



## Original Article

## Use of sildenafil citrate in cases of intrauterine growth restriction (IUGR); a prospective trial

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## ABSTRACT

**Objective:** Intrauterine growth restriction (IUGR) is one of the most serious complications of pregnancy. Up to date, there is no evidence of achieving antenatal treatment of IUGR with abnormal placentation. Although, Sildenafil citrate has shown promising results, there are no firm conclusion till now. The aim of our study is to evaluate the use of Sildenafil citrate in the treatment of IUGR cases associated with impaired placental circulation.

**Materials and methods:** This was a prospective non-randomized study conducted at Mansoura university hospitals starting from March 2016 till October 2017. The studied population included singleton pregnancy and suffering from IUGR associated with impaired placental circulation.

**Results:** This study included 50 pregnant women. Cases were divided into two groups. The first group received sildenafil citrate and the second control group did not receive sildenafil citrate. After 4 weeks after the 1st dose of Sildenafil significant decrease in umbilical artery Doppler indices. There was a statistically significant difference in the mean birth weight at delivery and neonatal admission to the newborn nursery in sildenafil group.

**Conclusion:** sildenafil citrate treatment may present a new hope towards better perinatal outcomes for pregnancies complicated by IUGR and impaired placental circulation that may help to decrease neonatal admission to the newborn nursery.

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## Introduction

Being one of the major complications of pregnancy, intrauterine growth restriction (IUGR) is commonly caused by abnormal placentation and impaired placental blood circulation [1].

Growth-restricted fetuses have increased the risk of intrauterine fetal death (IUFD), together with increased neonatal morbidity and mortality [2] and even may lead to childhood sequels [3].

The trophoblast releases nitric oxide (NO) in normal pregnancy, which is a potent vasodilator. However, decreased release of NO may be present in pregnancies complicated by pre-eclampsia or IUGR.

Nitric oxide (NO) is produced from the amino acid (L-arginine) by nitric oxide synthases. NO increases the concentration of cyclic guanosine monophosphate (cGMP), which causes relaxation of the vascular smooth muscle [4].

Drugs increasing the effect of NO may be possible therapeutic agents for IUGR. Sildenafil citrate acts by blocking phosphodiesterase-5 inhibitor that breaks down cGMP, consequently, mediating the vasodilator effects of NO. A promising effect of sildenafil citrate was seen in animal studies in the treatment of IUGR [5–7].

In human, the use of sildenafil citrate in some pregnancy-related disorders as preeclampsia (PET) [8] and IUGR revealed encouraging results [9–14].

Up to date, there is no evidence of the benefit of using sildenafil citrate in the treatment of IUGR associated with impaired placental circulation. This study was carried out to evaluate the effect of sildenafil citrate in patients with IUGR associated with impaired placental circulation.

## Patients &amp; methods

This was a prospective non-randomized study conducted at Mansoura university hospitals from March 2016 till October 2017. The Ethics Committee approved our study (code no. (MS/16.10.36)) and written informed consent was obtained from all patients.

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This study included fifty pregnant women with gestational age (GA) between 24 and 32 weeks having singleton pregnancy and suffering from IUGR attending the antenatal clinic.

The study concerned patients who fulfilled the following inclusion criteria:

1. Pregnant women with single fetus with IUGR
2. Age  $\geq 19$  and  $\leq 45$  years.
3. Patients with regular menstrual pattern before pregnancy
4. Patients are able to attend follow up as planned.

Exclusion criteria:

1. Patients with uncertain GA
2. Patients with known or suspected fetal anomalies
3. Patients with obstetrical complications (intrauterine infection, bleeding, premature rupture of membranes)
4. When urgent delivery is indicated
5. Usage of any vasodilator medication
6. Multiple pregnancies.
7. Smoking, drug or alcohol abusers

The diagnosis of IUGR was based on clinical suspicion (history and examination) confirmed by ultrasound diagnosis: less than the 10th percentile fetal weight for corresponding GA or abdominal circumference (AC) less the 10th percentile value for corresponding GA with abnormal Umbilical artery (UA) Doppler indices.

Sildenafil treatment was given after the diagnosis of IUGR pregnancy. Each participant received a 20 mg tablet of sildenafil citrate orally and if no significant side effects were recorded, the dose was increased to 20 mg sildenafil three times daily until delivery. Patients refused the treatment or stopped it due to in compliance or side effects in the first days of treatment were advised to stop it and were considered the control group.

Each patient was instructed for bed rest and nutritional supplementation including excessive oral fluid. Pregnancy was allowed to continue until fetal maturity as long as fetal growth continues and fetal evaluation remains normal. Each participant was weekly submitted to:

- 1) Fetal movements count
- 2) Biophysical profile.
- 3) UA Doppler indices.

Outcome measures:

1. UA Doppler indices.
2. Maternal and fetal safety.
3. GA at delivery.
4. Birth weight.
5. Neonatal outcomes.

#### Doppler ultrasonographic measurements

Ultrasonography and Doppler velocimetric studies were performed by a trained sonographer and were performed with Toshiba SSH 140 A/G ultrasonographic machine with a 3.5-MHZ convex transducer. All Doppler velocimetric studies were performed in the semirecumbent position of the patient and during fetal quiescence. To minimize interobserver errors, all the measurements in this study were performed by one investigator. We measured pulsatility index (PI), resistance index (RI) and systolic/diastolic (S/D) ratio.

#### Examination of the newborn

After resuscitation and establishment of respiration, Apgar score was calculated and the newborn was examined carefully for any congenital malformation or any disorder as birth trauma.

#### Statistics

The terms of data description were mean, range, standard deviation ( $\pm$ SD), frequencies and relative frequencies. The mean and standard deviation of the collected data were calculated and the Comparison of variables between the two groups in the present study was done using Student t-test. A probability value (P value) less than 0.05 was considered statistically significant.

Statistical calculations were done by SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program.

#### Results

This study included 50 pregnant women with GA between 24 and 32 weeks. Cases were divided into two groups. The first group received sildenafil citrate and the second control group did not receive sildenafil citrate.

Maternal baseline characteristics revealed that the mean of the age, body mass index (BMI) and GA at the start of treatment in sildenafil group and control group showed no significant difference (Table 1).

UA Doppler indices between studied groups at the start of treatment showed no significant difference. After 4 weeks of the 1st dose of sildenafil, there was a significant decrease in the S/D ratio in sildenafil group, compared to control group. There was also a significant decrease in (RI) and (PI) in sildenafil group, compared to control group (Table 2).

The mean GA at delivery in sildenafil group (35.3 weeks) was higher than that of the control group (34.8 weeks) with no significant difference. There was a statistically significant difference in the mean birth weight at delivery; it was 2066.8 gm in sildenafil group compared to 1732.8 gm in control group (Table 3).

Live birth was encountered in 24 cases in sildenafil group and 22 cases in the control group. Stillbirth was encountered in one case in sildenafil group and 3 cases in the control group. There were no apparent causes of stillbirth, such as congenital anomalies or hydrops or sign of infection. All live births delivered by cesarean section in both groups. Apgar score at 5 min were significantly increased in sildenafil group. Neonatal deaths were encountered in one case in sildenafil group and 3 cases in the control group. 7 of neonates in sildenafil group and 15 of neonates in control group were admitted to the newborn nursery (Table 3).

#### Discussion

The standard options for management of IUGR are expectant management till pregnancy termination. This involves modification

**Table 1**  
Maternal baseline characteristics.

characteristic	Sildenafil group (n=25)	control group (n=25)	P-value
	Mean $\pm$ SD (Range)	Mean $\pm$ SD (Range)	
Age (Y)	27.3 $\pm$ 7.5 (18–40)	28.7 $\pm$ 6 (18–40)	0.484
BMI (kg/m <sup>2</sup> )	28.5 $\pm$ 5.9 (21.5–40.1)	26.9 $\pm$ 5.1 (20.2–39.3)	0.301
G.A. at start (weeks)	27.4 $\pm$ 1.6 (25–31)	28.1 $\pm$ 1.5 (26–32)	0.223

**Table 2**  
Umbilical artery Doppler indices at baseline and 4 weeks after 1st dose of sildenafil.

N	Umbilical artery Doppler indices at baseline		t	P	Umbilical artery Doppler indices 4 weeks after 1st dose of sildenafil		t	P
	Sildenafil group (n=25)	Control group (n = 25)			Sildenafil group (n=25)	Control group (n=25)		
S/D	4.5 ± 0.1 (4.4–4.7)	4.6 ± 0.2 (4.4–4.7)	0.96	0.337	4.3 ± 0.09 (4.2–4.6)	4.6 ± 0.11 (4.4–4.8)	7.2	<0.001
RI	0.78 ± 0.02 (0.75–0.84)	0.759 ± 0.02 (0.75–0.84)	1.12		0.75 ± 0.02 (0.72–0.80)	0.81 ± 0.02 (0.78–0.85)	9.11	<0.001
PI	1.92 ± 0.02 (1.89–1.96)	1.93 ± 0.01 (1.90–1.96)	1.43		1.88 ± 0.02 (1.83–1.92)	1.94 ± 0.01 (1.91–1.97)	10.4	<0.001

**Table 3**  
Peripartum characteristics and Neonatal outcomes.

	Sildenafil group (n = 25)	Control group (n = 25)	P
G.A at delivery (weeks)			
Mean ± SD (Range)	35.3 ± 1.8 (30–38)	34.8 ± 1.9 (31–38)	0.359
Birth weight (gm)			
Mean ± SD (Range)	2066.8 ± 351.6 (1200–2800)	1732.8 ± 360.8 (1000–2300)	0.002
Live birth			
Number-percentage	24–96	22–88	0.305
Still birth			
Number-percentage	1–4	3–12	0.305
Neonatal death			
Number-percentage	1–4	3–12	0.305
Apgar score at 5 min			
Mean ± SD	6.2 ± 2.2	3.7 ± 2.3	<0.001
Admission to newborn nursery			
Number-percentage	7–28	15–60	0.023
Days in newborn nursery	4.7 ± 8.17	11.4 ± 11.58	0.028

of maternal lifestyle together with fetal surveillance. Since impaired placental circulation is a major cause, vasodilators may have their role. Sildenafil citrate started was emerged as a drug helping vasodilation.

Samangaya et al. did not support the use of sildenafil citrate in patients with pre-eclampsia however, the drug showed some effect on fetal growth [8]. On continuing trials, sildenafil may represent an effective intervention for IUGR pregnancies.

The decreased vascular resistance after sildenafil administration that we have encountered in our study was evident by the significant decrease in Doppler indices. Comparable results were recorded by Panda et al., and Lin et al., in their case reports of [11,12]. The same results were recorded from randomized controlled trials done by El-Sayed et al., Trapani et al., and Dastjerdi et al., [9,13,14].

Despite not evaluating the effect on vascular resistance, Dadelszen et al. showed a significant increase in AC when using sildenafil citrate in pregnancies complicated by the severe type of IUGR (AC < 5th percentile) [10].

It is worth to mention that, mean birth weight at delivery was increased significantly in sildenafil group. Of course, this had its value in decreasing admission to the newborn nursery unit in sildenafil group. A point of special interest, particularly in resource-limited countries as ours, where the newborn nursery admission is costly for both the individuals and the community. These results are similar to the study of El-Sayed et al., [14].

Regarding Maternal safety of sildenafil citrate, Headache was the commonest side effect followed by visual disturbance and gastrointestinal tract symptoms. Overall Sildenafil was well-tolerated. In our study, only a few cases stopped sildenafil due to its side effects. These findings were similar to that reported by of Dunn et al., 2017 [15].

Considering fetal safety, the available evidence suggests that sildenafil is safe with neither increase in fetal morbidity or mortality nor congenital malformations [15].

Although it's safe for mother and fetus with improving effect on IUGR, the use of sildenafil doesn't protect from IUFD. Throughout the study, we have seen one case of IUFD in sildenafil group.

Our study was a prospective and focused one including only cases of IUGR associated with impaired placental circulation. We didn't include IUGR cases with normal Doppler as they consider small for gestational age with good perinatal morbidity and mortality. We also excluded IUGR cases from other causes due to the unpredictable course of the pathology. Additionally, we evaluated the effect of sildenafil not only on Doppler but also on early neonatal outcomes. These issues may add strength to our study.

On the other hand, we didn't randomize our cases and couldn't include a large number of cases also maternal sildenafil concentration was not measured in the serum.

For ethical consideration, this trial wasn't a randomized one as we didn't want to deprive some patients from the beneficial effect of sildenafil. However, for comparison, we used control groups from cases that refused or didn't tolerate sildenafil.

We recommend larger multicentric studies evaluating the long-term neonatal outcomes to assess the beneficial effect of sildenafil in IUGR.

In conclusion, sildenafil citrate treatment may present a new hope towards better perinatal outcomes for pregnancies complicated by IUGR that may help to decrease neonatal admission to newborn nursery.

## Conflict of interest

The authors declare that they have no conflict of interest.

## Authors' contribution

M Maged: Data collection.

M Shams: Data analysis.

A wageh: Methodology and Manuscript writing.

A Abdlgawad: Project administration and general supervision.

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## References

- [1] Obstetricians ACo, Gynecologists. ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol* 2013;121(5):1122.
- [2] Vergani P, Roncaglia N, Locatelli A, Andreotti C, Crippa I, Pezzullo JC, et al. Antenatal predictors of neonatal outcome in fetal growth restriction with absent end-diastolic flow in the umbilical artery. *Am J Obstet Gynecol* 2005;193(3):1213–8.
- [3] Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intra-uterine growth restriction. *Clin Obstet Gynecol* 2006;49(2):257–69.

- [4] Miller SL, Loose JM, Jenkin G, Wallace EM. The effects of sildenafil citrate (Viagra) on uterine blood flow and well being in the intrauterine growth-restricted fetus. *Am J Obstet Gynecol* 2009;200(1):102.e1–7.
- [5] López-Tello J, Arias-Alvarez M, González-Bulnes A, Astiz S, García-García R, Rodríguez M, et al. 91 sildenafil citrate modifies fetoplacental development in a rabbit model of intrauterine growth restriction. *Reprod Fertil Dev* 2015;27(1):138–9.
- [6] George EM, Palei AC, Dent EA, Granger JP. Sildenafil attenuates placental ischemia-induced hypertension. *Am J Physiol Regul Integr Comp Physiol* 2013;305(4):R397–403.
- [7] Villanueva-García D, Mota-Rojas D, Hernandez-Gonzalez R, Sanchez-Aparicio P, Alonso-Spilsbury M, Trujillo-Ortega M, et al. A systematic review of experimental and clinical studies of sildenafil citrate for intrauterine growth restriction and pre-term labour. *J Obstet Gynaecol* 2007;27(3):255–9.
- [8] Samangaya RA, Mires G, Shennan A, Skillern L, Howe D, McLeod A, et al. A randomised, double-blinded, placebo-controlled study of the phosphodiesterase type 5 inhibitor sildenafil for the treatment of preeclampsia. *Hypertens Pregnancy* 2009;28(4):369–82.
- [9] Dastjerdi MV, Hosseini S, Bayani L. Sildenafil citrate and uteroplacental perfusion in fetal growth restriction. *J Res Med Sci – Offic J Isfahan Univ Med Sci* 2012;17(7):632.
- [10] Von Dadelszen P, Dwinnell S, Magee L, Carleton B, Gruslin A, Lee B, et al. Sildenafil citrate therapy for severe early-onset intrauterine growth restriction. *BJOG An Int J Obstet Gynaecol* 2011;118(5):624–8.
- [11] Panda S, Das A, Nowroz HM. Sildenafil citrate in fetal growth restriction. *J Reproduction Infertil* 2014;15(3):168.
- [12] Lin T, Su Y, Shih J, Hsu H, Lee C. Resolution of high uterine artery pulsatility index and notching following sildenafil citrate treatment in a growth-restricted pregnancy. *Ultrasound Obstet Gynecol* 2012;40(5):609–10.
- [13] Trapani A, Gonçalves L, Trapani T, Franco M, Galluzzo R, Pires M. Comparison between transdermal nitroglycerin and sildenafil citrate in intra-uterine growth restriction: effects on uterine, umbilical and fetal middle cerebral artery pulsatility indices. *Ultrasound Obstet Gynecol* 2016;48(1):61–5.
- [14] El-Sayed MA, Saleh SA-A, Maher MA, Khidre AM. Utero-placental perfusion Doppler indices in growth restricted fetuses: effect of sildenafil citrate. *J Matern Fetal Neonatal Med* 2017;1–6.
- [15] Dunn L, Greer R, Flenady V, Kumar S. Sildenafil in pregnancy: a systematic review of maternal tolerance and obstetric and perinatal outcomes. *Fetal Diagn Ther* 2017;41(2):81–8.