, and cerebroplacental ratio (CPR) (6–9), is known to be associated with IUGR [5–8].

To the best of our knowledge, there is no specific useful medication for IUGR, and tight monitoring of high-risk pregnancies until delivery is essential to minimize the potential adverse events [9]. Sildenafil citrate is a vasodilator drug that acts by inhibiting the phosphodiesterase type 5 inhibitor, ultimately leading to reducing the breakdown of cGMP and increasing NO production [10]. Several publications have appeared in recent years investigating the potential role of Sildenafil citrate for improving the clinical or ultrasound-related outcomes in IUGR-complicated pregnancies. Given the helpful role of ultrasound parameters in predicting IUGR, many of these studies have used the changes in these parameters as a measure of response to sildenafil citrate [11–16]. In seeking to reach the integrated result and resolve contradictory results across studies, we conducted a systematic review and meta-analysis to determine the efficacy of sildenafil citrate on ultrasound-related indices in IUGR-complicated pregnancies.

Methods

We performed a systematic search of PubMed, Scopus, Embase, Pro-Quest, ISI web of science, and Google scholar from inception to 30 June 2020 using the search strategy combining the keywords related to *Sildenafil citrate*, *IUGR*, and *ultrasound indices.* Published textbooks and systematic reviews and the reference lists of selected studies

were also searched for additional articles. Our search was limited to English studies. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the search flowchart is shown in Fig. 1.

We included the randomized clinical studies evaluating the efficacy of sildenafil citrate on ultrasound-related outcomes of pregnancies complicated with early or late-onset IUGR. The studies were excluded if: 1) they were not clinical trials, 2) they had a non-randomized design, 3) their language was non-English, 4) they had inadequate data for quantitative analysis. Two researchers were independently screened studies by the title and abstracts and then selected eligible studies following evaluating the full-texts. The essential data on study characteristics (e.g., study design and duration), participants (e.g., sample number and their age range), interventions (e. g type of intervention and comparison), and outcomes (e.g., all ultrasound-related outcomes and their methods of measurement) were extracted from each selected study.

The quantitative meta-analysis was performed using CMA software (version 2). Statistical heterogeneity of the results among studies was evaluated using I^2 Statistics, in which I^2 values of 50% and over were considered significant heterogeneity according to statistical studies [17]. In the case of statistically significant heterogeneity, the random-effects model was used to estimate the effect size of treatment; otherwise, the fixed-effects model was applied to get the study's pooled results. Mean difference (MD) (95% CI) was used as the statistical index for estimating the pooled effects of quantitative and qualitative outcomes, respectively. The quality assessment of the selected studies was performed using the Cochrane risk of bias tool. Publication and related biases were evaluated by visual inspection of funnel plot and statistical tests of Egger's regression and *Begg's* rank. A P-value less than 0.05 was considered significant.

Results

The Prisma flowchart for study selection is presented in Fig. 1. Our initial search found 793 studies, of which 40 studies were included by screening their titles and abstracts. After screening the remaining studies full-text, six trials evaluating seven ultrasound-related outcomes were included in the final quantitative meta-analysis [11–16].

Table 1 summarizes the characteristic of included studies. The sample number of selected studies ranged from 30 to 93, and the total number of participants in all studies was 332. The number of women whose results were pooled for each outcome was 147 for MCA RI, 264 for MCA PI, 188 for MCA S/D ratio, 197 for UA RI, 284 for UA PI, 238 for UA S/D ratio, and 84 for CPR. The gestational age (GA) of women was 24 weeks and more.

Table 1
Study characteristics

References	country	Sample size (N of loss to F/U)	Gestational age	Intervention	comparison	outcomes
Dastjerdi MV et al (2012) (17)	Iran	59 (18)	24–37 weeks	tablet of Sildenafil citrate (50 mg)	placebo tablets	Changes in PI, RI and S/D of MCA and UMA, 2 hour following treatment
El-Sayed MA et al (2017) (18)	Egypt	54 (0)	24 weeks or more	tablet of Sildenafil citrate (50 mg)	placebo tablets containing starch	Changes in PI, RI and S/D of MCA, UMA and UTA, and CPR 2 hour following treatment
khan MI et al (2017) (19)	India	93 (0)	28 weeks or more	tablet of Sildenafil (25mg TID for a week and then increased to 50mg TID till delivery).	placebo tablets	Changes in PI, RI and S/D of MCA and UMA, 1 week following initiation of treatment
Maged M et al (2018) (20)	Egypt	50 (0)	24–32 weeks	Tablet of Sildenafil (20 mg daily and then, if no side effects occurred, the dose increased to 20 mg TID till delivery).	N/A	Changes in PI, RI and S/D of UMA, 4 week following initiation of treatment
Mohammad EE et al (2017) (21)	Egypt	30 (0)	26–32 weeks	Tablet of Sildenafil (20 mg daily for 6 weeks)	placebo tablets	Changes in PI and S/D of MCA and UMA, 4–6 week following initiation of treatment

References	country	Sample size (N of loss to F/U)	Gestational age	Intervention	comparison	outcomes
Shehata NA et al (2020) (22)	Egypt	46	24–34 weeks	Tablet of Sildenafil (20 mg daily TID + fish oil + zinc supplementation	placebo tablets + fish oil + zinc supplementation	Changes in PI of MCA and UMA, 2 hour and 2 weeks following initiation of treatment
Abbreviations. CPR, cerebroplacental ratio; MCA, middle cerebral artery; mg, milligram; N/A, not applicable; TID, Three times a day; RI, resistive index; S/D, systolic to the diastolic ratio; UA, umbilical artery.						

The main intervention component in all selected studies was the oral tablet of sildenafil citrate, given to women in a dose range between 50 to 75 mg daily until delivery [11–16]. In one study, supplementation with fish oil and zinc has been added to the treatment and comparison group [13]. Regarding the comparison group, in five studies, women received a placebo [11–15], and only in one study was nothing given to women [16].

The assessment of the risk of bias in the selected studies is presented in Table 2. Each study bias has been judged as low risk, unclear, and high risk of bias. Overall, 42 responses were recorded, of which 69.04 % was a low risk of bias presenting in all seven domains of the Cochrane tool. The status of four types of biases, including those related to random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors, was unclear in 28.57 % of responses. The risk of attrition bias was high in only one study, which had a loss to a follow-up rate of 30 % [15]. The funnel plot was almost symmetric, showing no publication bias (Fig. 2). The statistical evaluation of publication bias through Egger's regression and *Begg's* rank test was not-significant (p-value = 0.78 and p-value = 0.99, respectively).

Table 2
Quality assessment of selected studies

References	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding to outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dastjerdi MV et al (2012) (17)	Unclear	Unclear	Low risk	Low risk	High risk	Low risk	Low risk
El-Sayed MA et al (2017) (18)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
khan MI et al (2017) (19)	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Maged M et al (2018) (20)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Mohammad EE et al (2017) (21)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Shehata NA et al (2020) (22)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Two studies reported data on MCA RI, five on MCA PI, three on MCA S/D, three on UA RI, five on UA PI, four on UA S/D, and two on CPR. Table 3 shows the summary of pooled results for the effect of sildenafil citrate on ultrasound indices. The visual presentation of individual studies using forest plots for these outcomes is shown in Fig. 3, Fig. 4, Fig. 5, Fig. 6, Fig. 7, Fig. 8, Fig. 9, and Fig. 10. The pooled MD for improvement of MCA RI and MCA S/D was significantly higher in the sildenafil group than the comparison group (Pooled MD = 0.07, 95% CI:0.03 to 0.1, p-value < 0.001; and Pooled MD = 0.8, 95% CI: 0.18 to 0.45, p-value < 0.001, respectively). Although there was a higher pooled MD for MCA PI in the sildenafil citrate group than the comparison group, this difference was not statistically significant. Regarding the UA related outcomes, the women received sildenafil citrate had higher pooled MD for RI, and lower pooled MD for PI and S/D than the comparison group; however, these effects was not statistically significant (Pooled MD = 0.07, 95% CI: -0.05 to 0.19, p-value = 0.26, Pooled MD=-0.08, 95% CI: -0.23 to 0.07, p-value = 0.28, and Pooled MD=-0.02, 95% CI:-0.45 to 0.41, p-value = 0.93, respectively). No significant difference occurred in the mean value of CPR for women who received sildenafil citrate and those who did not (Pooled MD = 0.29, 95% CI: -0.22 to 0.81, p-value = 0.27).

Table 3
The summary of pooled results for estimating the effect size of treatment

Outcome	Model	N of Studies	Effect size and 95% confidence interval				Heterogeneity	
			Mean Difference	Lower limit	Upper limit	P-value for overall effect	P-value for heterogeneity	I-squared
MCA RI	Fixed	2	0.07	0.03	0.10	0.00	0.69	0.00
MCA PI	Random	5	0.55	-0.16	1.26	0.13	< 0.01	99.28
MCA S/D ratio	Fixed	3	0.80	0.45	1.16	0.00	0.63	0.00
UA RI	Random	3	0.07	-0.05	0.19	0.26	< 0.01	96.96
UA PI	Random	5	-0.08	-0.23	0.07	0.28	< 0.01	95.78
UA S/D ratio	Random	4	-0.02	-0.45	0.41	0.93	< 0.01	93.89
CPR	Random	2	0.29	-0.22	0.81	0.27	< 0.001	91.23

Abbreviations. CPR, cerebroplacental ratio; MCA, middle cerebral artery; grRI, resistive index; S/D, systolic to the diastolic ratio; UA, umbilical artery.

Discussion

This study aimed to assess the effectiveness of sildenafil citrate in improving the indices changes detected in MCA and UA ultrasound among IUGR-complicated pregnancies. Six trials evaluated the effects of sildenafil citrate compared with a placebo or no intervention in women with IUGR-complicated pregnancies. The combined results suggest that sildenafil citrate improves the RI and S/D of MCA but has no significant effects on the other ultrasound indices.

The change in MCA indices, including RI, PI, and S/D, has a nonlinear pattern depending on gestational age in ultrasound evaluation of normal pregnancy, probably due to different brain demands to blood supply during different gestational periods [18]. MCA indices abnormality is an indicator of fetoplacental circulation and is associated with an increased risk of adverse outcomes in IUGR-complicated pregnancies [19, 20]. Our study pooled results found that sildenafil citrate significantly increased the RI [12, 14] and S/D [12, 14, 15]. The heterogeneity of combined studies for RI and S/D was not significantly different, and all of them reported the increasing or no effects of sildenafil citrate for these outcomes. No significant difference was found between the group receiving sildenafil citrate or placebo regarding the MCA PI index. As the combined studies for the PI index of MCA had high heterogeneity, we used a random model to estimate pooled effect size in the final quantitative analysis.

Previous shreds of evidence have demonstrated that abnormality in UA indices including RI, PI, and S/D had predictive value for the occurrence of IUGR in the high-risk population [8] and predictive value for the occurrence of adverse outcomes in IUGR-complicated pregnancies [21, 22]. Several trials evaluated the effect of sildenafil citrate on UA indices in IUGR-complicated pregnancies. In our analysis, the pooled results for the impact of sildenafil citrate on UA indices were not statistically significant; nevertheless, the selected studies showed high heterogeneity, and more studies are needed to evaluate this effect.

CPR, measured by the ratio of PI in MCA to UA, has been known as a helpful ultrasound indicator for fetoplacental circulation. Reduced CPR has been proven to be associated with increased risk of IUGR and its related adverse events [23, 24]. Two studies evaluated the effects of sildenafil citrate on CPR. Our analysis showed that the pooled effect size for treatment was not statistically significant; however, further studies are needed to clarify these results considering the small number of samples and high heterogeneity of these studies.

There were some limitations in this meta-analysis. First, we had high heterogeneity for assessing five outcomes, which limited the synthesis of the evidence; however, although the limitation partly remains, we used the random models for these analysis cases to overcome this problem. Second, the number of included studies was minimal, and further trials with higher sample numbers should be designed in the future. Finally, there were some differences in the design of selected studies, and we could not perform subgroups analysis due to the small number of included studies for each outcome. One of the differences was the time interval between the measurement of the index and the initial treatment. Furthermore, the cumulative daily dose of sildenafil citrate was slightly different. Further studies in the future will allow us to compare different subgroups.

Declarations

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Conflicts of interest: The authors have no conflicts of interest to declare

Ethics approval: The protocol for this research project has been approved by the ethics committee of Tabriz University of Medical Science.

Consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and material: Not applicable

Code availability: Not applicable

Authors contributions: All authors contributed significantly as follow: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

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Figures

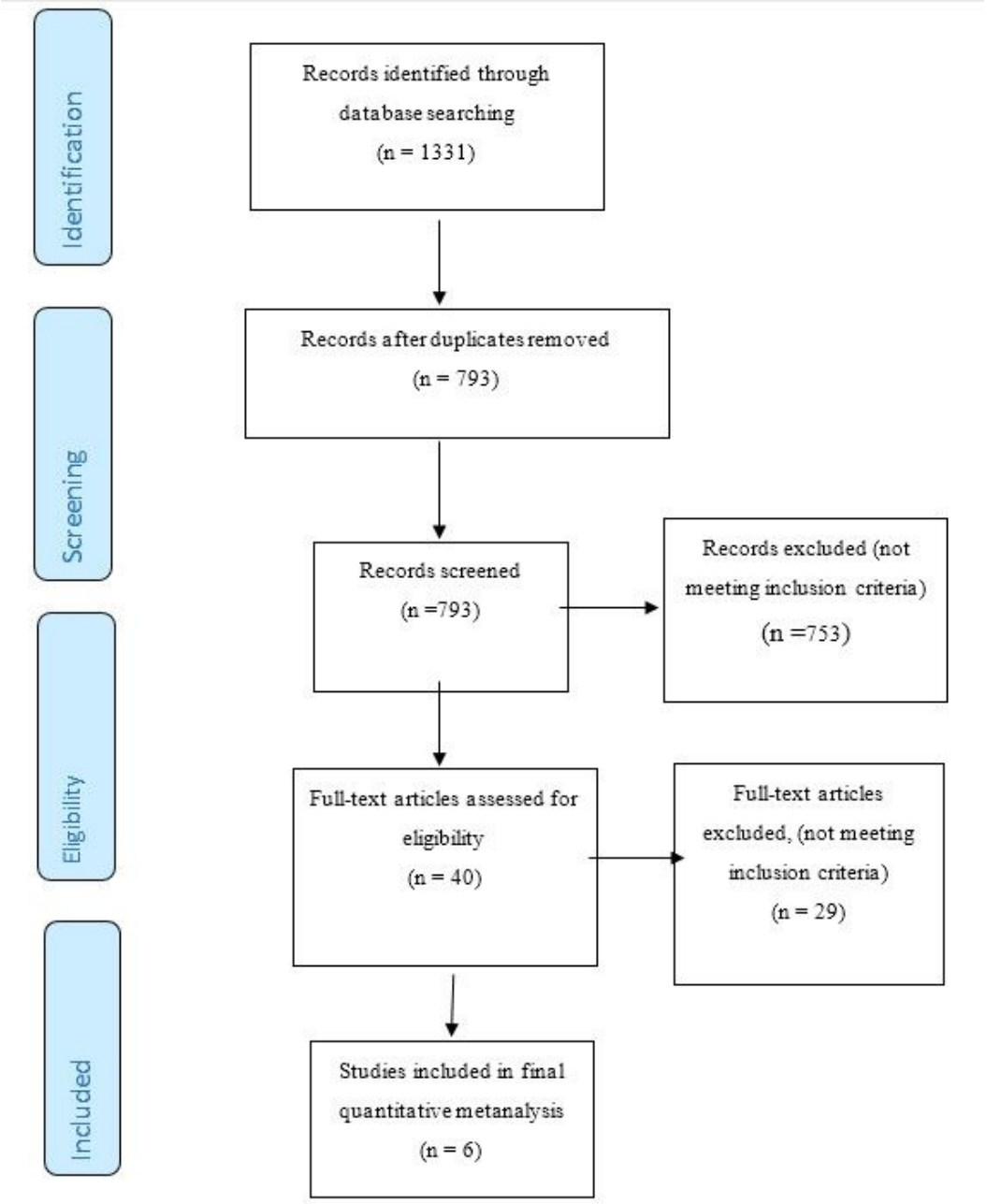

Figure 1

The Prisma flowchart of study selection

Figure 2

Funnel plot for assessment of publication bias

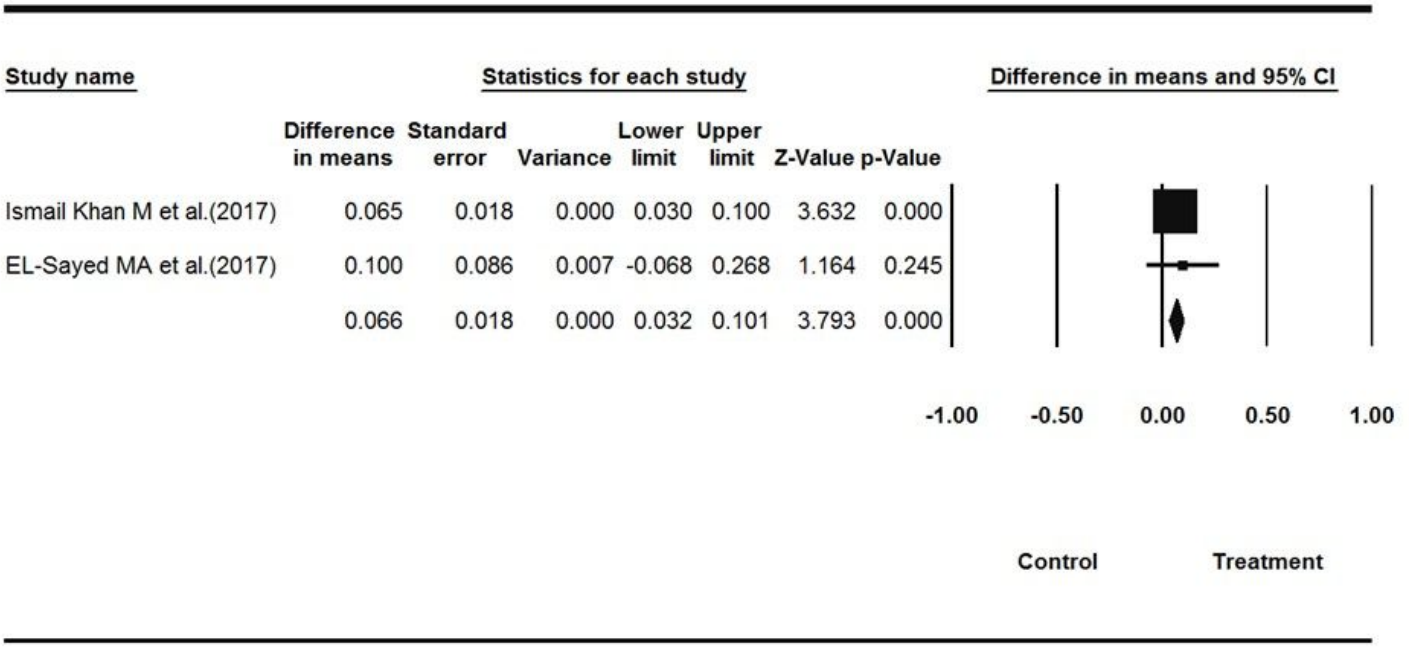

Figure 3

Effect of sildenafil citrate on MCA RI

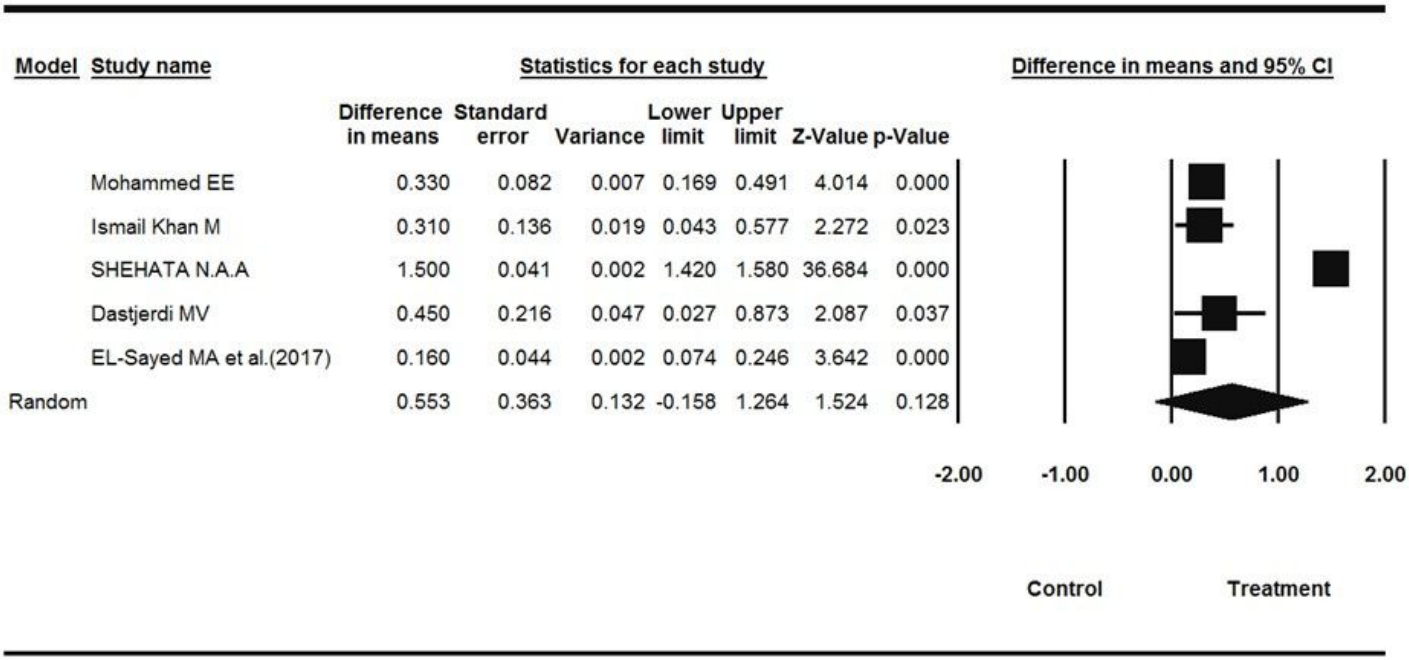

Figure 4

Effect of sildenafil citrate on MCA PI

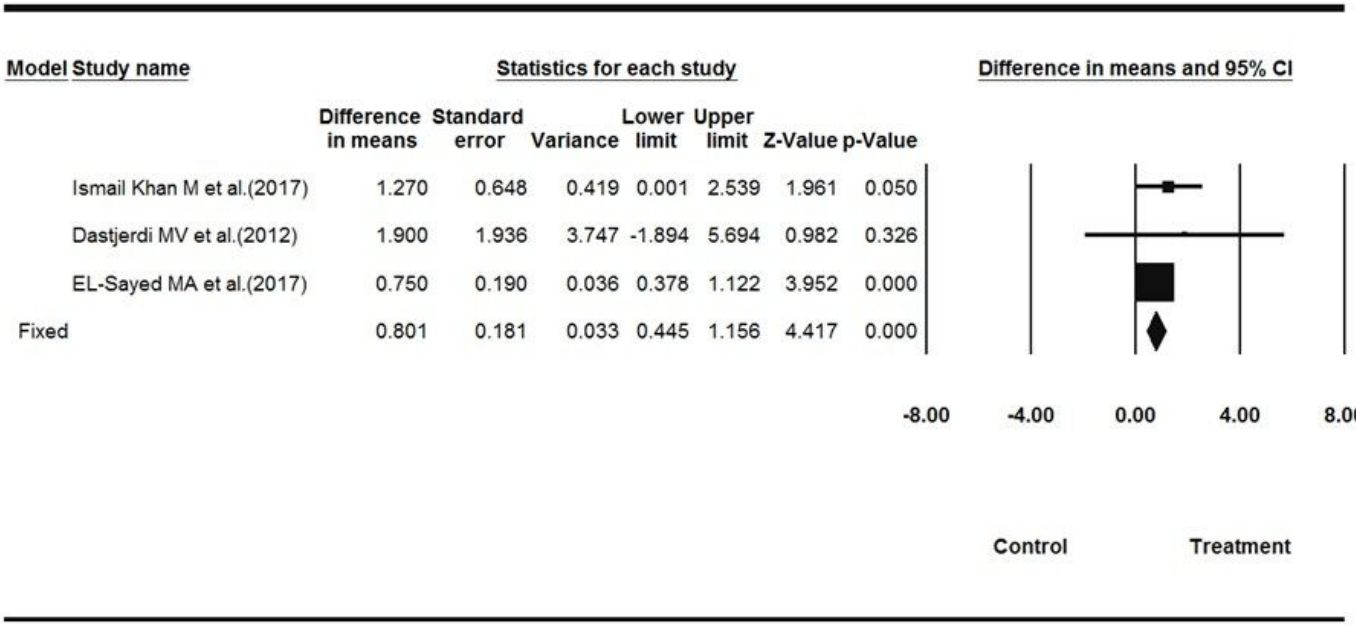

Figure 5

Effect of sildenafil citrate on MCA S/D

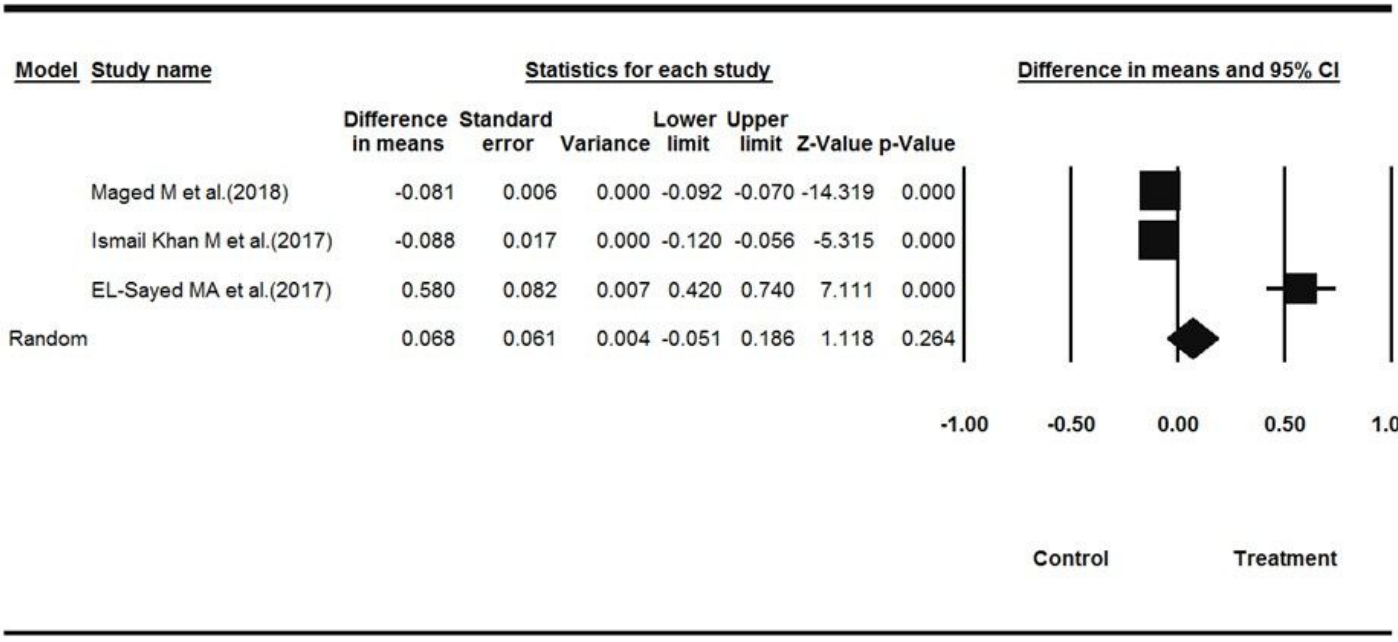

Figure 6

Effect of sildenafil citrate on UA RI

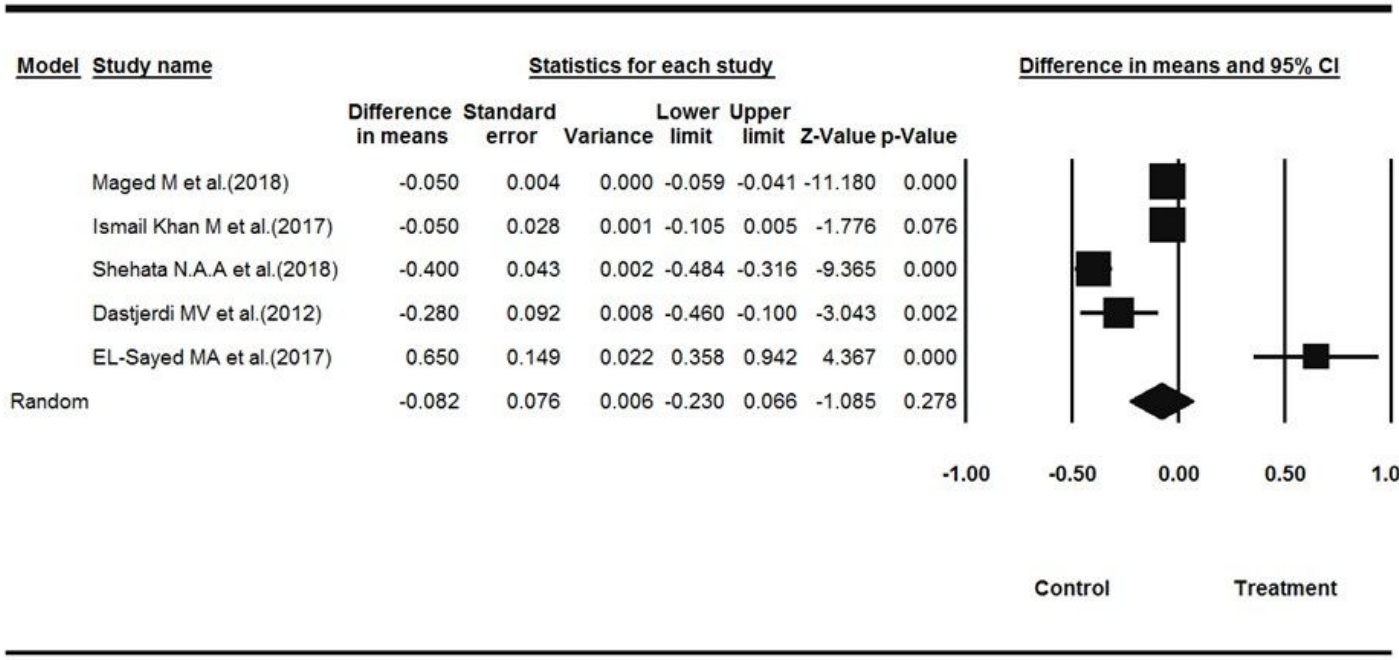

Figure 7

Effect of sildenafil citrate on UA PI

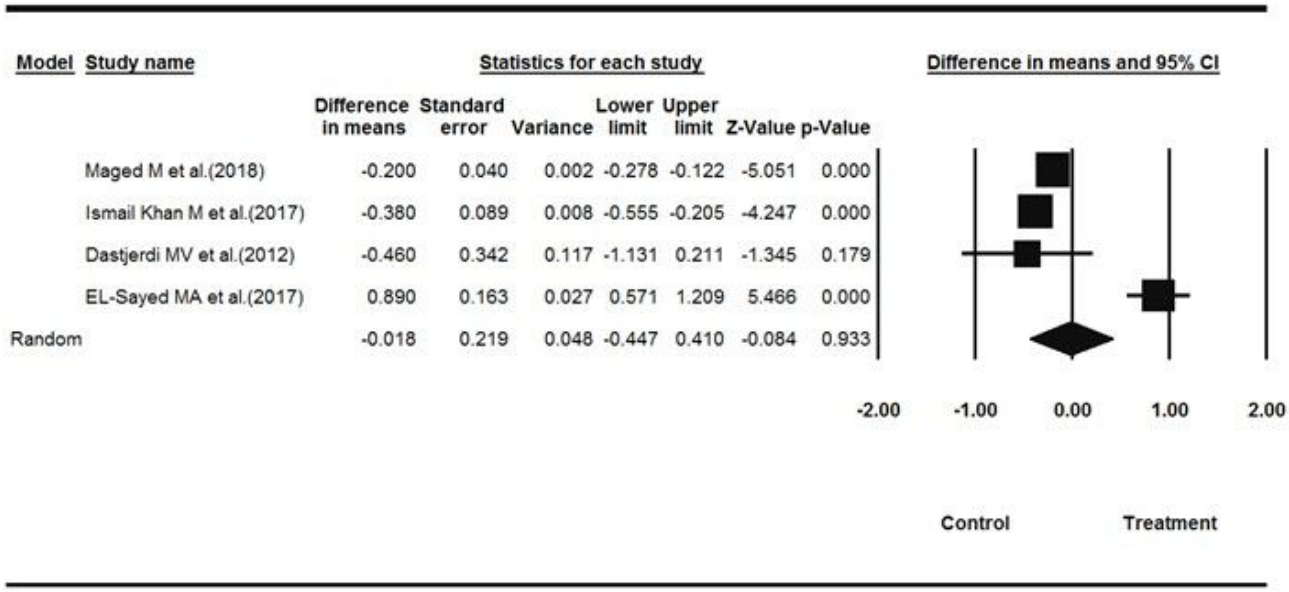

Figure 8

Effect of sildenafil citrate on UA S/D

Figure 9

Effect of sildenafil citrate on CPR