# Sildenafil Citrate for Treatment of Growth Restricted Fetuses: A Randomized Controlled Trial

Thesis

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# List of Contents


| Subject | Page No. |
|---|---|
| **List of Abbreviations** | **i** |
| **List of Tables** | **iii** |
| **List of Figures** | **iv** |
| **Introduction** | **1** |
| **Aim of the Work** | **5** |
| **Review of Literature** | |
| Fetal Growth Restriction | 6 |
| Sildenafil | 45 |
| **Patients and Methods** | **57** |
| **Results** | **66** |
| **Discussion** | **82** |
| **Summary and Conclusion** | **92** |
| **Recommendations** | **95** |
| **References** | **96** |
| **Arabic Summary** | **—** |

# List of Abbreviations

| Abbr. | Full-term |
|---|---|
| **AC** | : Abdominal circumference |
| **AEDV** | : Absent end-diastolic forward velocity |
| **AEs** | : Adverse effects |
| **AFP** | : Alpha-feto proteins |
| **AFV** | : Amniotic fluid volume |
| **AGA** | : Appropriate for gestational age |
| **AUC** | : Area under curve |
| **BPD** | : Biparietal diameter |
| **cGMP** | : Cyclic guanosine mono phosphate |
| **CI** | : Confidence interval |
| **DV** | : Ductus venosus |
| **ED** | : Erectile dysfunction |
| **EDV** | : End diastolic velocity |
| **EFW** | : Estimated fetal weight |
| **FGR** | : Fetal growth restriction |
| **FHR** | : Fetal heart rate |
| **FL** | : Femur length |
| **GA** | : Gestational age |
| **HCG** | : Human chorionic gonadotrophin |
| **HPL** | : Human placental lactogen |
| **IQ** | : Intelligence quotient |
| **IUFD** | : Intrauterine fetal death |
| **IUGR** | : Intrauterine growth restriction |

**MCA** : Middle Cerebral Artery
**NO** : Nitric oxide
**PDE** : Phosphodiesterase
**PI** : Pulsatility index
**RCOG** : Royal College of Obstetricians and Gynecologists
**REDV** : Reversed end-diastolic forward velocity
**RI** : Resistance index
**S/D** : Systolic/ Diastolic ratio
**SD** : Standard deviation
**SGA** : Small–for–gestational age
**SPET** : Severe preeclampsia
**SPSS** : Statistical Package for Social Sciences
**TCD** : Transverse cerebellar diameter
**UA** : Umbilical artery
**UV** : Umbilical vein
**UTA** : Uterine artery
**VTE** : Venous thromboembolism

# List of Tables


| Table No. | Title | Page No. |
|---|---|---|
| **Table (1):** | Adverse events reported by ≥ 2% of patients treated with (sildenafil citrate) and more frequent on drug than placebo in flexible-dose phase ii/iii studies. | 49 |
| **Table (2):** | Demographic characteristics among the studied groups | 67 |
| **Table (3):** | Comparison between both groups as regard Umbilical artery resistive index | 68 |
| **Table (4):** | Comparison between both groups as regard fetal gestational age (weeks) at time of delivery | 70 |
| **Table (5):** | Comparison between both groups as regard fetal weight (gm) at time of delivery | 72 |
| **Table (6):** | Comparison between both groups as regard the change in the SBP (mmHg) | 74 |
| **Table (7):** | Comparison between both groups as regard the change in the DBP (mmHg) | 76 |
| **Table (8):** | Comparison between both groups as regard maternal side effects | 78 |
| **Table (9):** | Comparison between both groups as regard neonatal condition | 80 |

# List of Figures


| Figure No. | Title | Page No. |
|---|---|---|
| **Figure (1):** | Relation between gestational age and AFI | 29 |
| **Figure (2):** | Organic structure of sildenafil | 45 |
| **Figure (3):** | Silden® | 59 |
| **Figure (4):** | Placebo | 59 |
| **Figure (5):** | Consort, Patient flow chart. | 66 |
| **Figure (6):** | Umbilical artery resistive index among the studied groups | 69 |
| **Figure (7):** | Fetal gestational age among the studied groups | 71 |
| **Figure (8):** | Fetal weight among the studied groups | 73 |
| **Figure (9):** | SBP among the studied groups | 75 |
| **Figure (10):** | DBP among the studied groups | 77 |
| **Figure (11):** | Maternal side effects among the studied groups | 79 |
| **Figure (12):** | Neonatal condition among the studied groups | 81 |

## Abstract

**Background:** Fetal growth restriction is a major obstetrical problem, which represents a main cause of perinatal morbidity and mortality; it is defined as a fetal weight below the $10^{th}$ percentile for gestational age or more specifically failure of a fetus to reach its genetically determined growth potential for pathological causes. It affects approximately 3 to 7% of all pregnancies. **Aim of the work:** The aim of this study is to assess the effect of Sildenafil citrate therapy on neonatal outcomes in women with FGR. **Patients and Methods:** This prospective, double-blind, randomized, placebo-controlled clinical trial was conducted at Ain Shams University Maternity Hospital on Sixty Pregnant women with FGR and color Doppler velocimetry changes in the umbilical artery, in the period from April 2017 to December 2017 after approval of the Research and Ethics Committee of Ain Shams University Maternity Hospital, Cairo, Egypt in accordance with local research governance requirements. **Results:** The Sildenafil citrate group showed a statistically significant decrease in the umbilical artery resistance index (mean ± SD 0.09 ± 0.02), with a statistically significant increase in the fetal weight progress during pregnancy (76.0 ± 34.4) g/week and fetal gestational age at delivery (35.9 ± 0.7) weeks. But there was no statistically significant difference in the maternal side effects except for vertigo and flushing with a significant decrease in the maternal SBP and DBP. **Conclusion:** Sildenafil citrate has an effective role in the improvement of neonatal outcome in cases of FGR as regards umbilical artery Doppler indices, fetal weight progress during pregnancy and gestational age at delivery. **Recommendations:** Its usage with subcutaneous heparin is more effective than the use of heparin only. Administration of sildenafil citrate as empirical drug in the cases of FGR, as it improves the fetal outcomes and Doppler indices and has mild side effects.


**Key words:** sildenafil citrate, treatment, GRF

# Introduction

A small for gestational age (SGA) infant may be growth restricted or constitutionally small. As many as 70 percent of fetuses who are estimated to weigh below the 10th percentile for gestational age are small simply due to constitutional factors such as female sex or maternal ethnicity, parity, or body mass index. They are not at high risk of perinatal mortality and morbidity. There is a real possibility of misclassifying these normally nourished, healthy, but constitutionally small fetuses as growth restricted ***(Manning, 1995)***.

**FGR** is defined as failure of a fetus to reach its genetically determined growth potential, which means that failure to grow along a consistent centile is more important than an absolute size. This definition intentionally excludes fetuses that are small for gestational age (SGA) but are not pathologically small ***(Alberry et al., 2007).***

FGR affects approximately 3 to 7% of all pregnancies ***(Neilson et al., 2003)***.

Fetal growth restriction (FGR) may be caused by fetal, placental, or maternal factors, often with contributions from multiple, overlapping factors ***(Eggermann et al., 2004)***.

Although the primary pathophysiologic mechanisms underlying these conditions are different, they often (but not

always) have the same final common pathway: suboptimal uterine–placental perfusion and fetal nutrition ***(Eydoux et al., 2012)***

Karyotypic abnormalities account for up to 20 percent of all FGR. These abnormalities are most common among growth restricted fetuses with congenital anomalies, at least 50% of fetuses with trisomy 13 or trisomy 18 have fetal growth restriction (***Eggermann et al., 2004)***.

Intrauterine infection may be the primary etiology underlying approximately 5–10% of cases of fetal growth restriction ***(Iqbal et al., 2010).***

Maternal medical conditions that may result in fetal growth restriction include any chronic disorder that is associated with vascular disease, such as pregnancy-related hypertensive diseases, Antiphospholipid syndrome, and an acquired immunemeditated thrombophilic state ***(Creasy et al., 2009).***

Clinical assessment is a reasonable screening tool for FGR in low risk pregnancies; Clinical assessment is based on assessment of past and present risk factors, physical examination, and ultrasound studies ***(Harkness et al., 2004)***.

So to diagnose fetal growth restriction information from maternal history and physical examination should be integrated with information from sonographic evaluation of the fetus, placenta, and amniotic fluid. The combined information helps

to both confirm the diagnosis and establish the etiology for the growth abnormality ***(Harkness et al., 2004)***.

The ultrasound diagnosis of FGR is based on discrepancies between actual and expected biometric measurements for a given gestational age ***(Duncan et al., 2005)***.

The combination of an estimated fetal weight less than the 10th percentile for gestational age and abnormal umbilical artery Doppler velocimetry is highly predictive of FGR and is the best tool available for identifying the growth restricted fetus at risk of adverse outcome ***(Morris et al., 2011).***

In a normal pregnancy, the trophoblast produces nitric oxide (NO) which plays an important role in vasodilatation in the fetoplacental circulation to improve oxygen and nutritional supply to the fetus. Nitric oxide relaxes arterial and venous smooth muscle potently and might inhibit platelets aggregation and adhesion ***(Ramsay et al., 1996)***.

So, Nitric oxide donors, as vasodilating agents, can be the possible therapeutic approach for embryo development and fetus growth. The umbilical vein endothelial cells in FGR do not respond to chronic hypoxia, which may lead to fetoplacental vasoconstriction. As a locally potent vasodilator, nitric oxide helps regulate perfusion by counter balancing the effects of other vasoactive agents ***(Nanetti et al., 2008)***.

Sildenafil citrate is a selective inhibitor of cyclic guanosine mono phosphate (cGMP)–specific phosphodiesterase (PDE)-5 and enhances cGMP accumulation elicited by exogenous and neural-released nitric oxide which enhances smooth muscle relaxation, thus causes vasodilatation. So it increases uterine blood flow and potentiates estrogen-induced vasodilation ***(Ballard et al., 1998; Jerzak et al., 2008)***.

There does not appear to be any severe adverse maternal side effects nor any increase in the rate of stillbirths, neonatal deaths, or congenital anomalies attributed to sildenafil citrate ***(Dunn et al., 2016)***.

A double-blind, placebo-controlled study was conducted in Iran to study the effect of Sildenafil citrate on women with fetal Growth Retardation (FGR) as regard color flow Doppler guidance on the umbilical and middle cerebral, before and after 2 hours of tablet ingestion ***(Marzieh et al., 2012).***

They found that means of the umbilical artery (UA) pulsatility index (PI) and Systolic/ Diastolic ratio (S/D) significantly decreased after Sildenafil ingestion as compared to the placebo group. In middle cerebral arteries, a significant increase was noted in mean Pulsatility Index (PI), resistance index (RI) and Systolic/Diastolic ratio (S/D) after Sildenafil administration, with no significant improvement was detected in the control group ***(Marzieh et al., 2012).***

# Aim of the Work

## *Research Hypothesis*

In women with FGR, Sildenafil citrate therapy may improve neonatal outcomes.

## *Research Question*

In women with FGR, does Sildenafil citrate improve neonatal outcomes?

## *Study objective*

The aim of this study is to assess the effect of Sildenafil citrate therapy on neonatal outcomes in women with FGR.

# Fetal Growth Restriction

## ➢ *Definitions:*

**Low birth weight (LBW)** refers to an infant with a birth weight < 2500 g ***(Clausson et al., 2001)***.

**Small–for–gestational age (SGA)** refers to an infant born with a birth weight less than the 10th centile for gestational age. Definitions of SGA birth and severe SGA vary. SGA birth is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th centile and severe SGA as an EFW or AC less than the 3rd centile ***(Clausson et al., 2001)***.

**Fetal growth restriction (FGR)** is not synonymous with SGA. **FGR** is defined as failure of a fetus to reach its genetically determined growth potential, which means that failure to grow along a consistent centile is more important than an absolute size. This definition intentionally excludes fetuses that are small for gestational age (SGA) but are not pathologically small. Some, but not all, growth restricted fetuses/infants are SGA, while 50–70% of SGA fetuses are constitutionally small, with fetal growth appropriate for maternal size and ethnicity. The likelihood of FGR is higher in severe SGA infants ***(Alberry et al., 2007).***