

Research Article

# The use of low dose sildenafil citrate in cases of intrauterine growth restriction

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## Abstract

**Introduction:** Intrauterine growth restriction [IUGR] is defined as a birth weight less than the 10th percentile for gestational age. It has a prevalence of the 5–8% in the general population. It represents the second cause of perinatal mortality, after prematurity. Sildenafil citrate is a phosphodiesterase5 (PDE-5) inhibitor, delaying the breakdown of cyclic guanosine monophosphate (cGMP) and enhancing nitric oxide (NO)-dependent vasodilatation. Sildenafil citrate is increasingly used for pulmonary hypertension in pregnancy, and is also emerging as a potential candidate for the treatment of intra-uterine growth retardation and for premature labour.

**Aim of work:** The aim of this work was to evaluate the effect of the use of low dose sildenafil citrate in cases of IUGR.

**Patients and methodology:** This study involved 30 patients who presented to Shatby Maternity University Hospital from August- December 2016, they were 26-32 weeks with singleton spontaneous pregnancy, who were diagnosed as intrauterine growth restriction by any of the following criteria:

1. Lag of two weeks or more between the current biometric measures and the documented pregnancy dating in the first trimester.
2. Estimated fetal weight less than the 10<sup>th</sup> percentile for gestational age.

Cases were subjected to full history taking, general and obstetric examination, laboratory investigations including blood grouping, Rh typing, complete blood count (CBC), blood urea, serum creatinine, liver function tests and complete urine analysis. Ultrasonographic examination was done including Serial fetal biometry (BPD, HC, AC, HC/AC ratio, FL, EFW) to monitor fetal growth and assessment of biophysical profile weekly. Doppler ultrasound: Doppler study of fetal blood vessels including umbilical artery (UA), middle cerebral arteries (MCA) and ductus venosus (DV) weekly. Who are divided into two groups: study group (n=15); women who received 20 mg sildenafil citrate oral tablets for 6 weeks, control group (n=15); women who received placebo. Follow-up was done for 4-6 weeks.

**Results:** Cases of both groups were matched in age, gestational age, gravidity, parity, blood pressure, weight, body mass index, estimated fetal weight, amniotic fluid index [AFI]. Comparing both groups regarding weekly increase of abdominal circumference [AC] and AFI after treatment; there was no statistically significant difference. Comparing both groups regarding umbilical artery systolic:diastolic ratio, pulsatility index [PI]; there was significant improvement in these indices in the study groups, however there was no statistically significant difference between both groups regarding gestational age at birth [mean 35 weeks versus 34 weeks] nor birth weight mean 1553 gm versus 1439 gm].

**Conclusion:** The administration of oral sildenafil tablets 20 mg twice a day for 6 weeks improved Doppler indices in umbilical artery and cerebroplacental ratio, yet it had no effect on gestational age at birth nor birth weight.

## Introduction

Intrauterine growth restriction (IUGR) is defined as a birth weight less than the 10th percentile for gestational age. With a prevalence of the 5–8% in the general population, IUGR can complicate 10% to 15% of all pregnancies [1,2]. IUGR represents the second cause of perinatal mortality, after prematurity, and it is related to an increased risk of perinatal complication as hypoxemia, low Apgar scores, and cord blood acidemia, with possible negative effects for neonatal outcome [3,4].

IUGR is a wide-ranging pregnancy problem with a number of possible mechanisms leading to reduced fetal growth [5]. Frequently the etiology of IUGR is unknown; however in several cases it is possible to identify fetal (infection, malformation, and chromosomal aberration), placental (chorioangioma, infarction, circumvallated placenta, confined placental mosaicism, obliterative vasculopathy of the placental bed, etc.), maternal (chronic hypertension, pre-gestational diabetes, cardiovascular disease, substance abuse, autoimmune conditions, etc.), and external factors that modulate the normal fetal growth, by acting on a genetically predetermined potential growth [6-8].

Hemodynamic changes involve maternal uterine, fetal umbilical, and middle cerebral arteries and precordial veins for cardiac effects of placental dysfunction [9,10]. The circulatory adaptation consists in an increased umbilical artery and decreased middle cerebral artery blood-flow resistance [11].

Despite the significant risks associated with IUGR-affected pregnancies, there remains no treatment. The only option currently available to clinicians is early delivery of the baby which is itself associated with increased morbidity and/or mortality [12].

Furthermore, there are still no drugs developed specifically for obstetric conditions currently in clinical trials. This has led to the

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assessment of drugs currently used in clinical practice for other diseases, to be assessed on a re-purpose basis as potential therapeutics in the treatment of IUGR [13].

Sildenafil citrate is a phosphodiesterase5 inhibitor, delaying the breakdown of cyclic guanosine monophosphate (cGMP) and enhancing nitric oxide (NO)-dependent vasodilatation. Sildenafil citrate is increasingly used for pulmonary hypertension in pregnancy, and is also emerging as a potential candidate for the treatment of intra-uterine growth retardation and for premature labour [14]. Sildenafil has also been proposed as a potential therapeutic strategy to maintain placental function in pre-eclampsia [15].

Recent studies have demonstrated that sildenafil citrate significantly enhances vasodilation of myometrial small arteries and is also associated with fetal weight gain which offers a potential therapeutic possibility for IUGR [16].

## Aim of the work

The aim of this work was to evaluate the effect of the use of low dose sildenafil citrate in cases of IUGR.

## Patients and methodology

This study involved 30 patients who presented to Shatby Maternity University Hospital from August- December 2016, they were 26-32 weeks with singleton spontaneous pregnancy, who were diagnosed as intrauterine growth restriction by any of the following criteria:

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Cases were subjected to full history taking, general and obstetric examination, laboratory investigations including blood grouping, Rh typing, complete blood count (CBC), blood urea, serum creatinine, liver function tests and complete urine analysis. Ultrasonographic examination was done including Serial fetal biometry (BPD, HC, AC, HC/AC ratio, FL, EFW) to monitor fetal growth and assessment of biophysical profile weekly.

Doppler ultrasound: Doppler study of fetal blood vessels including umbilical artery (UA), middle cerebral arteries (MCA) and ductus venosus (DV) weekly using Voluson P8 ultrasound machine [GE].

Who are divided into two groups: study group (n=15); women who received 20 mg sildenafil citrate oral tablets for 6 weeks, control group (n=15); women who received placebo. Follow-up was done for 4-6 weeks.

## Statistical analysis of the data

Data were fed to the computer using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test. The distributions of quantitative variables were tested for normality using Shapiro-Wilk test and D'Agostino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests were applied. If the data were abnormally distributed, non-parametric tests were used. Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data was

expressed using median, minimum and maximum. For normally distributed data, comparison between two independent population were done using independent t-test.

For abnormally distributed data, Correlations between two quantitative variables were assessed using Spearman coefficient. Multivariate logistic regression was used. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

## Results

Cases of study and control groups were matched in age [29.07 ± 5.39 versus 27.73 ± 5.55 years] , gestational age [28.13 ± 2.07 versus 28.80 ± 2.11 weeks], gravidity [3.33 ± 1.40 versus 3.53 ± 1.85], parity [1.07 ± 1.22 versus 1.53 ± 1.64] abortion [1.27 ± 1.39 versus 1.0 ± 1.47], blood pressure [systolic 127.33 ± 11.0 versus 120.67 ± 13.87, diastolic 78.67 ± 11.25 versus 80.0 ± 8.45 mmHg], weight [81.07 ± 14.42 versus 88.0 ± 9.61 kg] , body mass index [30.32 ± 4.99 versus 33.49 ± 3.67], estimated fetal weight [689.73 ± 207.35 versus 777.0 ± 316.50 gm] , amniotic fluid index [5.50 ± 3.08 versus 6.93 ± 3.79].

Comparing study and control groups regards changes in umbilical artery S/D ratio, PI, middle cerebral artery and cerebroplacental ratio, there was significant difference showing improvement of placental perfusion in the study group compared to the control group; as shown in tables 1-8.

## Discussion

Intrauterine growth restriction (IUGR) is defined as a fetus who is at or below the 10th percentile in weight for its gestational age as adopted by the ACOG and the RCOG [1,2].

**Table 1.** Showing S/D ratio in study and control groups before and after therapy, showing statistically significant decrease in the ratio in study group compared to control group after therapy.

UA S/D	Cases (n=15)	Control (n=15)	t	P
<b>Before</b>				
Min. – Max.	2.30 – 3.90	2.50 – 4.20 3.36 ± 0.55	0.022	0.982
Mean ± SD.	3.0 ± 0.48			
<b>After</b>				
Min. – Max.	2.30 – 3.70	2.60 – 3.70 3.01 ± 0.33	1.031	0.314
Mean ± SD.	3.14 ± 0.47			
<b>P<sub>i</sub></b>	0.322	0.047*		

t, p: t and p values for Student t-test for comparing between the two groups; p<sub>i</sub>: p value for Paired t-test for comparing between before and after in each group; \*: Statistically significant at p ≤ 0.05

**Table 2.** Showing umbilical artery PI in study and control groups before and after therapy showing statistically significant decrease in PI in study group compared to control group after therapy.

UA PI	Cases (n=15)	Control (n=15)	t	P
<b>Before</b>				
Min. – Max.	0.93 – 1.32	0.90 – 1.30	0.472	0.640
Mean ± SD.	1.04 ± 0.13	1.06 ± 0.10		
<b>After</b>				
Min. – Max.	0.89 – 1.30	0.90 – 1.40	2.297*	0.031*
Mean ± SD.	1.04 ± 0.15	1.17 ± 0.13		
<b>P<sub>i</sub></b>	0.917	0.026*		

t, p: t and p values for Student t-test for comparing between the two groups; p<sub>i</sub>: p value for Paired t-test for comparing between before and after in each group; \*: Statistically significant at p ≤ 0.05

Our results show significant statistical difference between umbilical artery[UA] indices in sildenafil treated cases and control. Mean umbilical artery systolic/diastolic ratio (UA S/D) significantly decreased in the Sildenafil group as compared to the placebo group at the end of trial (P=0.047). Also, mean umbilical artery pulsatility index (UA PI) significantly decreased in the Sildenafil group in comparison with the placebo group (P=0.026).

**Table 3.** Showing middle cerebral artery PI before and after therapy; showing statistically significant difference.

MCA PI	Cases (n=15)	Control (n=15)	t	P
<b>Before</b>				
Min. – Max.	1.30 – 1.90	1.30 – 2.50	1.238	0.226
Mean ± SD.	1.62 ± 0.19	1.87 ± 0.29		
<b>After</b>				
Min. – Max.	1.80 – 2.40	1.88 – 2.40	2.817*	0.009*
Mean ± SD.	2.10 ± 0.20	2.02 ± 0.16		
p <sub>i</sub>	0.065	<0.001*		

t, p: t and p values for Student t-test for comparing between the two groups; p<sub>i</sub>: p value for Paired t-test for comparing between before and after in each group; \*: Statistically significant at p ≤ 0.05

**Table 4.** Showing improvement in cerebroplacental ratio in study group compared to control group after therapy.

CPR	Cases (n=15)	Control (n=15)	t	P
<b>Before</b>				
Min. – Max.	1.46 – 2.58	1.38 – 2.67	0.358	0.723
Mean ± SD.	1.97 ± 0.30	2.01 ± 0.34		
<b>After</b>				
Min. – Max.	1.49 – 2.66	1.01 – 2.0	4.020*	0.001*
Mean ± SD.	1.94 ± 0.34	1.42 ± 0.31		
p <sub>i</sub>	0.689	<0.001*		

t, p: t and p values for Student t-test for comparing between the two groups; p<sub>i</sub>: p value for Paired t-test for comparing between before and after in each group; \*: Statistically significant at p ≤ 0.05

**Table 5.** Comparing both groups regarding gestational age at delivery; there was no statistically significant difference between both groups.

	Cases (n=15)	Control (n=15)	Test of sig.	p
<b>GA at delivery (weeks)</b>				
Min. – Max.	30.0 – 38.0	32.0 – 37.0	t=0.711	0.483
Mean ± SD.	35.47 ± 2.47	34.87 ± 2.13		

χ<sup>2</sup>, p: χ<sup>2</sup> and p values for Chi square test for comparing between the two groups; t, p: t and p values for Student t-test for comparing between the two groups.

**Table 6.** Regarding rate of increase in Abdominal circumference in both groups after therapy, there was no statistically significant difference.

	Cases (n=15)	Control (n=15)	Test of sig.	P
<b>AC/W (mm)</b>				
Min. – Max.	0.60 – 0.90	0.50 – 0.99	t=0.815	0.422
Mean ± SD.	0.75 ± 0.10	0.71 ± 0.16		

MW, p: p values for Mann Whitney test for comparing between the two groups; t, p: t and p values for Student t-test for comparing between the two groups

**Table 7.** Regarding rate of increase of estimated fetal weight per week in both study and control groups, there was no statistically significant difference.

	Cases (n=15)	Control (n=15)	Test of sig.	P
<b>EFW/W (g)</b>				
Min. – Max.	62.50 – 121.50	65.0 – 115.0	t=1.724	0.096
Mean ± SD.	98.77 ± 20.98	87.20 ± 15.34		

**Table 8.** Regarding changes in AFI in both groups after therapy, there was no statistically significant difference.

AFI .cm	Cases (n=15)	Control (n=15)	MW	p
<b>Pre-treatment</b>				
Min. – Max.	3.0 – 15.0	5.0 – 20.0	1.668	0.095
Mean ± SD.	5.50 ± 3.08	6.93 ± 3.79		
<b>Post treatment</b>				
Min. – Max.	5.0 – 13.0	3.0 – 15.0	0.662	0.508
Mean ± SD.	6.07 ± 2.09	5.73 ± 3.33		
p <sub>i</sub>	0.224	0.073		

MW, p: p values for Mann Whitney test for comparing between the two groups; p<sub>i</sub>: p value for Wilcoxon signed ranks test for comparing between preoperative and postoperative in each groups

**Table 9.** Comparing birthweight of newborns in both groups, there was no statistically significant difference between the two groups.

	Cases (n=15)	Control (n=15)	Test of sig.	p
<b>EFW delivery (g)</b>				
Min. – Max.	912.0 – 2300.0	850.0 – 2120.0	t=0.754	0.457
Mean ± SD.	1551.80 ± 468.49	1439.73 ± 334.05		

χ<sup>2</sup>, p: χ<sup>2</sup> and p values for Chi square test for comparing between the two groups; t, p: t and p values for Student t-test for comparing between the two groups

Regarding MCA Doppler study our results show significant statistical difference between MCA PI between cases and control, mean MCA PI significantly higher in sildenafil group in comparison with placebo group P=0.001. Also, cerebroplacental ratio significantly decreased at the end of study in control group compared to cases group (p=0.001).

Results suggest that sildenafil improved uteroplacental circulation among sildenafil treated group. However, there was no significant statistical difference between the rate of increase in AC per week or EFW per week between case and control group. Also, there was no significant statistical difference between measurements of AFI between cases and control group at the end of the study.

Von Dadelszen *et al.* [17] tested the potential for sildenafil to improve fetal growth in an open-label pilot study. Ten women with pregnancies affected by severe early-onset FGR, where the chance of intact fetal survival was felt to be less than 50%, accepted the option of taking 25-mg sildenafil TDS. Outcomes were compared with those from matched contemporaneous sildenafil-naïve pregnancies (n=17).

Sildenafil treatment was associated with increased post-treatment fetal growth velocity in the AC [9/10 (treated) vs7/17 (control); odds ratio, 12.9; 95% CI, 1.3, 126]. However, it is unclear if the higher levels of termination and permissive stillbirth in the sildenafil-naïve group reflect poorer prognosis or altered management.

E. Ferreira *et al.* [18] performed a retrospective and descriptive case series of all hospitalized pregnant women who received sildenafil for severe IUGR. Study included 19 hospitalized pregnant women who received sildenafil for severe IUGR. Sildenafil was started at an average of 25 weeks +3 days (median: 25, [20+1, 30+6]) in average dosage of 20 mg orally 3 times/day until delivery. Before sildenafil, estimated average fetal weight was 558g [237, 1208] and increased to an average of 807g (median: 820, [320, 1360]) at delivery and with an average weight gain of 249g (median:123, [-46, 732]). However, there was no control arm in his study.

In agreement to our findings, Trapani *et al.* [19] conducted a double-blind, placebo-controlled trial To evaluate the effects of transdermal nitroglycerin (GTN) and sildenafil citrate on Doppler

velocity waveforms of the uterine (UtA), umbilical (UA) and fetal middle cerebral (MCA) arteries in pregnancies with intrauterine growth restriction (IUGR).

This was a prospective study of 35 singleton pregnancies (gestational age, 24–31 weeks) with IUGR and abnormal UtA and UA Doppler waveforms. They compared maternal arterial blood pressure and Z-scores of the pulsatility index (PI) of UtA, UA and fetal MCA before and after application of a transdermal GTN patch (average dose, 0.4mg/h), oral sildenafil citrate (50mg) or placebo.

There was a significant decrease in UtA-PI after application of GTN (21.0%) and sildenafil citrate (20.4%). A significant reduction in UA-PI was also observed for both GTN (19.1%) and sildenafil citrate (18.2%). There was no difference in UtA- and UA-PI when the GTN and sildenafil groups were compared. No changes in Doppler velocimetry were observed in the placebo group and no significant change in MCA-PI was observed in any group. Maternal arterial blood pressure decreased with administration of both GTN and sildenafil citrate in those with pre-eclampsia. No effect was noted on birthweight in both groups.

Dastjerdi *et al.* also performed a randomized double-blinded and placebo-controlled trial, forty one pregnant women with documented intrauterine growth retardation at 24-37 weeks of gestation who were evaluated for the effect of a single dose of Sildenafil citrate on uteroplacental circulation as determined by Doppler ultrasound study of the umbilical and middle cerebral arteries.

Sildenafil group fetuses demonstrated a significant decrease in systolic/diastolic ratios and pulsatility index for the umbilical artery and a significant increase in middle cerebral artery pulsatility index (MCA PI). They concluded that sildenafil citrate can improve fetoplacental perfusion in pregnancies complicated by intrauterine growth restriction. It could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR). Again, this agrees with our work.

Also, Lin *et al.* [21] reported a decrease in uterine artery pulsatility and resolution of uterine artery notching following administration of sildenafil citrate to a case of IUGR diagnosed at 26 weeks of gestations. Contradictory to our findings, they also observed increase in EFW without maternal or neonatal adverse outcomes.

Despite a few negatives studies, sildenafil citrate has shown promise in vitro as well as in animal studies in the treatment of both IUGR and pre-eclampsia. Wareing *et al.* [22] conducted a study where small artery dissected from myometrial biopsies obtained at cesarean section from normal pregnant women (n=27) or women whose pregnancies were complicated by FGR (n=12) were mounted on wire myographs. Vessels were constricted (with arginine vasopressin or U46619) and relaxed (with bradykinin) before and after incubation with a phosphodiesterase-5 inhibitor, sildenafil citrate. They concluded that sildenafil citrate improves endothelial function of myometrial vessels from women whose pregnancies are complicated by intrauterine growth restriction. Sildenafil citrate may offer a potential therapeutic strategy to improve uteroplacental blood flow in FGR pregnancies.

## Conclusion

The administration of oral sildenafil tablets 20 mg twice a day for 6 weeks improved Doppler indices in umbilical artery and cerebroplacental ratio, yet it had no effect on gestational age at birth nor birth weight.

Further studies with larger sample size are needed to fully verify the efficacy of sildenafil citrate in the management of IUGR.

## Conflict of interest

Authors declare that there is no conflict of interest regarding publication of this article.

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