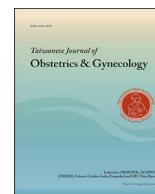




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## Original Article

## 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 preeclampsia 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

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