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*Full Length Research Paper*

# The Role of Sildenafil Citrate (20 mg) In Treatment of Intrauterine Growth Restriction

**Mahmoud Salah Mahmoud**
*Obstetrics and Gynecology Department, Al-Azhar Faculty of Medicine, Egypt.*

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**Corresponding Author:**
**Mahmoud S. Mahmoud**
*Obstetrics and Gynecology Department, Al-Azhar Faculty of Medicine, Egypt.*

***Abstract***
*Intrauterine growth restriction represented a major health problem with non-evidence based supportive treatments. Thus, the search for other clinical based effective treatments is mandatory.to examine if sildenafil citrate can prevent intrauterine growth restriction (IUGR) development in females with high risk for this condition and if the drug can reverse the IUGR when diagnosed. This study was designed and carried out at Al-Azhar University hospital (New Damietta); Obstetrics and Gynecology Department.one hundred pregnant females; 50 with high risk for development of IUGR and 50 with proved IUGR. Both groups received the same treatment and followed up till their delivery. Pregnancy outcome, serial Doppler ultrasound examinations were done and documented. Then, results were compared between both groups. Therapy by sildenafil citrate leads to better pregnancy outcome in both preventive and therapeutic groups. There was enhancement of restricted growth in females with IUGR. In addition, prophylactic treatment with sildenafil citrate was linked with prevention of IUGR development in high risk pregnancies. These results were confirmed by enhancement of uterine and umbilical artery indices, and increased abdominal circumference with decreased rates of still birth and prematurity in both groups. Results in preventive group were better than treatment group indicating that early identification of females at risk of IUGR and prompt start of sildenafil citrate prophylaxis could be reasonable and opens a new hope for those patients.*

***Keywords:*** *Intrauterine fetal demise; sildenafil citrate, pulsatility index, systolic/diastolic ratio; rate of growth; abdominal circumference.*

## Introduction

From pregnancy complications, intrauterine growth restriction (IUGR) is one of the most common and represents a major cause of iatrogenic prematurity. Abnormal placentation with placental blood flow impairment is the most frequent cause for IUGR (ACOG Practice bulletin, 2013). Fetuses with growth-restriction and severe impairment of umbilical artery blood flow are at high risk of adverse outcomes such as intrauterine fetal demise (IUFD), neonatal death, and increased neonatal morbidity, including jaundice, hypoglycemia, hypothermia, intra-ventricular bleeding, seizures, sepsis, necrotizing enterocolitis and respiratory distress syndrome (Vergani et al., 2005). In addition, studies have shown that IUGR fetuses are susceptible to development of cognitive delay in childhood as well as adulthood diseases (e.g., obesity, type 2 diabetes mellitus, coronary artery disease, and stroke) (Pallotto and Kilbride, 2006). Uterine artery Doppler sonography and a diversity of proteins & hormones have been investigated as possible early biomarkers of intra-uterine growth restriction (Cnossen et al., 2008). However, after recognizing high-risk patients, treatment policies are confined to increasing rate of screening. The only available choice to clinicians is early delivery of the baby which is itself associated with increased rate of morbidity and/or mortality (Dilworth et al., 2013).

In addition, there are still no therapeutic drugs developed specifically for intrauterine growth restriction. Such drugs are in clinical studies (Fisk and Atun, 2008). This has led to the evaluation of drugs used in clinical practice for other conditions, to be evaluated as potential therapeutics in the management of IUGR. There are two earlier studies demonstrated that sildenafil citrate significantly increases vasodilation of myometrial small vessels and fetal weight gain (Satterfield et al., 2010; von Dadelszen et al., 2011), which offers a possible therapy for IUGR. The present study was designed to evaluate the potential role of sildenafil citrate in treatment of intrauterine fetal growth restriction.

## Materials and methods

*Patients and methods*

This study was designed and carried out at Al-Azhar University hospital (New Damietta); Obstetrics and Gynecology Department. It included 100 pregnant females, with singleton pregnancy; 50 with confirmed diagnosis of IUGR and other 50 without IUGR, but has higher risk to develop IUGR. Females with singleton pregnancy with or without IUGR; gestational age between 24 weeks and 31 weeks; intact membranes; normal amniotic fluid volume; and abnormal uterine and umbilical artery Doppler waveforms were included in the study. On the other hand, females with or more of the following criteria were excluded from the study. These criteria are: confirmed congenital anomalies, TORCH infection, twin pregnancies, maternal anemia, maternal diabetes, previous hypertension or other chronic diseases, patients receiving magnesium sulfate, sensitivity to sildenafil, serum creatinine >1.0

mg/dL, fetal death, reversed blood flow of umbilical artery Doppler waveform, and eclampsia.

IUGR was defined as estimated fetal weight <10$^{th}$ percentile (ACOG Practice bulletin, 2013). Uterine artery and umbilical artery Doppler velocity waveforms considered abnormal when the PI was greater than the 95$^{th}$ percentile for gestational age (Acharya et al., 2005). Gestational age was calculated from the date of the last menstrual period and confirmed by ultrasound examination performed in the first half of the pregnancy. Maternal body mass index was defined as maternal weight divided by the square of their height (kg/m$^2$) (Kabiru and Raynor, 2004). According to study protocol, patients were allocated into one of two groups: Preventive group: included 50 pregnant females, who started administration of the drug (20mg, twice daily) after the end of first trimester and continued to the end of pregnancy or development of IUGR. Treatment group: included 50 pregnant females presented with IUGR; and started administration of the drug (20 mg, twice daily) as soon as IUGR was confirmed.

Firstly, Explanation of the study, its aim and protocol to all participants and an informed consent was attained from each female. Then full history taking and clinical examination were done. The maternal age, parity, gravidity, body mass index and gestational age at the examination were documented at the initial visit. Included females were followed until delivery and outcome and side effects were documented. Doppler velocimetry was performed during the period of absence of fetal movements and breathing. Six uniform Doppler waveforms as a minimum were measured. Pulsatility index (PI) was automatically calculated. Measurements were done on the ascending branches of the right and left uterine arteries at the point of apparent crossing with the external iliac arteries. Umbilical artery Doppler was obtained on a free loop.

Trans-abdominal color flow mapping and pulsed wave Doppler analysis of uterine and umbilical arteries was done using the GE voluson 730 Pro V (Al-Azhar University hospital) real-time machine with a 5–2-MHz transducer; and by GE logic P5 real time machine with 5-2MH transducer (General Damietta Hospital). Each sequence of measures was done three times during each examination and the results were averaged for inclusion in statistical analysis. Maternal screening included maternal arterial blood pressure measurements, proteinuria (dipstick and random protein: creatinine ratio), pulse oximetry, complete blood count, creatinine, uric acid, aspartate transaminase, bilirubin and albumin. Arterial blood pressure measurements of studied females were done using a mercury sphygmomanometer. Mean arterial blood pressure (MAP) (diastolic pressure + $^1/_3$ [Pulse pressure]) was used for comparisons. Decisions about termination of pregnancy (delivery or therapeutic abortion) were done using standard clinical assessments. For fetal maturation, antenatal betamethasone was administered once 'viability' was reached. The primary outcome for this study was the percentage of females in each group for whom fetal abdominal circumference (AC), growth velocity increased post-eligibility. Fetal growth rate (velocity) was defined as the mean daily increase in ultrasound-estimated AC. The measurements of AC were done by standardized ultrasound technique and repeated at least four times per scan, with the average AC reported (Lessoway et al., 1998). AC (in millimetres) measured at study inclusion was compared with the most recent measures of AC at least 12 days previously. The rate of the observed to expected AC increase in millimetres (δAC) was used to define the growth velocity. Thus, if the interval between ultrasound examinations was 18 days, and the actual AC increased by the equivalent of 9 days (in millimetres), the mean daily growth was believed to be 0.5. Other outcome variables included a change in PI measures of the uterine or umbilical compared with values obtained at inclusion before medication; the effect of treatment on maternal blood pressure and immediate side effects of sildenafil. In addition, occurrence of IUGR in first group and the outcome of pregnancy in both groups were considered.

*Statistical analysis of data:* Statistical presentation and analysis of the present study was conducted by statistical package for social science (SPSS) version 17 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean (mean of concentration) and standard deviation (measure of dispersion), while categorical variables were expressed as frequency and percent distribution. For comparison between both groups, unpaired (t) test and Chi square test were used for quantitative and qualitative data respectively. P value < 0.05 was considered significant.

**Results**

In the present work, maternal age ranged from 20 to 31 years; and there was statistically non-significant difference between preventive and treatment groups as regard to age (26.50± 2.10 vs 26.28±2.42 respectively). In addition, there was no statistically significant difference between preventive and treatment groups as regard weight, height or BMI. Parity ranged from 1 to 4 and there was statistically non-significant difference between preventive and treatment groups (2.14±0.53 vs 2.06±0.59 respectively). Proteinuria in studied females was reported in 22% of preventive group and 28% of treatment group with no statistically significant difference between both groups. Protein/creatinine ratio ranged from 30 to 100 mg/g protein and there was no statistically significant difference between preventive and treatment group (51.84±14.69 vs 54.06±12.95 mg/g protein respectively) (Table 1).

At inclusion, maternal heart rate ranged from 74 to 84 beats/minutes, while just before delivery, it ranged from 73 to 88 and there was no statistically non-significant difference between preventive and treatment groups at inclusion or just before delivery. In addition, values of heart rate at the end were no statistically significant difference when compared to corresponding values at inclusion in each of studied groups. Mean arterial pressure at inclusion ranged from 73.33 to 95.0 mmHg, while just before delivery, MAP ranged from 73.33 to 83.33 mmHg; and there was no significant difference between both preventive and treatment groups either at inclusion or just before the delivery. On the other hand, mean arterial pressure was significantly decreased just before delivery when compared to corresponding values at inclusion in preventive group (78.13±2.68 vs 83.63±5.48 respectively) and treatment group (78.23±2.70 vs 84.73±6.02 respectively). Gestational age at inclusion ranged from 24 to 31 weeks, and there

was no significant difference between group A and B; and at delivery, gestational age ranged from 27 to 39 weeks of gestation and there was statistically significant increase of gestational age at preventive when compared to treatment group (36.62±2.22 vs 35.58±2.49 weeks respectively) (Table 2). Both groups were comparable (no significant difference as regard to RBCs, hemoglobin, WBCs, platelets, creatinine, uric acid, AST, bilirubin and albumin.

Birth weight (g) ranged from 900 to 3420; and there was statistically significant increase of birth weight in preventive when compared to treatment group (2704.48±384.55 vs 2462.62±484.77 respectively). Prematurity was reported in 36.0% of preventive group compared to 66.0% of treatment group, with statistically significant increase of prematurity in treatment when compared to preventive group. Still birth in studied groups was reported in 4.0% of preventive group compared to 8.0% in treatment group; with no significant difference between both groups (Table 3). Pulsatility index at inclusion ranged from 1.08 to 1.32; while just before delivery, PI ranged from 0.80 to 1.30 and there was no significant difference between preventive and treatment groups either at inclusion or just before delivery. On the other hand, there was statistically significant decrease in PI just before delivery when compared to corresponding values at inclusion in preventive group (1.01± 0.06 vs 1.189±0.06 respectively) or in treatment group (1.02±0.07 vs 1.209±0.06 respectively). SD ratio of uterine artery at inclusion, it ranged from 2.40 to 3.50; and there was statistically significant decrease in preventive group when compared to treatment group (2.98±0.25 vs 3.18±0.13 respectively). In addition, SD ratio just before delivery ranged from 2.30 to 3.0 with significant decrease in preventive when compared to treatment group (2.56±0.16 vs 2.63±0.16 respectively). Furthermore, there was statistically significant decrease of SD ratio at the end when compared to basal values in each of studied groups. Pulsatility index of umbilical artery at inclusion ranged from 1.08 to 1.40; while just before delivery, PI ranged from 0.80 to 1.12 and there was no significant difference between preventive and treatment groups either at inclusion or just before delivery. On the other hand, there was statistically significant decrease in PI just before delivery when compared to corresponding values at inclusion in preventive group or in treatment group. Umbilical artery SD ratio at inclusion ranged from 2.30 to 3.50; and there was statistically significant decrease in preventive group when compared to treatment group. In addition, umbilical SD ratio just before delivery ranged from 2.20 to 3.0 with significant decrease in preventive when compared to treatment group. Furthermore, there was statistically significant decrease of SD ratio at the end when compared to basal values in each of studied groups (Table 4).

AC at inclusion ranged from 13 to 19 cm with statistically significant increase in preventive when compared to treatment group (16.68±1.53 vs 15.72±1.44 cm respectively). Just before delivery, AC ranged from 13 to 24 cm with significant increase in preventive when compared to treatment group (21.80±1.74 vs 19.02±1.49 cm respectively). Rate of growth (Increase of abdominal circumference) was ranged from 0 to 9.0 cm; and there was statistically significant increase in preventive group when compared to treatment group (5.12±2.17 vs 3.30±1.65 respectively). Thus, the rate of growth was significantly higher in preventive group (Table 4). As regard to side effects, it was in the form of headache (6.0% and 4.0% in groups A and B respectively), facial flushing (8.0% and 10.0% in groups A and B respectively), maternal tachycardia (2.0% and 0.0% in groups A and B respectively), and while fetal tachycardia was not reported in any of studied females. There was no statistically significant difference between both groups.

**Table 1:** Patient characteristics in studied groups

| Variable | Group A: preventive | Group B: therapeutic | P value |
|---|---|---|---|
| Age (year) | 26.50±2.10 | 26.28±2.42 | 0.62 |
| Weight (kg) | 66.26±3.12 | 65.92±3.09 | 0.58 |
| Height (m) | 1.650±0.026 | 1.645±0.025 | 0.40 |
| BMI (kg/m$^2$) | 24.31±0.56 | 24.32±0.48 | 0.97 |
| Parity | 2.14±0.53 | 2.06±0.59 | 0.47 |
| Proteinuria | 11(22.0%) | 14(28.0%) | 0.49 |
| Protein/cr ratio | 51.84±14.69 | 54.06±12.95 | 0.42 |

**Table 2:** Maternal heart rate, mean arterial pressure and gestational age, at inclusion and just before delivery in studied groups

| | | Group A | Group B | p |
|---|---|---|---|---|
| Heart | At inclusion | 79.30±2.99 | 79.42±3.52 | 0.85 |
| rate | Just before delivery | 79.10±2.76 | 79.44±3.55 | 0.59 |
| Mean arterial | At inclusion | 83.63±5.48 | 84.73±6.02 | 0.34 |
| Pressure | Just before delivery | 78.13±2.68$^{\#}$ | 78.23±2.70$^{\#}$ | 0.35 |
| Gestational | At inclusion | 27.54±1.43 | 27.64±1.57 | 0.70 |
| Age | Just before delivery | 36.62±2.22 | 35.58±2.49 | 0.030* |

*#=Significant decrease just before delivery when compared to corresponding values at inclusion' * = significant difference between both groups.*

**Table 3:** Fetal outcome in studied groups

| Variable | Group A: preventive | Group B: Therapeutic | P value |
|---|---|---|---|
| Birth weight | 2704.48±384.55 | 2462.62±484.77 | 0.007* |
| Prematurity | 18(36.0%) | 33(66.0%) | 0.003* |
| Still birth | 2(4.0%) | 4(8.0%) | 0.40 |

** = significant difference between both groups.*

**Table 4:** Doppler indices and rate of growth in studied groups

| | | Group A | Group B | p |
|---|---|---|---|---|
| PI of uterine artery | At inclusion | 1.189±0.06 | 1.209±0.06 | 0.11 |
| | Just before delivery | 1.01±0.06# | 1.02±0.07# | 0.39 |
| S/D ratio of uterine | At inclusion | 2.98±0.25 | 3.18±0.13 | <0.001* |
| artery | Just before delivery | 2.56±0.16# | 2.63±0.16# | 0.030* |
| Umbilical artery | At inclusion | 1.20±0.07 | 1.23±0.06 | 0.08 |
| PI | Just before delivery | 0.98±0.05# | 1.0±0.07# | 0.15 |
| Umbilical artery SD | At inclusion | 2.85±0.29 | 3.05±0.14 | <0.001* |
| ratio | Just before delivery | 2.48±0.14# | 2.55±0.17# | 0.049* |
| Abdominal | At inclusion | 16.68±1.53 | 15.72±1.44 | 0.002* |
| circumference | Just before delivery | 21.80±1.74# | 19.02±1.49# | <0.001* |
| Rate of growth | | 5.12±2.17 | 3.30±1.65 | <0.001* |

*#=Significant difference between values just before delivery when compared to corresponding values at inclusion' * = significant difference between both groups.*

**Discussion**

The idea about the present study is that, the smooth muscle relaxant actions of sildenafil in male erectile dysfunction are well established (Briganti et al., 2005). Other therapeutic indications are now being examined including therapy of pulmonary hypertension (Leibovitch et al., 2007). A systematic review done by Villanueva-García et al. (2007) found no evidence of deleterious effects on pregnant women or offspring in animal studies and human case reports. Thus, it would seem that sildenafil is safe to be used in infants and pregnant females (Nagdyman et al., 2006). The objective of this study is to investigate the action of sildenafil citrate on a specific group of women with proved or probable IUGR. Results of the present study proved that, sildenafil citrate was associated with better pregnancy outcome in both studied groups. The interesting results were the enhancement of restricted growth in females with IUGR. In addition, prophylactic treatment with sildenafil citrate was associated with prevention of development of IUGR in high risk pregnancies. These results were reflected by enhancement of uterine artery indices, and increased abdominal circumference with decreased rates of still birth and prematurity in both groups. However, results in preventive group were better than treatment group indicating that early identification of females at risk of IUGR and prompt start of sildenafil citrate prophylaxis could be reasonable and opens a new hope for such patients.

Results of the present work are comparable to those reported by Trapani et al. (2016) who reported that, their study showed that sildenafil citrate use is efficient to decrease resistance to the uteroplacental blood flow and fetoplacental circulations, as well as mean maternal blood pressure. In addition, sildenafil citrate use has shown promise both in vitro as well as in animal studies in the context of IUGR (López-Tello et al., 2014; Stanley et al., 2012) and pre-eclampsia (that share the pathophysiological mechanisms with IUGR) (George et al., 2013; Karasu et al., 2012). The vasodilator properties of sildenafil were of concern, since a drop in maternal blood pressure without a concomitant increase in the uterine artery blood flow could aggravate placental under perfusion. In a previous case-control study by von Dadelszen et al. (2011), the use of sildenafil citrate (20 mg, twice daily until delivery) in pregnancies complicated by severe IUGR (defined as abdominal circumference < 5$^{th}$ percentile and either gestational age < 25 weeks or estimated fetal weight < 600 grams) was associated with a significant increase in abdominal circumference compared to the control group. However, hemodynamic changes to the uteroplacental, fetoplacental, or fetal cerebral circulations were not evaluated in that study.

The decrease in uterine and umbilical artery PIs with the use of sildenafil has been previously shown in case reports (Lin et al., 2012) as well as in randomized double blinded placebo-controlled study in IUGR fetuses by Dastjerdi et al. (2012). Going with results of the present work, Panda et al. (2014) concluded that, to obtain ideal fetal growth, satisfactory blood flow in uteroplacental vascular effects is essential. Abnormal vasculature alteration, leading to abnormal blood flow, has been concerned as a potential cause of fetal growth demise though Samangaya et al. (2009) ruled out prolonged gestation in female with preeclampsia using Sildenafil. Sildenafil, as a vasodilator has also arose as a possible management choice in the management of fetal growth restriction (FGR) and preeclampsia by later normalization in velocimetric profile. Results of the present study confirmed previous results of an animal study, where low doses of Sildenafil favored fetal tolerability to induced intrapartum asphyxia and high doses of Sildenafil increased the fetal weight by 1.5 times (Sánchez-Aparicio et al., 2008). In addition, improved growth of a fetus with growth restriction whose mother is treated with Sildenafil for pulmonary hypertension is noted (Lacassie et al., 2004). Incubation with Sildenafil citrate limits the actions of vasoconstrictors on myometrial small vessels of normal gestation women and pregnant female with fetal growth restriction. So that phosphodiesterase inhibitors appear to increase

uterine perfusion with high safety in gestations with fetal growth restriction. In addition, it was reported that, decreased flow / increased resistance in uterine and umbilical vessels, indicative of decreased uteroplacental flow in gestations with fetal growth restriction, has been documented by non-invasive Doppler ultrasound velocimetry (Wareing et al., 2005). Furthermore, Dastjerdi et al. (2012) reported that, their study evaluated the action of Sildenafil citrate on uteroplacental perfusion in fetal growth restriction gestations and concluded that Sildenafil 50mg was linked with significant changes in the fetoplacental Doppler flow velocimetry waveforms, when compared to controls. This theory arises from the similarities between the pathophysiology link between preeclampsia and FGR due to a potential placental hypoperfusion. The study revealed that FGR gestations managed by Sildenafil revealed significant enhancements in umbilical and middle cerebral vessels Doppler velocimetry. Other study revealed that birth weight was significantly reduced in patients with persistent abnormal velocimetric profile versus those with normal velocimetry at 24 weeks gestation or those with later normalization. Efforts for later normalization of fetoplacental perfusion in FGR gestations with placental aberrations might increase fetal birth weight. Growth restriction due to placental irregularities is usually the consequence of insufficient substrates for fetal metabolism and reduced oxygen availability (Resnik, 2002).

Availability of nutrients to the baby exerts a vital role in fetal growth, and fetal overgrowth detected in diabetic gestations results from augmented substrate availability that induces fetal insulin production and fetal growth. To attain optimum fetal growth, satisfactory blood flow in uteroplacental vascular function is vital. Abnormal vasculature adaptation, leads to abnormal blood flow, has been involved as a potential cause of fetal growth restriction. Sildenafil, as a vasodilator, should be an alternative in the management of intrauterine growth Retardation and preeclampsia by later normalization in velocimetric outline. As a therapeutic drug in FGR pregnancies by enhancing myometrial small artery vasodilatation, decreasing in maternal peripheral resistance and increasing flow within the uteroplacental bed, can hasten uteroplacental perfusion. PDE-5 inhibitors can decrease vasoconstriction and hasten relaxation of FGR myometrial small vessels (Dastjerdi et al., 2012).

As regard to side effects, results of the present study are in agreement with previous work stated that, although there is no study on its placental transfer, Sildenafil has a potentially low molecular weight and might cross the placenta and exert a direct action on fetoplacental circulation as a mild NO donor in the peripheral vessels. No significant difference was found in drug complications ascribed to Sildenafil in single 50 mg. Common unwanted reactions of the administration of Sildenafil citrate in erectile dysfunction include headache, flushing, dyspepsia, congestion of nasal mucosa, urinary tract infection, aberrant vision and diarrhea, which have been described in clinical studies, may also be found in its prospective use in pregnancy (Boyce and Umland, 2001). The importance of this study is that, the treatment modalities for IUGR are limited and their benefits are not documented. Therefore, Sildenafil may represent a new therapy for these gestations. Currently, females and their families confronted with severe early-onset IUGR have two standards-of-care choices: expectant management with maternal lifestyle adjustment and maternofetal surveillance or gestation termination. Neither is pretty. Currently, there is no specific evidence-based therapy for severe early-onset IUGR. Nonspecific maneuvers include primarily the lifestyle changes of decreased work, stopping work, stoppage of aerobic exercise, rest at home and hospital admission for rest and surveillance. Although these broadly accepted interferences are not based on evidence from randomized controlled studies, they are used in the belief that rest will decrease the steal by the glutei and quadriceps from the uteroplacental circulation (von Dadelszen et al., 2011).

In conclusion, results of the present study proved the effectiveness of sildenafil citrate in treatment of and prevention of IUGR. However, due to small sample size, the results must be dealt with in caution, and future double blind randomized studies on a wide scale of patients are warranted before generalization of results of the present work.

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