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**Original Research Article**

# The role of sildenafil citrate in the treatment of fetal growth restriction: a randomized controlled trial

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## ABSTRACT

**Background:** This study was aimed to evaluate the effect of sildenafil citrate on Doppler velocity indices in patients with fetal growth restriction (FGR) associated with impaired placental circulation.
**Methods:** A double-blinded, parallel group randomized clinical trial (clinicaltrials.gov NCT02590536) was conducted in Ain Shams Maternity Hospital, in the period between October 2015 and June 2017. Ninety pregnant women with documented intrauterine growth retardation at 24-37 weeks of gestation were randomized to either sildenafil citrate 25 mg orally every 8 hours or placebo visually-identical placebo tablets with the same regimen. The primary outcome of the study was the change in umbilical artery and fetal middle cerebral artery indices.
**Results:** There was a significant improvement in umbilical and middle cerebral artery indices after sildenafil administration $p<0.001$. Present study observed that, sildenafil group, in comparison to placebo, has a significantly higher mean neonatal birth weight. 1783±241g vs 1570±455g ($p<0.001$). There was a significantly higher mean gestational age at delivery in women in sildenafil group 35.3±1.67 weeks, whereas it was lower in the placebo group 33.5±1.7 weeks. The side effects as headache, palpitation and facial flushing were significantly higher in sildenafil group compared to placebo group.
**Conclusions:** The use sildenafil citrate in pregnancies with fetal growth restriction (FGR) improved the feto-placental Doppler indices (pulsatility index of umbilical artery and middle cerebral artery) and improved neonatal outcomes.

**Keywords:** Fetal growth restriction (FGR), Middle cerebral artery doppler, Sildenafil citrate, Umbilical artery doppler

## INTRODUCTION

Early onset fetal growth restriction (FGR) increases the risk of perinatal morbidity and mortality with increase the rate of iatrogenic premature delivery.[1,2] It is highly associated with severe placental insufficiency and with chronic fetal hypoxia, this explains why umbilical artery Doppler is abnormal in a high proportion of cases and If left untreated, the fetal condition deteriorates with progression to decompensated hypoxia and acidosis.[3,4]

The risk of adverse outcome is proportional to the degree of growth restriction with those below the 3rd percentile and/ or abnormal umbilical artery Doppler measurements having the greatest risk of morbidity or mortality.[5] Until now there is no available effective treatment for fetal growth restriction otherwise close monitoring of fetal growth rates and well-being.[6]

Preterm delivery is indicated when fetal growth or well-being become so poor that the risks of intrauterine fetal demise are greater than the risks of prematurity.[3] Reduced flow and increased resistance in uterine and umbilical arteries, indicative of reduced uteroplacental flow in pregnancies with fetal growth restriction, have been

documented by non-invasive Doppler ultrasound velocimetry.[5]

Placental perfusion is enhanced by nitric oxide (NO), which promotes vasodilatation of maternal vessels. cGMP, the second messenger of nitric oxide, is degraded by the phosphodiesterase enzyme.[7] Sildenafil citrate is an inhibitor of phosphodiesterase type 5 subsequently, it results in a rise in cGMP and consequent vasodilatation.[8]

Sildenafil citrate could be a potential therapeutic strategy to improve uteroplacental blood flow in pregnancies with fetal growth restriction (FGR); moreover, it has shown promising results in various studies of fetal growth restriction.[5,9-11]

This study was carried out to evaluate the effect of sildenafil citrate on Doppler velocity indices in patients with IUGR associated with impaired placental circulation.

## METHODS

This randomized controlled clinical trial was conducted in Ain Shams Maternity Hospital, Cairo, Egypt in the period between October 2015 and June 2017 after approval of the hospital ethical review board (ERB) in and registration under (NCT02590536 on clinicaltrials.gov).

A total of 90 pregnant women with singleton pregnancy, between 24-37 weeks, with small for gestational age (SGA) and placental insufficiency were enrolled in present study and randomized to either sildenafil citrate or placebo.

Patients with SGA diagnosed by ultrasonography measurement when the estimated fetal weight falls below the 10$^{th}$ percentile for gestational age and abnormal umbilical artery Doppler velocimetry.

### *Exclusion criteria*

- Pregnant women with undetermined gestational age, Intrauterine infection, high Risk for aneuploidy (e.g., maternal age≥40 years, detected congenital fetal anomalies in the current or previous pregnancies), Maternal cardiovascular morbidity, users of any vasodilator agents or known allergy to sildenafil were excluded from present study.

After obtaining informed consent, patients were randomized to either the Sildenafil group, or the placebo group using a computer-generated list concealed by sequentially numbered, otherwise identical, sealed envelopes (SNOSE), each containing a paper with a written code designating the assigned group. Double-blinding was ensured by using visually-identical tablets for both the active drug and the placebo.

Patients received either 25 mg of sildenafil citrate (Sildin® 25 mg, EIPICO pharma, Cairo, Egypt) orally every 8 hours starting at diagnosis until delivery in the Sildenafil group or a visually-identical placebo tablets with the same regimen in the placebo group.

Then authors compared the pulsatility index (PI) of the umbilical artery and fetal middle cerebral artery, twice weekly.

### *Ultrasonographic features and Doppler assessment*

Fetal scan was done using a medison x5 ultrasound machine with 4.0 MHZ trans-abdominal probe at the special care center for fetus Unit at Ain-Shams University Maternity hospital by the same experienced sonographer twice weekly.

### *Umbilical artery Doppler*

All patients were placed in a semi recumbent position with a left lateral tilt, and then the uterine content was scanned to select an area of amniotic cavity with several loops of cord. Then using a pulsed wave Doppler on a free loop of cord, the characteristic sound and shape of the umbilical artery identified. When the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and Doppler umbilical artery pulsatility index (UA-PI) was estimated. A minimum of 3 separate reading was averaged before the final value were obtained.

### *Middle cerebral artery Doppler*

Transverse view of the fetal brain was obtained at the level of the biparietal diameter. The transducer was then moved towards the base of the skull at the level of the lesser wing of the sphenoid bone. Using color flow imaging, the middle cerebral artery was seen as a major lateral branch of the circle of Willis, running anterolaterally at the borderline between the anterior and the middle cerebral fosse. The pulsed Doppler sample gate is then placed on the middle portion of this vessel to obtain flow velocity waveforms. When the screen showed at least 3 consecutive wave forms of similar height, the image was frozen and Doppler middle cerebral artery pulsatility index (MCA-PI) was estimated. A minimum of 3 separate reading was averaged before the final values were obtained care should be taken to apply minimal pressure to the maternal abdomen with the transducer, as fetal head compression is associated with alterations of intracranial arterial waveforms.[12]

The pulsatility indices of the middle cerebral artery and umbilical artery were recorded. All Doppler recordings were performed by an expert sonologist. The patients with decreased middle cerebral artery PI and absent or reversed diastolic flow in umbilical artery were admitted for further evaluation and delivery.

Conservative treatment that was offered to the patients in the hospital with low end diastolic velocimetry consisted of bed rest, daily fetal movement count (DFMC), non-stress test and biweekly amniotic fluid estimation.

***Follow up***

Then the patients have been followed up until delivery and the effect of sildenafil on Doppler velocity indices of the umbilical arteries and fetal middle cerebral artery in patients were detected

***Statistical analysis***

Data were analyzed using SPSS version 24.0 (SPSS Inc, Chicago, IL, USA). Data were analyzed on intention-to-treat basis. Parametric numerical data are presented as mean ± standard deviation, whereas non-parametric numerical data are presented as median with interquartile range. Categorical data are presented as number and percentage. Two-group comparisons for numerical data was done using the student t test for parametric data and using the Mann-Whitney test for non-parametric data. Categorical data were compared using chi-square test or fisher exact test. Significance level was set at $p \leq 0.05$.

***Sample size justification***

The required sample size has been calculated using the IBM© sample power© software (IBM© Corp., Armonk, NY, USA), setting the confidence level at 95% (type I error, $\alpha$=0.05) and the power at 0.95 (type II error, $\beta$=0.05).

The primary outcome measure was set as the pulsatility index (PI) of the umbilical artery (UA) before and after treatment. According to the results of Unterscheider J et al, reported that the UA PI decreased from (1.13±0.10) to (1.01±0.13) after administration of sildenafil with a mean difference of (0.12±0.15), calculation according to the UA PI values produced a sample size of 40 cases for each group.[5] A10% drop-out rate was taken into consideration, giving a total sample of 45 cases in each arm (90 cases in total).

## RESULTS

A 90 women with a singleton pregnancy, between 24-34 weeks, with SGA and placental insufficiency which was diagnosed by ultrasonography measurement when the estimated fetal weight falls below the 10$^{th}$ percentile for gestational age and abnormal umbilical artery Doppler velocimetry, were randomly assigned into either Sildenafil (n=45) or placebo group (n=45). The process of recruitment and handling the study population during the course of the study is shown in the Consort flow diagram (Figure 1).

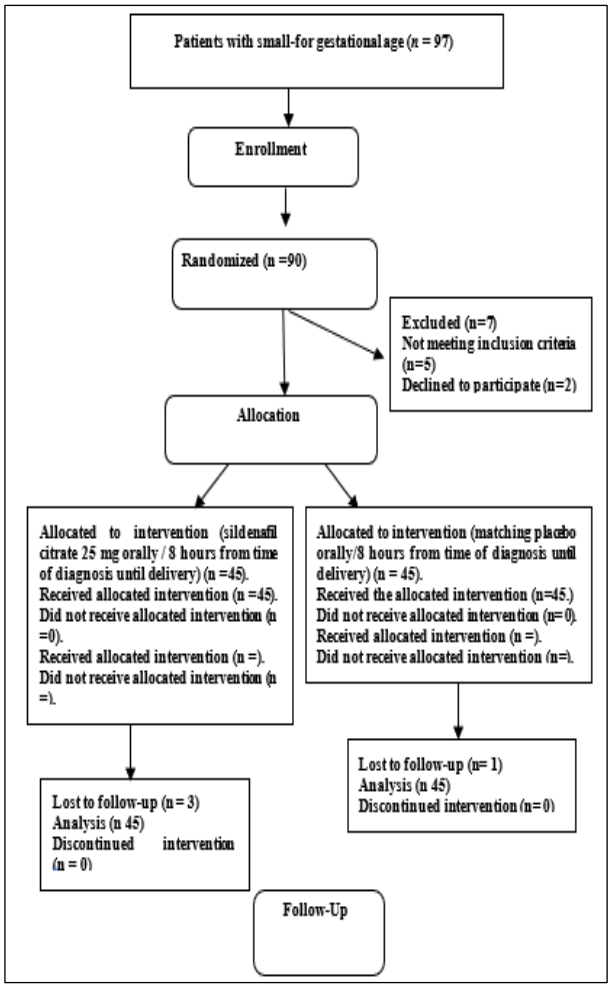


**Figure 1: Consort 2010 flow diagram showing the recruitment and handling of the study population during the course of the study.**

No statistically significant differences were found between both groups regarding basal demographic, and clinical characteristics (Table 1).

Umbilical artery pulsatility index was significantly lower in sildenafil group compared to placebo group and this was obvious after 3 weeks administration of sildenafil (Table 2).

Middle cerebral artery pulsatility index was significantly higher in sildenafil group compared to placebo group and this was obvious after 4 weeks administration of sildenafil (Table 3).

As shown in (Table 4) gestation at delivery and mean neonatal birth weight were higher in sildenafil group.

There was a significantly higher in headache and palpitation regarding possible side effects of sildenafil by using continuity-corrected chi-squared test (Table 5).

**Table 1: Basal characteristics in the two study groups.**

| | Group I (Sildenafil group) (n=45) | Group II (Placebo group) (n=45) | P- value |
|---|---|---|---|
| Age (years) | 22 - 36 | 22-39 | 0.521 |
| Range mean ±SD | 26.76±4.28 | 27.35±4.42 | NS |
| Weight (kg) | 55-93 | 58-93 | 0.147 |
| Range mean ±SD | 68.69±8.95 | 71.51±9.33 | NS |
| BMI (kg/m$^2$) | 19.94-35.2 | 20.38-39.47 | 0.158 |
| Range mean± SD | 26.7±3.67 | 27.89±4.29 | NS |
| Parity | 0-4 | 0-4 | 0.067 |
| Range median (IQR) | 1 (1-2) | 2 (1-2) | NS |
| No. of previous miscarriages | 0-4 | 0-11 | 0.089 |
| Range median (IQR) | 0 (0-1) | 1 (0-1) | NS |

Data presented as range, mean ± SD, or range, median (IQR), NS non-significant.

**Table 2: Umbilical artery doppler assessment in the two study groups.**

| UA-PI | Group I (Sildenafil group) | Group II (Placebo group) | MD 95% CI | P* |
|---|---|---|---|---|
| 30 weeks | 1.39 ± 0.08 | 1.42 ± 0.21 | -0.02-0.15 to 0.12 | 0.372 |
| 30$^{+3}$ weeks | 1.35 ± 0.10 | 1.38 ± 0.21 | -0.04-0.15 to 0.07 | 0.389 |
| 31 weeks | 1.28± 0.11 | 1.34 ± 0.19 | 0.00-0.09 to 0.08 | 0.070 |
| 31$^{+3}$ weeks | 1.26 ± 0.10 | 1.32 ± 0.20 | 0.02-0.05 to 0.10 | 0.075 |
| 32 weeks | 1.24 ± 0.11 | 1.22 ± 0.17 | -0.02-0.09 to 0.06 | 0.509 |
| 32$^{+3}$ weeks | 0.97 ± 0.13 | 1.03 ± 0.17 | 0.01-0.06 to 0.08 | 0.063 |
| 33 weeks | 1.42± 0.15 | 1.48 ± 0.16 | 0.02-0.04 to 0.09 | 0.069 |
| 33$^{+3}$ weeks | 1.08 ± 0.10 | 1.92 ± 0.17 | 0.02-0.05 to 0.10 | <0.001* |
| 34 weeks | 1.05 ± 0.09 | 1.42 ± 0.18 | 0.00-0.09 to 0.08 | <0.001* |
| 34$^{+3}$ weeks | 1.00 ± 0.09 | 1.6 ± 0.19 | -0.03-0.12 to 0.06 | <0.001* |
| 35 weeks | 0.95 ± 0.10 | 1.27 ± 0.13 | -0.10-0.20 to -0.01 | <0.001* |
| 35$^{+3}$ weeks | 0.90 ± 0.11 | 1.06 ± 0.13 | -0.16-0.27 to -0.04 | 0.009* |
| 36 weeks | 0.85 ± 0.13 | 1.03 ± 0.14 | -0.18-0.33 to -0.04 | 0.017* |
| 36$^{+3}$ weeks | 0.79 ± 0.15 | 1.01 ± 0.14 | -0.21-0.38 to -0.05 | 0.017* |
| 37 weeks | 0.70 ± 0.16 | 0.95 ± 0.16 | -0.26-0.55 to -0.04 | 0.037* |

UA umbilical artery, PI pulsatility index, Data presented as mean ± SD, *Analysis using Independent Student's t-Test, MD (95% CI) mean difference and its 95% confidence interval, NS non-significant-S significant.

**Table 3: Middle cerebral artery Doppler assessment in the two study groups.**

| MCA - PI | Group I (Sildenafil group) | Group II (Placebo group) | MD95% CI | P* |
|---|---|---|---|---|
| 30 weeks | 1.48 ± 0.04 | 1.49 ± 0.03 | -0.01-0.04 to 0.01 | 0.218 |
| 30$^{+3}$ weeks | 1.51 ± 0.04 | 1.52 ± 0.05 | -0.01-0.03 to 0.02 | 0.656 |
| 31 weeks | 1.53 ± 0.04 | 1.56 ± 0.05 | -0.03-0.06 to 0.00 | 0.028 |
| 31$^{+3}$ weeks | 1.55 ± 0.06 | 1.60 ± 0.07 | -0.05-0.08 to -0.02 | 0.002 |
| 32 weeks | 1.58 ± 0.07 | 1.61 ± 0.07 | -0.03-0.07 to 0.00 | 0.085 |
| 32$^{+3}$ weeks | 1.59 ± 0.08 | 1.64 ± 0.07 | -0.05-0.09 to 0.01 | 0.078 |
| 33 weeks | 1.64 ± 0.09 | 1.65 ± 0.08 | -0.01-0.06 to 0.03 | 0.587 |
| 33$^{+3}$ weeks | 1.69 ± 0.10 | 1.65 ± 0.06 | 0.04-0.01 to 0.09 | 0.148 |
| 34 weeks | 1.60 ± 0.13 | 1.65 ± 0.05 | -0.06-0.13 to 0.02 | 0.132 |
| 34$^{+3}$ weeks | 1.67 ± 0.05 | 1.50 ± 0.15 | -0.17-0.26 to -0.08 | 0.001* |
| 35 weeks | 1.69 ± 0.06 | 1.37 ± 0.18 | -0.32-0.45 to -0.19 | <0.001* |
| 35$^{+3}$ weeks | 1.70 ± 0.05 | 1.30 ± 0.20 | -0.40-0.57 to -0.23 | <0.001* |
| 36 weeks | 1.72 ± 0.04 | 1.15 ± 0.17 | -0.57-0.72 to -0.42 | <0.001* |
| 36$^{+3}$ weeks | 1.74 ± 0.03 | 1.06 ± 0.19 | -0.68-0.85 to -0.51 | <0.001* |
| 37 weeks | 1.83 ± 0.02 | 1.04 ± 0.14 | -0.74-0.95 to -0.53 | <0.001* |

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

**Table 4: Gestation at delivery and birth weight.**

| | Group I (Sildenafil group) (n=45) | Group II (Placebo group) (n=45) | MD 95% CI | P* |
|---|---|---|---|---|
| Gestation at delivery(week | 35 - 37 | 32 - 36.57 | 1.12 | <0.001* |
| Range mean±SD | 35.33±1.67 | 33.54±1.78 | 0.4 to 1.84 | S |
| Birth weight (g) | 2300 - 2700 | 750 - 2250 | 210.6 | <0.001* |
| Range mean±SD | 1783.33±241.57 | 1570.78±455.72 | 7.56 to 431.5 | S |

SD standard deviation, Data presented as range, mean ± SD, *Analysis using independent student's t-Test, S significant MD 95% CI mean difference and its 95% confidence interval.

**Table 5: Side effects.**

| Side effects | Group I (Sildenafil group) (N=45) | | Group II (Placebo group) (N=45) | | P-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Dizziness/postural hypotension | 1 | 2.2 | 0 | 0.0 | 0.315 NS |
| Headache | 8 | 17.8 | 2 | 4.4 | 0.044*S |
| Palpitation | 4 | 8.9 | 0 | 0.0 | 0.041* S |
| Nausea /vomiting | 0 | 0.0 | 2 | 4.4 | 0.153 NS |
| Backache/arthralgia | 2 | 4.4 | 3 | 6.7 | 0.645 NS |
| Flushing/Rash | 5 | 11.1 | 1 | 2.2 | 0.041 S |
| Dyspepsia | 3 | 6.7 | 1 | 2.2 | 0.306 NS |
| Nasal congestion | 2 | 4.4 | 0 | 0.0 | 0.153 NS |
| Abnormal vision | 1 | 2.2 | 0 | 0.0 | 0.315 NS |
| Diarrhea | 3 | 6.7 | 1 | 2.2 | 0.306 NS |

Data presented as number (percentage), *Analysis using continuity-corrected chi-squared test, S significant, NS non-significant.

## DISCUSSION

Adequate placental blood flow is essential for the optimal delivery of nutrients from mother to fetus and for growth of conceptus. Restricted fetal growth results from pathophysiological and environmental factors, which alters utero-placental blood flow, placental function and therefore, nutrient availability to the fetus.[13]

Sildenafil citrate, a specific phosphodiesterase-5 inhibitor, has been proposed as a potential therapeutic strategy to maintain placental function and emerging as a potential candidate for the treatment of intrauterine growth restriction.[14]

Several reports have suggested that, phosphodiesterase (PDE-5) inhibition results in an increase in c-GMP and consequent vasodilatation. Authors should emphasize that this study was carried out with cases of IUGR associated with placental vasculopathy already evident on Doppler examination.

According to our results, administration of sildenafil citrate improved the feto-placental Doppler indices of umbilical artery and middle cerebral artery in addition to neonatal outcomes.

Authors found that, there was a significant improvement in umbilical and middle cerebral artery indices after sildenafil administration This difference became evident after 3 weeks of gestation from sildenafil administration mainly after 33 weeks of pregnancy where mean umbilical artery pulsatility index (UAPI) significantly decreased in the sildenafil group in comparison with the placebo group. Regarding the middle cerebral artery velocity indices, there was significant increase in mean MCA pulsatility index (PI) after sildenafil administration in comparison with the placebo group at term p<0.001.

Present study observed that, sildenafil group, in comparison to placebo, has a significantly higher mean neonatal birth weight.1783±241grams vs1570±455grams (p<0.001).

Authors found that, there was a significantly higher mean gestation at delivery in women of sildenafil group 35.3±1.67 weeks, whereas it was lower in the placebo group 33.5 ±1.7 weeks.

In concordance with our results, several studies demonstrated the efficacy of sildenafil to improve the placental functions in FGR. Comparable results were reported by Unterscheider J et al, who reported a significant improvement in umbilical artery and middle cerebral artery indices after 2 hours of 50 mg sildenafil administration; however, they neither examined the prolonged effect of sildenafil on birth weight nor the neonatal outcomes.[5] Improvement in doppler indices, pregnancy prolongation, increased gestational age at

delivery, improved neonatal weight were also described by El Sayed MA et al, and his colleagues.[10]

Dadelszen PV et al, showed a significant increase in AC when using sildenafil citrate in pregnancies complicated by the severe type of IUGR (AC <5$^{th}$ percentile), However, they did not examine the effect of sildenafil on uteroplacental, fetoplacental or fetal cerebral circulation.[9]

As regards teratogenicity, many clinical trials could not demonstrate any evidence of teratogenicity by Sildenafil, even at doses much higher than that evaluated in present study, Samangaya RA et al, found that Sildenafil in the escalating dose regimen 20-80 mg three times daily (tid) was well tolerated, without increasing in maternal or fetal morbidity or mortality.[15]

On the contrary, Sharp A et al, reported that when sildenafil was administered to pregnant women with a severely growth-restricted fetus, it did not prolong pregnancy, improve survival, or reduce short-term neonatal morbidity, this was mostly because they recruited more than half of the fetal growth-restricted babies before 26 weeks'gestation and all fetuses had severely compromised umbilical circulation with absent or reversed end-diastolic flow.[16]

We reported in our results that side effects as headache, palpitation and facial flushing were significantly higher in sildenafil group compared to placebo group, whereas other side effects showed no significant difference between both groups our findings are matching with Nurnberg HG et al, who found that main adverse effects of sildenafil citrate were headache, flushing, rhinitis, nausea, visual disturbances, and dyspepsia, which were generally mild to moderate in nature.[17]

The main strength of this study is that it was a double blinded randomized control trial with low risk of bias; however, it was limited by not assessing the long term effect of sildenafil on the neonatal morbidity and mortality, it is hopeful that future trials would be designed assess those outcomes. Also, we did not measure the serum maternal Sildenafil concentrations during therapy to reach the most appropriate dose of sildenafil citrate therapy with the effective concentrations known to dilate maternal uteroplacental vascular endothelium.

## CONCLUSION

In the light of the above results, we concluded that administration of Sildenafil 25 mg 8 hourly in pregnancies with fetal growth restriction (FGR) improved the feto-placental Doppler indices (pulsatility index of umbilical artery and middle cerebral artery) and improved neonatal outcomes. Therefore, sildenafil treatment may offer a promising therapy for fetal growth restriction with placental insufficiency.

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## REFERENCES

1. Bilardo CM, Wolf H, Stigter RH, Ville Y, Baez E, Visser GH, et al. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet Gynecol. 2004;23(2):119-25.
2. Manning E, Corcoran P, Meaney S, Greene RA. On behalf of the perinatal mortality group: perinatal mortality in Ireland Annual Report 2011. National Perinat Epidemiol Centre Cork. 2013.
3. Turan S, Miller J, Baschat AA. Integrated testing and management in fetal growth restriction. In Seminars Perinatol. 2008:32(3):194-200.
4. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol. 2007;109(2):253-61.
5. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'donoghue K, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013; 208(4):290-e1.
6. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al. 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 Obstetr Gynecol. 2013;42(4):400-8.
7. Lin CS, Lin G, Xin ZC, Lue TF. Expression, distribution and regulation of phosphodiesterase 5. Current Pharm Design. 2006;12(27):3439-57.
8. Wareing M, Myers JE, O'hara M, Baker PN. Sildenafil citrate (Viagra) enhances vasodilatation in fetal growth restriction. J Clinic Endocrinol Metabol. 2005;90(5):2550-5.
9. Von Dadelszen P, Dwinnell S, Magee LA, Carleton BC, Gruslin A, Lee B, et al. Sildenafil citrate therapy for severe early-onset intrauterine growth restriction. BJOG: Int J Obstetr Gynaecol. 2011;118(5):624-8.
10. El-Sayed MA, Saleh SA, Maher MA, Khidre AM. Utero-placental perfusion Doppler indices in growth restricted fetuses: effect of sildenafil citrate. J Maternal Fetal Neonat Med. 2018;31(8):1045-50.
11. Trapani Jr A, Gonçalves LF, Trapani TF, Franco MJ, Galluzzo RN, Pires MM. Comparison between transdermal nitroglycerin and sildenafil citrate in intrauterine growth restriction: effects on uterine, umbilical and fetal middle cerebral artery pulsatility indices. Ultrasound Obstet Gynecol.2016;48(1):61-5.
12. Maged AM, Hashem AM, Gad Allah SH, Mahy ME, Mostafa WA, Kotb A. The effect of loading dose of magnesium sulfate on uterine, umbilical, and fetal middle cerebral arteries Doppler in women with

severe preeclampsia: a case control study. Hypertens Pregancy. 2016;35(1):91-9.
13. Levine RJ, Karumanchi SA. Circulating angiogenic factors in preeclampsia. Clinic Obstet Gynecol. 2005;48(2):372-86.
14. Villanueva-Garcia D, Mota-Rojas D, Hernandez-Gonzalez R, Sanchez-Aparicio P, Alonso-Spilsbury M, Trujillo-Ortega ME, 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.
15. 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. Hypertension Pregnancy. 2009;28(4):369-82.
16. Sharp A, Cornforth C, Jackson R, Harrold J, Turner MA, Kenny LC, et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. Lancet Child Adolesc Health. 2018;2(2):93-102.
17. Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. JAMA. 2008;300(4):395-404.

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