



Dose Sildenafil Citrate Reduce the Incidence of Emergency Cesarean Section and Fetal Distress During Labor? A Randomized Double-Blinded Clinical Trial

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Abstract

Background: Fetal distress (FD) is one of the most frequent causes of emergency cesarean section (CS) due to the insufficient uteroplacental blood supply during labor. There is a theory that Sildenafil citrate (SC) may improve the uteroplacental blood supply and decrease fetal hypoxia and FD.

Methods: In a randomized double-blinded clinical trial, a total of 208 low-risk subjects who met our stringent inclusion criteria were randomly assigned into two groups: the Sildenafil citrate group (n=104) and the placebo group (n=104). These participants were referred to our referral gynecology and obstetrics department for delivery between July 2022 to September 2022. The SC group received oral SC at a dose of 50 mg every 6 hr, up to a maximum of three times. The final maternal-fetal-neonatal results were recorded and all data were analyzed using SPSS version 23.

Results: The mean age of mothers was 28.98 ± 5.6 years and 120 cases were primigravid (57.7%). Out of a total of 208 pregnant subjects, 168 subjects delivered through normal vaginal delivery (80.8%) and 40 cases underwent emergency CS (19.2%). The number of NVD in Sildenafil group was significantly more than placebo group (87.5% vs. 74%) and SC decreased the rate of emergency CS to 87.5% (RR=2.46%, 95%CI 1.19-5.08). Also, SC decreased the rate of FD to 53.8% (RR=2.83%, 95%CI of 1-8.24).

Conclusion: The results showed that SC can effectively decrease the rate of emergency CS and FD during labor.

Keywords: Cesarean section, Fetal distress, Labor, Sildenafil citrate.

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Introduction

Labor is defined as the occurrence of regular uterine contractions with equal duration and intensity, resulting in cervical dilation and effacement (1). During labor, the intense contractions exert huge pressure on placenta, leading to a reduction of up to 60% in uterine blood flow. This reduction in blood flow puts the fetus at risk of experiencing fetal distress (FD) (2). FD is a major

alarm for intrauterine fetal death (IUFD) and is a critical situation for both mother and fetus (3) which is one of the most important indications of emergency cesarean section (CS) in Australia (23%), United States (27%), and United Kingdom (22%) (2-4).

In most pregnancies, uteroplacental perfusion is typically sufficient to support the proper growth

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of the fetus. However, this level of perfusion may not be adequate to meet the additional demands during labor (5). As a result, this reduced uteroplacental blood flow during labor impairs the placental function, leading to placental hypoxia and trophoblast apoptosis. This, in turn, can cause fetal hypoxia and FD, which is often manifested by compromised fetal heart rate (FHR) or the passage of meconium (5-6). In more severe cases, this reduced uteroplacental blood flow results in hypoxic ischemic encephalopathy or acidemia with long-term mental and neurodevelopmental complications (6).

During labor, the evaluation of fetal well-being is based on fetal heart rate (FHR) monitoring and the occurrence of meconium passage. It is generally assumed that an abnormal FHR pattern, particularly in conjunction with meconium, is a substantial indicator of fetal distress (6-7). Despite this tight monitoring, there is currently no solid evidence supporting interventions that effectively reduce the occurrence of FD during labor, and the only available option is emergency delivery through CS or vaginal birth using assisted techniques such as forceps or vacuum extraction (7).

Unfortunately, comparing with vaginal delivery, such emergency modalities result in higher incidence of morbidities for both the mother and neonate (8). There are several reports of the global increase in the use of emergency CS (9) which is an invasive method with various morbidities such as postpartum depression, an increased risk of uterine rupture in subsequent pregnancies, preterm labor, incisional ectopic pregnancy, difficulties in lactation, future adhesion bands, bleeding, urinary tract infection, metritis, and respiratory distress syndrome (9). Also, maternal mortality is 4-5 times more in CS vs. normal vaginal delivery (NVD). On the other hand, instrumental vaginal delivery with forceps or vacuum may result in perineal trauma, urinary incontinence, fecal incontinence, sexual disorders, and neonatal intracranial hemorrhage (8-9). Such morbidities highlight the significance of cost-effective and safe strategies aimed at reducing the incidence of emergency deliveries, making it one of the most important challenges worldwide.

Sildenafil citrate (SC) is a phosphodiesterase-5 (PDE-5) inhibitor that primarily acts on vascular smooth muscle cells. By increasing the bioavailability of nitric oxide, it promotes vasodilation, which manifests in the myometrial vessels. This leads to increased uterine blood flow and thickening

of endometrium (10). There is a theory that SC may improve the uteroplacental blood flow during labor and prevent FD. There are several studies that investigated the effects of SC on different pregnancy-related morbidities such as infertility, recurrent abortion, maternal pulmonary hypertension, preeclampsia, preterm labor, intrauterine growth retardation, congenital diaphragmatic hernia, neurological development, and fetal distress (11-22). SC is classified as Category B medication, indicating its safety during pregnancy with no adverse effects on the fetus. It is immediately absorbable, reaching maximum plasma level concentration during the first *hr* and has a half-life of 3-5 *hr*. SC has no significant effects on systemic blood pressure, which is particularly important in pregnant women who typically experience lower blood pressure levels. Also, the hepatic isoenzymes involved in SC metabolism (CYP2C19, CYP3A) are effectively active during pregnancy (23). While SC may have some side effects, such as headache (7-32%), flushing (7-33%), dyspepsia (1-13%), rhinitis (19%), and visual disturbance (10%), these side effects are generally milder compared to the potential side effects associated with emergency CS (24).

In a recent clinical trial conducted by Turner et al. (22), it was concluded that SC administration can decrease the risk of emergency operative delivery by 51% and SC can serve as a simple and well-tolerated pharmacological intervention to reduce fetal compromise resulting from inadequate placental perfusion, thereby reducing the need for emergency CS during labor. Another recent survey indicated that SC reduces the risk of operative birth when used for intrapartum fetal distress. Furthermore, the survey found no association between SC use and the development of new-onset preeclampsia, fetal growth restriction (FGR), or antepartum hemorrhage (23). In this study, the objective was to analyze the potential of SC in reducing the risk of fetal distress (FD) and emergency cesarean section (CS) during labor.

Methods

This randomized double-blinded clinical trial included pregnant women between the ages of 18 to 40, with singleton pregnancies and gestational age ranging from 37-41 weeks, who were referred to our referral gynecology and obstetrics department for delivery from 23 July, 2022 to 23 September, 2022. All subjects were enrolled in the study after receiving a detailed explanation of the protocol

and assurances about the confidentiality of their information. It was emphasized that there would be no changes in the treatment process and no additional costs would be imposed on the participants. The study protocol was thoroughly reviewed and approved by the Ethics Committee of Guilan University of Medical Sciences (Registration number: IRCT20100303003485N5; ethics approval ID: IR.GUMS.1401.114) and all subjects signed the informed consent forms.

The study excluded subjects who met any of the following criteria: maternal age below 18 or above 40 years; previous cesarean section; multiple gestations (twins or triplets); gestational age less than 37 weeks or more than 41 weeks; body mass index greater than 40; fetal anomalies; non-cephalic presentations; documented drug reaction to Sildenafil; preeclampsia; hypertension requiring antihypertensive medication; diabetes mellitus requiring insulin therapy; presence of any metabolic, cardiac, renal, hepatic, or ophthalmic diseases; fetal growth retardation (FGR); evidence of cephalopelvic disproportion; and estimated fetal weight below 2500 grams or above 4000 grams.

Sampling: The sample size calculation was conducted based on the data from the trial conducted by Turner et al. (22), which resulted in a sample size of 104 cases in each group, with 10% drop rate.

Study protocol: Over a period of four months (July 2022 to September 2022), a total of 523 pregnant women were gradually referred to our referral obstetrics and gynecology department for delivery. After excluding those who did not meet the inclusion criteria or those who were not interested in participating, a final enrollment of 220 subjects was achieved. All mothers were randomly assigned into two groups using the random block method with a computer-generated sequence in a 1:1 ratio. The first group was the Sildenafil group ($n=110$), which received 50 mg of oral Sildenafil every 6 hr, up to maximum of 3 times. The second group was the placebo group ($n=110$), which received placebo capsules that had the same appearance as Sildenafil. Six mothers in the placebo group and 4 in Sildenafil group withdrew their consent after randomization and did not receive the assigned capsules. Also, two subjects in Sildenafil group vomited after the first dose and refused to continue receiving the medication. Finally, a total of 104 subjects were enrolled. Subsequently, each mother was labeled and capsules

were provided, ensuring that both the patients and doctors were blinded to the contents of the capsules (Figure 1).

Study procedure: First, demographic data was collected using a data sheet. Subsequently, based on the Modified Bishop's Score, labor was initiated either spontaneously or with induction methods such as cervical balloon catheters, prostaglandin E1 tablets, oxytocin, or a combination of these therapies. Upon arrival during the latent phase of labor, the first dose of the trial medication was administered and repeated every 6 hr, up to 3 times. Throughout the process, both the mother and fetus were monitored at intervals of 15 to 30 min, and the final maternal-fetal-neonatal outcomes were recorded on the data sheet. FD was defined as category III or II of FHR, tracing with no improvement despite oxygen therapy, left lateral positioning, or hydration (25).

The variables assessed in the study included demographic factors such as age, weight, height, body mass index (BMI), parity, and gestational age at the time of labor admission. During labor, the main variables monitored were pulse rate, systolic blood pressure, the mode of labor initiation (spontaneous or induction), indications for induction (such as decreased fetal movement with a low biophysical profile score or rupture of membranes), the method of induction (including balloon catheters, prostaglandin E2 tablets, oxytocin, or combined therapy), duration of the latent and active phases of labor, and the number of capsules administered. The final results recorded encompassed the mode of delivery (vaginal or cesarean section), indications for cesarean section (such as thick meconium passage, failure to progress, placental abruption, or fetal distress), blood transfusion, mean hemoglobin levels before the study commenced and 6 hr after delivery. Neonatal outcomes included sex, birth weight, neonatal resuscitation, instances of intrauterine fetal death during labor, neonatal mortality, hypoxic ischemic encephalopathy, admission to the neonatal intensive care unit (NICU), umbilical artery pH levels, and Apgar scores at 1 and 5 min after birth.

Statistical analysis: For statistical analysis, quantitative variables were presented as mean $\pm$ standard deviation (SD), while categorical variables were summarized using frequency (percentage). Continuous variables were compared using t-test or Mann-Whitney U test whenever the data did not appear to have normal distribution or when the



CONSORT 2010 Flow Diagram

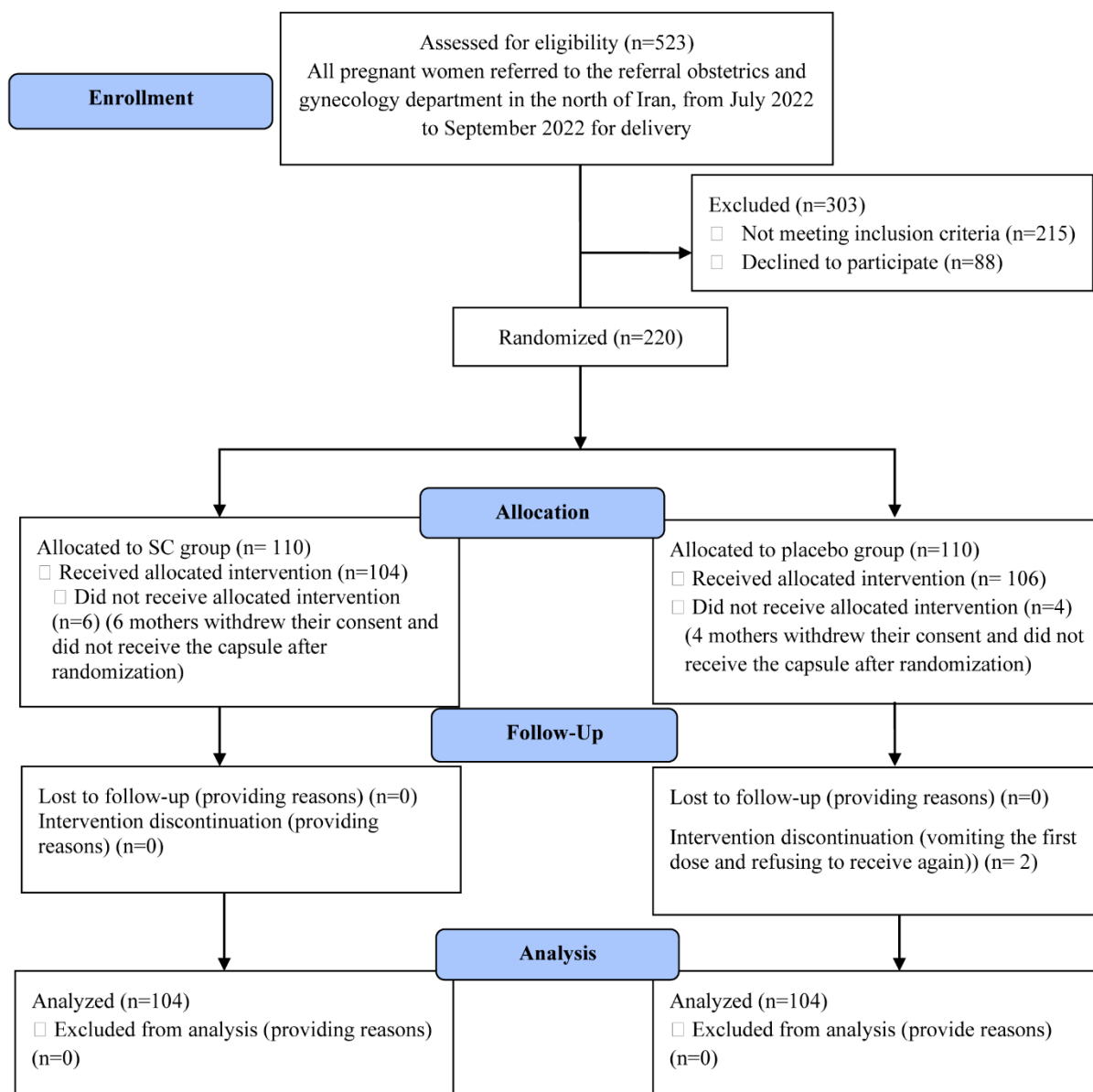


Figure 1. The study flowchart

assumption of equal variances was violated across the study groups. Categorical variables were compared using either chi-squared test or Fisher's exact test. The p-values of ≤ 0.05 were considered statistically significant. For the statistical analysis, SPSS software version 23.0 (IBM, USA) was used.

Results

In this clinical trial, a total of 208 pregnant women were divided into two study groups as Sildenafil group (n=104) and placebo group (n=104). Since the study had a relatively short duration, encompassing the period from admission day

to 48 hr after delivery, no participants were lost to follow-up during this time frame. Additionally, it is worth mentioning that the babies remained with their mothers in this hospital throughout the study period.

Table 1 demonstrates the demographic features of subjects which shows no statistically significant difference between the two study groups. In the study population, the mean age of mothers was 28.98 ± 5.6 years. Out of the total cases, 120 (57.7%) were primigravid. The mean body mass index (BMI) of all mothers was 30.99 ± 5.25 . Also, there were no instances of decrease in blood pressure or pulse rate (Table 1).

Table 2 shows the variables during labor. The onset mechanism of the labor did not show a statistically significant difference between the two study groups (138 cases (66.34%) spontaneous and 70 cases (33.66%) induced; $p=0.301$). Regarding the indication for induction, there were 37 (52.85%) subjects with a decrease in fetal movement and 33 (47.14%) subjects with rupture of membranes, with an equal distribution observed between the study groups ($p=0.229$).

About the mechanism of induction, the results show that 47.16% of cases were induced with oxytocin, 24.28% with PGE1, 8.57% with a combination of PGE1 and cervical balloon, 1.42% with oxytocin and cervical balloon, and 2.85% with cervical balloon, PGE1, and oxytocin combined.

The mean duration of labor showed no statistically significant difference between the two study groups. The mean duration of latent phase among the subjects was 223.815 ± 63.24 min, while the mean duration of the active phase was 50.66 ± 12.4 min. Also, the mean dose of administered Sildenafil and placebo showed no significant difference between the groups ($p=0.435$).

Out of the total of 208 pregnant subjects included in the study, 168 subjects (80.8%) delivered through normal vaginal delivery (NVD), while 40 (19.2%) cases underwent emergency CS. The number of NVD cases in Sildenafil group was significantly higher than placebo group (87.5% vs. 74%). Statistical analysis using the chi-squared test revealed that Sildenafil administration was associated with a decreased rate of emergency CS to 87.5% with a relative risk (RR) of 2.46% and a 95%CI of 1.19-5.08 ($p=0.014$).

Among all subjects, 5.28% experienced thick meconium passage, 2.88% had progression arrest, 1.44% presented with heavy vaginal bleeding and suspicion of placental abruption, and 9.1% with FD underwent emergency C/S.

In Sildenafil group, as shown in table 3, out of the total of 104 pregnant women, only 13 cases (12.5%) underwent emergency CS. Among these cases, three were due to thick meconium passage, two were due to progression failure, two were suspected cases of placental abruption, and six were

Table 1. Patients' demographic characteristics

	Groups (n=104 per group)	Mean±SD (range)	p-value
Maternal age (years)	Sildenafil	28.14±6.15 (16-40)	0.061
	Placebo	29.85±5.84 (18-44)	
Weight (kg)	Sildenafil	83.05±16.64 (53-135)	0.729
	Placebo	82.37±10.97 (55-105)	
Height (cm)	Sildenafil	164.03±7.61 (152-185)	0.265
	Placebo	162.92±6.62 (154-186)	
Body mass index (kg/m ²)	Sildenafil	30.86±5.92 (21.48-55.25)	0.730
	Placebo	31.12±4.58 (22.41-43.15)	
Gestational age at the time of labor admission (week)	Sildenafil	38.65±1.10 (36.29-40.86)	0.846
	Placebo	38.68±1.13 (35.57-41.00)	
Pulse rate (min)	Sildenafil	81.69±4.77 (70-98)	0.221
	Placebo	78.98±6.62 (60-97)	
Systolic blood pressure (mmHg)	Sildenafil	112.28±6.84 (100-140)	0.694
	Placebo	111.65±6.80 (85-130)	
Nulliparous	Sildenafil	62 (59.61%)	0.245
	Placebo	42 (40.39%)	

Table 2. The features during labor

		Sildenafil	Placebo	Total	p-value
		n (%)	n (%)	n (%)	
Onset of labor	Spontaneous	67 (64.43)	71 (68.27)	138 (66.34)	0.301
	Induction of labor	37 (35.57)	33 (31.73)	70 (33.66)	
	Total	104 (100.0)	104 (100.0)	208 (100.0)	
Indication of induction	Decreased fetal movement	19 (51.35)	18 (54.54)	37 (52.85)	0.229
	Rupture of membrane	18 (48.64)	15 (45.45)	33 (47.14)	
	Total	37 (100.0)	33 (100.0)	70 (100.0)	
The method of induction	Oxytocin	21 (56.75)	12 (36.36)	33 (47.16)	0.439
	Prostaglandin E1 (PGE1)	4 (10.81)	13 (39.39)	17 (24.28)	
	Cervical balloon (CB)+ PGE1+ Oxytocin	2 (5.41)	-	2 (2.85)	
	CB+PGE1	1 (2.70)	5 (15.15)	6 (8.57)	
	PGE1+Oxytocin	8 (21.62)	3 (9.1)	11 (15.72)	
	CB+Oxytocin	1 (2.71)	-	1 (1.42)	
	Total	37 (100.0)	33 (100.0)	70 (100.0)	
Dose of administered capsule	1	47 (45.2)	46 (44.23)	93 (44.71)	0.435
	2	46 (44.23)	42 (40.38)	88 (42.31)	
	3	11 (10.6)	12 (11.54)	33 (15.85)	
	Total	104 (100.0)	104 (100.0)	208 (100.0)	
Duration of labor (min)	Stage-1	459.45±80.66	448.18±45.82		0.201
	Stage-2	139.89±15.07	151.43±9.73		0.805

Table 3. Comparison of the results among the two study groups

		Groups			p-value
		Sildenafil (n=104)	Placebo (n=104)	Total (n=208)	
The process of final delivery (%)	NVD	91 (87.5)	77 (74.0)	168 (80.8)	0.014 *
	C/S	13 (12.5)	27 (26.0)	40 (19.2)	
Blood transfusion (%)	No	102 (98.07)	103 (99.04)	205 (98.55)	0.50
	Yes	2 (1.93)	1 (0.96)	3 (1.45)	
The causes of the emergency CS (%)	Thick meconium	3 (23.1)	8 (29.6)	11 (27.5)	0.121
	Failure to progress	2 (15.4)	4 (14.8)	6 (15.0)	0.361
	Placental abruption	2 (15.4)	1 (3.7)	3 (7.5)	0.50
	Fetal distress	6 (46.2)	14 (51.8)	20 (50.0)	0.049 *

due to fetal distress.

In contrast, in placebo group, out of the total of 104 subjects, 27 cases (26%) underwent emergency CS. Among these cases, eight were due to thick meconium passage, four were due to progression arrest, one was a suspected case of placental abruption, and fourteen were due to fetal distress. Statistical analysis using the chi-squared test indicated that Sildenafil administration was associated with a decreased rate of fetal distress to 53.8%

with a relative risk of 2.83% and a 95%CI of 1-8.24 (p=0.049). The results showed no significant relationship with the administered dose of Sildenafil.

Table 4 compares the hemoglobin (Hb) levels before and after delivery. The mean serum titer of Hb before delivery showed no significant difference between groups. However, 6 hr after delivery, the mean serum Hb titer was significantly higher in Sildenafil group compared to the placebo group.

Table 4. Comparison of the hemoglobin level among the two study groups before and after delivery

		Sildenafil	Placebo	p-value
Mean hemoglobin	Before delivery	12.02±1.07	11.83±0.86	0.19
	After delivery	11.06±1.26	10.75±1.14	0.01*

Table 5. Comparison of the neonatal results among the two study groups

		Groups			p-value
		Sildenafil	Placebo	Total	
Sex	Girl	53 (51.0)	66 (63.5)	119 (57.2)	0.066
	Boy	51 (49.05)	38 (36.5)	89 (42.28)	
Neonatal resuscitation		2 (1.9)	2 (1.9)	4 (1.84)	0.50
NICU admission		-	1 (1.0)	1 (0.5)	0.50
Apgar 5th score <7		2 (1.9)	2 (1.9)	4 (1.84)	0.50
Apgar 1st min		8.67±0.60	8.28±0.98		0.001*
Apgar 5th min		9.70±0.52	9.40±0.65		0.001*
Umbilical artery pH		7.25±0.05	7.24±0.07		0.765
Birth weight		3243.08±388.72	3329.52±355.52		0.083

bo group (11.06±1.26 vs. 10.75±1.14, respectively; $p=0.049$).

Table 5 shows the fetal-neonatal results comparing the two study groups. There was no report of IUFD, neonatal death, or HIE. In each group, one neonate underwent cardiopulmonary resuscitation, and NICU admission was only necessary for one case in placebo group. There was no statistically significant difference observed between the two study groups in terms of mean neonatal weight and cord pH measurement. However, the results showed higher Apgar scores at both the 1st and 5th min after delivery in Sildenafil group ($p=0.001$). However, these differences did not reach clinical significance.

Discussion

In this study, the safety and efficacy of Sildenafil (SC) were assessed as a pharmacological intervention to prevent FD and decrease the rate of emergency CS. Our study showed that the number of NVD cases in SC group was significantly higher than placebo group (87.5% vs. 74%) and SC administration decreased the rate of emergency CS to 87.5% (RR=2.46%, 95%CI of 1.19-5.08, $p=0.014$). Also, a significant reduction in the rate of FD was observed in SC group, with the rate decreasing to 53.8% (RR=2.83%, 95%CI of 1-

8.24, $p=0.65$). The mean duration of labor showed no statistically significant difference between the two study groups but the mean serum titer of hemoglobin was significantly higher in SC group 6 hr after delivery ($p=0.049$). Also, the results showed higher Apgar scores at both the 1st and 5th min after delivery in SC group ($p=0.001$).

In a similar recent clinical trial in Australia in 2020 (22), SC administration reduced the risk of operative birth by 51.0% (18.0% vs. 36.7%; RR=0.49, 95%CI of 0.33-0.73, $p=0.0004$). The lower CS rate in our study may be related to some other intervening variables, such as age and body mass index. As it is known, advanced maternal age and increased prevalence of obesity may contribute to increased caesarean delivery rates (6). However, in our study, mothers aged below 18 years old or above 40 years old, as well as those with body mass index above 42 were excluded. Also, participants with underlying diseases were not included in the study, which could be another contributing factor to the low incidence of emergency CS.

Moreover, a significant reduction in the rate of FD was found in SC group, with the rate decreasing to 53.8% (RR=2.83%, 95%CI of 1-8.24, $p=0.65$). Same to our findings, Turner et al. (22) showed that SC decreases the risk of emergency CS by 51% (18% vs. 36.7%; RR=0.49, 95%CI of

0.33-0.73, $p=0.004$). Both studies showed no decrease in blood pressure after SC administration.

SC is a well-tolerated vasodilator agent with no teratogenic or toxic effects. Importantly, its selective effect on pelvic vessels does not lead to a drop in systemic blood pressure. This selective effect is particularly important in pregnant women as they commonly have lower baseline blood pressure levels due to physiological changes (18). On the other hand, SC increases uteroplacental perfusion and reverses vasoconstriction of pelvic varicose veins (22). In fact, SC has demonstrated an anti-remodeling effect which inhibits placental mal-development, especially in cases of fetal growth restriction (FGR) or preeclampsia (26).

Another mechanism of SC is to decrease the smooth muscles vascularization and increase blood supply in ischemic tissues (24). In a clinical trial conducted by Dastjerdi et al. (29), an increase in pulsatility index (PI) was observed in middle cerebral artery two *hr* after SC administration, leading to a decrease in brain sparing. Also, there was a decrease in the umbilical artery pulsatility index (PI), indicating reduced peripheral vascular resistance. In fact, SC administration reduces peripheral vascular resistance, resulting in a "low-resistance, greater-caliber" uteroplacental vascular unit. This improvement in vascular dynamics enhances fetomaternal blood supply (28). Also, relaxation of myometrial smooth muscles is another mechanism by which SC decreases the rate of preterm labor (15-16). This relaxation effect removes the heavy pressure on the fetal head and decreases the incidence of FD.

A study on pregnant rats indicated that SC decreases the uterine contractions which is a good solution for preterm labor (26); however, our results revealed no significant difference between the two study groups in terms of labor duration. This finding suggests that SC does not prolong either the latent or active phase of labor, indicating that it does not interfere with the effective contractions necessary for a timely and efficient labor progression.

The other main finding in our study was the significantly higher serum hemoglobin level in SC group 6 *hr* after delivery (11.06 ± 1.26 vs. 10.75 ± 1.14 , respectively; $p=0.049$). As a result of lower rate of cesarean section in SC group, a decrease in the mean amount of bleeding volume was observed in comparison to placebo group.

Furthermore, there is a prevalent theory that by decreasing the peripheral vascular resistance, SC

increases the bleeding during labor. However, our results showed the opposite; SC did not increase bleeding during labor. Also, the mean amount of postpartum hemorrhage was similar in the two groups. These findings align with a meta-analysis conducted by Dunn et al. (30) who reported that in some randomized controlled trials (RCT), postpartum hemorrhage rate was comparable between SC and the control groups.

Also, SC group exhibited higher Apgar scores at both the 1st and 5th *min* after delivery ($p=0.001$) which is consistent with the findings of Turner et al. (22). This improvement in Apgar scores can be explained by the enhanced fetoplacental blood supply.

The strength of our study was the rigorous study protocol, since it was a double blinded, placebo-controlled trial and its design minimized the bias. Another strength of the study was its short duration, which minimized the potential for participants to be lost to follow-up and limited the exposure to the drug. Sildenafil citrate (SC) was administered solely during labor, further mitigating any prolonged drug exposure. Another advantage was the high number of referred patients to our obstetrics and gynecology department, which allowed us to efficiently collect the study sample in less than four months. However, a limitation of this study is the lack of recorded SC side effects. Nevertheless, it is worth noting that only a few cases experienced slight frontal headaches as a potential side effect of SC administration.

Conclusion

The result of our study showed that Sildenafil (SC) is an effective and safe pharmacological intervention to prevent fetal distress (FD) and reduce the need for emergency CS during labor. However, larger trials are urgently needed to further validate these results and establish its widespread usage in labor management.

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Conflict of Interest

We hereby declare that we have no conflicts of interests.

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