Original Article

The Effect of Sildenafil Citrate on the Neonatal Outcome of Growth Restricted Foetuses

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ABSTRACT

Background: Poor growth of a foetus during pregnancy is referred to as intrauterine growth restriction (IUGR), also known as intrauterine growth retardation. There are several potential reasons, but inadequate maternal nutrition or insufficient oxygen delivery to the foetus are the most frequent ones.

The purpose of the work is to determine how sildenafil citrate affects newborn outcomes such as birth weight and admission to the neonatal intensive care unit (NICU).

Patients and Methods: A total of 120 pregnant women between the ages of 28 and 30 who were attending antenatal care clinics or being admitted to the obstetrics and gynaecology department and had FGR,defined as a lag of two weeks or more between the current biometric measurements and the documented pregnancy dating to the first trimester and anestimated foetal weight less than the 10th percentile for gestational age, were included in this randomised controlled trial study.

Results: In comparison to 40.0% and 73.3% in the control group, 21.7% of neonates in the sildenafil group have an APGAR5 score 7 and 48.3% of them are admitted to the NICU, a significant difference between the two groups(p=0.030 &0.005, respectively). In the sildenafil group, sildenafil reduced the relative risk of both by 0.62&0.60.

Conclusion: One of the biggest problems in maternity care today, as well as one of the leading causes of perinatal morbidity and death, is intrauterine growth restriction (IUGR). notwithstanding the significant strain it places on maternity and paediatric healthcare. We are still looking for a cure that will last forever. In the current study, it was discovered that sildenafil increases gestational age, prolongs pregnancy,improves birth weight, lowers the incidence of CS, and lessens IUGR-related problems.

Key Words: Intrauterine growth restriction, neonatal outcome -, sildenafil citrate-.

Received: 06 February 2023, **Accepted:** 03 March 2023

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ISSN: 2090-7265, May 2023, Vol.13, No. 2

INTRODUCTION

Low birth weight (LBW), which is brought on by intrauterine growth restriction (IUGR), preterm labour,and genetic/chromosomal abnormalities, is linked to at least 60% of the 4 million neonatal deaths that occur annually throughout the world, proving that undernutrition is already a significant health issue at birth[1]. A baby that has intrauterine growth restriction may be small for gestational age (SGA), which is often characterised as having a weight below the 10th percentile for the gestational age[2].

It may cause a low birth weight at the conclusion of the pregnancy. The utero-placental blood flow, which significantly rises throughout the second and third trimesters of pregnancy, is primarily responsible for transporting nutrients from the mother to her foetus. 7-15% of pregnancies are complicated by foetal growth restriction (FGR),which increases the risk of perinatal morbidity and death when it appears early and in severe form[3].

Because FGR can be predicted by prenatal measurements of placental size, utero-placental blood flows, expression of angiogenic and vasoactive factors, and these factors are reduced or altered in pregnancies that are compromised, clinicians have proposed using therapeutic agents that target placental blood flow to alleviate these pathological effects[4].

Sildenafil citrate, a selective inhibitor of the type V cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase, is one of several novel vasodilator medications that have recently been proposed to improve blood flow to tissues. By blocking the activity of phosphodiesterase type 5, which breaks down cGMP,sildenafil increases the effects of nitric oxide[4].

cGMP levels stay raised when taking sildenafil, which causes arterial relaxation and enhanced uterine blood flow[5]. As it enhances endothelial function of these women's myometrial arteries, some studies hypothesised

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that sildenafil citrate may be a possible treatment option to increase utero-placental blood flow in pregnancies complicated by FGR[6].

A case control study was conducted at the Avicenna Research Institute on a pregnant woman who was 26 weeks and 3 days along with clinical suspicion of oligohydramnios. After an ultrasound, sildenafil citrate was administered in doses of 50 mg BD and gradually increased to 50 TDs over the course of 7 days with ongoing monitoring of the foetus. The foetus weighed about 800 grammes, and the pregnancy continued for another 3 weeks[7].

The purpose of this study was to evaluate sildenafil citrate's impact on neonatal outcomes, including growth-restricted foetuses' birth weight and admission to the neonatal intensive care unit (NICU).

Outcome of the study

A. Primaryoutcome: The birth weight of those foetuses.

B. Secondary outcome: Neonatal outcomes such as newborn ICU admission, neonatal respiratory distress syndrome, baby's Apgar score, umbilical artery pH, GA at birth, delivery method, and incidence of medication adverse effects were secondary end measures.

PATIENTS AND METHODS

Study settings

Ain Shams Maternity University Hospital.

Study design

A randomized controlled trial.

Study population

120 pregnant women between 28 and 30 weeks gestation who were attending antenatal care clinics or being admitted to the obstetrics and gynaecology department and had FGR, which was defined as (Lag of two weeks or more between the current biometric measures and the documented pregnancy dating in the first trimester and Estimated foetal weight less than the 10th percentile for gestational age)[8]. Patients were divided into two treatment groups, sildenafil and non-sildenafil, in a ratio of one to two. In the sildenafil group, sildenafil 25 mg was administered three times daily, while the non-sildenafil group did not receive it. The dose was adjusted in accordance with results from a prior study. Women were randomly assigned to one of the two groups, and random sampling was carried out by a random sample generator[7].

Sample size justification

Using the PASS software, the sample size was estimated with the power set to 90% and the type-1 error () at 5%. El-Sayed *et al*. consider foetal weight to be the main result[8]. The outcome is 873142 in the non-sildenafil group against 1320 +_240 in the sildenafil group. The study size was 120 patients (60 in each group)

Inclusion criteria

Singleton viable pregnancy

Gestational age between 28 and 30 weeks suffering from FGR defined by (Lag of two weeks or more between the current biometric measures and the documented pregnancy dating in the first trimester and Estimated fetal weight less than the 10th percentile for gestational age[8].

BMI 20-30

Age 20-35 years

Exclusion criteria

Women with multiple gestation

FGR due to fetal causes as congenital abnormalities or fetal infection.

Maternal diseases or medications contraindicate or interact with sildenafil as:

1. Patients suffering from cardiac problems as arrhythmias, vulve stenosis, coronary stenosis or pulmonary hypertension.
2. Patients suffering from hepatic or renal diseases as renal or hepatic failure.
3. Patient taking nitroglycerin.
4. Patient taking Guanyl atecyclase stimulator.
5. Patients have known hyper sensitivity reaction against sildenafil citrate.

" All the women included in this study were not taking heparin.

Methodology

All included women were subjected to the following:

1. All participants were recruited into the study after receiving their signed informed consent,which was obtained following an explanation of the objectives,

potential risks, and potential consequences of the various procedures used in the study.

2. Taking the patient's history with a focus on the medical, menstrual, obstetric, and family histories, as well as the cause of FGR and a review of their medications.

3. A general assessment.

4. Symphysis-fundal height measurement and abdominal inspection.

5. Ultrasound during the first trimester and the last period to confirm the gestational age.

The analysisis of fetal growth restriction was considered if EFW and/or AC <10th percentile by ultrasound (U/S).

The participants in the study were distributed into 2 group:

" Sildenafil group: 60 pregnant women receiving sildenafil citrate 25 mg 3 times daily till delivery.

" Non sildenafil group: 60 pregnant women not receiving sildenafil.

Both groups underwent strict fetal surveillance in the form of:

Umbilical artery Doppler (UA) was the primary surveillance tool in the FGR fetus:

a. The surveillance was repeated every seven days in the form of uterine artery Doppler (UAD), middle cerebral artery (MCA) Doppler, ultrasound for (AC, EFW, and amniotic fluid index (AFI) for amniotic fluid), non-stress test, and Biophysical profile (BPP) twice weekly. This was done when the umbilical artery Doppler flow indices were normal.

b. Umbilical artery Doppler flow indices were repeated twice weekly in the form of UAD/MCA Doppler and weekly ultrasound for (AC, EFW, and amniotic fluid index), non-tress test, and BPP when they were abnormal (pulsatility or resistance index>+2 S/Ds for gestational age) and end-diastolic velocities were present but decreased.

The surveillance was performed every day in the form of UAD, MCA Doppler, DV Doppler,BPP,and non-stress test until umbilical artery Doppler indicated absent frequencies at 32 weeks' gestation. Weekly ultrasound for (AC,EFW, and amniotic fluid index) and daily foetal kick counts are also advised. Once cephalization in the MCA or reversal of flow in the UA were evident, hospitalisation was performed along with continuous oxygen treatment, bed rest, daily BPP, and daily Doppler. In preparation for a quick termination, steroids for foetal lung maturity were given.c)The following also underwent termination

Circumstances (no end diastolic velocities above 34 weeks of gestation, end diastolic velocities that were reversed at any moment, unintentional haemorrhage, early membrane rupture, or severe preeclampsia occurred)[9].

c. The number of neonatal ICU admissions, birth weight, Apgar score, mode of delivery, gestational age at birth, and occurrence of medication side effects for each delivered foetus were recorded.

d. Randomization:

Randomization was carried out utilising a computer-generated randomization method to make sure that everyone has an equal chance of participating.

Allocation and concealment

Each of the 120 opaque envelopes held the appropriate number that was serially assigned, and the allocation was made in accordance with a randomization table.

After that, all of the envelopes were sealed and placed in a single box. When the first lady arrived, the box was opened, and the patient was assigned based on the note inside the envelope (Tables 1,2).

Table 1: Sildenafil group

41	50	110	77	63	105	98	30	17	120
22	90	109	53	69	86	35	66	64	101
7	88	119	61	114	39	47	28	89	115
16	60	79	117	5	107	3	102	40	108
62	12	14	24	48	99	118	44	9	113
92	74	31	78	61	111	116	104	58	80

Table 2: Non-Sildenafil group

49	81	51	19	82	13	11	76	33	73
57	91	20	112	68	56	4	8	84	10
97	34	70	52	15	94	100	26	93	103
36	23	37	55	95	29	106	42	46	1
54	21	45	96	38	87	32	85	6	75
25	71	27	59	83	43	2	72	67	18

The method

If the pregnancy is a singleton, between 28 and 30 weeks gestation or more, and the age of the women is between 20 and 35 years old with a body mass index between 20 and 30, we included a group of 120 women with intrauterine growth limited foetuses.

60 of these women received sildenafil citrate 25 mg three times daily till the conclusion of their pregnancies as therapy for this issue.

According to a previous case study[7], the number of neonatal ICU hospitalisations between the delivered foetuses, and their birth weight at delivery, the dose was changed. The 60 remaining women did not get this treatment, and they were allowed to carry their pregnancies to term. Documented factors were Apgar scores, delivery method, gestational age at birth, and the prevalence of medication adverse effects.

Data Management and Analysis

Statistical package for Social Science was used to review, code, tabulate, and introduce the acquired data to a computer (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). For quantitative parametric data, the data were displayed as mean and standard deviation (SD), and for quantitative non-parametric data, median and interquartile range. The presentation of qualitative data utilised frequency and percentage. In line with the type of data acquired, the appropriate analysis was conducted.

While chi square and fisher exact tests were used to analyse qualitative data, the Student T Test or Mann Whitney test was used to analyse quantitative data.

P-value indicates the degree of significance. The difference is statistically significant (P=.007).

P0.05:Not Significative (NS).

P<0.05:Significant(S).

P<0.01:Highly-significant (HS).

RESULTS

137 pregnant females were assessed for their eligibility to be included in this study, 17 cases were excluded either due to not meeting inclusion criteria (n=13) or refused to participate (n=4). And remaining 120 cases were randomized to equal 2 groups (60 cases each). During the study 15 cases (10 in control group and 5 in cases group) did not complete the study and replaced by another suitable case and their results were removed (Figure 1).

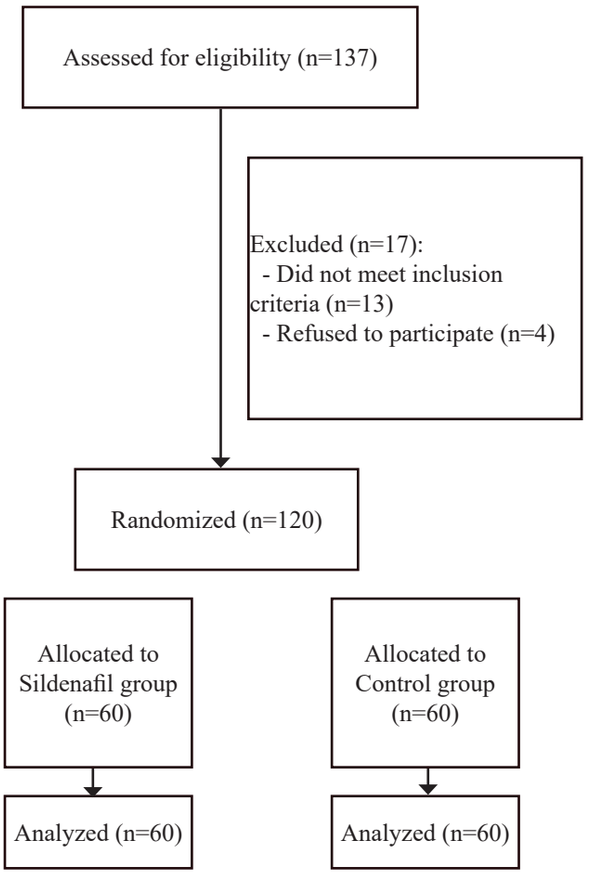

Fig. 1: CONSORT,Patient flow chart.

No significant difference between sildenafil and control groups regarding demographic characteristics (Table 3).

Table 3: Demographic characteristics among the studied groups

Variables		Sildenafil(N=60)	Control(N=60)	*P*
Age (years)	Mean±SD	27.8±4.0	26.9±3.8	0.245
	Range	20.0-35.0	20.0-35.0	
BMI (kg/m^2)	Mean±SD	25.9±2.2	26.2+2.4	0.387
	Range	20.4-29.7	20.7-29.6	
Parity (n,%)	Primi	21(35.0%)	17(28.3%)	0.432
	Multi	39(65.0%)	43(71.7%)	
GA (weeks)	Mean±SD	29.1±0.4	28.9±0.5	0.164
	Range	28.0-30.0	28.0-30.0	

Independent t-test,Chi square test

Table (4) shows that: the mean value of GA & pregnancy prolongation was 34.5±1.5 weeks &37.2±11.2 days respectively in sildenafil group versus 32.6±0.8weeks &25.3±5.5 days respectively in control group, with prolongation of pregnancy by 11.6±1.6 days and increase the GA by 1.8±0.2 weeks by sildenafil effect (*p*<0.001 for both).

Table 4: Gestational age at delivery and pregnancy prolongation among the studied groups

Variable	Measures	Sildenafil (N=60)	Control(N=60)	*P*
GA (weeks)	Mean±SD	34.5±1.5	32.6±0.8	<0.001
	Range	33.0-39.0	32.0-37.0	
Prolongation (days)	Mean±SD	37.2±11.2	25.3±5.5	<0.001
	Range	22.0-70.0	18.0-56.0	
Value of sildenafil over control				
Items			Mean±SE	95% CI
GA elevation(weeks)			1.8±0.2	1.4-2.3
Prolongation elevation(days)			11.6±1.6	8.5-14.8

Independent t-test,Significant,CI:Confidence interval

Table (5) shows that: Different complications were more frequent among Sildenafil group than among control group, the differences were significant in headache, flushing and visual disturbances.

Table 5: Maternal complications among the studied groups

Complications	Sildenafil (N=60)	Control (N=60)	*P*	RR (95%CI)
Headache	15(25.0%)	6(10.0%)	0.031	1.57 (1.11-2.22)
Flushing	14(23.3%)	2(3.3%)	<0.001	1.98 (1.49-2.63)
Visual disturbances	10(16.7%)	3(5.0%)	0.040	1.65 (1.15-2.36)
Nasal congestion	3(5.0%)	1(1.7%)	&0.619	1.53 (0.84-2.77)

^Chi square test,#Fisher's Exact test,RR:Relative risk,CI:Confidence interval

Follow up Doppler indices, mode of delivery and indication of termination. There were no significant differences between women of both groups regarding the initial (pre-treatment) mean values of UA-RI, UA-PI,MCA-RI and MCA-PI (Table 6).

Table 6: Initial UA and MCA Doppler Indices in Both Groups

Initial	Group I [Sildenafil Group] (n=60)	Group II [Control Group] (n=60)	MD (95%CI)	*P*1
UA-RI Range Mean±SD	 0.52-0.71 0.61±0.05	 0.52-0.72 0.62±0.06	 -0.01 (-0.03 to 0.01)	 0.323 NS
UA-PI Range Mean±SD	 1.02-1.29 1.16±0.09	 1.01-1.27 1.14±0.08	 0.02 (-0.02 to 0.05)	 0.201 NS
MCA-RI Range Mean±SD	 0.52-0.74 0.61±0.06	 0.50-0.71 0.62±0.05	 -0.01 (-0.03 to 0.01)	 0.321 NS
MCA-PI Range Mean±SD	 1.32-1.59 1.44±0.08	 1.33-1.62 1.46±0.08	 -0.02 (-0.05 o0.01)	 0.174 NS

UA umbilical artery, MCA middle cerebral artery, RI resistance index,PI pulsatility index, Data presented as range, mean ± SD,MD (95% CI) mean difference and its 95% confidence interval, 1 Analysis using Independent Student's t-Test,NS non-significant

The mean values of post-treatment UA-RI and UA-PI were significantly lower, while those of post-treatment MCA-RI and MCA-PI were significantly higher, among women of group I [Sildenafil Group] when compared to women of group II [Control Group] (Table 7).

Table 7: Post-Treatment UA and MCA Doppler Indices in Both Groups

Post-Treatment	Group I [Sildenafil Group] (n=60)	Group II[Control Group] (n=60)	MD (95%CI)	*P*1
UA-RI Range Mean±SD	 0.52-0.63 0.57±0.03	 0.52-0.71 0.61±0.06	 -0.04 (-0.06 to-0.02)	 <0.001 HS
UA-PI Range Mean±SD	 1.02-1.19 1.10±0.05	 1.02-1.29 1.13±0.08	 -0.03 (-0.05 to-0.01)	 0.015 S
MCA-RI Range Mean±SD	 0.58-0.87 0.72±0.08	 0.52-0.71 0.62±0.06	 0.10 (0.07 to 0.13)	 <0.001 HS
MCA-PI Range Mean±SD	 1.36-1.73 1.57±0.10	 1.32-1.59 1.45±0.07	 0.12 (0.09 to 0.15)	 <0.001 HS

UA umbilical artery,MCA middle cerebral artery, RI resistance index, PI pulsatility index,Data presented as range, mean ±SD, MD (95% CI) mean difference and its 95% confidence interval, 1 Analysis using Independent Student's t-Test,HS highly significant-S significant

The median difference between pre- and post-treatment were significantly higher among women of group I [Sildenafil Group] when compared to women of group II [Control Group] (Table 8).

Table 8: Changes in UA and MCA Doppler Indices in Both Groups

Post-Treatment Changes	Group I [Sildenafil Group] (n=60)	Group II [Control Group] (n=60)	*P*1
UA-RI Range Median(IQR)	 -0.17-0.1 -0.07(-0.03-0.01)	 -0.19-0.18 -0.06(-0.01-0.04)	 0.032 S
UA-PI Range Median(IQR)	 -0.25-0.17 -0.14(-0.07-0.02)	 -0.25-0.25 -0.12(-0.04-0.06)	 0.033 S
MCA-RI Range Median(IQR)	 -0.1-0.32 0.04(0.11-0.19)	 -0.16-0.17 -0.04(-0.01-0.04)	 <0.001 HS
MCA-PI Range Median (IQR)	 -0.23-0.41 0.02(0.16-0.26)	 -0.21-0.24 -0.1(0.0-0.07)	 <0.001 HS

UA umbilical artery, MCA middle cerebral artery,RI resistance index,PI pulsatility index,IQR interquartile range,Data presented as range, median (interquartile range), 1 Analysis using Mann-Whitney's U-Test, S significant- NS non-significant-HS highly significant

There were no significant differences between women of both groups regarding the mode of delivery, or indications for CS. The rates of non-elective CS were significantly higher among women of group II [49 (81.7%) vs. 38 (63.3%)), p=0.025]. The rates of CS for antenatal fetal compromise, hypertensive disorders and intrapartum fetal compromise were higher among women of group II, but not to statistically significant levels (Table 9).

Table 9: Mode of Delivery in Included Women

	Group I [Sildenafil Group] (n=60)	Group II [Control Group] (n=60)	*P*1
Vaginal Delivery	4(6.7%)	1(1.7%)	0.361
Cesarean Delivery	56(93.3%)	59(98.4%)	NS
Vaginal Delivery			
Spontaneous	2(3.3%)	1(1.7%)	0.999(NS)
Induced	2(3.3%)	0(0%)	0.467(NS)
PROM	1(1.7%)	0(0%)	0.999(NS)
Hypertensive Disorder	1(1.7%)	0(0%)	0.999(NS)
Cesarean Delivery			
Elective CS	18(30%)	10(16.7%)	0.084(NS)
Non-Elective CS	38(63.3%)	49(81.7%)	0.025(S)
PROM(non-vertex)	5(8.3%)	6(10%)	0.752(NS)
Labor (non-vertex/previous CS)	11(18.3%)	12(20%)	0.817(NS)
Antenatal Fetal Compromise	9(15%)	14(23.3%)	0.246(NS)
Hypertensive Disorder	8(13.3%)	10(16.7%)	0.609(NS)
Failed Induction of Labor	2(3.3%)	2(3.3%)	0.611(NS)
Intrapartum Fetal Compromise	3(5%)	5(8.3%)	0.714(NS)

Data presented as frequency percentage)
1 Analysis using Continuity-Corrected Chi-Squared Test
NS non-significant

Table (10) shows that: Birth weight was significantly higher (p<0.001) among Sildenafil group (1.7±0.2) than among control group (1.4±0.2).

Table 10: Neonatal condition among the studied groups

Variables		Sildenafil (N=60)	Control (N=60)	*P*	RR (95% CI)
Birth weight (kg)	Mean±SD	1.7±0.2	1.4±0.2	<0.001	--
	Range	1.3-2.1	1.1-1.8		
APGAR5<7 (n,%)		13(21.7%)	24(40.0%)	0.030	0.62 (0.39-0.99)
Umbilical artery PH<7.2(n,%)		7(11.7%)	11(18.3%)	0.306	0.75 (0.41-1.38)
Respiratory distress (n,%)		5(8.3%)	10(16.7%)	0.168	0.64 (0.30-1.33)
NICU admission (n,%)		29(48.3%)	44(73.3%)	0.005	0.60 (0.42-0.85)

Independent t-test,&Chi square test,Fisher's Exact test,RR:Relative risk,CI:Confidence interval

21.7% of cases in sildenafil group have APGAR5 score <7 and 48.3% of them admitted to NICU versus 40.0% and 73.3% respectively in control group with significant difference between both groups (p=0.030 & 0.005 respectively). Sildenafil decreases the relative risk of both by 0.62 &0.60 in sildenafil group.

Umbilical artery PH<7.2 was reported in11.7% of cases in sildenafil group and in 18.3% in control group. 8.3% of cases in sildlenafil group developed respiratory distress versus 16.7% in control group were non-significantly decrease among Sildenafil group than among control group(p=0.306 &0.168 respectively) as Sildenafil decreases the relative risk of umbilical artery blood acidosis or respiratory distress by 0.75 and 0.64 respectively.

DISCUSSION

Numerous unfavourable pregnancy outcomes, such as foetal and neonatal death[10], necrotizing enterocolitis, respiratory issues, neurodisability, and long-term risks to the health of the affected child, such as obesity and hypertension, are linked to foetal growth restriction and subsequent preterm birth[11].

The core of care for foetal growth restriction is extensive observation to optimise the date of birth because there is no effective treatment[12].

Nitric oxide(NO), which encourages vasodilatation of maternal arteries, increases placental perfusion. The phosphordiesterase enzyme class breaks down the NO second messenger, cGMP.PDE-5, the most prevalent PDE type present in the reproductive tract, is inhibited by sildenafil citrate[13].

In cohort studies, randomised trials, pre-eclampsia, foetal growth restriction, animal models, 23-28, and ex *vivo* human tissue, sildenafil has demonstrated potential[8].

The purpose of this study was to evaluate sildenafil citrate's impact on neonatal outcomes, including growth-restricted foetuses' birthweight and admission to the neonatal intensive care unit (NICU).

120 pregnant participants between 28 and 30 weeks gestation were divided into sildenafil and non-sildenafil medication groups for the research.

All of the patients had thorough history-taking (personal history, obstetric history,including prior history of small for gestational age, menstrual history, and history of the current pregnancy), examination, and menstrual history (either general examination, abdominal examination to assess the fundal height and maternal weight and height). The number of neonatal ICU admissions, birth weight, Apgar score, mode of delivery, gestational age at birth, and occurrence of medication side effects for each delivered foetus were recorded.

In the current study, the mean value of GA and pregnancy prolongation were 34.51.5 weeks and 37.211.2 days, respectively, in the sildenafil group versus 32.60.8 weeks and 25.65.5 days, respectively, in the control group. The sildenafil effect resulted in an 11.61.6-day pregnancy prolongation and an increase of 1.80.2 weeks in GA (p0.001 for both).

Compared to the control group's birth weight of 1.40.2,the Sildenafil group's birth weight of 1.70.2 was substantially greater (p0.001).Furthermore,compared to 40.0% and 73.3% respectively in the control group, 48.3% of neonates in the sildenafil group had an APGAR5 score below 7, and there is a statistically significant difference between the two groups (p=0.030 & 0.005, respectively). In the sildenafil group, sildenafil reduces the relative risk of both by 0.62 & 0.60.

This study found that 18.3% of the control group and 11.7% of the sildenafil group had umbilical artery PH levels below 7.2. Sildenafil decreased the relative risk of umbilical artery blood acidity or respiratory distress by 0.75 and 0.64, respectively,while 8.3% of the sildenafil group experienced respiratory distress compared to 16.7% in the control group.

Regarding the initial (pre-treatment) mean values of the umbilical artery resistance index (UA-RI), the umbilical artery pulsatility index (UA-PI), the middle cerebral artery RI resistance index (MCA-RI), and the middle cerebral artery RI resistance index pulsatility index, there were no significant differences between the women of the two groups in the current study (MCA-PI). After treatment, group I (the sildenafil group) had considerably lower UA-RI and UA-PI whereas group II (the control group) had significantly higher MCA-RI and MCA-PI(p0.001 for all).

Additionally, women in group I (the Sildenafil Group) had substantially higher median pre-to-post-treatment values for UA-RI, UA-PI, MCA-RI, and MCA-PI than did women in group II (Control Group).

Regarding the manner of delivery or CS indicators, there were no appreciable variations between the women in the two groups in the current research. Women in group II experienced considerably higher non-elective CS rates (49 (81.7%) vs. 38 (63.3%); p=0.025). Women in group II had greater rates of CS for prenatal foetal compromise, hypertensive disorders, and intrapartum foetal compromise, albeit notat statistically significant levels.

Complications like headaches, flushing, visual disturbances, and nasal congestion were more common in the Sildenafil group compared to the control group (RR was 1.57,1.98,1.65,and 1.53).The differences were significant for headaches, flushing, and visual disturbances (p=0.031,0.001,and 0.040, respectively).

The Egyptian research by El-Sayed *et al*.[8], which sought to determine the impact of the use of low dosage sildenafil citrate in instances of IUGR on newborn outcomes, concurs with these findings. In this study, 30 patients with singleton spontaneous pregnancies with intrauterine growth restriction who reported to Shatby Maternity University Hospital between August and December 2016 were examined. Cases were split into two groups: study group (n=15); women who got 20 mg sildenafil citrate oral tablets for 6 weeks; control group (n=15); women who received a placebo. Both groups had thorough history-taking,general and obstetric examinations, and laboratory tests. For 4-6 weeks,there was follow-up.

They discovered that sildenafil was also linked to higher gestational age at birth (p =.004),better newborn weight (p = 0.0001), and fewer admissions to neonatal critical care units (p = 0.03). No negative consequences were recorded.

The case control study undertaken by Singh *et al*.[14], whose findings confirmed the findings of our investigation, identified and included all women whose pregnancies at the Dr. B.R.A.M. Hospital in Raipur between July 2014 and July 2016 were complicated by IUGR.

The therapy with Sildenafil split the ladies into two groups (Study group included women taking Sildenafil, control group had women who were not taking Sildenafil). Both groups' outcomes, including birth weight, AC, and problems due to IUGR, were compared after being monitored up to delivery.

In the study group, 16% of women delivered prematurely, whereas in the control group, 38% of women had preterm births, which was significant. Singh *et al*.[14], who observed the perinatal outcome, also discovered that in the sildenafil-treated group,63% of mothers had babies with birth weights above the 10th percentile,whereas in the sildenafil non-treated group, only 20% did. The significance of this was established (*p-value* 0.001).

The non-treated group's mean birth weight was 2200gm, or less than 2500gm, compared to the treated group's mean birth weight of 2594gm, or more than 2500gm. Singh *et al*.[14], reported that IUGR complications such as meconium aspiration and intrapartum asphyxia were less common in Sildenafil-treated women even though there was no statistically significant difference. They also discovered that the incidence of caesarean sections for pre-term in the study group was 8% while it was significantly higher, or 38% in the control group, which is a lower caesarean section rate in agreement with the current study.

In pregnancies affected by severe early-onset IUGR, Von Dadelszen *et al*.[7] evaluated the potential benefit of sildenafil treatment intended to enhance perinatal outcomes. They provided 10 women with severe early-onset IUGR

(referred to as "Sildenafil-treated") Sildenafil citrate (25 mg three times per day till birth) as an avant-garde therapy from 2004 to 2009. For analytical reasons, the results of 17 women who met the treatment requirements but chose not to take Sildenafil or were not given it (referred to as "Sildenafil-naive") were compared to those of those who received Sildenafil therapy. When compared to women who remained Sildenafil-naive, sildenafil medication was linked to better foetal growth velocity as measured by serial ultrasound. Additionally, sildenafil therapy was linked to a tendency towards improvement in both perinatal survival and intact survival.

They retrospectively analysed 11 Japanese singleton pregnant women with FGR who received tadalafil (sildenafil along) (tadalafil group) along with conventional management for FGR at Mie University Hospital from July 2015 to February 2016 and found that the duration of pregnancy was >3 weeks longer in the tadalafil group than in the conventional management group. This study is also in agreement with the current study (tadalafil group, 10 mg or 20 mg tadalafil daily continued until delivery in all participants without severe adverse events). At enrolment, these women were matched to 14 singleton pregnant women in 2014 who solely got the usual therapy for FGR in terms of maternal age, parity, gestational age, and projected foetal weight (conventional management group).

The standard management of FGR was carried out in accordance with Japanese obstetric practise standards. Birthweights in the study (median 17.7 g/day; IQR,10.6-23.0 g/day versus 12.8 g/day,0-17.2 g/day; median 1990 g; IQR, 1488-2168 g vs 1384 g, 870-1949 g, respectively; P 0.05) were substantially greater in the tadalafil group than in the traditional treatment group. The birth weight for GA and sex of each infant in the usual treatment group was below the 10th percentile. One infant in the tadalafil group had a birthweight score above the 10^{th} percentile (11.6^{th} percentile), whereas the rest had birthweight scores below the 10^{th} percentile.

The tadalafil group had substantially higher newborn Apgar ratings at 1 and 5 minutes after birth, according to Kubo *et al*.[15]. However, their research found no discernible variation in umbilical artery pH between the two groups. In comparison to the tadalafil group, the conventional management group had a considerably greater rate of RDS. The other short-term baby outcomes did not change much. They also discovered that the caesarean birth rate was almost twice as high in the traditional care group as it was in the tadalafil group.

The conventional management group (58.3%) performed caesarean sections on seven pregnant women, but none in the tadalafil group (P 0.05; chi-squared test, which is consistent with our findings).

A retrospective and descriptive case series of all hospitalised pregnant women who took sildenafil for severe IUGR was conducted by Ferreira *et al*.[16], which is also in agreement with this study. 19 hospitalised pregnant women who got sildenafil for severe IUGR participated in the study. The typical dosage of sildenafil was 20 mg taken three times per day until birth, starting at an average of 25 weeks plus three days (median: 25, 20+1,30+6). Prior to the use of sildenafil, it was estimated that the average foetal weight was 558g (median:820, 320, 1360) with an average weight rise of 249g (median: 123, -46, 732). At delivery, the average weight was 807g(median: 820, 320, 1360). However, his study lacked a control group.

A research by Samangaya *et al*.[17] discovered that sildenafil therapy for pregnant women with pre-eclampsia resulted in a decreased incidence of negative neonatal short-term outcomes. This finding is consistent with the earlier data. According to Samangaya *et al*.[17], kids delivered to women who had taken sildenafil citrate antenatally had cord arterial pH measurements. In it, there was no cord arterial pH 7.1 in any of the 17 infants in the sildenafil citrate group. Furthermore, there were no clinically significant changes between the placebo (7.29, range: 7.26-7.3) and sildenafil citrate (7.25, range: 7.17-7.31) groups in terms of the median cord arterial pH.

One more was A prospective randomised control research by El-Shalakany *et al*.[18], which assessed the efficacy and safety of sildenafil citrate for the treatment of intrauterine growth restriction (IUGR) Eighty pregnant women with gestational ages between 24 and 34 weeks, singleton pregnancies, and IUGR who attended an antenatal clinic were randomly assigned to sildenafil (n=40) 25mg tid or placebo (n=40), with plenty of fluids until delivery. This study was conducted at Ain Shams University Hospital and Kafr Aldwwar Main Hospital in the El-Beheria governorate.

The length of pregnancy,newborn weight, and ICU hospitalisation were the primary outcome measures. According to their findings, sildenafil medication was linked to a substantial increase in pregnancy duration (P 0.05), a significant rise in ultrasound-estimated foetal weight (P 0.05), and a significant decrease in neonatal ICU hospitalisation (P = 0.218).

A Trial of Randomized Umbilical and Fatal Flow in Europe research, which provided funding for this investigation, revealed that 97% of caesarean deliveries in pregnant women with early-onset FGR were done for foetal purposes[12].

Additionally, according to 2 case reports, 35 infants (67.3%,35/52) were admitted to the neonatal critical care unit[6,19]. Small arteries were dissected from myometrial biopsies taken at caesarean sections from

27 normal pregnancies and 12 women with IUGR in Wareing *et al* investigation .'s[20], which validated these findings. Sildenafil citrate, they discovered, enhanced the endothelial function of the myometrial arteries in women whose pregnancies were affected by IUGR. This medication greatly enhanced IUGR small artery relaxation and decreased vasoconstriction.

Similar to this, four trials compared sildenafil and placebo groups using the umbilical artery pulsatility index (PI).They discovered that the sildenafil group had a 12% drop (ranging from 7% to 18%) in the umbilical artery PI on average[17,21,22].

Along with these findings, Trapani *et al*.[21], in 35 singleton pregnancies affected by FGR,examined maternal UA, and MCA before and after administration of either a transdermal nitroglycerin patch (average dosage 0.4 mg/h), oral sildenafil citrate (50 mg), or placebo. Both nitroglycerin (21.3% and 19.2%, respectively) and sildenafil citrate (20.2% and 18.4%, respectively) significantly reduced UA PI as compared to placebo. But in contrast to the current findings, none of the therapy groups showed a significant change in MCA PI.

In accordance with the current findings, Groom *et al*.[23], discovered that using Sildenafil was linked to a decreased mean uterine artery pulsatility index after 48 hours of therapy(1.56 versus 1.81; P=0.02).

A research by Maged *et al*.[24], which included 50 pregnant women and separated them into two control groups without sildenafil citrate, is also consistent with the current findings. At the beginning of therapy, there was no discernible change between the examined groups' UA Doppler indices. Significant reduction in umbilical artery Doppler indices was seen 4 weeks after the first dosage of Sildenafil. Additionally, the sildenafil group's (RI) and (PI) values were much lower than those of the control group.

Studies by Panda *et al*.[6] and Choudhary *et al*.[25] and others have demonstrated a considerable improvement in uterine and UA Doppler indices in FGR when sildenafil is used.

Similar findings were made by Shehata *et al*.[26], who discovered that after taking sildenafil,the Doppler indices in the umbilical and middle cerebral arteries significantly differed between groups. While the middle cerebral artery pulsatility index increased considerably in the intervention group (*p value* = 0.00), the umbilical artery pulsatility index dramatically reduced (*p value* =.001). Also shown that there was no discernible change over time in the control group.

The results of this investigation concur with A single dose of sildenafil citrate was tested on 41 pregnant women with documented FGR at 24-37 weeks of gestation in a randomised double-blind and placebo-controlled study by Dastjerdi *et al*.[22]; the results showed that the sildenafil group's foetuses showed signs of increased uteroplacental circulation. After taking sildenafil for two hours, the means of the umbilical artery (UA) pulsatility index (PI) and systolic/diastolic ratio (S/D) considerably reduced as compared to the placebo group. (P=0.019)and a substantial rise in the mean Pulsatility Index (PI), Resistance Index (RI), and Systolic/Diastolic Ratio (S/D) was seen in the middle cerebral arteries (P = 0.008).They came to the conclusion that sildenafil can improve fetoplacental perfusion in pregnancies complicated by IUGR and that this potential therapeutic approach could improve uteroplacental blood flow in pregnancies with FGR. Doppler velocimetry index values also reflect decreased placental bed vascular resistance after sildenafil administration. The systolic/diastolic ratio and mean (95% CI) pulsatility index of the middle cerebral and umbilical arteries were comparable before and after placebo.

Additionally,incidence of headaches were comparable between the Sildenafil citrate(SC) and control groups in the 2RCTs Samangaya *et al*.[17] and Trapani *et al*.[21].

Four investigations examined the effects of sildenafil on visual disturbances: Von Dadelszen *et al*.[7]; Samangaya *et al*.[17]; Trapani *et al*.[21]; and El-Far *et al*.[27]

However, no participant withdrew from either of the RCTs conducted by Samangaya *et al*.[17] or Trapani *et al*.[21], and visual problems happened at rates comparable to those in the placebo groups.

Additionally,the three RCTs noted arthralgia, myalgia, face flushing, dizziness, diarrhoea, and neurological problems[17,21,22].

In clinical trials for the treatment of erectile dysfunction, sildenafil users frequently experienced side effects such as headaches (7-32%),flushing (7-33%), dyspepsia (1-13%), rhinitis (0-19%), and abnormal vision/visual disturbances (0-10%). These side effects may also be present if sildenafil is used during pregnancy in the future[28].

In contrast to the findings of the current study, Sharp *et al*.[29] conducted a study in 19 foetal medicine units in the UK on women who were carrying singletons between 22 weeks and 0 days and 29 weeks and 6 days and had severe early-onset foetal growth restriction. These women were randomly assigned to receive either sildenafil 25 mg three times per day or a placebo until 32 weeks and 0 days of pregnancy or delivery. They enlisted 135 women between November 21,2014,and July 6,2016, and then randomly allocated 70 to sildenafil and 65 to a placebo.

They came to the conclusion that sildenafil did not cause pregnancy to be prolonged when given to expectant mothers who had significantly growth-restricted foetuses. Because at randomization, the median gestation was 24.4 weeks (IQR 24.0275). In the sildenafil group, the median interval from randomization to delivery was 17 days (7-24), while in the placebo group, it was 18 days (8-28) (p=0.23). According to a linear regression analysis, there was no difference in the average time to delivery for any of the participants (2.7 days,95% CI-1.3 to 6.8; p=0.19). This discrepancy can be attributed to the fact that Sharp *et al*.[29], who recruited more than half of the foetuses with foetal growth restrictions before 26 weeks of gestation, all had severely compromised umbilical circulation with absent or reversed end-diastolic flow, and overall mortality was around 45%.

Although the trial was underpowered for these secondary outcomes, Sharp *et al*.[29], research found no clinically significant differences in death or short-term infant morbidity between the two groups. Additionally, Sildenafil had no negative effects on the blood flow in the umbilical and uterine arteries, according to Sharp *et al*.[29].

Trapani *et al*.[21], in a randomised double-blind, placebo-controlled trial, randomly assigned 100 singleton pregnancies with preeclampsia between 24 and 33 weeks of gestation to 50 mg oral sildenafil citrate every 8 hours or a placebo. The trial was not powered to detect differences in neonatal outcomes. The length of pregnancy from randomization to delivery was the main result. Negative neonatal outcomes, foetal and maternal problems, and alterations in the resistance indices of the uterine, umbilical, and middle cerebral arteries by Doppler were secondary outcomes. According to power calculations, 43 patients would need to be randomly assigned to each group in order to detect a difference of 5 days in pregnancy length. When compared to the control group, infants born in the SC cohort had a reduced rate of admissions to a neonatal critical care unit (66%, 33/50 vs. 74%, 37/50). Of these, 4 instances (7.1%,4/56) with Apgar scores below 7 at 5 minutes were all reported in one RCT. In addition, the SC group had a reduced percentage of Apgar scores 7 at 5 minutes compared to the placebo group (8%, 4/50 vs. 12%, 6/50), according to the same RCT.

Samangaya *et al*.[17] tested the effects of sildenafil in patients with preeclampsia-complicated pregnancy and found that there were no significant changes in UA PI after 2 weeks of sildenafil ingestion. This can be explained by the fact that all of their patients had preeclampsia-complicated pregnancy, and the maternal syndrome of preeclampsia precipitated delivery in 66% of their patients. Similar outcomes were seen in the trial by Groom *et al*.[23], where the rate of caesarean delivery for all live newborns was 82/103 (79.6%) in the placebo group and there was no statistically significant difference between the two groups allocated to sildenafil or placebo.

Additionally, according to Sharp *et al*.[29], caesarean sections did not differ between the two groups given sildenafil or a placebo, with 98% (90 of 92) of all live deliveries occurring by this method in both groups.

Additionally, in a study by Rasheedy *et al*.[30], 100 pregnant women with placentally induced FGR between 28 and 35 weeks of gestation were randomly allocated to receive SC or LMWH starting at the beginning of pregnancy and continued until delivery. Regarding further CS indicators, there was no statistically significant difference between the two groups. Every woman underwent a caesarean section either at the mother's desire, in response to foetal compromise discovered during prenatal care, or as an emergency CS for abnormal cardiotocography while labour was being monitored.

Contrarily, Dunn *et al*. found that caesarean sections were more common (83.3%,55/66) than vaginal births (16.7%, 11/66) in women exposed to SC[31]. 42 women reported side effects overall in the trial by Sharp *et al*.[29]; 24 (34%) of them were in the sildenafil group and 18 (28%) were in the placebo group (RR 1.24,95% CI 0.74-2.06;p=0.41). The most common negative effect,reported by 45 (48% of 94),was face flushing. Other side effects mentioned were nasal congestion, dry mouth, and headaches.

CONCLUSION

According to the study's findings, intrauterine growth restriction (IUGR) continues to be a significant problem in maternity care and a significant contributor to perinatal morbidity and death. notwithstanding the significant strain it places on maternity and paediatric healthcare. We are still looking for a cure that will last forever. In the current study, it was discovered that sildenafil increases gestational age, prolongs pregnancy, improves birth weight, lowers the incidence of CS, and lessens IUGR-related problems.

Future research needs to take into account the effects of sildenafil on boosting foetal weight in FGR pregnancies. Selected women with IUGR may benefit from using sildenafil.

CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCES

1. Lawn JE, Cousens S, Zupan J, *et al*. (2005): 4 million neonatal deaths: when? Where? Why?.The lancet; 365(9462):891-900.

2. Mercer BM, Goldenberg RL, Moawad AH, *et al*. (1999): The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. American journal of obstetrics and gynecology; 181(5):1216-21.

3. Petersen SG,Wong SF, Urs P, *et al*. (2009): Early onset, severe fetal growth restriction with absent or reversed end-diastolic flow velocity waveform in the umbilical artery: Perinatal and long-term outcomes. Australian and New Zealand Journal of Obstetrics and Gynaecology; 49(1):45-51.

4. Wareing M,Myers JE,O'Hara M, *et al*. (2005): Sildenafil citrate (Viagra) enhances vasodilatation in fetal growth restriction.The Journal of Clinical Endocrinology & Metabolism; 90(5):2550-5.

5. Zoma WD, Baker RS, Clark KE *et al*. (2004): Effects of combined use of sildenafil citrate (Viagra) and 17β-estradiol on ovine coronary and uterine hemodynamics. American journal of obstetrics and gynecology; 190(5):1291-7.

6. Panda S, Das A, Nowroz HM *et al*. (2014): Sildenafil citrate in fetal growth restriction. Journal of reproduction & infertility; 15(3):168.

7. Von Dadelszen P, Dwinnell S,Magee LA, *et al*. (2011):Sildenafil citrate therapy for severe early-onset intrauterine growth restriction. BJOG: An International Journal of Obstetrics &Gynaecology; 118(5):624-8.

8. El-Sayed MA, Saleh SA, Maher MA, *et al*. (2018):Utero-placental perfusion Doppler indices in growth restricted fetuses: effect of sildenafil citrate. The Journal of Maternal-Fetal & Neonatal Medicine;31(8):1045-50.

9. Royal College of Obstetricians and Gynaecologists (RCOG) (2013): The investigation and management of the small-for-gestational-age fetus. London: Green-top Guideline No.31.

10. Lawin-O'Brien AR, Dall'Asta A, Knight C, *et al*. (2016): Short-term outcome of periviable small-for-gestational-age babies: is our counseling up to date?. Ultrasound in Obstetrics & Gynecology; 48(5):636-41.

11. Lees CC,Marlow N, van Wassenaer-Leemhuis A, *et al*. (2015): 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. The Lancet; 385(9983):2162-72.

12. Lees C, Marlow N, Arabin B, *et al*. (2013):Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound in Obstetrics & Gynecology;42(4):400-8.

13. Lin CS, Lin G, Xin ZC, *et al*. (2006): Expression, distribution and regulation of phosphodiesterase 5. Current pharmaceutical design; 12(27):3439-57.

14. Singh A,Daharwal A,Kujur A, *et al*. (2017): Effect of sildenafil on IUGR. International Journal of Reproduction, Contraception, Obstetrics and Gynecology;6(5):1807.

15. Kubo M, Umekawa T, Maekawa Y, *et al*. (2017): Retrospective study of tadalafil for fetal growth restriction: Impact on maternal and perinatal outcomes. Journal of Obstetrics and Gynaecology Research.;43(2):291-7.

16. Ferreira E, Léveillée D, Iglesias MH, *et al*. (2016):O-OBS-MFM-PhD-065 Sildenafil Use During Pregnancy for Intrauterine Growth Restriction: A Case Series. Journal of Obstetrics and Gynaecology Canada;38(5):486.

17. Samangaya RA, Mires G,Shennan A, *et al*. (2009): A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor sildenafil for the treatment of preeclampsia. Hypertension in pregnancy; 28(4): 369-82.

18. El-Shalakany AH, Abd El Aleem MM, Bawady MZ (2018): Sildenafil Citrate and Uteroplacental Perfusion in Fetal Growth Restriction. The Egyptian Journal of Hospital Medicine; 71(4): 2989-95.

19. Molelekwa V, Akhter P, McKenna P, *et al*. (2005): Eisenmenger's syndrome in a 27 weekpregnancy--management with bosentan and sildenafil. Irish Medical Journal; 98(3): 87-8.

20. Wareing M, Myers JE, O'Hara M, *et al*. (2006): Phosphodiesterase-5 inhibitors and omental and placental small artery function in normal pregnancy and pre-eclampsia. European Journal of Obstetrics & Gynecology and Reproductive Biology;127(1):41-9.

21. Trapani A, Gonçalves LF, Trapani TF, *et al*. (2016): Comparison between transdermal nitroglycerin and sildenafil citrate in intrauterine growth restriction: effects on uterine, umbilical and fetal middle cerebral artery pulsatility indices. Ultrasound in Obstetrics & Gynecology;48(1):61-5.

22. Dastjerdi MV,Hosseini S,Bayani L (2012): Sildenafil citrate and uteroplacental perfusion in fetal growth restriction. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences;17(7):632.

23. Groom KM,Mccowan LM, Mackay LK, *et al*. (2019): STRIDER NZAus: a multicentre randomised controlled trial of sildenafil therapy in early-onset fetal growth restriction. BJOG: An International Journal of Obstetrics & Gynaecology; 126(8):997-1006.

24. Maged M, Wageh A, Shams M, *et al*. (2018): Use of sildenafil citrate in cases of intrauterine growth restriction (IUGR); a prospective trial. Taiwanese Journal of Obstetrics and Gynecology; 57: 483-486.

25. Choudhary R,Desai K,Parekh H, *et al*. (2016): Sildenafil citrate for the management of fetal growth restriction and oligohydramnios. Internationa1 Journal of Women's Health; 8: 367.

26. Shehata N, Ali H, Fahim A, *et al*. (2018): Addition of sildenafil citrate for treatment of severe intrauterine growth restriction: a double blind randomized placebo controlled trial. The Journal of Maternal-Fetal & Neonatal Medicine:1-7.

27. El-Far M, El-Motwally AE, Hashem IA, *et al*. (2009): Biochemical role of intravaginal sildenafil citrate as a novel antiabortive agent in unexplained recurrent spontaneous miscarriage: first clinical study of four case reports from Egypt.Clinical Chemistry and Laboratory Medicine; 47(11): 1433-8.

28. Boyce EG, Umland EM (2001): Sildenafil citrate:a therapeutic update. Clinical Therapeutics; 23(1): 2-3.

29. Sharp A, Cornforth C, Jackson R, *et al*. (2018):Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled,double-blind trial.The Lancet Child&Adolescent Health;2(2):93-102.

30. Rasheedy R,El Bishry G, Tarek R (2019): Maternal low molecular weight heparin versus sildenafil citrate for fetal growth restriction: a randomized, parallel groups, open-label clinical trial. Journal of Perinatology:1-9.

31. Dunn L, Greer R, Flenady V, *et al*. (2017): Sildenafil in Pregnancy: A Systematic Review of Maternal Tolerance and Obstetric and Perinatal Outcomes.Fetal Diagnosis and Therapy;41:81-88.