Original

Evaluation of Sildenafil Citrate Therapy in the Management of Fetal Growth Restriction

Running Title: Sildenafil Citrate for Fetal Growth Restriction

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Abstract

Objective: The objective of this study was to evaluate the effectiveness of sildenafil citrate in the treatment of intrauterine growth restriction (IUGR).

Methods: This research constituted a single-group, non-randomized clinical trial with 258 pregnant women diagnosed with intrauterine growth restriction (IUGR), aged 19 to 35 years, with a gestational age of 27 weeks or greater. Each subject was administered sildenafil citrate (20 mg) thrice day until the conclusion of pregnancy. The research was performed in the Department of Obstetrics and Gynecology at Beni-Suef University Hospital and Beni-Suef General Hospital between January 2020 and December 2021. Fetal biometric measurements and Doppler ultrasound evaluations were performed before to and during sildenafil administration. The principal outcome measurements comprised fetal weight, amniotic fluid index (AFI), and Doppler indices. Statistical analysis was conducted utilizing SPSS version 25, with a significant threshold established at $P < 0.05$.

Results: Maternal age varied from 19 to 35 years (mean 26.39 ± 5.29 years), whereas gestational age ranged from 27 to 35 weeks (mean 33.08 ± 2.25 weeks). The treatment of sildenafil citrate led to notable enhancements in fetal biometric measures. The biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), estimated fetal weight (EFW), and amniotic fluid index (AFI) exhibited statistically significant increases. Doppler ultrasonography results revealed increased blood flow in the cerebral, umbilical, and uterine arteries, accompanied by decreased resistance and pulsatility indices, indicating enhanced uteroplacental perfusion and fetal circulation. The rate of change analysis corroborated these enhancements, emphasizing the prospective advantages of sildenafil in instances of IUGR.

Conclusion: The findings of this study suggest that sildenafil citrate significantly improves fetal growth parameters and uteroplacental blood flow in pregnancies complicated by IUGR. The observed enhancements in fetal biometric measurements and Doppler indices indicate that sildenafil may contribute to better pregnancy outcomes. However, further randomized controlled trials with larger sample sizes and long-term follow-up are necessary to establish the safety and efficacy of sildenafil citrate for managing IUGR.

Keywords: Intrauterine growth restriction, sildenafil citrate, fetal growth, Doppler ultrasound, uteroplacental circulation.

Introduction

When a baby is born weighing less than the 10th percentile for their gestational age, it is known as intrauterine growth restriction (IUGR). In the general population, it affects 5-8% of babies, making it the second most prevalent cause of low birth weight, behind preterm. According to ACOG (2013),

IUGR can cause complications in 10% to 15% of pregnancies. Perinatal problems include hypoxemia, low Apgar scores, and cord blood acidemia can adversely affect neonatal outcomes; this condition is linked to an increased risk of these complications and is a major cause of perinatal mortality, second only to preterm (Gardosi et al., 2013).

In addition to the risks that are already present during pregnancy, research in both animals and humans has linked low birth weight to an increased risk of cardiovascular complications later in life, such as diabetes, high blood pressure, abnormal lipid profiles, and abnormal blood clotting (Tideman et al., 2007). It is not always possible to determine what causes IUGR, but there are a number of factors that can be considered. External factors that impede normal foetal growth include chorioangiomas and infarctions, as well as fetal factors like infections and congenital malformations, maternal conditions like chronic hypertension and pre-gestational diabetes, and placental abnormalities (Shah et al., 2011). There are two types of placental vascular insufficiency—non-placenta-mediated and placenta-mediated growth restrictions—but the most prevalent one is intrauterine growth restriction (IUGR) (Villar et al., 2013).

Doppler evaluations of the uterine arteries, maternal blood biomarkers, and medical and obstetric history are the three main components of early IUGR screening (Baschat et al., 2000). The gold standard for predicting foetal distress and delivery outcomes is uteroplacental Doppler ultrasonography (Baschat et al., 2014). In order to gain valuable information about the placental function and the fetal well-being, the most frequent fetal vessels that are checked are the umbilical artery, the middle cerebral artery, and the ductus venosus (Harman et al., 2003). Changes in hemodynamics during intrauterine growth restriction (IUGR) include malfunction in the placenta, which causes changes in the blood flow to the middle cerebral arteries, the fetal umbilical artery, and the mother's uterus (Turan et al., 2012). As a result of fetal compensatory mechanisms, the hallmark of intrauterine growth restriction (IUGR) is an increase in resistance to blood flow in the umbilical artery and a decrease in resistance to blood flow in the middle cerebral artery (Baschat, 2011).

Despite the severe risks associated with IUGR, no effective treatment currently exists. The primary management strategy remains early delivery, which is itself associated with significant neonatal morbidity and mortality (Bernstein et al., 2009). Furthermore, there are no pharmaceutical agents specifically developed for obstetric conditions currently undergoing clinical trials. As a result,

existing drugs used for other medical conditions are being repurposed as potential therapeutic options for IUGR (Fisk et al., 2010).

By controlling arterial relaxation and hence enhancing the fetus's supply of oxygen and nutrients, nitric oxide (NO) plays an important function in foetal development. Nitric oxide synthases (NOS) produce NO, which relaxes smooth muscles by raising levels of cyclic guanosine monophosphate (cGMP). According to Jancoa Chen et al. (2016), IUGR may have its pathogenesis connected to an insufficiency of NO availability. The selective phosphodiesterase type 5 (PDE5) inhibitor sildenafil citrate promotes vasodilation by increasing NO activity through blocking the breakdown of cyclic guanosine monophosphate (cGMP). According to Wareing et al. (2005), sildenafil has a vasodilatory effect that could boost fetal oxygen and nutrient delivery, relax the tiny arteries of the myometrium, and increase blood flow to the uteroplacenta. Nevertheless, additional research is required because there is a lack of comprehensive clinical data on the safety and effectiveness of sildenafil during pregnancy. The research team behind this study set out to find out how well sildenafil citrate worked for treating IGR.

Methodology

Study Design and Population

This clinical experiment included 258 pregnant women who were diagnosed with intrauterine growth restriction (IUGR). It was a single-group, non-randomized research. At the time of registration, participants' gestational ages were 27 weeks or older, and their ages ranged from 19 to 35 years. From the beginning of the trial to the end of the pregnancy, all participants took 20 mg of sildenafil citrate three times day.

Study Setting

The study was conducted in the Department of Obstetrics and Gynecology at Beni-Suef University Hospital and Beni-Suef General Hospital. Data collection took place over a two-year period, beginning in January 2020 and concluding in December 2021.

Recruitment and Sample Selection

Participants were identified based on predefined inclusion and exclusion criteria. Eligible women were invited to participate in the study, and written informed consent was obtained before enrollment. The sample size was determined based on the primary outcome of fetal growth, specifically the abdominal circumference (AC). According to previous studies, the mean fetal AC growth rate increased from approximately 0.08 ± 0.4 pre-treatment to 0.15 ± 0.3 post-treatment. A sample size of 258 patients was calculated to detect a difference of 0.07 with 80% power at a significance level of $\alpha = 0.05$, using a paired t-test. Sample size calculations were performed using StatsDirect statistical software (version 2.7.2, StatsDirect Ltd., Cheshire, UK).

Inclusion and Exclusion Criteria

Participants were included if they had a confirmed last menstrual period (LMP), were diagnosed with asymmetrical IUGR via fetal biometry, had a singleton pregnancy, were at least 27 weeks gestational age, and were capable of attending scheduled follow-ups. Women with maternal cardiovascular conditions, known or suspected fetal anomalies, urgent indications for delivery, history of smoking, drug, or alcohol abuse, obstetric complications such as intrauterine infection, bleeding, or premature rupture of membranes, or difficulty adhering to follow-up visits were excluded from the study.

Clinical Assessment and Data Collection

A detailed medical history was taken from each participant, including personal information, presenting complaints, menstrual and obstetric history, and past and family medical history. Physical examinations were performed, including general assessments of vital signs and local obstetric examinations, such as fundal height measurement. Laboratory investigations were conducted, including complete blood count (CBC), fasting blood sugar (FBS), two-hour postprandial blood sugar (2HPP BS), and urine analysis.

Treatment Protocol

All enrolled participants received sildenafil citrate at a dosage of 20 mg three times daily. Patients were advised to maintain bed rest and increase oral fluid intake to enhance amniotic fluid levels and optimize placental circulation. The treatment regimen continued until fetal maturity or until termination of pregnancy, as clinically indicated.

Fetal Monitoring and Follow-Up

Fetal Doppler ultrasound assessments were conducted every four weeks before and after sildenafil administration. The pregnancy was allowed to continue as long as fetal growth was sustained and fetal evaluations remained within normal parameters. If growth restriction worsened or other complications arose, clinical management was adjusted accordingly.

Doppler Ultrasound Technique

Patients were positioned in a supine, slightly left-lateral position to avoid supine hypotension syndrome, which could affect Doppler readings. The umbilical artery was identified based on its characteristic waveform pattern. Measurements were taken twice for each vessel, and the mean value was recorded to ensure accuracy.

Doppler Parameters Measured

Doppler parameters were evaluated before and four weeks after sildenafil administration. The primary assessments included placental and fetal Doppler parameters, pulsatility index (PI) and resistance index (RI) of the umbilical artery, and blood flow analysis using a triplex system incorporating two-dimensional imaging, color Doppler, and pulsed Doppler. Measurements were taken from the midpoint of the umbilical artery, between the placental and abdominal insertions.

Potential Risks

Potential adverse effects of sildenafil citrate, including headache, hypotension, and tachycardia, were explained to all participants before enrollment. Patients were monitored for any side effects throughout the study.

Outcome Measures

The primary outcome measures included fetal weight, amniotic fluid index (AFI), and Doppler indices. Secondary outcomes included gestational age at delivery, the duration between randomization and delivery, and birth weight.

Statistical Analysis

All collected data were coded, entered, and analyzed using SPSS software (version 25). Descriptive statistics were applied, with categorical variables presented as percentages and continuous variables summarized as mean and standard deviation. Cross-tabulation and chi-square ($\chi 2$) tests were used to compare categorical variables. The paired sample t-test was used to compare pre- and post-intervention means, while rate of change calculations were conducted to assess the magnitude of improvement. Pearson correlation analysis was performed to evaluate linear relationships between variables, with statistical significance set at $P < 0.05$.

Ethical Considerations

The study was approved by the Ethics & Research Committee (ERC) of the Department of Obstetrics and Gynecology, Faculty of Medicine, Beni-Suef University. It was conducted in compliance with institutional policies and national regulatory guidelines. Participants were fully informed of the study's objectives, potential risks, and their rights before providing written informed consent. Confidentiality was maintained by anonymizing all patient records, reports, and evaluation forms to ensure the privacy of study participants.

Results

This study included 258 pregnant women diagnosed with intrauterine fetal growth restriction (IUGR). The maternal age at the beginning of the study ranged from 19 to 35 years, with a mean age of 26.39 ± 5.29 years. The gestational age at the start of the study ranged from 27 to 35 weeks, with a mean of 33.08 ± 2.25 weeks.

Following sildenafil citrate administration, significant improvements were observed in fetal biometric measurements. The biparietal diameter (BPD) increased significantly after four weeks of treatment. Similarly, head circumference (HC) showed marked improvement, indicating enhanced fetal growth. Abdominal circumference (AC) exhibited a statistically significant increase, reflecting improved nutritional status and fetal development. Femur length (FL) also increased, further supporting the positive impact of sildenafil on fetal growth. Estimated fetal weight demonstrated a notable rise, suggesting improved overall fetal well-being. Additionally, the amniotic fluid index (AFI) significantly increased after treatment, indicating better intrauterine conditions for fetal development.

Table (1): Fetal Biometry before and two weeks after Sildenafil citrate administration; (N= 258)

Fetal Biometry	Pre-Sildenafil (Mean ±SD)	4W Post-Sildenafil (Mean ±SD)	p-value
BPD	13.67 ±20.56	15.32 ±20.57	0.030*
HC	278.79 ±26.34	295.43 ±29.82	0.002*
AC	25.34 ±1.78	28.39 ±1.79	<0.001*
FL	5.78 ±0.71	6.48 ±0.81	0.004*
Wt.	1561.87 ±316.27	1912.57 ±361.27	<0.001*
AFI	7.78 ±1.24	10.51 ±1.28	<0.001*

**p-value ≤0.05 is considered statistically significant by Paired Sample t-test. BPD (biparietal diameter), HC (head circumference), AC (abdominal circumference), FL (femur length), AFI: (Amniotic Fluid Index)*

Doppler ultrasound findings showed significant changes in blood flow parameters, further supporting the effectiveness of sildenafil citrate. In the cerebral artery, blood flow velocity significantly increased, while the resistance and pulsatility indices decreased, reflecting improved cerebral perfusion. The umbilical artery exhibited a decrease in both the resistance and pulsatility indices, suggesting improved placental circulation. Similarly, in the uterine artery, blood flow increased significantly, while both the resistance and pulsatility indices decreased, indicating enhanced uteroplacental circulation.

Table (2): Doppler Findings before and four weeks after Sildenafil citrate administration:

Doppler	Artery	Pre-Sildenafil (Mean ±SD)	4W Post-Sildenafil (Mean ±SD)	p-value
BF	Cerebral	35.93 ±5.91	40.80 ±6.63	<0.001*
RI	Cerebral	0.82 ±0.03	0.76 ±0.03	<0.001*
PI	Cerebral	1.88 ±0.08	1.57 ±0.14	<0.001*
RI	Umbilical	0.80 ±0.02	0.75 ±0.03	0.003*
PI	Umbilical	1.89 ±0.06	1.77 ±0.10	<0.001*
BF	Uterine	452.39 ±90.99	538.51 ±94.32	<0.001*
RI	Uterine	0.55 ±0.07	0.48 ±0.04	<0.001*
PI	Uterine	0.80 ±0.22	0.75 ±0.20	0.044*

**P-value ≤0.05 is considered statistically significant by Paired Sample t-test. Resistance index (RI), Pulsatory index (PI), blood flow (BF).*

The rate of change in Doppler findings before and after sildenafil administration further confirmed these improvements. Cerebral artery blood flow showed a substantial increase, while the resistance and pulsatility indices displayed a notable decline. The umbilical artery exhibited a decrease in resistance and pulsatility indices, further supporting better placental function. In the uterine artery, blood flow increased markedly, while the resistance and pulsatility indices showed a decrease, demonstrating enhanced maternal-fetal blood exchange.

Table (3): Rate of Change in Doppler Findings before and four weeks after Sildenafil citrate administration:

Doppler	Artery	Minimum	Maximum	Mean	±SD
BF	Cerebral	1.7	10	4.86	2.32
RI	Cerebral	-0.14	-0.02	-0.05	0.03
PI	Cerebral	-0.59	-0.11	-0.31	0.12
RI	Umbilical	-0.12	0	-0.04	0.03
PI	Umbilical	-0.2	0.05	-0.11	0.04
BF	Uterine	7.62	40.55	20.23	11.89
RI	Uterine	-0.17	-0.02	-0.07	0.03
PI	Uterine	-0.11	0.1	-0.04	0.05

Rate of change was calculated by calculating the difference between pre- and post- assessment then divided by the original pre assessment and finally multiplied by 100.

Overall, these findings suggest that sildenafil citrate administration significantly improved fetal growth parameters and blood flow characteristics. The observed enhancements in fetal biometric measurements and Doppler parameters indicate that sildenafil may contribute to better pregnancy outcomes in cases of IUGR by improving uteroplacental and fetal circulation, thereby supporting fetal development and overall well-being.

Discussion

Intrauterine growth restriction (IUGR) is a significant contributor to perinatal morbidity and mortality, often necessitating referral to tertiary care centers (Shehata et al., 2020). Despite various treatment approaches, no single therapy has been conclusively proven to be effective. Current strategies focus on improving uteroplacental perfusion to enhance fetal growth and reduce hypoxemia (Kingdom et al., 2018). Phosphodiesterase inhibitors, such as sildenafil citrate, have demonstrated potential in increasing myometrial arterial tone and placental blood flow, making them a candidate for addressing IUGR (Ganla et al., 2019).

Sildenafil citrate is a potent phosphodiesterase type 5 (PDE5) inhibitor, widely used for vascular conditions such as erectile dysfunction and pulmonary hypertension (Scaglione et al., 2017). Its mechanism of action enhances the effects of nitric oxide, leading to vasodilation and improved blood circulation. While its effects on fetoplacental circulation remain under investigation, several studies suggest that it may induce vasodilation in myometrial arteries, potentially alleviating placental insufficiency and promoting fetal growth (Cruz-Burgos et al., 2021; Coksuer et al., 2019; Renshall et al., 2020).

In this study, we evaluated the effectiveness of sildenafil citrate in managing IUGR through a single-group, non-randomized clinical trial involving 258 pregnant women diagnosed with IUGR. Each participant received 20 mg of sildenafil citrate three times daily until the termination of pregnancy. The results revealed significant improvements in fetal growth parameters, including abdominal circumference (AC), estimated fetal weight (EFW), and amniotic fluid index (AFI). AC increased significantly, with a rate of change of 3.05%, while EFW exhibited a 23.78% increase, and AFI improved by 2.73%.

These findings align with previous studies investigating sildenafil's role in IUGR. Research comparing sildenafil citrate with transdermal nitroglycerin found that sildenafil significantly increased fetal growth parameters (El-Bheirey, 2018). However, other studies reported no statistically significant changes in fetal biometry after sildenafil administration, suggesting variability in individual response or differences in study design (Mohammed et al., 2017; Samangaya et al., 2009).

Doppler assessments in our study indicated substantial improvements in uterine, umbilical, and cerebral artery blood flow following sildenafil administration. A significant decrease in resistance index (RI) and pulsatility index (PI) was observed in the umbilical and uterine arteries, indicative of improved placental perfusion. Similar findings have been reported in previous studies, where sildenafil increased blood flow in fetal circulation, potentially restoring normal fetal development (Abo-El Roose & Ghoneim, 2020; El-Sayed et al., 2015; von Dadelszen et al., 2011; Lin et al., 2012).

Despite these positive findings, concerns have been raised regarding sildenafil's safety during pregnancy. A Dutch study was halted after adverse neonatal outcomes, including pulmonary complications, were observed in infants exposed to sildenafil in utero. This underscores the necessity for further research to clarify the safety profile of sildenafil in pregnancy and identify potential risks associated with its use in IUGR management (Wareing et al., 2005).

Limitations

This study had several limitations. First, it was a single-arm trial without a control group, limiting the ability to compare sildenafil's effects against standard care or placebo. Second, maternal and fetal side effects were not comprehensively documented, which could have provided further insights into

the drug's safety profile. Third, long-term neurodevelopmental outcomes of infants exposed to sildenafil were not assessed, leaving uncertainties about potential delayed effects. Fourth, Doppler parameters were recorded primarily at the initiation of therapy, and more frequent measurements could have provided a clearer picture of hemodynamic changes over time. Fifth, maternal sildenafil concentration was not measured, preventing an evaluation of dose-response relationships. Additionally, only one dosage regimen was used, whereas exploring different dosages might have yielded different outcomes. Furthermore, the study exclusively included women with abnormal Doppler findings, making it unclear whether similar benefits would be observed in IUGR cases with normal Doppler results. Lastly, maternal compliance with the prescribed treatment regimen was not explicitly monitored, which could influence treatment effectiveness.

Conclusion

The findings of this study, combined with evidence from prior research, suggest that sildenafil citrate has potential benefits in improving fetal growth and uteroplacental circulation in pregnancies complicated by IUGR. The observed improvements in fetal biometry and Doppler indices indicate that sildenafil may contribute to better pregnancy outcomes by enhancing placental perfusion. However, the results must be interpreted cautiously, given the limitations of this study and the conflicting evidence from other research. Further studies with larger sample sizes, randomized controlled designs, and long-term follow-up are necessary to establish the safety and efficacy of sildenafil for managing IUGR.

Recommendations

Future research should focus on conducting randomized controlled trials with larger cohorts to validate the findings of this study. Investigating alternative dosing regimens and earlier initiation of sildenafil therapy may provide insights into optimizing treatment efficacy. Additionally, long-term follow-up studies are required to assess the neurodevelopmental outcomes of infants exposed to sildenafil in utero. Monitoring maternal sildenafil levels could help determine optimal dosing and minimize potential risks. Given the emerging concerns regarding neonatal safety, clinicians should exercise caution when considering sildenafil for IUGR management, weighing potential benefits against risks. Until further evidence is available, sildenafil should be used within research settings rather than routine clinical practice for treating IUGR.

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