The effects of sildenafil on fetal Doppler indices: A systematic review and meta-analysis

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Abstract:

Background & Objective: Sildenafil citrate is a potential new strategy for the management of intra-uterine growth restriction (IUGR) and preeclampsia, although its efficacy still needs to be approved. This study has been tried **t**o systematically assess evidence on the effectiveness of sildenafil on improving fetal Doppler indices as well as the most common adverse effects of sildenafil.

Materials & Methods: Online databases PubMed, Web of Science, Scopus, Embase, and Cochrane reviews were searched from their date of creation up until 26 Jan. 2019. We conducted two Meta-analyses, one for fetal Doppler indices and other for adverse events of sildenafil. Eligible studies were randomized controlled trials (RCTs) in which the effects of sildenafil on fetal Doppler indices have been evaluated. The quality of studies was appraised through five components of Cochrane's checklist for quality appraisal of RCT studies by two of the authors.

Results: Out of 1087 reviewed sources, seven studies were included for meta-analysis. The following results were observed for the effect of sildenafil on the umbilical artery: significant effect on Umbilical Artery Pulsatility Index (UA PI) (P=0.03), which was observed in dosages more than 60 mg/day (P=0.008). Sildenafil was effective in UA PI of the individuals suffering from Eclampsia (P=0.008); however, no significant effect was observed on IUGR disorder. Furthermore, sildenafil had no effect on the umbilical artery systolic/diastolic ratio (UA S/D ratio). Sildenafil was not effective on middle cerebral artery pulsatility index (MCA PI) or on middle cerebral artery systolic/diastolic ratio (MCA S/D Ratio). Regarding adverse events, headaches occurred significantly more in mothers consuming sildenafil (P=0.03).

Conclusion: Obviously, we need more accurate RCTs in this issue before any judgments can be made.

Key Words: Sildenafil, Doppler Indices, IUGR, Preeclampsia, Meta-Analysis.

INTRODUCTION

In the first half of pregnancy, utero-placental arteries, especially spiral arteries, undergo a series of pregnancy-specific changes to meet the requirements of the fetus. Spiral artery modification reduces maternal blood flow resistance and increases utero-placental perfusion (1). Reduced trophoblast invasion and the absence of pregnancy-specific changes of utero-placental arteries have a crucial role in IUGR and are often combined with preeclampsia. In addition, in a normal pregnancy, the trophoblast produces nitric oxide (NO), which acts as a vasodilator in feto-placental circulation. It has been shown that NO can improve perfusion in IUGR pregnancies and preeclampsia by relaxing the arteries and improving oxygen and nutritional supplies (2).

Consequently, it is assumed that sildenafil citrate can be a potential strategy to aid women suffering from IUGR and preeclampsia during pregnancy by releasing NO (3).
Sildenafil citrate in tablet form and under the name Viagra was initially used to treat erectile dysfunction in men. The physiologic mechanism of sildenafil involves the release of NO, and it enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE-5). This process can relax the muscles of blood vessels and other areas of the body, such as the uterine vessel (3, 4). This finding has inspired many researchers to use sildenafil for the management of preeclampsia and IUGR (5-12).
Due to an increase in the prevalence of preeclampsia, as well as the massive physical, psychological, and economic burdens of preeclampsia and IUGR, sildenafil can be of great interest as an innovative approach, even though its efficacy still needs to be approved (13-16). Every medication should be prescribed with extreme caution. To date, the use of sildenafil in human pregnancy has not been clinically approved; it is confined to research studies.
Unfortunately, due to a lack of adequate RCTs, different reported outcomes, or unqualified research works, only two systematic reviews exist in this field. The first one evaluated the effect of sildenafil on IUGR with in-vitro studies, and the other reported the adverse effects of sildenafil usage in pregnancy, along with some obstetrical and perinatal outcomes (17, 18). For evaluating sildenafil efficacy in pregnancy, one of the most reported outcomes has been Doppler ultrasonography indices. Two common Doppler indices for predicting and evaluating IUGR and preeclampsia are related to the umbilical artery (UA) and the middle cerebral artery (MCA) (19, 20).
In our search, the outcome that led to the recruitment of the most qualified RCTs was associated with Doppler ultrasonography indices. It seems that if the effect of the sildenafil on fetal Doppler indices is known, then the effect of sildenafil on IUGR and preeclampsia can be predicted through evidence-based studies. It may also be useful for understanding the mechanism of effects more accurately.

Objective: Considering the importance of evidence-based research studies for clinical decision-making, this meta-analysis aimed to evaluate sildenafil's efficacy in improving fetal Doppler indices. It also describes the most common adverse effects of sildenafil. Specifically, the umbilical artery pulsatility index (UA PI), umbilical artery systolic/diastolic ratio (UA S/D ratio), middle cerebral artery pulsatility index (MCA PI), and middle cerebral artery systolic/diastolic ratio (MCA S/D ratio) were evaluated in mothers suffering from preeclampsia and IUGR during pregnancy.

METHODS:

Search Strategy

Online databases PubMed, Web of sciences, SCOPUS, EMBASE, and Cochrane reviews were searched from their date of creation (up until 26 Jan. 2019). The MESH terms for "Sildenafil", "Pregnancy", "Preeclampsia", "IUGR", "Amniotic fluid", "Apgar score", and "mode of delivery" were extracted from PubMed.

Selection Process

Studies lacking control groups or that were not related to the main subject were excluded. Two of the authors reviewed the title and abstract of the papers individually, extracted the full text of the related studies, and ultimately the required data. Disagreements about inclusion or exclusion were

discussed and resolved by consensus or arbitration. The percent agreement of the two researchers was 97.5%, and the Kappa statistic was 91.9%. The extracted data included the name of the author, year of publication, country, type of study, study population, age of mother, term of pregnancy upon receiving sildenafil, dose of received sildenafil, and the population size in intervention groups and control groups, as well as indices related to fetal Doppler, UA, and MCA.

Sub-group Analysis

Sub-groups of fetal Doppler indices (UA and MCA) were analyzed based upon the dose of the used medication, term of effect assessment, study population, and quality of the conducted studies.

Adverse Events

The reported adverse events included headache, hot flash, nausea and vomiting, epigastric pain, neurologic disorders, visual disturbances, dizziness, abruption, postpartum hemorrhage, HELLP Syndrome, eclampsia, and backache. These were compared in both groups.

Quality Appraisal of Studies

The quality of each study was appraised based on five components of Cochrane's checklist for quality appraisal of RCT studies, including random sequence generation, allocation concealment, blinding, incomplete reporting, and selective outcome reporting. According to the checklist, the studies were scored between 0 and 2 (high-risk, unknown, and low-risk). In cases where all the above-mentioned criteria were present, the respective study was selected as a high-quality study. A score of 8 to 9 represented a medium-quality study; if a study did not meet more than two of the criteria (yielding a score of less than 8), it was categorized as a low-quality study. None of the studies were excluded due to their quality.

Data Analyses

RevMan software (version 5.3) was employed for the meta-analysis of data. The mean and standard deviation of the fetal Doppler indices, including fetal Doppler indices PI index and the S/D ratios of UA and MCA, were extracted from the studies. Also, the adverse effects of sildenafil were extracted from qualified studies. Two meta-analyses were conducted on fetal Doppler indices and maternal adverse effects ~~as a result of sildenafil consumption~~. The first meta-analysis on Doppler indices was conducted using standardized mean difference (SMD) and random effects. SMDs were measured per Cohen regulations: any value lower or equal 0.2 was denoted as a "minor effect"; a value between 0.2 and 0.8 was denoted as a "medium effect"; and any value equal to or higher than 0.8 was denoted as a "major effect" (21). The I^2 statistic was employed for the examination of the study's heterogeneity (22). In the second meta-analysis, the effect of sildenafil on maternal adverse events was analyzed using an odds ratio and the random effect between the two intervention and control groups. Also, Begg and Egger statistical tests were used to measure publication bias (24, 23). An ethical committee's approval and participants' informed consent were not required.

RESULTS

Selection Process

A search among electronic resources yielded 1084 references from databases and three from references of papers. Out of 1087 reviewed sources, 804 studies were excluded for repetition, and 511 were excluded for other reasons. Moreover, 463 studies were not related to the main subject,

and 48 were excluded from the systematic review and meta-analysis for not being a clinical trial. Out of the 101 studies remaining for full-text evaluation, 94 studies were excluded for not containing adequate data, and another two were excluded for not having any control or waiting groups. Ultimately, seven studies were included in the meta-analysis (Figure 1).

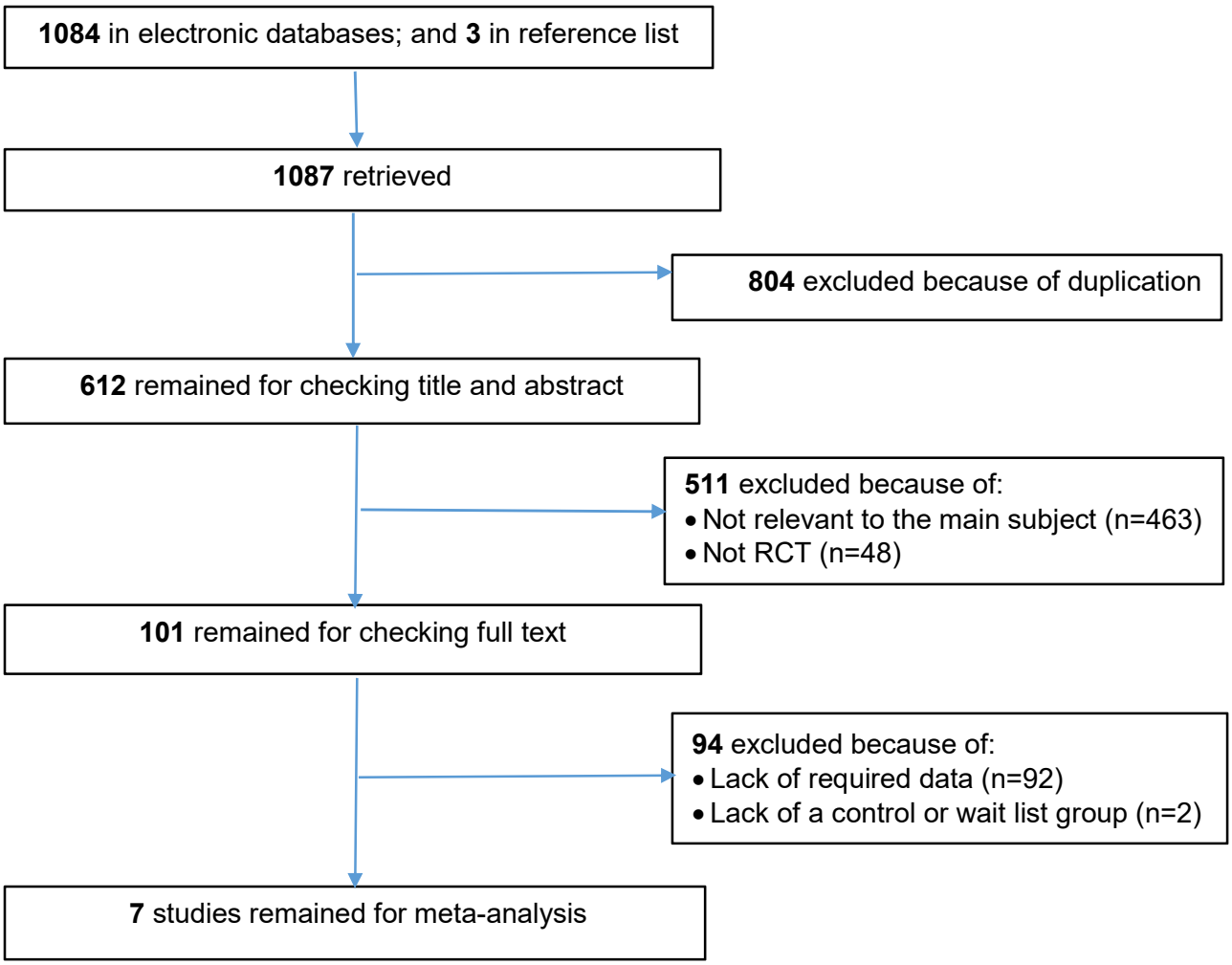

Figure 1. Flow diagram showing the phases of development through the meta-analysis

Study Characteristics

Seven papers had the required criteria for inclusion in meta-analysis (3-9). The total number of participants in these studies was 361. Of these, 180 individuals were in intervention groups and 181 individuals were in control group. The mean ages of mothers in intervention and control groups were 26.4 and 28.6 years, respectively. The mean ages of pregnancy upon admission to the study in the intervention and control groups were 29.8 and 30.4 weeks, respectively. Most studies were conducted on IUGR (five studies), and the rest examined preeclampsia (two studies). The quality of most of the studies was high (57%) (Table 1).

The funnel plots in both meta-analyses were symmetrical, and it seems that the probability of publication bias is very low.

Table 1.Characteristics of included studies in meta-analysis

Author	Year	country	Design	Study population	Maternal age		GA (week)		SC regimen	Sample size		Study quality	PI of Umbilical Artery	
					Int.	Cont.	Int.	Cont.		Int.	Cont.		Int.	Cont.
Vahid Dastjerdi	2012	Iran	RCT	IUGR	25.6	32	35	35	50 mg	29	30	Low	1.01 (0.13)	1.02 (0.31)
El-Sayed	2017	Egypt	RCT	IUGR	26.3	28.1	29.7	29.3	50 mg daily	27	27	High	0.79 (0.59)	0.14 (0.5)
Samangaya	2009	UK	RCT	Preeclampsia	28*	27*	31*	29*	20 - 80 mg TDS	17	18	High	1.17 (0.22)	1.27 (0.14)
Shehata	2018	Egypt	RCT	IUGR	30.4	30.7	29.5	30.1	20 mg TDS	23	23	Moderate	1.8 (0.03)	1.9 (0.03)
Trapani	2016	Brazil	RCT	IUGR	23.6	25.8	28.5	30.1	50 mg single dose	12	12	High	1.21 (0.13)	1.40 (0.11)
Trapani	2016	Brazil	RCT	Preeclampsia	25.3	26.4	29.1	30.2	5o mg TDS	47	46	High	1.19 (0.17)	1.38 (0.13)
Maged	2018	Egypt	Non random RCT	IUGR	27.3	28.7	27.4	28.1	20 mg daily to 20 mg TDS	25	25	Low	1.88 (0.02)	1.94 (0.01)

RCT: Randomized Controlled Trial, IUGR: Intra Uterine Growth Restriction, PI: Pulsatility Index, TDS: Three Times a day, GA: Gestational Age, SC: Sildenafil Citrate, Int: Intervention, Cont: Control, *Data are Median

Subgroup Analyses

The effects of sildenafil on the Umbilical Artery (UA) Indices:

- **UA PI**

The results yielded by the studies revealed that Sildenafil significantly decreases the UA PI to a value of 1.28 in the intervention group in comparison with the control group (SMD= -1.28; 95% CI, -2.44, -0.12; P=0.03) (Table 2). The Sildenafil effect on UA PI was observed in dosages of more than 60 mg per day (SMD= -.0.94; 95% CI, -1.63, -0.25; P=0.008), and in durations of 24 hours (SMD= -1.24; 95% CI, -1.69, -0.80; P<0.001), two weeks (SMD= -0.90; 95% CI, -1.59, -0.20; P=0.01), and four weeks (SMD= -3.74; 95% CI, -4.68, -2.79; P<0.001), but it was ineffective in durations of two hours (Table 2 and Figure 2). From a study population perspective, Sildenafil was effective in preeclampsia (SMD= -0.94; 95% CI, -1.63, -0.25; P=0.008), but had no effect on IUGR (Table 2 and Figure 3). From a study quality perspective, only medium quality studies showed such an effect (SMD= -3.28; 95% CI, -4.18, -2.37; P<0.001) (Table 2).

Table 2.The effects of Sildenafil on the Doppler indices in different sub-groups of the study (based on SMD and random effect)

Adverse events	Umbilical Artery						Middle Cerebral Artery					
	PI			S/D ratio			PI			S/D ratio		
	SMD	95% CI	P Value	SMD	95% CI	P Value	SMD	95% CI	P Value	SMD	95% CI	P Value
Dose of the Sildenafil												
50 mg Single dose	-0.74	-2.20, 0.71	0.32	-0.14	-0.78, 0.51	0.68	-0.06	-0.57, 0.44	0.80	0.15	-0.50, 0.80	0.65
20 - 60 mg daily	-1.93	-5.35, 1.49	0.27	-0.73	-5.04, 3.59	0.74	19.91	-17.66, 57.47	0.30	1.06	0.49, 1.63	<0.001
> than 60 mg daily	-0.94	-1.63, -0.25	0.008	-	-	-	-0.20	-0.61, 0.21	0.34	-	-	-
Time of outcome assessment												
2 hours	-0.89	-2.72, 0.94	0.34	0.67	-0.90, 2.24	0.40	2.89	0.43, 5.35	0.02	0.62	-0.27, 1.51	0.17
24 hours	-1.24	-1.69, -0.80	<0.001	-	-	-	-0.20	-0.61, 0.21	0.34	-	-	-
2 weeks	-0.90	-1.59, -0.20	0.01	-	-	-	57.83	45.46,70.20	<0.001	-	-	-
4 weeks	-3.74	-4.68, -2.79	<0.001	-2.94	-3.76, -2.12	<0.001	-	-	-	-	-	-
Study population												
IUGR	-1.46	-3.33, 0.41	0.13	-0.52	-2.89, 1.85	0.67	2.89	0.43, 5.35	0.02	0.62	-0.27, 1.51	0.17
Preeclampsia	-0.94	-1.63, -0.25	0.008	-	-	-	-0.20	-0.61, 0.21	0.34	-	-	-
Quality of the studies												
High	-0.52	-1.75, 0.72	0.41	1.47	0.86, 2.07	<0.001	0.18	-0.64, 0.99	0.67	1.06	0.49, 1.63	<0.001
Moderate	-3.28	-4.18, -2.37	<0.001	-	-	-	39.31	30.89,47.74	<0.001	-	-	-
Low	-1.87	-5.49, 1.75	0.31	-1.53	-4.27, 1.22	0.28	0.08	-0.57, 0.72	0.82	0.15	-0.50, 0.80	0.65
Total effect	**-1.28**	**-2.44, -0.12**	**0.03**	-0.52	-2.89, 1.85	0.67	1.38	-0.22, 2.98	0.09	0.62	-0.27, 1.51	0.17

PI: Pulsatility Index, S/D: systolic/diastolic, IUGR: Intra Uterine Growth Restriction, SMD: Standardized Mean Difference

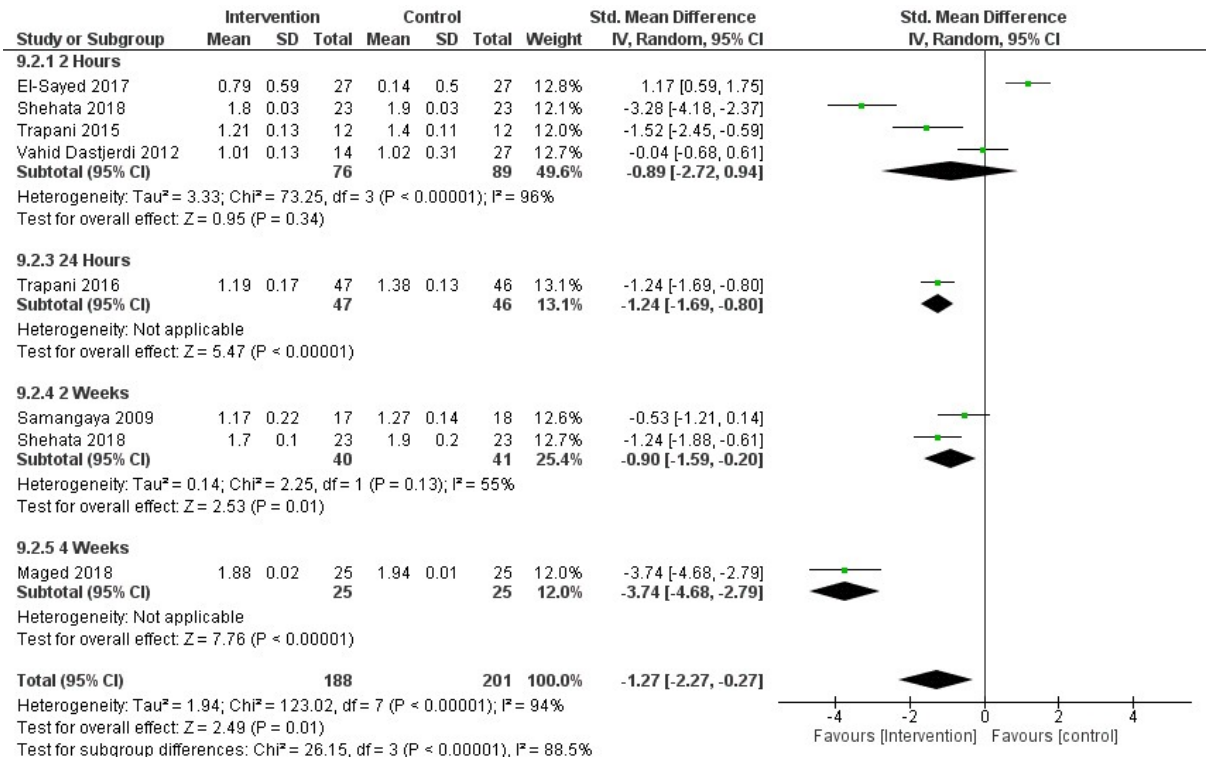

Figure 2. Forest plot compare the mean difference of UAPI between sildenafil and control group based on assessment time (2 hours, 24 hours, 2 weeks, 4 weeks after sildenafil use).

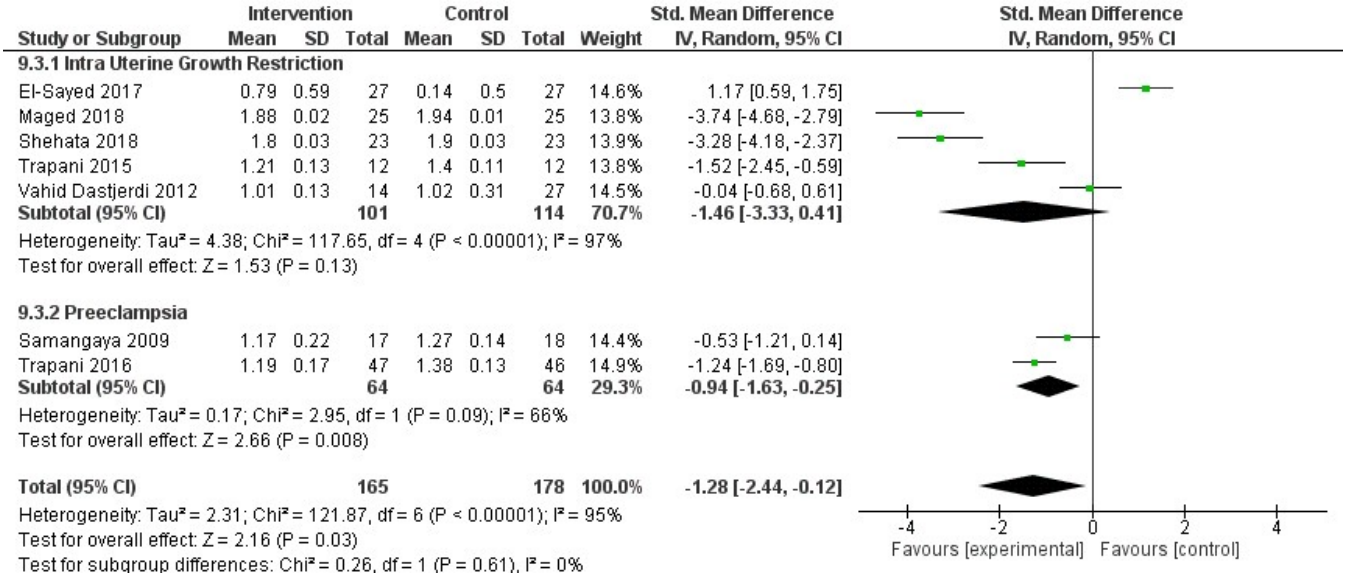

Figure 3.Forest plot compare the mean difference of UAPI between sildenafil and control group in the two subgroups of IUGR and Pre-eclampsia.

- **UA S/D Ratio**

Sildenafil exerted no effect on UA S/D Ratio. The effect was significant only in a four-week follow-up subgroup (SMD= -2.94; 95% CI, -3.76, -2.12; P<0.001) and in high quality studies (SMD= 1.47; 95% CI, 0.86, 2.07; P<0.001) (Table 2).

The effect of sildenafil on the Middle Cerebral Artery (MCA) Indices:

- **MCA PI**

Sildenafil had no effect on MCA PI of the embryo. The effect was significant only in a two-hour follow-up (SMD= 2.89; 95% CI, 0.43, 5.35; P=0.02), a two-week follow-up (SMD= 57.83; 95% CI, 45.46, 70.20; P<0.001) and in IUGR (SMD= 2.89; 95% CI, 0.43, 5.35; P=0.02) subgroups and in low quality studies (SMD= 39.31; 95% CI, 30.89, 47.74; P<0.001) (Table 2).

- **MCA S/D Ratio**

Sildenafil had no effect on MCA S/D ratio. The effect was significant only at the dosage of 20-60 mg per day (SMD= 1.06; 95% CI, 0.49, 1.63; P<0.001) and in high quality studies (SMD= 1.06; 95% CI, 0.49, 1.63; P<0.001) (Table 2).

The heterogeneity values for different types of studies are as follows: 95% (P<0.001) for studies conducted on UA PI, 97% (P<0.001) for studies conducted on UA S/D ratio, 96% (P<0.001) for studies conducted on MCA PI, and 77% (P=0.04) for studies conducted on MCA S/D ratio. A subgroup analysis decreased the heterogeneity to 55% in studies conducted on UAPI (Table 3).

Table 3.Heterogeneity assessment using Chi-square test in different sub-groups of the study (based on I^2 statistics)

Heterogeneity	Umbilical Artery				Middle Cerebral Artery			
	PI		S/D ratio		PI		S/D ratio	
	I^2	P Value	I^2	P Value	I^2	P Value	I^2	P Value
Dose of the Sildenafil								
50 mg Single dose	85	0.01	-	-	0	0.49	-	-
20 to 60 mg daily	98	<0.001	99	<0.001	99	<0.001	-	-
> than 60 mg daily	66	0.09	-	-	-	-	-	-
Time of outcome assessment								
2 hours	96	<0.001	92	<0.001	97	<0.001	77	0.04
24 hours	-	-	-	-	-	-	-	-
2 weeks	55	0.13	-	-	-	-	-	-
4 weeks	-	-	-	-	-	-	-	-
Study population								
IUGR	97	<0.001	97	<0.001	97	<0.001	77	0.04
Preeclampsia	66	0.09	-	-	-	-	-	-
Quality of the studies								
High	94	<0.001	-	-	83	0.002	-	-
Moderate	-	-	-	-	-	-	-	-
Low	98	<0.001	96	<0.001	-	-	-	-
Total effect	95	<0.001	97	<0.001	96	<0.001	77	0.04

PI: Pulsatility Index, S/D: systolic/diastolic, IUGR: Intra Uterine Growth Restriction.

Adverse Events

The meta-analysis conducted on maternal adverse events revealed a 3.57-times increase (CI: 1.14, 11.18; P=0.03) in the occurrence of headache in the intervention group in comparison with the

control group. The other maternal adverse events presented no statistically significant differences between the two groups. Furthermore, no significant heterogeneity existed among the studies conducted on maternal adverse events (Table 4).

Table 5.The effects of Sildenafil on the reported maternal adverse events (based on Odds ratio and random effect)

Adverse events	Total effects			Heterogeneity	
	Odds ratio	95% CI	P Value	I^2	P Value
Headache	3.57	1.14-11.18	0.03	57	0.06
Nausea or Vomiting	1.29	0.42-3.93	0.66	46	0.14
Flushing	4.26	0.45-40.58	0.21	0	0.83
Epigastric pain	0.73	0.33-1.62	0.44	0	0.56
Diarrhea	0.94	0.23-3.82	0.93	4	0.35
Neurological disturbances	0.61	0.22-1.69	0.34	0	0.88
Visual disturbances	0.91	0.40-2.09	0.83	0	0.48
Dizziness	0.75	0.16-3.59	0.72	0	0.68
Back pain	2.10	0.18-24.87	0.56	-	-
Placental abruption	2.13	0.37-12.16	0.40	0	0.94
Post-Partum Hemorrhage	1.02	0.14-7.53	0.99	0	0.97
HELLP syndrome	0.51	0.08-3.03	0.45	0	0.51
Eclampsia	0.32	0.05-2.09	0.23	0	0.97

Discussion

This systematic review summarized the fetal Doppler indices following sildenafil use in the pregnancy in the existence of RCTs. The outcomes are reported separately for UA and MCA indices in IUGR and preeclampsia studies.

The evaluation of UA PI revealed that, in general, UA PI is reduced significantly in pregnant women who used sildenafil in comparison with the control group.

In this meta-analysis, a sub-analysis was conducted to determine the "effective dosage of sildenafil in UA PI", "the best time for evaluating UA PI index after sildenafil use", "compare the effect size of UA PI on individuals suffering from IUGR and preeclampsia", and "the quality of studies".

Concerning effective dosage, the obtained data revealed that a significant difference in UA PI is observed only when the dose is increased to more than 60 mg per day. Meanwhile, a significant difference in UA PI was observed by Trapeni and Dastjerdi after a single dosage of 50 mg (10, 5). As no pharmacokinetic studies on sildenafil during pregnancy are available, it is not possible to discuss the proper dose that should be used in future studies.

Regarding the best time for evaluating the UA PI index after sildenafil use, an assessment made two hours after the use of sildenafil showed no meaningful effects on UA PI. In other words, when the sample size and power of the study were increased, assessments made two hours after the administration of sildenafil did not alter the significance of the effect. However, sildenafil was effective when other times of assessment, such as 24 hours, two weeks, or four weeks, were investigated. However, the presence of few existing studies in each group made the results unreliable. Assessments made two hours after using sildenafil have been deemed by most of the studies as the standard time for viewing the effects in UA PI. Such a standard time has been deemed

by Trapani to be one to four hours after use, while Shehata made assessments two hours and two weeks after use and Sharp made assessments one week after use (10, 9, 25).

The effect size of UA PI on populations suffering from IUGR and preeclampsia showed that UA PI decreased significantly after sildenafil consumption only in individuals suffering from preeclampsia and was insignificant in those suffering from IUGR. This finding yields various interpretations.

The first is that the five out of the seven studies focused on IUGR (Figure 3). It seems that, even though UA PI was significant in each of the RCT studies, the significance of the sildenafil effect on individuals suffering from IUGR faded as the sample size and power of the study increased. Therefore, studies with larger populations are required to draw accurate conclusions about the effect of sildenafil on UA PI. In other words, it is possible that if we had more RCTs (and a larger sample size) on preeclampsia, we would not see a significant effect. This finding somewhat conforms to those obtained by the study conducted by Sharp, in which sildenafil was found to be ineffective in IUGR. The population in Sharp's study (i.e., 65 individuals in the control group and 70 individuals in the intervention group) was larger than those of other RCT studies (25).

The second interpretation stems from the difference in the heterogeneity of the IUGR and preeclampsia studies. In the IUGR RCTs, heterogeneity of the studies was significant. That is, although the studies were different in terms of their procedure, the preeclampsia studies (two RCT) were similar in design. Sildenafil might have had a significant effect on UA PI on the IUGR group if they were of the same standard; this also could have decreased the heterogeneity.

The assessment of UA S/D ratio revealed that this index has not changed significantly as a result of sildenafil use. This might be explained through the insignificant effect of sildenafil on IUGR and preeclampsia, which conforms to Sharp's study (25). No significant differences were observed as a result of changing the dose of the sildenafil and study population. However, the UA S/D ratio became significant in high-quality studies assessing the outcome four weeks after use.

An evaluation of MCA PI showed that sildenafil did not affect this index as it relates to the embryo. Regarding this index, the effect was significant in medium quality studies at a two-hour follow-up, two-week follow-up, and for IUGR subgroups (Table 2). Sildenafil had no significant effect on MCA S/D ratio. Furthermore, in general, sildenafil did not affect MCA S/D ratio. Its effect was significant only for 20-60 mg per day dosage subgroups in high-quality studies (Table 2).

The meta-analysis conducted on maternal adverse events revealed that sildenafil significantly increased the occurrence of headaches in the intervention group by as much as 3.57 times (CI: 1.14, 11.18; P=0.03) in comparison with the control group. No statistically significant differences were found for other maternal adverse events between the two groups. The obtained results are of higher credibility, considering that no significant heterogeneity existed in the studies conducted on the maternal adverse effects. Conforming to these results, In a systematic review on the effect of sildenafil during pregnancy, Dunn showed that headaches are the most prevalent adverse effect (prevalence rate of 46%) in mothers (18).

Conclusion

Before any decisions can be made on the effect of sildenafil on fetal Doppler indices and ultimately on preeclampsia and IUGR, more high-quality RCTs with adequate study populations are required. On the other hand, more credible results on the effectiveness of sildenafil in preeclampsia and IUGR might be obtained via information registration systems (26).

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