Effects of sildenafil citrate on impedance to flow in the umbilical and fetal middle cerebral arteries in pregnancies at high risk for fetal growth restriction

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Objective:

To assess whether sildenafil citrate improves blood flow in fetal umbilical arteries and middle cerebral arteries in pregnancies at high risk for fetal growth restriction.

Methods:

A quasi-experimental study was carried out at the Department of Obstetrics and Gynecology, Suez Canal University Hospital in Ismailia over the period from June 2017 to April 2018. Trans-abdominal obstetric ultrasonography (U/S) was done for 30 pregnant women aged24 to 35 years, gestational age ranged between 33- 36 weeks, at high risk for fetal growth restriction (mild pre-eclampsia, diabetes mellitus, history of previous pregnancy with a small for gestational age, stillbirth, severe pre-eclampsia or pregnancies with abnormal umbilical artery indices-above 90th centile). Fetal umbilical and middle cerebral artery blood flow Doppler indices were determined before and 2 and 6 hours after ingestion of sildenafil citrate 20 mg tablet.

Results:

There was a statistically significant decrease in umbilical artery Doppler indices before, two hours and six hours following sildenafil citrate therapy in the studied patients ($P<0.05$) and a statistically significant increase in middle cerebral artery Doppler indices before, two hours and six hours following sildenafil citrate therapy in the studied patients ($P<0.05$).

Conclusions:

Sildenafil citrate significantly increases blood flow in the umbilical arteries and normalizes blood flow in fetal middle cerebral arteries in pregnancies at high risk for fetal growth restriction thereby restoring a normal fetal circulation and corrects the "brain sparing" adaptive mechanism.

Key words:

Sildenafil citrate, FGR, High-risk pregnancy, Doppler ultrasound, Umbilical artery, iddle Cerebral Artery

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INTRODUCTION

Excluding fetal anomalies, after prematurity, fetal growth restriction (FGR) is the second common cause of perinatal morbidity. It has been long recognized that in preeclampsia, a severe maternal endothelial dysfunction must be identical placental pathology to that underlying fetal growth restriction. Pregnancies with fetal growth restriction are associated with elevated peripheral resistance in the maternal arterial system as seen in pregnancies with preeclampsia[1], [2].

Several maternal demographic factors have been associated with FGR as maternal race, lower socioeconomic status, and living in a developing country also smoking in pregnancy is associated with a 3.5-fold increased risk of SGA compared with nonsmokers. Up to 19 % of term low birth weight (LBW) has been attributed to smoking during pregnancy. Fetal factors can vary from genetic causes, congenital malformations, fetal infection, or other causes, including multiple pregnancies. Placental insufficiency accounts for many cases of FGR and can affect up to 3 % or more of all pregnancies. The pathogenesis of FGR is not well defined; defects in the placental circulation and transport can affect the nutrient transport to the fetus, resulting in FGR. The relative decrease in placental mass and function can result in the development of FGR[3]–[5].

A fetus with FGR may be born small for gestational age (SGA) or appropriate for gestational age (AGA) according to population reference charts. Additionally, in developing countries, there is a direct correlation between the incidence of low birth weight (<2500 g) and FGR because in developing countries, the high incidence of low-birth-weight (LBW) infants is almost exclusively due to the incidence of FGR. Data from developed countries show the opposite, rates of low birth weight being explained almost exclusively by prematurity rates[6], [7].

Sildenafil citrate is a selective inhibitor of cyclic guanosine mono phosphate (cGMP)–specific phosphor-diesterase (PDE)-5 and enhances the relaxation and (cGMP) accumulation elicited by exogenous and neural-released nitric oxide in corpus cavernosum. The most common adverse reactions reported in clinical trials are headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness, and rash[1], [2].

Sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction and it could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR) [1], [4].

Reduced flow increased resistance in uterine and umbilical arteries, indicative of reduced uteroplacental flow in pregnancies with fetal growth restriction, has been documented by noninvasive Doppler ultrasound velocimetry. This adaptive mechanism, termed "brain sparing", is reflected on arterial Doppler ultrasound by increased impedance in the umbilical arteries and decreased impedance in the middle cerebral arteries. As metabolic deterioration occurs and the fetus loses the ability to adapt to hypoxemia, the middle cerebral artery Doppler indices will normalize, with an evident decrease in end-diastolic flow in the cerebral circulation[5], [8], [9].

Dastjerdi et al.determined whether the phosphodiesterase type 5 inhibitor, Sildenafil citrate, affects uteroplacental perfusion. They concluded that velocimetry index values reflect decreased placental bed vascular resistance after Sildenafil. Sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction[1]. It could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR) [9].

PATIENTS AND METHODS:

A quasi-experimental study was carried out at the Department of Obstetrics and Gynecology, Suez Canal University Hospital, Ismailia, Egypt. Thirty pregnant women with fetal growth restriction were included in the study. The patients were recruited from the prenatal outpatient clinicover the period from March 2018 to December 2018.Inclusion criteria were as follows:

- Maternal age ranged between 24 to 35 years
- Gestational age between 28- 37 weeks
- Singleton pregnancy
- Low risk pregnant women with ultrasound evidence of fetal growth restriction

- Pregnant women at high risk for fetal growth restriction:
  - Mild pre-eclampsia
  - Diabetes mellitus
  - History of previous pregnancy with; small for gestational age, stillbirth, severe pre-eclampsia
- Elevated umbilical artery Doppler indices above 90th percentile of norm
- Normal non-stress test at time of admission. Intact membranes.

Approval of the Ethics Committee of the Faculty of Medicine, SCU was obtained. A signed informed consent for participation in the study was also obtained from each of the enrolled patients.

Investigations: Trans abdominal Obstetric Ultrasonography (U/S) was done for 30 pregnant women in a semi-recumbent position (before and 2- and6-hours after of ingestion of sildenafil citrate 20 mg tablet) using a PHILIPS, ClearVue350 with a C5-2 Active Array transducer.

The ultrasound criteria for FGR included:

- Fetal body weight below 10th percentile.
  - An elevated ratio of Head Circumference (HC) to Abdominal Circumference (AC).It is normally drops almost linearly from 1.2 to 1.0. The ratio is normal in the fetus with symmetric growth restriction and elevated in the infant with asymmetric growth restriction.
  - An elevated ratio of femoral length to abdominal circumference. Growth retardation = >24% **(Crang-svalenius, 1991)**.
- Oligohydramnios.

Umbilical artery Doppler is identified at the fetal end, the free-floating loop of the umbilical cord at the apparent entrance point into the placenta.Absent or Reverse End-Diastolic Velocity (AREDV) was noted and the following waveform indices were determined;Systolic/Diastolic (S/D) ratio, Pulsatility Index (PI) and Resistance Index (RI).

Middle cerebral artery Doppler was found overlying the anterior wing of the sphenoid bone near the base of the skull in the transverse plane of the fetal head at the apparent entrance point into the Circle of Willis. The Systolic/Diastolic (S/D) ratio, Pulsatility Index (PI) and Resistance Index (RI) were determined. Doppler studies were done by the same investigator in all the patients.

Cerebroplacental ratio was calculated by dividing the Doppler pulsatility index of the middle cerebral artery (MCA)by the umbilical artery (UA) pulsatility index.

- Sildenafil was given orally 20 mg tablets/ tdsuntil delivery.
- Doppler studies were performed (before and at 2- and 6-hours after giving sildenafil) to assess its effectiveness and note any adverse reactions.
- Patients were asked about drug adverse reactions such as nausea, dizziness, headache, flushing, back pain, nasal congestion and asked about fetal movement changes after ingestion of the drug and weekly thereafter until delivery. Mild dizziness and headache were the only adverse side effects reported and sildenafil appeared to be well tolerated by our patients at the above-mentioned dosage.

Statistical Analysis

Data were analyzed by Statistical Package of Social Science (SPSS), software version 240.0 (SPSS Inc., 2016). Continuous data were presented as the Mean±SD or Median (Range). Normality of distribution of data was checked by Shapiro-Wilk test. Categorical data were presented by frequency and percentage.The one-way repeated measure ANOVA: was used to test for differences between groups when the dependent variable is normally distributed continuous variable. Post hoc analysis with a Bonferroni adjustment: is used for multiple comparisons following one-way repeated measure ANOVA to detect which occasion in particular differs from other occasions.

RESULTS

Table 1: Demographic characteristics of the studied patients (n=30)

Variables		
Maternal age (years)		
Mean ± SD	30.5±3.5	
Median (Range)	30(26-35)	
Gestational age at delivery (weeks)		
Mean ± SD	34.1±1	
Median (Range)	34(33-36)	
Maternal parity, n, (%)		
Multipara	N	%
2	9	30%
3	15	50%
4	3	10%
6	3	10%
Maternal risk factors:n, (%)		
• Mild pre-eclampsia	13	43%
• Diabetes mellitus	5	17%
• History of previous FGR, stillbirth or severe pre-eclampsia	9	30%
• Elevated umbilical artery indices above the 90th percentile of norm	3	10%

This table shows that mean age of studied population was Mean ± SD (34.1±1), and shows that 43% wereMild pre-eclampsia,17% werer diabetics and 30% had History of previous FGR, stillbirth or severe pre-eclampsia and only 10% of the participants had Elevated umbilical artery indices above the 90th percentile of norm.

Table 2: Umbilical artery Doppler indices before (baseline), 2 hours and 6 hours following sildenafil citrate therapy in the studied patients

Umbilical Artery Indices	**Baseline Indices** n=30	**2-hours post sildenafil** n=30	**6-hours post sildenafil** n=30	**Repeated measure ANOVA**	**P-value**
S/D ratio	3.3±0.49	3.0±0.39	2.7±0.22	F=23.8	<0.001
Pulsatility index	1.2±0.36	1.12±0.1	0.9±0.11	F=10.7	0.001
Resistance index	0.79±0.2	0.70±0.1	0.60±0.2	F=7.5	0.003

UA= umbilical artery

This table showed statistically significant differences in umbilical artery Doppler indices before sildenafil and2 and 6 hours following sildenafil citrate therapy in the studied patients (P<0.05).

Table 3: Post hoc analysis assessing umbilical artery pulsatility index at different time points (Pre-sildenafil, 2- and 6-hourspost sildenafil) in the studied patients

UA pulsatility index	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		> 0.99	**0.004**
2-hourspost-sildenafil			**<0.001**

Post hoc analysis with a Bonferroni adjustment revealed that umbilical artery pulstality index was not statistically significantly differentbetween pre-sildenafil therapy to two hour-post therapy (p>0.99). However, the pulsatility index was statistically significantly decreased in the6-hour post therapy as compared to pre-sildenafiland2-hour post-therapy were the probability values were 0.004 and 0.001 respectively.

Table 4: Post hoc analysis assessing umbilical artery resistance index at different time points (Pre-sildenafil, 2-hoursand 6-hourspost- sildenafil) in the studied patients

UA resistance index	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		.33	**0.008**
2-hours post-sildenafil			**0.022**

Post hoc analysis with a Bonferroni adjustment revealed that umbilical artery resistance index was not statistically significantly different between pre-sildenafil therapy to 2-hourspost therapy (p=0.33). However, the resistance index was statistically significantly decreased in the6-hour post therapy as compared to pre-sildenafil and the2-hour post therapy were the probability values were 0.008 and 0.022 respectively.

Table 5: Post hoc analysis assessing middle cerebral artery Systolic/diastolic ratio at different time points (Pre-sildenafil, 2- and 6-hourspost sildenafil) in the studied patients

MCA S/D ratio	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		0.003	**<0.001**
2-hours post-sildenafil			**0.006**

Post hoc analysis with a Bonferroni adjustment revealed that middle cerebral artery systolic/diastolic ratio was statistically significantly higherinthe 2-hourspost therapy, and 6-hourspost therapycompared-to pre-sildenafil therapywere the probability value was0.003 and<0.001 respectively. Also, the middle cerebral artery systolic/diastolic ratio was statistically significantly higherin the6-hourspost therapy as compared to 2-hourspost therapy (p= 0.006).

Table 6: Post hoc analysis assessing middle cerebral artery resistance index at different time points (Pre-sildenafil, Two hours-post sildenafil and Six hours-post sildenafil) in the studied patients

MCA resistance index	Pre-sildenafil n=30	2-hourspost- sildenafil n=30	6-hourspost- sildenafil n=30
Pre-sildenafil		**0.002**	**0.01**
2-hours post-sildenafil			>0.99

Post hoc analysis with a Bonferroni adjustment revealed that middle cerebral artery resistance index was statistically significantly higherinthe 2-hourspost therapy, and 6-hourspost therapy comparedto pre-sildenafil therapy were the probability value was<0.002 and<0.001 respectively. Also, the middle cerebral artery resistanceindex was not statistically significantly higherin the6-hourspost therapy as compared to 2-hourspost therapy (p>0.99).

Table 7: Cerebro-placental ratio before, two hours and six hours following sildenafil citrate therapy in the studied patients

Variable	Baseline n=30	2-hours post-sildenafil n=30	6-hours post-sildenafil n=30	Repeated measure ANOVA	p-value
Cerebro-placental ratio	**0.88±0.22**	**1.1±0.10**	**2.7±0.92**	***F=99.3***	**<0.001**

This table showed a statistically significant increase in cerebroplacental ratio before, two hours and six hours following sildenafil citrate therapy in the studied patients (P<0.001).

Table 8: Post hoc analysis cerebroplacental ratio at different time points (Pre-sildenafil, 2- and 6- hourspost-sildenafil) in the studied patients

Cerebroplacental ratio	Pre-sildenafil n=30	Two hourspost-sildenafil n=30	Six hourspost-sildenafil n=30
Pre-sildenafil			**<0.001**
2-hours post-sildenafil		**<0.001**	**<0.001**

Post-hoc analysis with a Bonferroni adjustment revealed that cerebro-placental ratio was statistically significantly increased from pre-sildenafil therapy to two hours post-therapy (P<0.001), and from pre-sildenafil therapy to six hourspost-therapy (P<0.001). Also, cerebro-placental ratio was statistically significantly increased from two hours post-therapy to six hours post-therapy (P<0.001).

Table 9: Birth weight of the babies

Variables	
Birth weight (g)	
Mean ± SD	2573.3±146.1
Median (Range)	2550(2400-2900)

DISCUSSION

This quasi-experimental study was carried out at the Department of Obstetrics and Gynecology, Suez Canal University Hospital, Ismailia, Egypt. Thirty pregnant women with risk factors for fetal growth restriction were included in the study. The patients were recruited from the prenatal outpatient clinicover the period from June 2017 to April 2018.

In our stud y, mean age of studied women is 30.5 years, with range from 26 to 35 years old.

Sildenafil, as a vasodilator, should be an alternative in the treatment of fetal growth restriction (FGR) and preeclampsia by later normalization in velocimetric profile. As a therapeutic agent in FGR gestations by promoting myometrial small artery vasodilatation, reducing in maternity peripheral resistance and increasing flow within the uteroplacental bed, can improve uteroplacental perfusion. PDE-5 inhibitors can reduce vasoconstriction and improve relaxation of FGR myometrial small arteries[1], [10].

Not only an extensive report of the preclinical evaluation could not demonstrate any evidence of teratogenicity by Sildenafil, even at doses much higher than that evaluated in the present study but also for preeclampsia treatment, Sildenafil in the escalating dose regimen 20-80 mg tid was well tolerated, without increasing in maternal or fetal morbidity or mortality. It might safely reduce perinatal morbidity and mortality by increasing uteroplacental impaired perfusion[10], [11].

The current study findings consistent with those of Dastjerdi et al. which was conducted on 59 women with fetal growth restriction were divided into two groups, 30 in the placebo and 29 in the Sildena-

fil group .Unfortunately,3 patients in the placepo and 15 in the sildenafil group refused to undergo Doppler velocimetry for the second time. Among the41 pregnancies, there were 6 with oligohydramnios (4 in the case and 2 in the control group), 3 with hypertension (all in the control group) and 1 with previous stillbirth (in the placebo group). This study included 38 asymmetric and 3 symmetric fetuses with growth restriction. All symmetric ones were in the control group. No significant improvement was detected in the perfusion of umbilical and middle cerebral arteries in the control group before and after placebo[1], [9].

Two hours after tablet ingestion, 1 in the Sildenafil and 2 in the placebo group expressed headache and 1 in the placebo group reported flushing but there was no report of nausea, myalgia and arthralgia. However, nine in the placebo and 3 in the Sildenafil group reported better fetal movement. The means of the umbilical artery (UA) pulsatility index (PI) and Systolic/Diastolic ratio (S/D) significantly decreased 2 hours after Sildenafil ingestion as compared to the placebo group. Mean umbilical artery systolic/diastolic ratio (UA S/D) significantly decreased in the Sildenafil group as compared to the placebo group. Mean umbilical artery pulsatility index (UA PI) significantly decreased in the Sildenafil group in comparison with the placebo group. In middle cerebral arteries, a significant increase was noted in mean Pulsatility Index (PI), resistance index (RI) and Systolic/Diastolic ratio (S/D) after Sildenafil administration. Mean Middle Cerebral Artery Pulsatility Index (MCA PI) significantly increased in the Sildenafil group [12], [13].

Maharaj et al. studied the effects and mechanisms of action of sildenafil citrate in human chorionic arteries ex vivo. In a series of pharmacologic studies, the effects of sildenafil citrate in pre-constricted chorionic plate arterial rings were determined. They showed that phosphodiesterase-5-mRNA and protein was demonstrated in human chorionic plate arteries. Sildenafil produced dose dependent vasodilatation. They concluded that sildenafil citrate vasodilated the fetoplacental circulation via a cGMP dependent mechanism involving increased responsiveness to nitrous oxide[14].

Von Dadelszen et al. studied the role of sildenafil citrate therapy for severe early onset intrauterine growth restriction. Women were offered sildenafil citrate 25 mg three times daily until delivery if their pregnancy was complicated by early onset IUGR (AC\5th centile) and either the gestational age was less than 25 weeks or the fetal weight was 600 g. They found that sildenafil citratewas associated with increased AC growth. They suggested that Sildenafil treatment offer a new opportunity to improve perinatal outcomes for women whose pregnancies are complicated by severe early-onset IUGR [15].

Panda et al. stated that sildenafil, as a vasodilator has also emerged as a potential management option in the treatment of FGR and preeclampsia by later normalization in velocimetric profile[16].

This study is consistent with a study was conducted in Ain shams University hospital and Kafr Aldwwar main Hospital in El-Behera governorate showed that Sildenafil treatment was associated with a significant increase in length of pregnancy and a significant increase in estimated fetal weight by ultrasound , and was associated with a significant decrease in neonatal ICU admission and neonatal mortality[17].

CONCLUSION

Sildenafil citrate significantly increases blood flow in the umbilical arteries and normalizes blood flow in fetal middle cerebral arteries in pregnancies at high risk for fetal growth restriction in late.

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